

# Leitlinienreport S3-Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplem Myelom

Version 1.0 - Februar 2022

AWMF-Registernummer: 018/035OL

Leitlinienreport

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# 1. Informationen zum Leitlinienreport

## 1.1. Autoren des Leitlinienreports

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- Prof. Dr. Dr. Christof Scheid

## 1.2. Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Deutschen Krebsgesellschaft (DKG) und Deutschen Krebshilfe (DKH).

## 1.3. Federführende Fachgesellschaft der Leitlinie



Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

## 1.4. Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

## 1.5. Kontakt

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## 1.6. Zitierweise des Leitlinienreports

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplem Myelom, Leitlinienreport 1.0, 2022, AWMF Registernummer: 018/035OL, <https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom/> (Zugriff am TT.MM.JJJJ)

## 1.7. Gender-Disclaimer

Aus Gründen der besseren Lesbarkeit wird in dieser Leitlinie das generische Maskulinum verwendet. Weibliche und anderweitige Geschlechteridentitäten werden dabei ausdrücklich mitgemeint.

## 1.8. Weitere Dokumente zur Leitlinie

Die Leitlinie liegt als Lang- und Kurzversion vor. Außerdem wird es eine Patientenleitlinie (Laienversion der Leitlinie) geben. Alle Dokumente zur Leitlinie sind über die folgenden Seiten zugänglich:

- AWMF (<http://www.awmf.org/leitlinien/aktuelle-leitlinien.html>)
- Leitlinienprogramm Onkologie <https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom/>
- Guidelines International Network ([www.g-i-n.net](http://www.g-i-n.net))
- Beteiligte Fachgesellschaften (z. B. DGHO)

Die Leitlinie ist außerdem in der App des Leitlinienprogramms Onkologie enthalten.

Weitere Informationen unter: <https://www.leitlinienprogramm-onkologie.de/app/>



## 1.9. Abkürzungsverzeichnis

Abkürzung	Erläuterung
18-FDG	18-Fluorodesoxyglucose
AAPV	Allgemeine Ambulante Palliativversorgung
ACR	Albumine Creatinine Ratio
ADC-Parameterkarten	Apparent Diffusion Coefficient-Parameterkarten
ADL	Activities of Daily Living
AE	adverse event/ unerwünschtes Ereignis
AGIHO	Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie
AH-Amyloidose	Schwerketten-Amyloidose
AHB	Anschlussrehabilitation
AHL-Amyloidose	Heavy and light chain amyloidosis
AK	Antikoagulanz
AKI	Akutes Nierenversagen
AL-Amyloidose	Leichtketten-Amyloidose
APV	Amprenavir
AR	Außenrotation
ASCO	American Society of Clinical Oncology
ASCT	Autologe Stammzelltransplantation
ASS	Acetylsalicylsäure
ASZT	Autologe Stammzelltransplantation
Auto-TX	Auto-Transplantation
BAR	Bundesarbeitsgemeinschaft für Rehabilitation e.V.
BWS	Brustwirbelsäule
CAD	Cyclophosphamid, Adriamycin, Dexamethason
CCI	Charlson-Komorbiditätsindex
CCO	Cancer Care Ontario
CI	Konfidenzintervall
CipN	Chemotherapie-induzierte Poly-Neuropathie
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-MBD	Chronic Kidney Disease Mineral and Bone Disorder
CR	Complete response/ vollständige Remission
CRAB	Calcium, Renal insufficiency, Anaemia and Bone lesions
CRP	C-reaktives Protein
CR-Rate	Complete response rate
CT	Computertomografie

Abkürzung	Erläuterung
CZE	Capillarzonenelektrophorese
DFS	Disease-free survival
DGHO	Deutsche Gesellschaft für Hämatologie und medizinische Onkologie
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DKG	Deutsche Krebsgesellschaft
DRV	Deutsche Rentenversicherung
D-VTd	Daratumumab, bortezomib, thalidomid, dexamethason
DWI	Diffusion Weighted Imaging
EANM	European Association of Nuclear Medicine
EBM	Evidenz basierte Medizin
EBMT	The European Society for Blood and Marrow Transplantation
eCFR	Electronic Code of Federal Regulations
ECOG	Eastern Cooperative Oncology Group
EFNS	European Federation of Neurological Sciences
eGFR	epidermal growth factor receptor
EK	Expertenkonsens
EMN	European Myeloma Network
EMP	Extrameduläres Plasmozytom
EORTC	European Organization for Research and Treatment of Cancer
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDG	Fluordesoxyglukose
FDG-PET	Fluordesoxyglukose-Positronenemissionstomograph
FGFR	Fibroblast growth factor receptors
FISH	Fluoreszenz-in-Situ-Hybridisierung
FL	follikuläres Lymphom
FLC	Freie Leichtketten
G-BA	Gemeinsamer Bundesausschuss
GFR	glomeruläre Filtrationsrate
GK-CT	Ganzkörper-Computertomographie
GK-MRT	Ganzkörper-Kernspintomographie
GKV	Gesetzliche Krankenversicherung
GPT	Glutamat-Pyruvat-Transaminase

Abkürzung	Erläuterung
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GVHD	Graft-Versus-Host-Reaktion
Hb	Hämoglobin
HCV	Hepatitis-C-Virus
HD	Hochdosis
HIB	Haemophilus influenzae Typ b
HIV	Humane Immundefizienz-Virus
HR	Hazard ratio
IADL	Instrumental Activities of Daily Living
ICD-10	Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme
ICF	Internationalen Klassifikation der Funktionsfähigkeit, Behinderung und Gesundheit
IE	Internationale Einheiten
IFM	Intergruppe Francophone du Myélome
iFOBT	immunologische fäkale Okkultbluttest
IG	immunoglobulin
IL	Interleukin
IMiD	Immunmodulierende Substanzen
IMWG	International Myeloma Working Group
IMWG-FI	IMWG-Frailty Index
IPOS	Integrierte Palliative Outcome Scale
ISCN	International System for Human Cytogenetic Nomenclature
ISS	International Staging System
JACIE	Joined Accreditation Committee der ISCT (International Society for Cellular Therapy) und EBMT (European Group for Blood and Marrow Transplantation)
JÜR	Jahresüberlebensrate
KCD	Carfilzomib, Cyclophosphamide, Dexamethasone
KDIGO	Kidney Disease Improving Global Outcomes (KDIGO) initiative
KOF	Körperoberfläche
KPS	Karnofsky Performance Status
KRINKO	Kommission für Krankenhaushygiene und Infektionsprävention
LDH	Lactatdehydrogenase
LK	Leichtkette
LL	Leitlinie

Abkürzung	Erläuterung
LoE	Level of evidence
LWS	Lendenwirbelsäule
MGRS	Monoklonale Gammopathie renaler Signifikanz
MGUS	Monoklonale Gammopathie unklarer Signifikanz
MIDOS	Minimale Dokumentationsystem
MM	Multiple Myelom
MMR	Masern, Mumps, Röteln
MR	Minimales Ansprechen
MRD	Minimale Resterkrankung
MRI	Magnetresonanztomografie
MRT	Magnetresonanztomografie
MY-RADS	Myeloma Response Assessment and Diagnosis System
nCR	nahezu komplette Remission
NDMM	Neudiagnostiziertes Multiple Myelom
NGF	next generation flow
NGS	Next-Generation Sequencing
NICE	National Institute for Health and Clinical Excellence
NMA	Netzwerk Metaanalyse
NMH	niedermolekulare Heparine
NSAID	nichtsteroidales Antirheumatikum
NSAR	nichtsteroidales Antirheumatikum
OS	Overall Survival/ Gesamtüberleben
Osteo-CT	Knochendichtemessung
PCR	Polymerase-Kettenreaktion
PET	Positronenemissionstomographie
PFS	progression-free survival/ Progressionsfreies Überleben
PI	Proteasom Inhibitor
PNS	Peripheres Nervensystem
POEMS	Polyneuropathie, Organomegalie, Endokrinopathie, Monoklonale Gammopathie und Hautveränderungen (Skin)
POEMS-Syndrom	Polyneuropathie, Organomegalie, Endokrinopathie, Monoklonale Gammopathie und Hautveränderungen (Skin)-Syndrom
PR	partial response
PROM	Patient-Reported-Outcome-Messung
PZL	Plasmazelleukämie
QoE	Quality of Evidence



Abkürzung	Erläuterung
QoL	Quality of Life
qPCR	quantitative PCR
RANKL	Receptor Activator of NF- $\kappa$ B Ligand
REFS	Rehabilitation following lumbar fusion surgery
rFLC	free light chain ratio
R-ISS	revised international staging system
R-MCI	Revised Myeloma Comorbidity Index
RR	risk ratio
SAE	serious adverse events/ schwere unerwünschte Ereignisse
SAKK	Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
SAPV	Spezialisierte Ambulante Palliativ-versorgung
SCR	stringent complete response
SD	Standardabweichung
SGB	Sozialgesetzbuch
SID	Secondary Immunodeficiency
SOP	Standard Operating Procedure
SP	Solitary Plasmozytom
SPE	serum protein electrophoresis
SPV	spezialisierte Palliativversorgung
SRE	skeletal-related events/ skelettassoziierte Ereignisse
STIKO	Ständige Impfkommission
SUV	standardized uptake values
SZT	Stammzelltransplantation
TEMPI-Syndrom	Telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting-Syndrome
TTP	Thrombotisch-thrombozytopenische Purpura
TX	Transplantation
VEGF	Vaskulären endothelialen Wachstumsfaktoren
VGPR	Sehr gute partielle Remission
WHO	Weltgesundheitsorganisation
ZNS	Zentralnervensystem

## 2. Geltungsbereich und Zweck der Leitlinie

### 2.1. Adressaten

Primäre Zielgruppe sind folgende Ärzte, die Patienten mit einem Multiplen Myelom (MM) behandeln oder sie im Rahmen der Nachsorge langfristig betreuen. Hier seien Onkologen, Hämatologen, Pathologen, Strahlentherapeuten, Radiologen, Nuklearmediziner, Radioonkologen, Psychoonkologen, Internisten sowie Pflegekräfte genannt. Die Leitlinie dient weiterhin zur Information für Ärzte der hausärztlichen Versorgung und Patienten mit einem Multiplen Myelom, die direkt durch eine optimierte Versorgung profitieren werden, insbesondere jene Patienten, die außerhalb von klinischen Studien therapiert werden. Die Patientenleitlinie wird die Patienten außerdem in einer partizipativen Entscheidungsfindung unterstützen.

Die nach aktueller wissenschaftlicher Erkenntnis erstellte Leitlinie wird auch Einfluss auf die Planung zukünftiger randomisierter klinischer Studien haben. So werden die Leitlinienempfehlungen in den Studien der German Multicenter Myeloma Group (GMMG) und Deutschen Studiengruppe Multiples Myelom (DSMM) berücksichtigt und implementiert werden und gewährleisten, dass die partizipierenden Zentren der GMMG und DSMM die Leitlinienempfehlungen umsetzen. Die Leitlinie dient weiterhin zur Information für:

- Ärzte der ambulanten und stationären Versorgung
- Medizinische Fachgesellschaften
- Patienten
- Organisationen der Patientenberatung
- Selbsthilfegruppen
- Qualitätssicherungseinrichtungen
- Kostenträger
- Gesundheitspolitische Entscheidungsträger

Als Versorgungsbereich für die Leitlinie gilt sowohl der ambulante als auch der stationäre Versorgungssektor. Die Leitlinie gilt für alle Patienten, unabhängig vom Alter und Geschlecht, mit einem histologisch gesicherten MM. Die Leitlinie gibt sowohl Empfehlungen für neu diagnostizierte Patienten als auch für die mit einem Rezidiv, unabhängig von Stadium oder Risikofaktoren. Außerdem werden Empfehlungen für Patienten nach einer Therapie zur strukturierten Nachsorge gegeben.

### 2.2. Zielsetzung

Das multiple Myelom tritt in Deutschland mit einer Inzidenz von 8/100.000 auf und zeigt eine steigende Tendenz. Da das durchschnittliche Erkrankungsalter bei über 70 Jahren liegt und der Anteil der älteren Menschen an der Gesamtbevölkerung steigt, ist mit weiter zunehmenden Zahlen zu rechnen.

Nachdem in den 90er Jahren mit der autologen Stammzelltransplantation erstmals eine wirksame Therapie für das multiple Myelom eingeführt wurde, hat sich die Behandlungssituation seit der Jahrtausendwende durchgreifend verändert. Immer neuere Medikamentengruppen wurden eingeführt und können in vielfältigen Kombinationen eingesetzt werden. Dabei ist heute eine Ansprechdauer von mehreren Jahren möglich und die Vielfalt der Optionen erlaubt es, immer mehr Therapielinien hintereinander zu verabreichen.

All dies erfordert aber eine sorgfältige Auswahl der Therapieoptionen in sinnvoller Sequenz, um ein möglichst langes Ansprechen zu erreichen, Organkomplikationen durch das multiple Myelom zu vermeiden und die Überlebenszeit zu verlängern.

Bei der Auswahl der Therapie müssen aber auch Patienteneigenschaften und -wünsche berücksichtigt werden. Das kalendarische Alter spielt dabei eine immer geringere Rolle, sondern die Fitness, Begleiterkrankungen und die Einstellung zur Intensität der Therapie stehen im Vordergrund. Ebenso muss beachtet werden, durch die meist über Monate bis Jahre verabreichten Therapien möglichst keine Akut- oder Spätkomplikationen zu verursachen, die dann die Lebensqualität, die durch eine erfolgreiche Kontrolle der Myelomkrankung erreicht wurde, wieder verschlechtern kann.

Die besseren Behandlungsmöglichkeiten erhöhen auch die Anforderungen an die Diagnostik, welche dabei hilft durch eine frühzeitige Entdeckung einer behandlungsbedürftigen Neuerkrankung oder eines Rezidivs weitere Organkomplikationen durch das multiple Myelom zu vermeiden.

Neben der Vermeidung von Komplikationen ist es aber auch wichtig, ein optimales Management der bereits eingetretenen Beeinträchtigungen zu definieren, da sich neben einer effizienten Myelomtherapie auch hierdurch die Lebensqualität der Patienten entscheidend verbessern lässt. Beispielhaft seien hier die Strahlentherapie, Schmerztherapie, Physio- und Bewegungstherapie sowie die onkologische Rehabilitationsbehandlung genannt.

Ziel dieser Leitlinie soll daher sein, das aktuelle Wissen zu diesem sehr umfassenden Bereich zusammenzustellen und daraus Standards für die aktuelle Diagnostik und Behandlung von Patienten mit multiplem Myelom in Deutschland abzuleiten.

## 2.3. Gültigkeitsdauer und Aktualisierungsverfahren

Die S3-Leitlinie ist bis zur nächsten Aktualisierung gültig. Die Gültigkeitsdauer beträgt maximal 5 Jahre. Vorgesehen sind regelmäßige Aktualisierungen bzw. eine kontinuierliche Überprüfung der Aktualität durch die beteiligten Fachexperten und Organisationen. Die jeweils aktuelle Version der Leitlinie kann auf den Seiten des Leitlinienprogramms Onkologie unter: <https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom/> heruntergeladen werden.

Kommentare und Hinweise für den Aktualisierungsprozess sind ausdrücklich erwünscht und können an das Leitliniensekretariat adressiert werden:

E-Mail: [multiples-myelom@leitlinienprogramm-onkologie.de](mailto:multiples-myelom@leitlinienprogramm-onkologie.de)

## 3. Zusammensetzung der Leitliniengruppe

### 3.1. Koordination und Redaktion

Prof. Dr. Nicole Skoetz	Klinik I für Innere Medizin, Uniklinik Köln
Prof. Dr. Dr. Christof Scheid	Klinik I für Innere Medizin, Uniklinik Köln
Vanessa Piechotta	Klinik I für Innere Medizin, Uniklinik Köln
Benjamin Scheckel	Klinik I für Innere Medizin, Uniklinik Köln

### 3.2. Leitliniensteuerguppe

Die folgenden Fachexperten der Leitliniensteuerguppe waren gemeinsam mit den Koordinatoren Herrn Prof. Dr. Dr. Scheid und Frau Prof. Dr. Skoetz an der konzeptionellen Leitliniengestaltung beteiligt:

- Prof. Dr. Monika Engelhardt (Freiburg, Hämatologin)
- Prof. Dr. Hartmut Goldschmidt (Heidelberg, Hämatologe)
- Prof. Dr. Hermann Einsele (Würzburg, Hämatologe)

### 3.3. Beteiligte Fachgesellschaften und Autoren

Federführende Fachgesellschaft bei der Leitlinienerstellung ist die Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO). Herausgeber der Leitlinie ist das Onkologische Leitlinienprogramm. In Tabelle 1 sind die an der Leitlinienerstellung beteiligten medizinischen Fachgesellschaften und sonstigen Organisationen sowie deren mandatierte Vertreter aufgeführt, die schriftlich vom jeweiligen Vorstand bestätigt wurden.

Tabelle 1: Beteiligte Fachgesellschaften und Organisationen

Beteiligte Fachgesellschaften und Organisationen	1. Mandatsträger	2. Mandatsträger (Vertreter)
Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	Prof. Dr. Dr. h. c. Christof Scheid Prof. Dr. med. Hartmut Goldschmidt Prof. Dr. med. Monika Engelhardt	PD Dr. Dr. med. Udo Holtick Dr. med. Marc-Steffen Raab Dr. Dr. med. Johannes Jung
AG Supportive Maßnahmen in der Onkologie (AGSMO)	PD Dr. Karin Hohloch	
AG Onkologische Rehabilitation und Sozialmedizin (AGORS)	Dr. Mario Schubert	PD Dr. Reiner Caspari
Arzneimittelkommission der deutschen Ärzteschaft (AKdÄ)	PD Dr. Sebastian Fetscher	
AG Radiologische Onkologie (ARO)	PD Dr. Robert Semrau	

Beteiligte Fachgesellschaften und Organisationen	1. Mandatsträger	2. Mandatsträger (Vertreter)
Bundesverband Deutscher Pathologen e.V. (BDP)/ Deutsche Gesellschaft für Pathologie (DGP)	Prof. Dr. med. Falko Fend	Prof. Dr. Andreas Rosenwald
Berufsverband der Niedergelassenen Hämatologen und Onkologen in Deutschland e.V. (BNHO)	Prof. Dr. med. Wolfgang Knauf	Dr. Georg Jacobs
Deutsche Arbeitsgemeinschaft für Knochenmark- und Blutstammzelltransplantation e.V. (DAG-KBT)	Prof. Dr. Nicolaus Kröger	Prof. Dr. Hermann Einsele
Deutsche Gesellschaft für Interventionelle Radiologie und minimal-invasive Therapie (DeGIR)	PD Dr. Claas Philip Nähle	
Deutsche Gesellschaft für Radioonkologie e.V. (DEGRO)	PD Dr. Daniela Trog	
Deutsche Gesellschaft für Nephrologie e.V. (DGfN)	Prof. Dr. Thomas Benzing	
Deutsche Gesellschaft für Geriatrie e.V. (DGG)	PD Dr. Valentin Goede	
Deutsche Gesellschaft für Innere Medizin e.V. (DGIM)	PD Dr. Markus Munder	
Deutsche Gesellschaft für Klinische Medizin und Laboratoriumsmedizin e.V. (DGKL)	Dr. Peter Eichhorn	
Deutsche Gesellschaft für Nuklearmedizin e.V. (DGN)	Prof. Dr. Thorsten Derlin	Prof. Dr. Constantin Lapa
Deutsche Gesellschaft für Orthopädie und Unfallchirurgie e.V. (DGOU)	Prof. Dr. Torsten Kluba	
Deutsche Gesellschaft für Palliativmedizin e.V. (DGP)	PD Dr. Steffen Simon	Dr. Christina Gerlach
Deutsche Gesellschaft für Pflegewissenschaft e.V. (DGP)	Heinrich Recken	
Deutsche Leukämie- & Lymphom-Hilfe e.V. (DLH)	Dr. Ulrike Holtkamp	Jan Lüneburg Klaus-Werner Mahfeld
Deutsches Netzwerk Versorgungsforschung e.V. (DNVF)	Dr. Walter Baumann	
Deutsche Röntgengesellschaft e.V. (DRG)	Prof. Dr. Stefan Delorme	Prof. Dr. Tim Weber
Deutsche Gesellschaft für Humangenetik e.V. (GfH)	Prof. Dr. Anna Jauch	Dr. Lana Harder

Beteiligte Fachgesellschaften und Organisationen	1. Mandatsträger	2. Mandatsträger (Vertreter)
Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e.V. (GMDS)	Dr. Borge Schmidt	
Konferenz Onkologischer Kranken- und Kinderpflege (KOK)/ Deutsche Krebsgesellschaft e.V. (DKG)	Matthias Hellberg-Naegele	
AG für Psychoonkologie (PSO)	Dr. Bianca Senf	Dirk Lang

An der Erarbeitung dieser S3-Leitlinie waren die beiden Studiengruppen aus Deutschland die German-speaking Myeloma Multicenter Group (GMMG) unter der Leitung von Herrn Professor Hartmut Goldschmidt und die Deutsche Studiengruppe Multiples Myelom (DSMM) unter der Leitung von Herrn Professor Hermann Einsele beteiligt.

An der Erarbeitung dieser S3-Leitlinie waren zudem zu einzelnen Aspekten mit sozialmedizinischer Relevanz Ärztinnen und Ärzte des Kompetenz Centrus Onkologie des GKV-Spitzenverbandes und der MDK-Gemeinschaft beratend beteiligt. Sie haben an den Abstimmungen zu den einzelnen Empfehlungen nicht teilgenommen und sind für den Inhalt dieser Leitlinie nicht verantwortlich.

Außerdem wurden folgende Fachgesellschaften für den Leitlinienprozess angeschrieben:

- Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)
- Arbeitsgemeinschaft Internistische Onkologie (AIO)
- Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)
- Deutsche Gesellschaft für Endoskopie und Bildgebende Verfahren (DGE-BV)
- Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM)
- Deutsches Netzwerk Evidenzbasierte Medizin (DNEbM)
- Gesellschaft der epidemiologischen Krebsregister in Deutschland (GEKID)
- Paul-Ehrlich-Gesellschaft für Chemotherapie e.V.

Diese haben jedoch auf Anfrage erklärt, sich nicht an dem Erstellungsprozess der Leitlinie zu beteiligen oder haben auf die Anfrage nicht reagiert.

### 3.4. Patientenbeteiligung

Bei der Leitlinienerstellung sind Vertreter der Selbsthilfeorganisation Deutsche Leukämie- und Lymphom-Hilfe (DLH) aktiv beteiligt, um die Perspektive der Patienten zu berücksichtigen. Die Vertreter der DLH haben mit eigenem Stimmrecht an der Konsensuskonferenz teilgenommen.

### 3.5. Methodische Begleitung

Die methodische Begleitung erfolgt durch:

1. Arbeitsgruppe Evidence-based Oncology (Prof. Dr. Nicole Skoetz, Vanessa Piechotta, Benjamin Scheckel, Ina Monsef)

2. Leitlinienprogramm Onkologie:
  - a. Dr. med. Markus Follmann, MPH, Dipl.-Soz. Wiss. Thomas Langer; Office des Leitlinienprogramms Onkologie c/o Deutsche Krebsgesellschaft.
  - b. Dr. rer. medic. Susanne Blödt, MScPH, AWMF-Institut für Medizinisches Wissensmanagement
3. Durch externe Auftragnehmer:
  - a. Dr. Simone Wesselmann, MBA; Aktualisierung der Qualitätsindikatoren

## 3.6. Arbeitsgruppen

Tabelle 2: Zusammensetzung Arbeitsgruppen

Arbeitsgruppe	Mitglieder der Arbeitsgruppe (AG-Leiter und Vertreter fett markiert)
Arbeitsgruppe 1: Ziele der Leitlinie	<b>Prof. Dr. Dr. Christof Scheid</b>
Arbeitsgruppe 2: Epidemiologie	<b>Dr. Borge Schmidt</b> , PD Dr. Sebastian Fetscher, M.Sc. Vanessa Piechotta, M.Sc. Angela Aldin
Arbeitsgruppe 3: Versorgungsstrukturen	<b>Dr. Walter Baumann</b> , Prof Dr. Wolfgang Knauf
Arbeitsgruppe 4: Diagnostik, Stadieneinteilung und Prognoseabschätzung	<b>Prof. Dr. Dr. Christof Scheid</b> , Dr. Marco Herling, Dr. Peter Eichhorn, Prof. Dr. Falko Fend, Prof. Dr. Anna Jauch, Dr. Lana Harder, Dr. Niels Weinhold, PD Dr. Katharina Kriegsmann, Prof. Dr. Michael Hundemer, Prof. Dr. Stefan Delorme, Prof. Dr. Thorsten Derlin, Prof. Dr. Tim Weber, PD Dr. Constantin Lapa, Dr. Bettina Beuthien-Baumann, Prof. Dr. Jens Hillengaß, Prof. Dr. Marc-Steffen Raab, PD Dr. Maximilian Merz , PD Dr. Daniela Trog, Dr. Stefanie Huhn
Arbeitsgruppe 5: Alter und Komorbidität	<b>Prof. Dr. Monika Engelhardt</b> , <b>PD Dr. Valentin Goede</b> , Sandra Maria Dold, Katja Schoeller, Sophia Scheubeck, Maximilian Holler, Heike Reinhardt, PD Dr. Karin Hohloch, Prof. Dr. Wolfgang Knauf
Arbeitsgruppe 6: Komplikationen	<b>PD Dr. Robert Semrau</b> , Prof. Dr. Thomas Benzing, Dr. Linus Alexander Völker, Prof. Dr. Torsten Kluba, PD Dr. Sebastian Fetscher, Prof. Dr. Katja Weisel, PD Dr. Claas Philip Nähle,
Arbeitsgruppe 7: Zeitpunkt und Wahl der Erstlinientherapie	<b>Prof. Dr. Hartmut Goldschmidt</b> , Dr. Lukas John, PD Dr. Robert Semrau, PD Dr. Daniela Trog, Prof. Dr. Markus Munder, PD Dr. Sebastian Fetscher, Prof. Dr. Nicolaus Kröger, Matthias Hellberg-Naegele, Dr. Marc Bärtsch, Dr. Elias Mai

Arbeitsgruppe	Mitglieder der Arbeitsgruppe (AG-Leiter und Vertreter fett markiert)
Arbeitsgruppe 8: Wahl der Rezidivtherapie	<b>Prof. Dr. Monika Engelhardt</b> , Prof. Dr. Hermann Einsele, Dr. Dr. Johannes Jung, PD Dr. Udo Holtick, Giulia Graziani, Dr. Heike Reinhardt, Veronika Riebl, Dr. Ralph Wäsch, Dr. Ulrike Holtkamp, PD Dr. Sebastian Fetscher, Matthias Hellberg-Naegele, Prof. Dr. Markus Munder, Prof. Dr. Wolfgang Knauf
Arbeitsgruppe 9: Rehabilitation	<b>Dr. Mario Schubert</b> , Heinrich Recken, PD Dr. Reiner Caspari
Arbeitsgruppe 10: Supportivtherapie, Psychoonkologie und Palliativmedizin	<b>PD Dr. Steffen Simon</b> , PD Dr. Karin Hohloch, Dr. Bianca Senf, Dirk Lang, Dr. Christina Gerlach, Dr. Christina Ramsenthaler, Matthias Hellberg-Naegele, PD Dr. Sebastian Fetscher, Heinrich Recken
Arbeitsgruppe 11: Zeitplan von Verlaufskontrollen (Survivorship)	<b>Prof. Dr. Monika Engelhardt</b> , Prof. Dr. Dr. Christof Scheid, Dr. Maximillian Schinke, Dr. Patrick Marschner, Dr. Matthias Weiß, Dr. Dr. Johannes Jung, Dr. Ralph Wäsch, Prof. Dr. Falko Fend, PD Dr. Daniela Trog, Dr. Lana Harder, Prof. Dr. Stefan Delorme, PD Dr. Tim Weber, Prof. Dr. Thorsten Derlin, PD Dr. Constantin Lapa, Dr. Walter Baumann, Dirk Lang
Arbeitsgruppe 12 Qualitätsindikatoren	<b>Dr. Markus Follmann</b> , <b>PD Dr. Simone Wesselmann</b> , Dr. Johannes Rückher, Dr. Ulrike Holtkamp, Eva Hilgenfeld, Dr. Christina Ramsenthaler, Dr. Christina Gerlach, Prof. Dr. Nicole Skoetz, Dr. Monika Nothacker, Claudia Winzler (ADT)

## 4. Fragestellungen und Gliederung

Die Leitlinie gliedert sich in die unten aufgeführten Themenkomplexe. Bei dem Kick-Off Meeting am 29.05.2018 wurden die jeweiligen Themen je Themenkomplex definiert und unter Berücksichtigung der verfügbaren Ressourcen die jeweils angestrebte Art der Bearbeitung (De novo, Leitlinienadaptation oder primär Expertenkonsens) durch die Mandatsträger konsentiert. De novo Recherche bedeutet in diesem Zusammenhang, dass nach systematischen Reviews und randomisiert kontrollierten Studien bzw. für einzelne Fragestellungen auch nach nicht-randomisiert-kontrollierten Studien gesucht wurde.

Das entsprechende Vorgehen ist in Kapitel 5 dargestellt.



## 4.1. Schlüsselfragen

Tabelle 3: Konsentierete zu bearbeitende Themen je Kapitel

AG	Fragestellung	SR	LA	EK
Ziele der Leitlinie	-			
Epidemiologie	-			
Versorgungsstrukturen	-			
Diagnostik, Stadieneinteilung und Prognoseabschätzung	Typische Symptome			X
	Diagnosesicherung			X
	Diagnostik für die Therapieeinleitung			X
	Diagnostik für die Medikamentenwahl			X
	Blutbild			X
	Werte der klinischen Chemie			X
	Paraproteine			X
	Knochenmarkdiagnostik			X
	Aspiration			X
	Biopsie			X
	Durchflusszytometrie			X
	Stellenwert der Zytogenetik			X
	Zytogenetische Verfahren			X
	Häufigkeit molekulargenetischer Diagnostik			X
	Stellenwert von Mutationsanalysen			X
	Stellenwert der Genomik			X
	Lokaler Befall			X
	Diagnostischer Ausschluss eines multifokalen Befalls			X
	Bildgebung zur Verlaufskontrolle			X
	Stellenwert des konventionellen Röntgens			X
Stellenwert der Computertomografie (i.V. zum Röntgen)			X	

AG	Fragestellung	SR	LA	EK
	Stellenwert der Magnetresonanztomografie			X
	Ganz-Körper-/Rumpf-Magnetresonanztomografie			X
	Stellenwert der Kombination Positronen-Emissions-Tomografie und Computertomografie (i.V.)	X		
	Qualitative Anforderungen an Bildgebung und Testgüteparameter			X
	Diagnostische Abschätzung des Therapieansprechens			X
	Notwendigkeitsbereich der Änderung der Therapie			X
	Maßnahmen der Verlaufsdagnostik			X
	Einsatzgründe der Verlaufsdagnostik			X
	Häufigkeit der Verlaufsdagnostik			X
	Besonderheiten der Subgruppen der älteren Patienten			X
	Stellenwert der Bestimmung der minimalen Resterkrankung	X		
	Messmethoden der minimalen Resterkrankung			X'
	Bildgebung zur Beurteilung der minimalen Resterkrankung			X'
	Maßnahmen zur Rezidivdiagnostik			X
	Diagnostische Maßnahmen zur Therapieeinleitung bei Rezidiven			X
	Diagnostische Maßnahmen zur Medikamentenwahl bei Rezidiven			X
Alter und Komorbidität	Spezifische Diagnostik für bestimmte Altersgruppen			X
	Notwendigkeit der Berücksichtigung des biologischen Alters			X
	Altersgrenze für Transplantationsentscheidungen			X
	Erfassung von Komorbidität, Fitness & deren Einfluss auf Therapieentscheidungen			X
Komplikationen	Besonderheiten bei Patienten mit Niereninsuffizienz			X

AG	Fragestellung	SR	LA	EK
	Indikation für High-Cut-Off-Dialyse			X
	Notwendigkeit der symptomatischen Bestrahlung bei multiplem Befall <sup>2</sup>	X		
	Stellenwert der Strahlentherapie (vs. andere Therapieverfahren) bei symptomatischer Schmerzbehandlung	X		
	Vorgehen bei Skelett-Läsionen	X		
Zeitpunkt und Wahl der Erstlinientherapie	Art der Bestrahlung bei lokalem Befall	X		
	Art der Bestrahlung bei multiplem Befall	X		
	Kombination der Strahlentherapie mit anderen Therapien			X <sup>1</sup>
	Kombination der Strahlentherapie mit neuen Substanzen			X <sup>1</sup>
	Relevanz der Transplantationseignung bei der Wahl der Induktionstherapie		X <sup>3</sup>	
	Beschränkung der Relevanz der Transplantationseignung auf VMP-basierte Regime		X <sup>3</sup>	
	Indikation für die Hochdosistherapie + autologe Stammzelltransplantation		X <sup>3</sup>	
	Dauer der Behandlung vor der Hochdosistherapie		X <sup>3</sup>	
	Patientengruppen für Hochdosistherapie + autologe Stammzelltransplantation		X <sup>3</sup>	
	Zeitlich unbegrenzte Fortsetzung der Induktionstherapie wenn keine Hochdosistherapie + autologe Stammzelltransplantation geplant	X		
	Patientengruppen für eine zweite Hochdosistherapie	X		
	Konsolidierung nach ein/zwei Hochdosistherapien			X <sup>1</sup>
	Stellenwert der allogenen Stammzelltransplantation		X <sup>3</sup>	
	Allogene Stammzelltransplantation bei der Erstlinientherapie	X <sup>4</sup>		
	Stellenwert der Erhaltungstherapie		X <sup>3</sup>	
Patienten, die nicht von einer Lenalidomid-Erhaltung profitieren & keine oder eine andere Erhaltung benötigen		X <sup>3</sup>		

AG	Fragestellung	SR	LA	EK
Wahl der Rezidivtherapie	Indikation & Ziel der Rezidivtherapie		X <sup>3</sup>	
	Art der Rezidivtherapie		X <sup>3</sup>	
	Allogene Stammzelltransplantation im Rezidiv		X <sup>3</sup>	
	Behandlungsoptionen für quadrupel-/penta-refraktäre Patienten			X <sup>1</sup>
Rehabilitation	Empfehlung von Sport(-arten)	X		
	Empfehlung von Physiotherapie			X <sup>1</sup>
	Empfehlung von Physiotherapie auch bei Skelett-Läsionen			X <sup>1</sup>
	Empfehlung von Ergotherapie (bei begleitender Polyneuropathie)			X <sup>1</sup>
	Anwendung von Lymphdrainage			X <sup>1</sup>
Supportivtherapie, Psychoonkologie und Palliativmedizin <sup>5</sup>				
	Einsatz antiresorptiver Antikörper	X		
	Stellenwert von Calcium & Vitamin D in der antiresorptiven Therapie			X <sup>1</sup>
	Anwendung von Bisphosphonaten bei skelettalen Komplikationen	X		
	A von Impfungen			X
	Verabreichung von Antibiotika			X
	Verabreichung von Immunglobulinen	X		
	Spezifische Thromboseprophylaxe i.A. von der systematischen Therapie			X
	Anwendung von Gallensäurebindern zur Behandlung von, durch Lenalidomid verursachter, Diarrhoe			X
	Zeitpunkt & Integration der palliativmedizinischen Versorgung			X
	Häufige Symptome & Probleme			X
Palliativmedizinische Maßnahmen & Strukturen			X	
Zeitplan von Verlaufskontrollen (Survivorship)	-			

AG	Fragestellung	SR	LA	EK
<p>Abkürzungen: EK = Expertenkonsens, LA = Leitlinienadaptation, SR = Systematische Recherche, i.V. = im Vergleich, vs.= versus, i.R. = im Rahmen, i.A. = in Abhängigkeit</p> <p>1: als SR geplant, keine Evidenz gefunden</p> <p>2: ursprünglich in Kapitel „Zeitpunkt und Wahl der Erstlinientherapie“ angesiedelt</p> <p>3: als SR geplant, qualitativ-hochwertige Leitlinie zur Adaptation identifiziert</p> <p>4: zur vollständigen Beantwortung der Schlüsselfrage wurde die zitierte Evidenz der NICE- und ASCO- Leitlinie mit einer Aktualisierungsrecherche ergänzt.</p> <p>5: ursprünglich in Kapitel „Rehabilitation“ angesiedelt</p>				

## 5. Methodisches Vorgehen

### 5.1. Allgemeines Vorgehen

Die Evidenzrecherche und Datenextraktion erfolgten in einem abgestuften Vorgehen. Zunächst wurde nach Leitlinien, Nutzendossiers, systematischen Übersichtsarbeiten und Einzelstudien gesucht. Die Ergebnisse der Recherchen wurden vorsortiert und mit den jeweiligen Instrumenten bewertet. Für die Datenextraktion wurde dann zunächst eine mögliche Leitlinienadaptation je Schlüsselfrage geprüft. Sofern keine Adaptation möglich war, wurde geprüft, ob systematische Übersichtsarbeiten und Nutzendossiers für die jeweiligen Schlüsselfragen extrahiert werden können. Wenn auch dies nicht möglich war, wurden passende Einzelstudien extrahiert.

### 5.2. Leitlinienadaptation

#### 5.2.1. Recherche

Im ersten Schritt wurde am 13.06.2018 in der Datenbank des Guideline International Networks ([www.g-i-n.net](http://www.g-i-n.net)) und MEDLINE ([www.pubmed.org](http://www.pubmed.org)) mit dem Suchbegriff „myeloma“ nach relevanten Leitlinien gesucht. Die Suche wurde am 05.04.2019, nach der Publikation der amerikanischen Leitlinie zur Behandlung des Multiplen Myeloms wiederholt (Mikhael, Ismaila et al. 2019).

#### 5.2.2. Auswahl der Leitlinien

Insgesamt wurden die 7 potentiell relevanten Leitlinien und Quellen aggregierter Evidenz über die Datenbank des Guideline International Networks und MEDLINE mit dem Suchbegriff „myeloma“ identifiziert. Leitlinien wurden vorerst eingeschlossen, wenn die Diagnose oder Therapie des Multiplen Myeloms thematisiert wurde. Dabei wurden folgende Leitlinien gefunden:

- Thalidomid in multiple myeloma (AHRQ) (Hicks, Haynes et al. 2010)
- Stem cell transplantation in multiple myeloma (AHRQ) (Kouroukis and Rumble 2012)
- Lenalidomide in multiple myeloma (AHRQ) (Lu, Chen et al. 2012)
- Guidelines for the diagnosis and management of multiple myeloma 2013 (AHRQ) (Bird, Owen et al. 2013)
- Bortezomib in multiple myeloma and lymphoma (AHRQ) (Kouroukis, Cheung et al. 2013)
- Myeloma: diagnosis and management (NICE) (National Institute for Health and Care Excellence (NICE) 2016)
- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline (Mikhael, Ismaila et al. 2019)

Zum Vergleich der Wirksamkeit und Risiken der einzelnen Substanzen wurde eine Netzwerk-Metaanalyse erstellt (Piechotta, Jakob et al. 2019). Daher wurden Leitlinien die ausschließlich den gesundheitlichen Nutzen und die Sicherheit einer einzelnen Substanz bewerten nicht für eine mögliche Leitlinienadaptation in Erwägung gezogen. Dies betrifft folgende Leitlinien:

- Thalidomid in multiple myeloma (AHRQ) (Hicks, Haynes et al. 2010)
- Lenalidomide in multiple myeloma (AHRQ) (Lu, Chen et al. 2012)

- Bortezomib in multiple myeloma and lymphoma (AHRQ) (Kouroukis, Cheung et al. 2013)

Alle anderen identifizierten Leitlinien wurden detailliert betrachtet und wie folgt bewertet.

Ausgeschlossen wurden Leitlinien, in denen nicht systematisch die verfügbare Evidenz aufbereitet wurde und, in denen nicht das Multiple Myelom thematisiert wurde.

### 5.2.3. Leitlinienbewertung

Die Volltexte der vier nachfolgend aufgeführten Leitlinien wurden von zwei der vier Methodiker (Vanessa Piechotta, Benjamin Scheckel, Angela Aldin, Lisa Umlauff) mit der entsprechenden Domäne des Deutschen Leitlinien-Bewertungsinstruments (DELBI) methodisch bewertet:

- Stem cell transplantation in multiple myeloma (AHRQ) (Kouroukis and Rumble 2012)
- Guidelines for the diagnosis and management of multiple myeloma 2013 (AHRQ) (Bird, Owen et al. 2013)
- Myeloma: diagnosis and management (NICE) (National Institute for Health and Care Excellence (NICE) 2016)
- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline (Mikhael, Ismaila et al. 2019)

Nach erfolgter Bewertung konnten zwei Leitlinien (National Institute for Health and Care Excellence (NICE) 2016, Mikhael, Ismaila et al. 2019) eingeschlossen werden. Eine Leitlinie wurde ausgeschlossen, da dort keine systematische Evidenzaufbereitung durchgeführt wurde (Bird, Owen et al. 2013). Eine Leitlinie wurde ebenfalls ausgeschlossen (Kouroukis and Rumble 2012), da zeitgleich ein Nutzendossier des IQWiG publiziert wurde (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2011). Dieses wurde von den Autoren primär verwendet.

### 5.2.4. Leitliniensynopsen / Extraktionen/ Adaptierungsprozess

In erster Instanz wurden die Aktualität und Gültigkeit der eingeschlossenen LL überprüft. Die zugrunde gelegte Literatur der ASCO LL (Mikhael, Ismaila et al. 2019) wurde durch eine bis zum 30. August 2018 durchgeführte systematische Literaturrecherche identifiziert und die Empfehlungen daher bezüglich der Aktualität uneingeschränkt für den Adaptierungsprozess für geeignet befunden. Die zugrunde gelegte Literatur der NICE LL (National Institute for Health and Care Excellence (NICE) 2016) wurde durch eine bis zum 08. Juni 2015 durchgeführte systematische Literaturrecherche identifiziert. Die Aktualität der Empfehlungen wurde für fraglich befunden und die ASCO Leitlinie vorwiegend zur Adaptierung herangezogen. Die identifizierten LL wurden thematisch den entsprechenden Kapiteln zugeordnet und weiter überprüft, ob die Empfehlungen zu den zu Beginn festgelegten Schlüsselfragen zugeordnet werden können. Für den Fall, dass Schlüsselfragen ausschließlich in der NICE LL abgedeckt waren, wurde eine Aktualisierungsrecherche durchgeführt. Die Empfehlungen wurden nicht formal adaptiert, sondern die identifizierte Evidenz vollständig und unabhängig beurteilt. Insgesamt konnten 12 Empfehlungen der eingeschlossenen ASCO LL adaptiert werden (s. Tabelle 4). Die zugrundegelegte Evidenz und Qualitätsbewertung der eingeschlossenen Studien ist in Abschnitt 12.4 dargestellt. Die GRADE Bewertung je Empfehlung ist in Abschnitt 12.5 abgebildet.

Tabelle 4: Adaptierte Empfehlungen

Originalempfehlung	Adaptierte Empfehlung
ASCO recommendation 1.1: Patients should be referred to a transplant center to determine transplant eligibility (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).	Alle Patienten, die potenziell für eine autologe Transplantation in Frage kommen, <b>sollten</b> in einem Transplantationszentrum zur Prüfung der Transplantationsfähigkeit vorgestellt werden.
ASCO recommendation 1.2: Chronologic age and renal function should not be the sole criteria used to determine eligibility for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).	Chronologisches Alter und Nierenfunktion <b>sollten nicht</b> allein die Transplantationsfähigkeit entscheiden.
ASCO recommendation 2.1: The optimal regimen and number of cycles remain unproven. However, at least three to four cycles of induction therapy including an immunomodulatory drug, proteasome inhibitor (PI), and steroids are advised prior to stem-cell collection (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).	Die Stammzellsammlung <b>sollte</b> nach 4 bis 6 Zyklen Induktionstherapie erfolgen.
ASCO recommendation 2.5: The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy—patients should be referred for SCT independent of depth of response (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).	Die Hochdosistherapie <b>sollte</b> unabhängig vom Ansprechen in der Induktionstherapie erfolgen.
ASCO recommendation 2.9: Allogeneic transplant for multiple myeloma is not routinely recommended but may be considered in select high-risk patients or in the context of a clinical trial (Type: evidence based; Evidence quality: intermediate, harm outweighs benefit; Strength of recommendation: strong).	Eine allogene Stammzelltransplantation in der Erstlinientherapie <b>soll</b> beim Multiplen Myelom <b>nicht</b> routinemäßig erfolgen.
ASCO recommendation 3.2: Lenalidomide maintenance therapy should be routinely offered to standard-risk patients starting at approximately day 90 to 110 at 10 to 15 mg daily until progression. A minimum of 2 years of maintenance therapy is associated with improved survival, and efforts to maintain therapy for at least this duration are recommended (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).	Als Erhaltungstherapie <b>soll</b> bei Standardrisikopatienten Lenalidomid gegeben werden. Und Die Lenalidomid-Erhaltungstherapie <b>soll</b> mindestens 2 Jahre und <b>sollte</b> bis zum Progress fortgeführt werden.



Originalempfehlung	Adaptierte Empfehlung
<p>ASCO recommendation 3.3: For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).</p>	<p>Patienten mit initialem Kreatinin &gt; 2mg/dl und/oder del 17p13 <b>kann</b> als Alternative zu Lenalidomid eine Erhaltungstherapie mit Bortezomib angeboten werden.</p>
<p>ASCO recommendation 7.2: All clinically relapsed patients with symptoms due to myeloma should be treated immediately (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).</p>	<p>Alle Patienten mit symptomatischem Myelom-Rezidiv <b>sollen</b> zeitnah therapiert werden.</p>
<p>ASCO recommendation 7.1: Treatment of biochemically relapsed myeloma should be individualized. Factors to consider include patient's tolerance of prior treatment, rate of rise of myeloma markers, cytogenetic risk, presence of comorbidities (ie, renal insufficiency), frailty, and patient preference. High-risk patients as defined by high-risk cytogenetics and early relapse post-transplant/initial therapy should be treated immediately. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse (Type: informal consensus/evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).</p>	<p>Patienten mit biochemischem Myelom-Rezidiv und Hochrisiko-Zytogenetik, frühem Rezidiv nach der initialen Therapie und/oder schnellem Anstieg der Myelom-Parameter <b>sollten</b> frühzeitig therapiert werden.</p> <p>Und</p> <p>Asymptomatische Patienten mit langsamem biochemischem Progress können engmaschig verlaufskontrolliert werden.</p>
<p>ASCO recommendation 7.4: Treatment of relapsed multiple myeloma may be continued until disease progression. There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD) (Type: evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).</p>	<p>Die Therapie im Rezidiv <b>sollte</b>, in Abhängigkeit des initialen Ansprechens, der Verträglichkeit, der Toxizität und des Patientenwunschs, bis zum Progress fortgeführt werden.</p>
<p>ASCO recommendation 7.3: Triplet therapy should be administered on first relapse, though the patient's tolerance for increased toxicity should be considered. A triplet is defined as a regimen with two novel agents (PIs, immunomodulatory drugs, or monoclonal antibodies) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).</p>	<p>Eine Triple-Kombinationstherapie mit zwei neuen Substanzen und einem Steroid <b>soll</b> bei Multiplen Myelom Patienten im ersten Rezidiv, unter Berücksichtigung der erhöhten Toxizität, angewendet werden.</p>
<p>ASCO recommendation 7.6: ASCT, if not received after primary induction therapy, should be offered to transplanteligible patients with relapsed multiple myeloma. Repeat SCT may be considered in relapsed multiple myeloma if progression-free survival after first transplant is 18 months or greater</p>	<p>Eine autologe Stammzelltransplantation <b>sollte</b> allen transplantationsfähigen Patienten angeboten werden, bei denen keine Transplantation im Rahmen der Erstlinientherapie durchgeführt wurde.</p> <p>Und</p>

Originalempfehlung	Adaptierte Empfehlung
(Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).	Eine autologe Re-Transplantation <b>kann</b> erfolgen, wenn das progressionsfreie Überleben nach erster Transplantation in der Regel mindestens 18 Monate andauerte.

### 5.3. Systematische Recherchen

Die systematische Literatursuche basiert auf dem Prinzip der besten verfügbaren Evidenz. Die methodischen und inhaltlichen Ein- und Ausschlusskriterien wurden prospektiv definiert (und von einer in der medizinischen Terminologie erfahrenen Bibliothekarin in sensitiven und hochkomplexen Suchstrategien für die jeweilig zu durchsuchende Datenbank umgesetzt. Für alle Suchstrategien wurden neben dem Datum der Suche auch die Anzahl der erzielten Treffer dokumentiert. Bei der de novo Recherche wurde nach Volltextpublikationen RCTs bzw. bei speziellen Fragestellungen auch nach nicht-randomisierten-kontrollierten Studien und Fallserien gesucht (für die detaillierten Suchstrategien siehe auch 11.2).

Alle Referenzen dieser umfassenden Suchen, die durch die Suchstrategien identifiziert wurden, sind in einem Literaturverwaltungsprogramm erfasst. Sie wurden durch zwei wissenschaftliche Mitarbeiter (Vanessa Piechotta und Benjamin Scheckel) der Evidence-Based Oncology unabhängig auf die potentielle Relevanz für die Leitlinie ausgewählt und von einem weiteren Mitarbeiter (Prof. Dr. Nicole Skoetz) überprüft. Unstimmigkeiten in der Vorauswahl der Referenzen wurden gelöst und die so ermittelten Publikationen in einer Literaturdatenbank als PDF-Volltexte abgelegt. In verschiedenen Telefonkonferenzen wurden alle so identifizierten Studien den Arbeitsgruppen vorgestellt. Im nächsten Schritt wurden die Studien, die als Volltext publiziert wurden und zur Beantwortung einer der Schlüsselfragen beitragen, in Evidenztabelle extrahiert. Für die Beantwortung der Schlüsselfragen wurden nach Möglichkeit qualitativ hochwertige systematische Übersichtsarbeiten herangezogen. Die Bewertung gefundener systematischer Übersichtsarbeiten erfolgte mit AMSTAR (Shea, Grimshaw et al. 2007). Bei hoher methodischer Qualität und inhaltlicher Relevanz wurden diese sowie die Einzelstudien in Evidenztabelle extrahiert. Die umfassende Qualitätsbewertung der eingeschlossenen Übersichtsarbeiten und Einzelstudien auf Endpunktebene mittels GRADE hat im letzten Schritt in Evidenztabelle stattgefunden.

Es wurden 1621 Treffer für die weitere Selektion eingeschlossen. Diese verteilen sich wie folgt auf die einzelnen Leitlinienkapitel:

- Kapitel 4.1.2.7.4: 114 Treffer
- Kapitel 4.3: 52 Treffer
- Kapitel 6: 132 Treffer
- Kapitel 7: 675 Treffer
- Kapitel 8: 437 Treffer
- Kapitel 9: 96 Treffer
- Kapitel 10: 115 Treffer

Die eingeschlossenen Treffer wurden weitersortiert und für die Schlüsselfragen extrahiert, für die keine Leitlinienadaptation möglich war.

### 5.3.1. Nutzendossiers

Zusätzlich zu eigenen systematischen Recherchen wurde auf der Seite des IQWiG mit dem Suchbegriff „Myelom“ nach Nutzendossiers gesucht. Es konnten insgesamt 9 Publikationen identifiziert werden.

- Pomalidomid – Nutzenbewertung gemäß § 35a SGB V (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2015)
- Elotuzumab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2016)
- Carfilzomib (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2017)
- Daratumumab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2017)
- Daratumumab (multiples Myelom) – Addendum zum Auftrag A17-40 (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2018)
- Pomalidomid – Bewertung gemäß § 35a Abs. 1 Satz 10 SGB V (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2013)
- Panobinostat – Bewertung gemäß § 35a Abs. 1 Satz 10 SGB V (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2015)
- Daratumumab – Bewertung gemäß § 35a Abs. 1 Satz 10 SGB V (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2016)
- Ixazomib (multiples Myelom) – Bewertung gemäß § 35a Abs. 1 Satz 10 SGB V (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2017)

Die gefundenen Publikationen wurden geprüft und anschließend wie systematische Übersichtsarbeiten in Evidenztabelle extrahiert, sofern bei den jeweiligen Schlüsselfragen keine Leitlinienadaptation möglich war.

## 5.4. Schema der Evidenzklassifikation

Die Bewertung der Evidenz erfolgte nach einem formalisierten Verfahren durch die Evidence-Based Oncology entsprechend den üblichen Kriterien der evidenzbasierten Medizin. Die in den systematischen Recherchen identifizierte und selektierte Literatur, die den Einschlusskriterien der jeweiligen Schlüsselfragen entsprach, wurde von Methodikern (Vanessa Piechotta, Benjamin Scheckel, Lisa Umlauff, Lara Mossakowski, Selin Altindis, Burcu Besiroglu) in Evidenztabelle extrahiert. Dabei wurden Unstimmigkeiten geklärt, gegebenenfalls unter Hinzuziehung eines weiteren Experten (Prof. Dr. Nicole Skoetz). Neben dem Studiendesign wurden auch die Qualität der Studiendurchführung, Auswertung und Berichterstattung beurteilt, analog zu den Publikationsrichtlinien PRISMA, REMARK und CONSORT. Die Resultate der Bewertung sind zusammen mit den Ergebnissen der Studien in Evidenztabelle zusammenfassend dargestellt und bieten die Diskussionsgrundlage zur internen Validität der Studienergebnisse im Hinblick auf die zu beantwortende Frage.

Die systematische Beurteilung des Vertrauens in die Evidenz wurde unter Verwendung des international anerkannten GRADE-Systems (Grading of Recommendations Assessment, Development and Evaluation) vorgenommen.

Hierbei handelt es sich um ein System mit speziell entwickelter, online verfügbarer Software, mittels dessen die Qualität der Evidenz formalisiert bewertet und die Güte der aus

der Evidenz abgeleiteten Empfehlungen eingeschätzt und übersichtlich dargestellt werden kann (<https://gradepro.org/>). In dieser Leitlinie erfolgte die Bewertung des Vertrauens in die Evidenz durch GRADE (siehe unten), nicht jedoch die formalisierte Ableitung der Empfehlungen (siehe hierzu Kapitel 5.6). GRADE kann sowohl für diagnostische als auch therapeutische Empfehlungen angewendet werden (Guyatt, Oxman et al. 2008).

Tabelle 5: Evidenzgraduierung nach GRADE (<http://www.gradeworkinggroup.org>)

Vertrauen in die Evidenz	Beschreibung	Symbol
Hohes Vertrauen	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.	⊕⊕⊕⊕
Moderates Vertrauen	Wir haben mäßig viel Vertrauen in den Effektschätzer: der wahre Effekt ist wahrscheinlich nahe bei dem Effektschätzer, aber es besteht die Möglichkeit, dass er relevant verschieden ist.	⊕⊕⊕⊖
Geringes Vertrauen	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.	⊕⊕⊖⊖
Sehr geringes Vertrauen	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.	⊕⊖⊖⊖

## 5.5. Durchführung einer Netzwerk-Metaanalyse

Im Rahmen von Kapitel 7: Zeitpunkt und Wahl der Erstlinientherapie, wurde eine Netzwerk-Metaanalyse durchgeführt (Piechotta, Jakob et al. 2019). Ziel war es den gesundheitlichen Nutzen und die Risiken der einzelnen Substanzen für neu diagnostizierte nicht-transplantierfähige Patienten zu vergleichen und eine klinisch relevante Rangordnung möglicher Substanzkombinationen zu generieren. Zusätzlich zur Unterscheidung zwischen den Therapieregimen wurde zwischen fixierter Therapiedauer und kontinuierlicher Therapiedauer (c) unterteilt. Insgesamt wurden die Patienten auf 21 verschiedene Therapieregime randomisiert: MP, MPc, RCD, RCPc, RD, RDc, RMP, RMPc, TCD, TDc, TMP, TMPc, VD, VDc, VMP, VMPc, VRD, VRDc, VTDC, VTMPc, VTPc.

Die Zusammenfassung der wichtigsten Ergebnisse, einschließlich der Bewertung nach GRADE ist in Abbildung 1, Abbildung 2 und Abbildung 3 dargestellt. Die Darstellung der Ergebnisse der Netzwerk-Metaanalyse erfolgte nach Rücksprache mit der Methodik-Gruppe der AWMF im finalen Leitlinienreport.

**SUMMARY OF FINDINGS**

**Summary of findings 1. Summary of findings**

**Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in transplant-ineligible multiple myeloma patients**

**Patient or population:** newly diagnosed, transplant-ineligible adults with symptomatic multiple myeloma

**Settings:** mostly outpatient; mostly multi-centre studies across Europe, Asia, North- and South America, Australia, and the Pacific region

**Intervention:** lenalidomide plus dexamethasone (RD), thalidomide plus melphalan and prednisone (TMP), bortezomib plus melphalan and prednisone (VMP), continuous bortezomib plus lenalidomide plus dexamethasone (VRDc)

**Comparison:** melphalan and prednisone (MP)

Outcomes	Effects and 95% confidence intervals in the effects. Main comparator is MP*				
	Risk with MP	Risk with RD	Risk with TMP	Risk with VMP	Risk with VRDc
Overall survival	Median overall survival over all studies in the network <sup>1</sup> : 34.8 months	NMA-median OS: 55.2 (35.2 to 87.0) months	NMA-median OS: 46.4 (35.9 to 60.0) months	NMA-median OS: 49.7 (32.5 to 77.3) months	NMA-median OS: 71.0 (37.8 to 133.8) months
		NMA-HR: 0.63 (95% CI 0.40 to 0.99)  ⊕⊕⊕⊕ moderate confidence in estimates due to inconsistency of I <sup>2</sup> = 53.9% (downgrade minus 1)	NMA-HR: 0.75 (95% CI 0.58 to 0.97)  ⊕⊕⊕⊕ moderate confidence in estimates due to inconsistency of I <sup>2</sup> = 53.9% (downgrade minus 1)	NMA-HR: 0.70 (95% CI 0.45 to 1.07)  ⊕⊕⊕⊕ low confidence in estimates due to inconsistency of I <sup>2</sup> = 53.9% (downgrade minus 1), imprecision (downgrade minus 1)	NMA-HR: 0.49 (95% CI 0.26 to 0.92)  ⊕⊕⊕⊕ moderate confidence in estimates due to inconsistency of I <sup>2</sup> = 53.9% (downgrade minus 1)
Progression-free survival	Median progression-free survival over all studies included in the network <sup>1</sup> : 16.2 months	NMA-median PFS: 24.9 (16.9 to 36.8) months	NMA-median PFS: 25.7 (20.8 to 32.4) months	NMA-median PFS: 28.9 (18.0 to 46.3) months	NMA-median PFS: 47.6 (27.9 to 81.0) months

Abbildung 1: Zusammenfassung der Ergebnisse der Netzwerk-Metaanalyse, übernommen aus (Piechotta, Jakob et al. 2019)

		NMA-HR: 0.65 (95% CI 0.44 to 0.96)	NMA-HR: 0.63 (95% CI 0.50 to 0.78)	NMA-HR: 0.56 (95% CI 0.35 to 0.90)	NMA-HR: 0.34 (95% CI 0.20 to 0.58)
		⊕⊕⊕⊕ <b>low</b> confidence in estimates due to high risk of bias (downgrade minus 1) and inconsistency of I <sup>2</sup> = 55.3% (downgrade minus 1).	⊕⊕⊕⊕ <b>low</b> confidence in estimates due to high risk of bias (downgrade minus 1) and inconsistency of I <sup>2</sup> = 55.3% (downgrade minus 1).	⊕⊕⊕⊕ <b>low</b> confidence in estimates due to high risk of bias (downgrade minus 1) and inconsistency of I <sup>2</sup> =55.3% (downgrade minus 1).	⊕⊕⊕⊕ <b>low</b> confidence in estimates due to high risk of bias (downgrade minus 1) and inconsistency of I <sup>2</sup> = 55.3% (downgrade minus 1).
Polyneuropathies	Mean risk over all studies included in the network <sup>2</sup> : 0.9% (10/1074)	NMA-risk: 0.5% (0.1 to 1.8)	NMA-risk: 4.0% (1.6 to 10.0)	NMA-risk: 79.4% (4.8 to 1306.0)	No study reported the amount of participants with grade ≥ 3 polyneuropathies for treatment with VRDc.
		NMA-RR: 0.57 (95% CI 0.16 to 1.99)	NMA-RR: 4.44 (95% C: 1.77 to 11.11)	NMA-RR: 88.22 (95% CI 5.36 to 1451.11)	
		⊕⊕⊕⊕ <b>low</b> confidence in estimates. Downgrade minus 1 for imprecision and minus 1 for high risk of bias.	⊕⊕⊕⊕ <b>moderate</b> confidence in estimates. Downgrade minus 1 for high risk of bias.	⊕⊕⊕⊕ <b>moderate</b> confidence in estimates. Downgrade minus 1 for high risk of bias.	
Serious adverse events	Mean risk over all studies included in the network <sup>2</sup> : 36.1% (177/490)	Risk not available, because RD is not connected to MP in the network.	Risk not available, because TMP is not connected to MP in the network.	NMA-risk: 46.2% (38.3 to 55.6)	Risk not available, because VRDc is not connected to MP in the network.
		NMA-RR not available, because RD is not connected to MP in the network.	NMA-RR not available, because TMP is not connected to MP in the network.	NMA-RR: 1.28 (95% CI 1.06 to 1.54)	NMA-RR not available, because VRDc is not connected to MP in the network.
		Confidence in estimates can not be assessed, because RD is not connected to MP in the network.	Confidence in estimates can not be assessed, because TMP is not connected to MP in the network.	⊕⊕⊕⊕ <b>moderate</b> confidence in estimates. Downgrade minus 1 for high risk of bias.	Confidence in estimates can not be assessed, because VRDc is not connected to MP in the network.
Withdrawals due to adverse events	Mean risk over all studies included in the network <sup>2</sup> : 9.2% (77/837)	NMA-risk: 38.5% (19.6 to 75.4)	NMA-risk: 37.7% (22.1 to 64.5)	NMA-risk: 9.75% (5.8 to 16.7)	NMA-risk: 82.1% (35.1 to 191.7)

Abbildung 2: Zusammenfassung der Ergebnisse der Netzwerk-Metaanalyse (Fortführung), übernommen aus (Piechotta, Jakob et al. 2019).

		NMA-RR: 4.18 (95% CI 2.13 to 8.20)	NMA-RR: 4.10 (95% CI 2.40 to 7.01)	NMA-RR: 1.06 (95% CI 0.63 to 1.81)	NMA-RR: 8.92 (95% CI 3.82 to 20.84)
		⊕⊕⊕⊕ <b>high</b> confidence in estimates.	⊕⊕⊕⊕ <b>high</b> confidence in estimates.	⊕⊕⊕⊕ <b>moderate</b> confidence in estimates. Downgrade minus 1 for imprecision.	⊕⊕⊕⊕ <b>high</b> confidence in estimates.
Quality of life	One study reported that health-related QoL scores increased steadily from baseline until completion of cycle 10	One study reported that global health status of patients improved from baseline over the duration of the study and disease symptoms decreased  RD was not compared to MP in this study	One study reported that global health status of patients improved from baseline over the duration of the study and disease symptoms decreased  TMP was not compared to MP in this study	No study reported the outcome QoL for treatment with VMP.	No study reported the outcome QoL for treatment with VRDc.

\*Basis for the assumed risks:

1: Median OS/PFS over all studies in the network were estimated, calculating the mean of all available MP-medians (OS and PFS, respectively).

2: mean risk over all studies included in the network was estimated, dividing the total events under MP-therapy by the total of patients treated with MP.

The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk Ratio; **MP:** Melphalan and Prednisone; **RD:** Lenalidomide and Dexamethasone; **TMP:** Thalidomide, Melphalan and Prednisone; **VMP:** Bortezomib, Melphalan and Prednisone; **VRDc:** continuous Bortezomib, Lenalidomide and Dexamethasone

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GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

Abbildung 3: Zusammenfassung der Ergebnisse der Netzwerk-Metaanalyse (Fortführung), übernommen aus (Piechotta, Jakob et al. 2019).



## 5.6. Formulierung der Empfehlungen und formale Konsensusfindung

### 5.6.1. Schema der Empfehlungsgraduierung

Die in der Leitlinie generierten Empfehlungen und wesentlichen Aussagen zu Diagnostik, Therapie und Nachsorge des MM sind thematisch bezogene handlungsleitende Kernsätze der Leitlinie. In der Leitlinie wurde zu allen Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung wurden in der Leitlinie drei Empfehlungsgrade unterschieden (siehe [Tabelle 5](#)), die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln und dem AWMF-Regelwerk entsprechen.

Es wurden weiterhin Expertenkonsens-Empfehlungen (in der Leitlinie mit EK gekennzeichnet) generiert, wenn beim Kick-Off Meeting entschieden wurde, eine spezifische Schlüsselfrage nicht über eine systematische Literaturrecherche und -bewertung zu beantworten.

Tabelle 5: Verwendete Empfehlungsgrade

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Zur Festlegung des Empfehlungsgrades erfolgte grundsätzlich eine Anlehnung der evidenzbasierten Empfehlungen hinsichtlich ihres Empfehlungsgrades an die Stärke der verfügbaren Evidenz (siehe), d.h. ein hoher Evidenzgrad (z.B. Metaanalysen/systematische Übersichten von RCTs oder mehrere methodisch hochwertige RCTs). Dies bedeutet, dass eine hohe Sicherheit bzgl. der Ergebnisse in der Regel auch zu einer starken Empfehlung (Empfehlungsgrad A, „soll“) führen soll.

Zusätzlich wurden weitere Kriterien bei der Wahl des Empfehlungsgrades berücksichtigt. Diese folgenden berücksichtigten Kriterien konnten zu einem Abweichen der Empfehlungsstärke nach oben oder unten führen:

- **Konsistenz** der Studienergebnisse  
Bsp.: Die Effektschätzer der Studienergebnisse gehen in unterschiedliche Richtungen und zeigen keine einheitliche Tendenz.
- **Klinische Relevanz** der Endpunkte und Effektstärken  
Bsp.: Es liegen zwar Studien mit Ergebnissen in eine Richtung vor, jedoch wird die Bedeutung der gewählten Endpunkte und/oder Effektstärken als nicht relevant eingeschätzt.
- Nutzen-Risiko-Verhältnis



Bsp.: Dem nachgewiesenen Nutzen einer Intervention steht ein relevanter Schadensaspekt gegenüber, der gegen eine uneingeschränkte Empfehlung spricht.

- Ethische Verpflichtungen

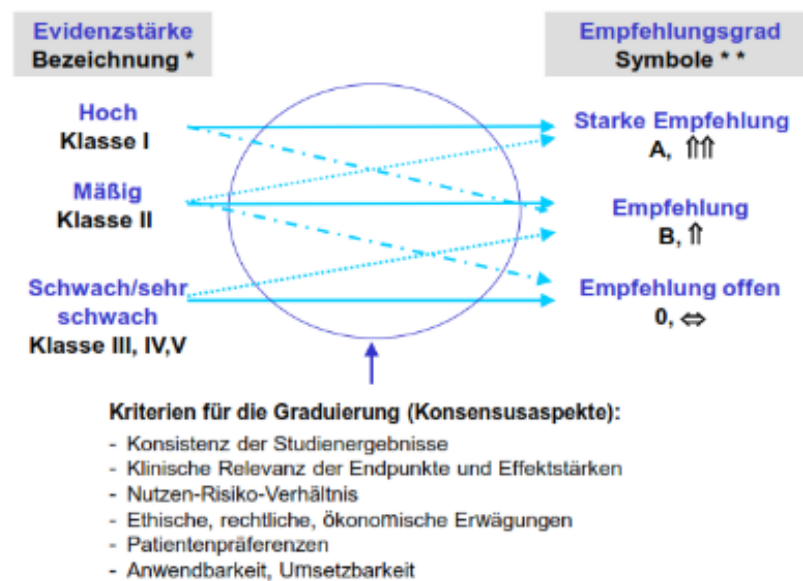
Bsp.: Downgrading: Aus ethischen Gründen kann eine Intervention mit nachgewiesenem Nutzen nicht uneingeschränkt angeboten werden. Upgrading: Starke Empfehlung auf Basis von z.B. Fall-Kontroll-Studien, da aus ethischen Gründen ein RCT nicht durchführbar ist.

- Patientenpräferenzen

Bsp.: Eine Intervention mit nachgewiesenem Nutzen wird nicht stark empfohlen, da sie von den Patienten als belastend oder nicht praktikabel abgelehnt wird.

- Anwendbarkeit, Umsetzbarkeit in der Versorgung

Bsp.: Eine Intervention mit nachgewiesenen positiven Effekten kann nicht empfohlen werden, weil sie im regionalen Versorgungssystem aus strukturellen Gründen nicht angeboten werden kann.



**Abbildung 4: Schema zur Darstellung der kriteriengestützten Entscheidungsprozesse bei der Wahl des Empfehlungsgrades.**

\*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence‘, schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford;

\*\* : Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien. Die Empfehlungen werden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll“; (abgeschwächte) Empfehlung: „sollte“; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht“ / „kann verzichtet werden“) bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden“ / „kann verzichtet werden“).

Quelle: Modifiziertes AWMF-Regelwerk (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften - Ständige Kommission 1. Auflage 2012)

## 5.6.2. Formale Konsensusverfahren und Konsensuskonferenz

Die Empfehlungen der Leitlinie wurden im Rahmen eines formalen Konsensusverfahrens verabschiedet. Hierzu fand eine zweitägige formale Konsensuskonferenz im Januar 2020 statt. Diese erfolgte unter neutraler Moderation durch Dr. S. Bloedt (AWMF-IMWi) und Dr. M. Follmann (OL-Office) wie folgt: Präsentation der abzustimmenden Empfehlungen im Plenum, Gelegenheit zu Rückfragen und Einbringung von begründeten Änderungsanträgen, Abstimmung der Empfehlungen und Änderungsanträge. Bei Bedarf: Diskussion, Erarbeitung von Alternativvorschlägen und endgültige Abstimmung.

Nach Abschluss der zweitägigen Konferenz wurden neun verbliebene Empfehlungen im Nachgang abgestimmt. Die Konsentierung dieser Empfehlungen erfolgte vom 10. bis zum 28. Juni 2020 über eine schriftliche, mehrstufige und anonyme Online-Abstimmung im Delphi-Verfahren. Zwei Tage vor Ablauf der Antwortfrist wurde eine Erinnerungsmail an die Mandatsträger mit bis dahin ausbleibender Rückmeldung versendet. Es wurden keine inhaltlichen Bedenken zu den Empfehlungsvorschlägen geäußert und alle Empfehlungen jeweils mit einer Zustimmung von >95% der teilnehmenden Mandatsträger konsentiert.

Auf Grund inhaltlich relevanter Kommentare und verbesserter Konsistenz mit der Datenlage und den weiteren Empfehlungen, wurden vier Empfehlungen im Zeitraum vom 17. Juli 2020 bis Februar 12. 2021 erneut in einem formellen E-Mail-Verfahren abgestimmt. Angebrachte Kommentare zu zwei der vier Empfehlungen wurden mit der Steuergruppe diskutiert, die Empfehlung gemeinsam mit den Kommentatoren revidiert und erneut zur Abstimmung gebracht. An der schriftlichen Abstimmung (per E-Mail) beteiligten sich 25 der 27 Mandatsträger. Zudem wurde vorab informiert, dass ausstehende Rückmeldungen als Zustimmung betrachtet werden. Alle Empfehlungen wurden jeweils mit einer Zustimmung von >95% der teilnehmenden Mandatsträger konsentiert.

**Tabelle 6: Festlegungen hinsichtlich der Konsensstärke**

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	>75 - 95% der Stimmberechtigten
Mehrheitliche Zustimmung	>50 - 75% der Stimmberechtigten
Dissens	<50% der Stimmberechtigten

## 6. Ableitung der Qualitätsindikatoren

Im Rahmen des Leitlinienprogramms Onkologie werden Qualitätsindikatoren in einem standardisierten Prozess aus den Empfehlungen der Leitlinien abgeleitet. Die detaillierte Beschreibung der Methodik findet sich auf der Homepage des Leitlinienprogramms Onkologie (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft 2017)).

Die Generierung der neuen Qualitätsindikatoren wurde in folgenden Schritten durchgeführt.

### 6.1. Bestandsaufnahme

Bei der Suche nach bereits definierten internationalen und nationalen Qualitätsindikatoren außerhalb des OL-Verfahrens erfolgte eine Einschränkung des Suchzeitraums auf die letzten zehn Jahre (2010 bis 07.2020). Es erfolgte eine Einschränkung auf die Sprachen Deutsch und Englisch.

Die Suche wurde in folgenden Quellen durchgeführt:

- Literaturdatenbanken:  
PubMed: <https://pubmed.ncbi.nlm.nih.gov/advanced>  
Cochrane: <https://www.cochranelibrary.com/advanced-search>
- Webseiten nationaler Agenturen im Bereich medizinische Qualitätssicherung/ Qualitätsmessung/ Qualitätsindikatoren
- Webseiten internationaler Agenturen im Bereich medizinische Qualitätssicherung/ Qualitätsmessung/ Qualitätsindikatoren
- Internetrecherche via [www.google.de](http://www.google.de)

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und sind in Anlage 12.3 aufgeführt.

Die Recherche führte zu einer Reihe von internationalen Qualitätsindikatoren, die ebenfalls in dem Dokument zusammengefasst wurden (Anlage 12.3).

### 6.2. Vorbereitung 1. Online-Sitzung (Erstellung einer Primärliste potentieller Qualitätsindikatoren)

Soweit möglich, wurden im Vorfeld der ersten Online-Sitzung (siehe 6.3) aus den starken Empfehlungen der Leitlinie (n= 104) potentielle Indikatoren mit Definition von Zähler und Nenner abgeleitet. Diese Liste und das Dokument mit den internationalen Qualitätsindikatoren wurden den Mitgliedern der Arbeitsgruppe im Vorfeld des Anwesenheitstreffens zugesandt.

### 6.3. 1. Online-Sitzung (Diskussion und primäre Sichtung)

Die 1. Sitzung der Arbeitsgruppe Qualitätsindikatoren (AG QI), die aus Mitgliedern der Leitliniengruppe und Vertretern der klinischen Krebsregister, des Zertifizierungssystems, der AWMF und des onkologischen Leitlinienprogramms (OL) bestand, fand am 16.09.2020 COVID-bedingt online und nicht als Anwesenheitssitzung statt. In dem Treffen wurde den Teilnehmern der Prozessablauf der Erstellung von Qualitätsindikatoren sowie das Bewertungsinstrument des OL erläutert.

Darüber hinaus wurde die unter 1.2 generierte Zusammenstellung aus den starken Empfehlungen der Leitlinie und der internationalen Qualitätsindikatoren diskutiert und entschieden, ob aus der jeweiligen Empfehlung ein potentieller Qualitätsindikator generiert werden könne. Folgende Ausschlusskriterien kamen bei diesem ersten Screening zur Anwendung.

**Tabelle 7: Gründe für einen Ausschluss der Empfehlung aus der Liste der potentiellen Qualitätsindikatoren**

Nr.	1	2	3	4
Begründung	Empfehlung ist nicht operationalisierbar (Messbarkeit nicht gegeben)	Fehlender Hinweis auf Verbesserungspotential	Fehlende Verständlichkeit u/o großer Erhebungsaufwand in Verhältnis zu Nutzen	Sonstiges (mit Freitexteingabe in Liste der Empfehlungen)

Auf Basis der starken Empfehlungen der Leitlinie wurden 3 potentielle Qualitätsindikatoren definiert.

Weitere Ergebnisse der Anwesenheitssitzung (16.09.2020): Für die folgenden Empfehlungen wird die Aufnahme in den Erhebungsbogen der Zentren für Hämatologische Neoplasien angeregt (Eingabe für Zertifizierungskommission), da die Empfehlungen Bereiche mit Verbesserungspotenzial adressieren, aber gleichzeitig nicht für einen QI operationalisiert werden können:

4.1.2.1.b Bei der körperlichen Untersuchung soll auch der neurologische Status erhoben werden, insbesondere zur Erfassung einer Polyneuropathie.

4.1.2.2.a Der Allgemeinzustand und die körperliche Aktivität des Patienten im Alltag sollen mit Hilfe des Karnofsky-Index oder des ECOG-Scores quantifiziert werden.

6.1.1.2 Bei Verdacht auf eine Nierenbeteiligung soll eine fachnephrologische Vorstellung erfolgen.

7.4.3 Bei Patienten, bei denen eine Hochdosistherapie nicht ausgeschlossen ist, soll Melphalan in der Induktionstherapie vermieden werden.

10.1.2.1 Eine Impfung gegen Streptococcus pneumoniae und Influenza soll bei Patienten mit Multiplem Myelom zusätzlich zu den Standardimpfungen (für chronisch kranke Menschen) erfolgen.

11.1.7.1 Bei allen Patienten soll im Rahmen der Nachsorge auf Impfungen, z.B. nach SOP, STIKO-Empfehlungen, geachtet und diese regelmäßig ergänzt bzw. aufgefrischt werden.

11.1.7.2 Der Impfstatus soll nach autologer und allogener Stammzelltransplantation entsprechend der Empfehlungen der EBMT aufgefrischt werden.

10.2.1 Bei Patienten mit einem Multiplen Myelom unabhängig des Krankheitsstadiums und mit Schmerzen soll eine wirksame und leitliniengerechte Schmerztherapie durchgeführt werden. → Verweis auf Kapitel „Tumorschmerz“ der S3-Leitlinie Palliativmedizin. → Übernahme QI Palliativ in den Kennzahlenbogen der HAEZ

10.4.2 Alle Patienten sollen nach der Diagnose eines Multiplen Myelom eine allgemeine Palliativversorgung (APV) durch die Primärbehandler erhalten, unabhängig davon, ob eine tumorspezifische Therapie durchgeführt wird.

## 6.4. Bewertung

Die 3 potentiellen Qualitätsindikatoren wurde mit dem Bewertungsinstrument des Leitlinienprogramms Onkologie durch die Mitglieder der AG QI bewertet. Jeweils mit dem unten abgebildeten Bogen erhielten die Bewertenden seitens der Krebsregister und des Zertifizierungssystems der DKG für den Indikatorvorschlag die Informationen zur Datenverfügbarkeit. Angenommen wurden die Qualitätsindikatoren, bei denen mind. 75% der Teilnehmer die Kriterien 1,2,3 und 5 mit „Ja“ und das Kriterium 4 mit „Nein“ bewertet haben. Die Auswertung dieser Abstimmungen erfolgte durch einen Methodiker, der nicht am Qualitätsindikatoren-Entwicklungsprozess teilgenommen hatte.

**Tabelle 8: Bewertungsinstrument des Leitlinienprogramms Onkologie**

QI-Nr.	Möglicher Qualitätsindikator	Empfehlung	
1.	Z		
	N		
<p><b>Information zur Datenverfügbarkeit (Stand 07/2020):</b>  <b>[dies wird von den Registern und den Zentren ausgefüllt]</b></p> <p>Die Erfassung ist seitens der Klinischen Krebsregister über den einheitlichen Onkologischen Basisdatensatz und seiner Module gewährleistet: ja / nein</p> <p>Die Erfassung ist Teil des Zertifizierungssystems der DKG: ja / nein</p> <p>Ggf. welche Ergänzungen wären erforderlich?</p>			
			<b>Nein</b>
			<b>Ja</b>
<p><b>Kriterium:</b> Der Qualitätsindikator erfasst für den Patienten relevante Verbesserungspotentiale.</p>			
<p><b>Kriterium:</b> Der Indikator ist klar und eindeutig definiert.</p>			
<p><b>Kriterium:</b> Der Qualitätsindikator bezieht sich auf einen Versorgungsaspekt, der von den Leistungserbringern beeinflusst werden kann.</p>			
<p><b>Kriterium:</b> Gibt es Risiken zur Fehlsteuerung durch den Indikator, die nicht korrigierbar sind?</p>			

QI-Nr.	Möglicher Qualitätsindikator	Empfehlung	
	<b>Kriterium:</b> Die Daten werden beim Leistungsbringer routinemäßig dokumentiert oder eine zusätzliche Erhebung erfordert einen vertretbaren Aufwand		

Zusätzlich bestand die Möglichkeit, zu den im Folgenden genannten Kriterien Kommentare abzugeben:

	Kommentar
<b>Risikoadjustierung</b> Können spezifische Merkmale von Patienten z.B. Alter, Komorbidität oder Schweregrad der Erkrankung die Ausprägung des QI beeinflussen?	
<b>Implementierungsbarrieren</b> Gibt es Implementierungsbarrieren, die es zu beachten gilt?	

#### 6.4.1. Telefonkonferenz

Nach der schriftlichen Bewertung erfolgte am 14.10.2020 eine 2. moderierte Online-Sitzung, in der die Ergebnisse der Bewertung diskutiert und teilweise modifiziert wurden. Auf Basis der Bewertungen und der Diskussion wurde das Set von 3 Qualitätsindikatoren konsentiert.

Im Anschluss an die Telefonkonferenz erfolgt eine Rückmeldung der Ergebnisse an die Gesamtleitliniengruppe. Hieraus ergaben sich Diskussionen bzw. Änderungen der den QI „Behandlung in einem zertifizierten Zentrum für Hämatologische Neoplasien“ und „Prätherapeutische Vorstellung in der Tumorkonferenz“ zugrundeliegenden Empfehlungen (Änderung „soll“ in „sollte“ und Ausschluss nach Neu-Interpretation der Zählerdefinition aus der Empfehlung). Aus diesem Grund wurden die genannten QI final gestrichen.

Qualitätsindikator	Zugrundeliegende Empfehlung	Anmerkungen
<b>QI Behandlung in einem zertifizierten Zentrum für Hämatologische Neoplasien</b>		
<b>Zähler:</b> Patienten des Nenners, die in einem zertifizierten Zentrum für Hämatologische Neoplasien behandelt werden  <b>Nenner:</b> Alle Patienten mit Multiplem Myelom (C90.0)	Die Patientenführung <i>soll</i> in den Händen von erfahrenen Fachärzten für Hämatologie und Onkologie liegen, die die Behandlung im Rahmen eines spezialisierten, interdisziplinären Myelom-Netzwerks koordinieren.	EK  <b>Qualitätsziel:</b> Behandlung möglichst vieler Patienten mit Multiplem Myelom in zertifizierten Zentren für Hämatologische Neoplasien
<b>QI Prätherapeutische Vorstellung in der Tumorkonferenz</b>		

Qualitätsindikator	Zugrundeliegende Empfehlung	Anmerkungen
<p><b>Zähler:</b> Patienten des Nenners mit prätherapeutischer Vorstellung in der Tumorkonferenz</p> <p><b>Nenner:</b> Alle Patienten mit Multiplem Myelom</p>	Alle behandlungsbedürftigen Patienten <b>sollten</b> einem spezialisierten Tumorboard vorgestellt werden	<p><b>EK</b></p> <p><b>Qualitätsziel:</b> Vorstellung möglichst vieler Patienten mit Multiplem Myelom in der prätherapeutischen Tumorkonferenz</p>
<p><b>Anmerkung:</b> Teilnehmer Tumorkonferenz = Hämatologie und Onkologie, Radiologie, Strahlentherapie, Pathologie; indikationsbezogen u.a. Orthopädie und Unfallchirurgie</p>		

Die Primärliste der potentiellen Qualitätsindikatoren inklusive der Ausschlussgründe, die o.g. Zusammenstellung der internationalen Qualitätsindikatoren und die Ergebnisse der schriftlichen Bewertung sind auf Anfrage im Leitliniensekretariat oder Office des Leitlinienprogramms Onkologie erhältlich.

## 7. Reviewverfahren und Verabschiedung

Die Leitlinie konnte im Rahmen einer 6-wöchigen Konsultationsphase (bis zum 12.08.2021) durch die (Fach)Öffentlichkeit kommentiert werden. Hierzu wurde eine Konsultationsfassung der Leitlinie auf der Homepage des Leitlinienprogramms Onkologie und der AWMF eingestellt und über mehrere Verteiler und Newsletter der beteiligten Organisationen zur Kommentierung der Konsultationsfassung aufgerufen. Zeitgleich wurde die formale Zustimmung der Vorstände der beteiligten Fachgesellschaften zur Publikation der Leitlinien eingeholt. Auf Anfrage sind alle eingegangenen Kommentare im Leitliniensekretariat einsehbar. Zusätzlich wurde ein Review-Verfahren sowohl bei klinisch als auch bei methodisch anerkannten Experten durchgeführt, u.a. durch Vertreter des OL und AWMF.

Die eingegangenen Kommentare wurden zunächst durch das Leitliniensekretariat gesichtet und hinsichtlich ihrer inhaltlichen Relevanz klassifiziert. Insgesamt gingen im Rahmen der öffentlichen Konsultation 33 Kommentare von 7 Personen oder Organisationen ein. Anschließend wurden in Zusammenarbeit mit der Steuergruppe und den jeweiligen Kapitelautoren Empfehlungen zum Umgang mit den Kommentaren diskutiert und konsentiert.

Inhaltliche Kommentare und die daraus resultierenden Änderungen mit Begründung ggf. auch bei Beibehaltung des ursprünglichen Textentwurfs können Tabelle 9 und Tabelle 10 entnommen werden. Das Layout betreffende und orthographische sowie syntaktische Kommentare wurden eingearbeitet und sind hier nicht gelistet.



Tabelle 9: Bearbeitung eingegangener Kommentare zu Empfehlungen und Statements

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung des Kommentierenden oder Statement dazu	Begründung (mit Literaturangaben)	Umgang mit Kommentar	Begründung der Entscheidung
1	Kapitel 14.4, Wahl der Rezidiv- therapie bei >3. Rezidiv, S. 160 ff	Konsensbasierte Empfehlung – <i>neue Einfügung</i>	Bei Patienten mit mindestens vier Vortherapien und progredientem Verlauf sollte geprüft werden, ob eine neue Therapieoption gegen eine bisher nicht adressierte Zielstruktur, wie z.B. BCMA eingesetzt werden kann.	Grund: Das anti-BCMA Antikörper-Wirkstoff-Konjugat Belantamab-Mafodotin ermöglicht eine weitere Therapieoption für das rezidierte/refraktäre Multiple Myelom (rrMM) und richtet sich gezielt gegen eine bisher noch nicht adressierte Zielstruktur auf Myelomzellen.  <b>Literaturangaben:</b>  Tai et al. 2015. Targeting B-cell maturation antigen in multiple myeloma. <i>Immunotherapy</i> 2015; 7: 1187-1199.  Lonial S. et al., Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. <i>Lancet Oncol</i> 2020; 21: 207-221.	Empfehlung nicht ergänzt; stattdessen Ausblick auf weitere Therapieoptionen, wie BCMA, im Hintergrundtext ergänzt	Die Ergänzung einer Empfehlung wird im Aktualisierungsverfahren der Leitlinie evaluiert. Ein Ausblick weiterer Therapieoptionen wurden gemäß Zulassungsstand im Hintergrundtext ergänzt.
2	Kapitel 16.1.1 Seite 170	Neuaufnahme	Neuaufnahme Zitat:  Evidenzbasierte Empfehlung aus S3-Leitli-	S3 Leitlinienempfehlung mit Relevanz für den Antiresorptiva-Verordnenden  Hasegawa, T., et al., The observational study of delayed wound healing after	Empfehlung wird nicht ergänzt, sondern stattdessen im Hintergrundtext auf auf die AWMF-	Durch den Querverweis wird der Anwender auf die jeweils gültige Leitlinie verwiesen.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Än- derung des Kom- mentierenden oder Statement dazu	Begründung (mit Literaturangaben)	Umgang mit Kommentar	Begründung der Entscheidung
			nie 007/091: Auf- grund des AR-ONJ Ri- sikos soll der AR-Ver- ordnende eine zahnärztliche Vor- stellung anregen, auch wenn sich der betreffende Patient in regelmäßiger Kon- trolle des Hauszahn- arztes befindet. Emp- fehlungsgrad A, LoE III	tooth extraction in patients receiving oral bisphosphonate therapy. J Cranio- maxillofac Surg, 2013. 41(7): p. 558- 63	Leitlinie 007/091: Anti- resorptiva-assoziierte Kiefernekrosen (AR-ONJ) verwiesen.	

Tabelle 10: Bearbeitung eingegangener Kommentare zu den Hintergrundtexten

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
3	14.4. Wahl der Re- zidivthera- pie S. 160 ff	Neue Einfügung	Patienten mit einem Rezidiv nach mindestens vier vorherigen Therapien, die refraktär gegenüber mindestens einem Proteasom-Inhibitor, einem Immunmodulator und einem monoklonalen Anti-CD38-Antikörper sind, können mit Belantamab-Mafodotin behandelt werden.	<p>Belantamab-Mafodotin ist zugelassen zur Behandlung des Multiplen Myeloms bei erwachsenen Patienten, die bereits mind. 4 Therapien erhalten haben und deren Erkrankung refraktär gegenüber mind. einem Proteasom-Inhibitor, einem Immunmodulator und einem monoklonalen Anti-CD-38-Ak ist, und die während der letzten Therapie eine Krankheitsprogression zeigten.<sup>1</sup></p> <p>In der Zulassungsstudie DREAMM-22 wurde Belantamab-Mafodotin bei dieser Patientengruppe durch intravenöse Infusion alle 3 Wochen bis zum Progress der Erkrankung oder inakzeptabler Toxizität verabreicht. Belantamab-Mafodotin wird als Monotherapie ohne Prämedikation und ohne begleitende Kortikosteroide verabreicht mit einer Dosierung von 2,5 mg/kg Körpergewicht, q3w.</p>	Änderungsvorschlag wurde im Hintergrundtext ergänzt.	Die Anregung ist nachvollziehbar und sinnvoll.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
				<p>Untersuchte Endpunkte waren ORR, DOR, TTR, PFS, OS, CBR.</p> <p>Nach einer medianen Nachbeobachtungszeit von 13 Monaten sprachen 32% der Patienten auf die Behandlung an (ORR: 32%, 31/97; 97,5% KI:22 % - 44 %). Von diesen erreichten 2% ein stringentes komplettes Ansprechen, 5% ein komplettes Ansprechen, weitere 11% ein sehr gutes partielles und 13% ein partielles Ansprechen.</p> <p>Die mediane DoR betrug 11 Monate (95% CI, 4,2 - nicht erreicht) und das mediane OS betrug 13,7 Monate (95% KI, 9,9 - nicht erreicht).</p> <p>Das mediane PFS (Studienpopulation mit 2,5 mg/kg Körpergewicht Dosierung) betrug 2,8 Monate.</p> <p>Die häufigsten Nebenwirkungen in der zulassungsrelevanten 2,5mg/kg-Kohorte waren Keratopathie / Veränderungen im kornealen Epithel, Anämie, Thrombozytopenie, Lymphozytopenie, Neutropenie, Hyperkalzämie, Pneumonie.</p>		

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
				<p>Literaturangaben:</p> <p>Fachinformation Blenrep, GSK, Stand Juni 2021</p> <p>Lonial et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol 2020; 21: 207-221.</p> <p>Lonial S. et al., Poster No. 436, ASCO 2020</p>		
4	Kapitel 16.1.1 Seite 170	Beim Vergleich der verschiedenen Bisphosphonate in einer Netzwerk-Metaanalyse (NMA) (Mhaskar, Kumar et al. 2017) zeigte sich keine unterschiedliche Häufigkeit im Auftreten einer Kieferosteonekrose.	Zusätzlich wird auf die S3- Leitlinie S3-Leitlinie 007/091: Antiresorptiva-assoziierte Kiefernekrosen (AR-ONJ) verwiesen (Kapitel Prophylaxe vor Antiresorptiva Therapie 3.3).	In der genannten Leitlinie sind 3 Empfehlungen genannt, die sich unmittelbar an den Antiresorptiva-Verordnenden richten.	Änderungsvorschlag wurde im Hintergrundtext ergänzt.	Die Anregung ist nachvollziehbar und sinnvoll.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
5	13.6 / S.148	Hier zeigte sich ein eindeutiger Vorteil	Hier zeigte sich ein eindeutiger Nachteil  (!!!)		Überarbeitung des Hintergrundtext.	Die Literaturdarstellung zur GMMG-MM5-Studie war aufgrund der Komplexität der Untersuchung irreführend und wurde zur besseren Verständlichkeit überarbeitet. Es wird der Überlebensvorteil von Patienten, die Lenalidomid unabhängig vom Ansprechen über 2 Jahre erhielten gegenüber jenen, die Lenalidomid bei Erreichen einer CR absetzten dargestellt.
6	9.2 / Seite 92	Es liegen 2 Metaanalysen aus den Jahren 2016 und 2017 vor.	Es liegen 3 Metaanalysen aus den Jahren 2016, 2017 und 2020 vor.  Die bisher größte Metaanalyse von Munshi aus dem Jahr 2020 basiert auf insgesamt 44 Studien und PFS-Daten von 8098 Patienten und OS-Daten von 4297	Diese Studie bestätigt den hohen prognostischen Stellenwert der MRD-Negativität für NDMM Patienten und zeigt gleichzeitig, dass dieser prognostische Wert ebenfalls auf RRMM zutrifft: „This meta-analysis showed that MRD negativity was associated with significant improvements in PFS and OS outcomes in a large cohort of patients with MM including both transplant-eligible and transplant-ineligible patients with NDMM and those with RRMM.“  Quelle: Munshi et al. Blood Adv 2020, 4 (23):5988–5999	Änderungsvorschlag wurde im Hintergrundtext ergänzt.	Die Anregung ist nachvollziehbar und sinnvoll.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
			Patienten. MRD-Negativität ist im Vergleich zum MRD-positivem Status mit einem signifikant verlängertem PFS (HR, 0,33; 95% CI, 0,29-0,37; P< 0,001) und OS (HR, 0,45; 95% CI, 0,39-0,51; P< 0,001) assoziiert, unabhängig von der Art der Erkrankung (NDMM und RRMM).			
7	14.3 / Seite 152	Dieses Kapitel behandelt die Therapie des rezidivierten Multiplen Myeloms. Zugrunde gelegt wurden die Empfehlungen der ASCO Leitlinie „Treatment of Multiple Myeloma:	EHA-ESMO Guidelines (Dimopoulos et al. 2021)  NCCN Version 7.2021 (Kumar et al. 2021)	Bitte aktuelle Guidelines (s. links) ergänzen.  Da es in den letzten Jahren zahlreiche Neuzulassungen und Indikationserweiterungen von effektiven Kombinationstherapien gab, wäre es sinnvoll diese in die S3 Leitlinien aufzunehmen.  Quellen:	Änderungsvorschlag wurde nicht übernommen.	Die EHA-ESMO und NCCN Leitlinien sind konsensbasierte Zusammenstellungen ohne dezidierten Leitlinienreport und nachvollziehbarem Interessenkonfliktmanagement. Ein Verweis auf Leitlinien, deren Erstellungsprozess nicht nachvollziehbar ist, ist in der S3-Leitlinie nicht vorgesehen.

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		ASCO and CCO Joint Clinical Prac- tice Guideline“ aus den Jahren 2016 und 2019.		Dimopoulos et al. Ann Oncol 2021, 32 (3):309-322  Kumar et al. 2021: NCCN Version 7.2021		
8	14.3 / Seite 154	In Anhang II ist eine exemplari- sche Übersicht der medikamentö- sen Rezidivthera- pie-Optionen, in Abhängigkeit des Ansprechens auf das jeweilige In- duktionsregime bzw. die voraus- gegangene Thera- pielinie, darge- stellt (Chim, Kumar et al. 2018).	EHA-ESMO Guide- lines (Dimopoulos et al. 2021)  NCCN Version 7.2021 (Kumar et al. 2021)  Anhang II:  Isatuximab-Poma- lidomid-Dexame- thason (Isa-Pd) basierend auf der ICARIA-MM Studie (Attal et al. 2019)  Isatuximab-Carfil- zomib-Dexame- thason (Isa-Kd) basierend auf der IKEMA Studie (Mo- reau et al. Lancet 2021)	Anhang II fehlt in der aktuellen Ver- sion.  Bitte aktuelle Guidelines (s. links) er- gänzen.    Bitte die zugelassenen Rezidivtherapie- Optionen Isatuximab-Pomalidomid- Dexamethason (Isa-Pd) basierend auf der ICARIA-MM Studie (Attal et al. 2019) und Isatuximab-Carfilzomib- Dexamethason (Isa-Kd) basierend auf der IKEMA Studie (Moreau et al. 2021) im Anhang II nach Bedarf ergänzen.   Quellen:  Dimopoulos et al. Ann Oncol 2021, 32 (3):309-322  Kumar et al. 2021: NCCN Version 7.2021	Übersicht wurde er- gänzt und gemäß Zu- lassungen überprüft (Stand 09 2021)	Übersicht fehlte in der wäh- rend der Konsultation öffent- lich zugänglichen Version.



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				Attal et al. Lancet 2019, 394:2096-2107  Moreau et al. Lancet 2021, 397:2361-2371		
9	14.3 / Seite 154	Eine Übersicht der für die Behandlung des Myeloms verwendeten Arzneistoffe mit Haupt-Nebenwirkungen, inkl. der für die Rezidivtherapie zugelassenen Wirkstoffkombinationen, ist im Anhang I dieser Leitlinie aufgeführt.	EHA-ESMO Guidelines (Dimopoulos et al. 2021)  NCCN Version 7.2021 (Kumar et al. 2021)  Anhang I:  Isatuximab-Pomalidomid-Dexamethason (Isa-Pd) basierend auf der ICARIA-MM Studie (Attal et al. 2019)  Isatuximab-Carfilzomib-Dexamethason (Isa-Kd) basierend auf der	Anhang I fehlt in der aktuellen Version.  Bitte aktuelle Guidelines (s. links) ergänzen.          Bitte Isatuximab (Sarclisa® Fachinformation Stand Juni 2021) und die zugelassenen Wirkstoffkombinationen Isatuximab-Pomalidomid-Dexamethason (Isa-Pd) basierend auf der ICARIA-MM Studie (Attal et al. 2019) und Isatuximab-Carfilzomib-Dexamethason (Isa-Kd) basierend auf der IKEMA Studie (Moreau et al. 2021) im Anhang I nach Bedarf ergänzen.   Quellen:  Dimopoulos et al. Ann Oncol 2021, 32 (3):309-322	Übersicht wurde ergänzt und gemäß Zulassungen überprüft (Stand 09 2021)	Übersicht fehlte in der während der Konsultation öffentlich zugänglichen Version.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
			IKEMA Studie (Moreau et al. Lancet 2021)	Kumar et al. 2021: NCCN Version 7.2021  Attal et al. Lancet 2019, 394:2096-2107  Moreau et al. Lancet 2021, 397:2361-2371		
10	14.4 / Seite 159	Die Gruppe wird penta-refraktär, wenn zusätzlich der CD38-Antikörper Daratumumab wirkungslos ist (Chim, Kumar et al. 2018).	Die Gruppe wird penta-refraktär, wenn zusätzlich die anti-CD38-Antikörper Isatuximab oder Daratumumab wirkungslos sind.	Isatuximab ist zugelassen und seit 01.02.2021 in Deutschland im Markt verfügbar (Sarclisa® Fachinformation Stand Juni 2021).	Änderungsvorschlag wurde im Hintergrundtext ergänzt.	Die Anregung ist nachvollziehbar und sinnvoll.
11	14.4 / Seite 159	Die Prognose bei stark vorbehandelten Patienten ist immer noch schlecht mit einem medianen Gesamtüberleben von 13 Monaten bei drei oder mehr Vorthera-	Die Prognose bei stark vorbehandelten Patienten ist immer noch schlecht mit einem medianen Gesamtüberleben von 13 Monaten bei drei oder mehr Vorthera-	Der Entwurfstext der Leitlinie spiegelt den Erfolg neuer Triplet-Therapien bei stark vorbehandelten Patienten nicht ausreichend wider, sodass diese hier Erwähnung finden sollten.	Änderungsvorschlag wurde nicht übernommen.	Die Triplet Therapie wird in zwei Empfehlungen empfohlen (14.6 und 14.11) und durch Erläuterungen im Hintergrundtext ausreichend belegt.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung																					
		<p>pien und Versagen eines ImiDs (Lenalidomid oder Pomalidomid) und eines Proteasom-Inhibitors (Bortezomib oder Carfilzomib) (Kumar, Dimopoulos et al. 2017).</p>	<p>pien und Versagen eines ImiDs (Lenalidomid oder Pomalidomid) und eines Proteasom-Inhibitors (Bortezomib oder Carfilzomib) (Kumar, Dimopoulos et al. 2017).</p> <p>Gleichzeitig verbessern neue effektive Triplet-Therapien die Prognose von stark vorbehandelten Patienten, sodass eine Verbesserung des medianes PFS auf über 11 Monate erreicht werden kann (Bringhen et al. 2021) (siehe zudem Hintergrund zu Empfehlung 14.11).</p>	<table border="1"> <thead> <tr> <th data-bbox="927 395 1182 427">Prior treatment</th> <th colspan="2" data-bbox="1182 395 1417 427">Isatuximab-pomalidomide-dexamethasone</th> </tr> <tr> <th data-bbox="927 475 1182 507">Prior lines</th> <th data-bbox="1182 475 1227 507">N</th> <th data-bbox="1227 475 1417 507">Median PFS, months</th> </tr> </thead> <tbody> <tr> <td data-bbox="927 547 1182 579">2-3<sup>a</sup></td> <td data-bbox="1182 547 1227 579">102</td> <td data-bbox="1227 547 1417 579">12.26</td> </tr> <tr> <td data-bbox="927 619 1182 651">2 prior</td> <td data-bbox="1182 619 1227 651">45</td> <td data-bbox="1227 619 1417 651">12.25</td> </tr> <tr> <td data-bbox="927 691 1182 722">At least 3 prior</td> <td data-bbox="1182 691 1227 722">109</td> <td data-bbox="1227 691 1417 722">11.40</td> </tr> <tr> <td data-bbox="927 762 1182 794">&gt; 3<sup>a</sup></td> <td data-bbox="1182 762 1227 794">52</td> <td data-bbox="1227 762 1417 794">9.40</td> </tr> <tr> <td data-bbox="927 834 1182 866">4<sup>b</sup></td> <td data-bbox="1182 834 1227 866">32</td> <td data-bbox="1227 834 1417 866">8.54</td> </tr> </tbody> </table> <p data-bbox="927 906 1417 970">Quelle: Bringhen et al. Leukemia Research 2021, 106576</p>	Prior treatment	Isatuximab-pomalidomide-dexamethasone		Prior lines	N	Median PFS, months	2-3 <sup>a</sup>	102	12.26	2 prior	45	12.25	At least 3 prior	109	11.40	> 3 <sup>a</sup>	52	9.40	4 <sup>b</sup>	32	8.54		
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12	14.4 / Seite 160	Erkenntnisgewinn gezogen werden kann aus Studien mit Myelom-Patienten, die letztlich im Median vier oder mehr Vortherapien aufwiesen. In der Phase 2- Studie mit Daratumumab als Monotherapie wurden Patienten mit im Median fünf Vortherapien (2-14) behandelt. Das Gesamtansprechen lag bei 29%. Das mediane Gesamtüberleben lag bei 17,5 Monaten (Lonial, Weiss et al. 2016). Es sollte die Möglichkeit geprüft werden, Daratumumab in Kombi-	Erkenntnisgewinn gezogen werden kann aus Studien mit Myelom-Patienten, die letztlich im Median vier oder mehr Vortherapien aufwiesen. In der Phase 2- Studie mit Daratumumab als Monotherapie wurden Patienten mit im Median fünf Vortherapien (2-14) behandelt. Das Gesamtansprechen lag bei 29%. Das mediane Gesamtüberleben lag bei 17,5 Monaten (Lonial, Weiss et al. 2016).  In der Phase 3- Studie ICARIA-MM wurde die Triplet-	„In patients with four prior lines of therapy, the median PFS was 8.54, (4.50–15.21 [isatuximab arm] versus 3.29 months (1.97–8.58 [control arm]); (HR 0.501; 95 % CI 0.259–0.971).“  “Of the 8 patients who were MRD negative at 10-5, [...] 2 had received 2 prior lines, 4 had received 3 prior lines, and 1 patient had received 4 prior lines of treatment. All of the MRD negative patients were PFS event-free at the date of the analysis cut-off.”  Quelle: Bringhen et al. Leukemia Research 2021, 106576	Hintergrundtext wurde überarbeitet.	Die Anregung ist nachvollziehbar und sinnvoll.

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		nation mit anderen aktiven Substanzen (Lenalidomid, Bortezomib) gemäß der Zulassung zu verabreichen, um das Ansprechen potenziell noch zu verbessern (siehe Kapitel 14.3).	Therapie Isatuximab, Pomalidomid, Dexamethason mit Pomalidomid, Dexamethason verglichen. Das Gesamtansprechen lag bei der Subgruppe der Patienten, die vier Vortherapien erhalten hatten im Isatuximab-Arm bei 56,3% und im Kontrollarm bei 28,6%. Hinzu kommt, dass auch in Patienten mit drei oder mehr Vortherapien mit einer Isatuximab-Pomalidomid-Dexamethason Therapie eine MRD-Negativität erreicht werden konnte (MRD-Negativität mit			

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			10-5). Patienten, die vier Vortherapien erhalten hatten, erreichten mit der Triplet-Kombination ein medianes PFS von 8,54 Monaten vs 3,29 Monate im Kontrollarm (HR 0,501 95% CI 0,259-0,971). (Bringhen et al. 2021).			
13	13.4/Seite 133	Zum Erreichen eines noch besseren Ansprechens in der Induktion werden aktuell Kombinationen von RVD mit einem monoklonalem Antikörper, wie dem anti-SLAMF-7-Antikörper Elotuzumab oder einem der	Bitte am Ende des Absatzes zu den Vierfachkombinationen mit VRD ergänzen:  „Gleichzeitig werden in Phase 3 Studien Kombinationen aus KRd mit einem monoklonalen Antikörper wie Elotuzumab oder Isatuxi-	Carfilzomib ist ein potenter Proteasomeninhibitor der zweiten Generation, der weniger periphere Neuropathien und gastrointestinalen Nebenwirkungen als Bortezomib aufweist. Aus diesem Grund gibt es zu den Studien mit Vierfachkombinationen bestehend aus Antikörper und VRD auch Phase 3 Untersuchungen zu Vierfachkombinationen mit KRd. Auch mit diesen Vierfachkombinationen erwartet man ein besseres und tieferes Ansprechen in der Induktion (clinicalTrials.gov Identifier: NCT03948035 (DSMM XVII),	Änderungsvorschlag wurde im Hintergrundtext übernommen.	Die Anregung ist nachvollziehbar und sinnvoll.

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		anti-CD-38-Anti- körper Daratu- mumab oder Isatuximab unter- sucht.	mab in der Induk- tion untersucht (clinicalTrials.gov Identifizier: NCT03948035 (DSMM XVII), NCT04483739 (IsKia), NCT04934475 (IFM 2020-02)).“	NCT04483739 (IsKia), NCT04934475 (IFM 2020-02)).		
14	13.4/Seite 135	Aktuell wird auch bei nicht trans- plantationsfähi- gen Patienten die Kombination von Lenalidomid und Proteasominhi- bitor (RVD) mit CD-38-Antikörper getestet, endgül- tige Daten hierzu stehen aber noch aus.	Aktuell wird auch bei nicht trans- plantationsfähi- gen Patienten die Kombination von Lenalidomid und Proteasominhi- bitor (RVD) mit den anti-CD-38- Antikörper Isatu- ximab und Darat- umumab getes- tet (Orlowski RZ et al. Zweegman S et al.), endgültige Daten hierzu ste- hen aber noch aus.	Um den genauen Stand der Studien er- mitteln und damit die Daten einordnen zu können, sollten die anti-CD38-Anti- körper und die NCT-Nummern genannt werden.  Neben den Beschreibungen der Stu- dien auf ClinicalTrials.gov können auch die folgenden Abstracts als Lite- ratur verwendet werden:  Orlowski RZ et al. Journal of Clinical Oncology 2018, 36:15_suppl, TPS8055-TPS8055 ClinicalTrials.gov Identifizier: NCT03319667 (IMROZ)  Zweegman S et al. Journal of Clinical Oncology 2019, 37:15_suppl, TPS8056-TPS8056 NCT03652064 (CEPHEUS)	Änderungsvorschlag wurde im Hinter- grundtext übernom- men.	Die Anregung ist nachvoll- ziehbar und sinnvoll.

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15	13.5/Seite 135	Außerdem kann eine lange Exposition insbesondere mit Melphalan und immunmodulierenden Substanzen zu einer reduzierten Stammzellsammlung führen, somit eine Hochdosis-therapie erschweren und sollte daher vermieden werden (Breitkreutz, Lokhorst et al. 2007, Kumar, Dispenzieri et al. 2007).	Ergänzung des Satzes:  „Bei Patienten, die nicht ausreichend Stammzellen mobilisieren, ist der Einsatz von Plerixafor in Kombination mit G-CSF indiziert.“	Aktuelle Ergebnisse aus der CASSI-OPEIA-Studie (Dara-VTD vs VTD) zeigen, dass weniger Stammzellen im Dara-VTD Arm im Vergleich zum Kontrollarm gesammelt werden konnten und daher vermehrt Plerixafor eingesetzt wurde. Durch den Einsatz von Plerixafor erhielten in beiden Armen genauso viele Patienten eine autologe Stammzelltransplantation (Moreau P, et al. Lancet. 2019. PMID: 31171419).  Auch in der GMMG-CONCEPT Studie wurde gezeigt, dass genug Stammzellen für eine autologe Stammzelltransplantation gesammelt werden konnten, wenn 3-6 Zyklen einer intensiven Induktionstherapie mit Isa-KRd eingesetzt wurden. 22% -33% der Patienten wurden jedoch als Poor Mobilizer eingestuft und bei insgesamt 34% der Patienten (n=21; total n=62) wurde Plerixafor für die Mobilisierung der Stammzellen eingesetzt. Bei nur 4 Patienten reichten die Stammzellen nicht für eine autologe Stammzelltransplantation im Anschluss aus (Asemisen AM, et al. EHA Congress 2020, Poster EP987).	Änderungsvorschlag wurde im Hintergrundtext übernommen.	Die Anregung ist nachvollziehbar und sinnvoll.



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				„Mozobil ist indiziert, in Kombination mit Granulozyten-Kolonie-stimulierenden Faktor (Granulocyte-Colony Stimulating Factor, G-CSF), die Mobilisierung von hämatopoetischen Stammzellen in das periphere Blut zur Entnahme und anschließenden autologen Transplantation bei erwachsenen Patienten mit Lymphom oder multiplen Myelom zu verbessern, die nicht ausreichend Stammzellen mobilisieren.“		
16	S 100	Einzelne altersas- soziierte Komorbi- ditäten können zudem negativ mit Komponenten der Myelomthera- pie interagieren und das Auftreten spezifischer ad- verser Ereignisse begünstigen (z.B. Diabetes mellitus - Dexamethason - hyperglykämische Stoffwechsellage, diabetische Poly-	Die Darstellung der Auflistung ist schwierig zu er- fassen- welche Nebenwirkung bezieht sich auf welches Medika- ment.  Vorschlag: Klam- mer löschen  In der Daratu- mumab Fachin- formation liegen keine Angaben zur NW mildes	Fachinformation Daratumumab iv, Fachinformation Daratumumab sc	Die Medikamenten- übersicht wurde über- arbeitet.	Die Anregung ist nachvoll- ziehbar und sinnvoll.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
		neuropathie – Bor- tezomib, Daratu- mumab oder Thalidomid - ag- gravierte Polyneu- ropathie mit Sturzzunahme, mildes kognitives Defizit - Dexamethason - hyperdy- names Delir, mil- des kognitives De- fizit - Lenalidomid - Einnahmefehler mit unzureichen- der Wirksamkeit oder unerwünsch- ten Nebenwirkun- gen)	kognitives Defizit vor.			
17	106	Bei Diagnose ei- ner Leichtketten Cast Nephropa- thie sollte die Erstlinientherapie	Diese Empfehlung wird im Text auf Seite 106 nicht begründet. Es fehlen Erläuterun- gen / Daten zu	ESMO Guideline supplement Renal impairment  Renal impairment (RI) is a common complication of myeloma present in up to 20% of patients at diagnosis [15].	Der Hintergrundtext wurde entsprechend ergänzt.	Die Anregung ist nachvoll- ziehbar und sinnvoll.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
		<p>bevorzugt Proteasom-Inhibitoren* in Kombination mit Dexamethason enthalten. Proteasom-Inhibitoren zeigen bei Ansprechen eine rasche Leichtkettenreduktion (Ludwig, Adam et al. 2010 Dimopoulos, Roussou et al. 2013).</p>	<p>den zugelassenen Regimen. Die Fachinformationsgerechte Gabe von IMiDen / Antikörpern sollte erwähnt werden.</p>	<p>Bortezomib-based regimens remain the cornerstone of the management of myeloma-related RI [I, B]. High-dose dexamethasone should be administered at least for the first month of therapy [II, B] [15]. In patients eligible for</p> <p>ASCT, bortezomib could be given in combination with thalidomide and dexamethasone [II, B] [16]. In patients who are ineligible for ASCT, bortezomib, melphalan and prednisone (VMP) can also be given [I, A] but no data exist for this regimen in dialysis patients [17]. Thalidomide is effective in myeloma patients with RI and can be given without dose modifications [II, B]. Lenalidomide is also effective and safe in patients with mild to moderate RI [II, B]. It should be administered with dose adjustments according to CrCl [18]. High-dose therapy (HDT)/ASCT is feasible in myeloma patients with RI; the dose of melphalan should be restricted to 100-140 mg/m<sup>2</sup> [III, C] [15]. Pomalidomide can be given at standard dose in patients with severe RI [II, B] [19]. Carfilzomib</p>		

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
				is another option for patients with re-lapsed/refractory MM (RRMM) and CrCl >15 ml/min [II, B] [20]. Ixazomib, lenalidomide and dexamethasone (IRd) can be safely administered in RRMM patients with CrCl $\geq$ 30 ml/min [I, A] [21]. Finally, daratumumab may be also given to patients with severe RI [III, C] [22]		
18	132	Daten der CASSIOPEIA-Studie zeigen jedoch ein tieferes Ansprechen in der Induktion für die Kombination Daratumumab/Bortezomib/Thalidomid/Dexamethason im Vergleich zu Bortezomib/Thalidomid/Dexamethason sowie ein besseres progressionsfreies Überleben	Dara-VTd ist seit dem 01.2020 in Deutschland zugelassen.  PFS nach einem medianen Follow-up von 44,5 Monaten: Not Reached in der D-VTd-Gruppe vs. 51,5 Monaten im Kontrollarm, HR 0,58 [95% CI 0,47-0,72].  Overall Survival nach einem medianen Follow-up	Fachinformation Daratumumab iv / sc  Moreau P., et al. DARATUMUMAB MAINTENANCE VS OBSERVATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH BORTEZOMIB, THALIDOMIDE, AND DEXAMETHASONE $\pm$ DARATUMUMAB AND ASCT: CASSIOPEIA PART 2 RESULTS, HemaSphere, 2021;5:(S2):45-46, Abstract Book, DOI: <a href="http://dx.doi.org/10.1097/HS9.0000000000000566">http://dx.doi.org/10.1097/HS9.0000000000000566</a>	Änderungsvorschlag wurde im Hintergrundtext übernommen.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierte Ent- scheidung	Begründung der Entschei- dung
		(PFS nach 18 Monaten 93% [95% CI 90-95] in der D-VTd-Gruppe vs. 85% [95% CI 81-88] im Kontrollarm) (Moreau, Attal et al. 2019). Bisher ist Dara-VTD in Deutschland aber noch nicht zugelassen. (Stand 06/2020)	von 44,5 Monaten: (D-VTd 41 Ereignisse, VTd 73 Ereignisse) Not Reached in der D-VTd-Gruppe vs. Not Reached im Kontrollarm, HR 0,54 [95% CI 0,37-0,79].			
19	132	Transplantationsfähige Patienten ohne Komorbiditäten, die eine intensive Therapie verhindern, sollen daher eine Drei- oder Vierfachtherapie erhalten. Dafür stehen die folgenden Schemata zur Verfügung:	Keine folgenden Schemata enthalten		Der Text wurde umgestellt und die Therapieschemata im Folgenden dargestellt	Die Anregung ist nachvollziehbar und sinnvoll.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
20	132	Carfilzomib ist im Moment ebenfalls noch nicht in der Erstlinientherapie zugelassen. Es gibt keine direkten Vergleiche mit bortezomibhaltigen Schemata, im Vergleich zwischen verschiedenen Carfilzomib-basierten Schemata scheint aber KRd hinsichtlich der ORR deutlich wirksamer zu sein als KCD oder KTD (Sheng, Li et al. 2017).	Es gibt mindestens zwei vergleichende Studien zwischen Carfilzomib und Bortezomib:  Clarion KMP vs VMP  Endurance KRd vs VRd	Literatur  Facon et al, Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma  Blood Publisher: American Society of Hematology  Publication Date: 5/2/2019 Volume: 133 Issue: 18 Pages: 1953-1963  DOI: 10.1182/blood-2018-09-874396 PMID: 30819926  Kumar S, Jacobus S, Cohen A, et al. Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma (NDMM): Results of ENDURANCE (E1A11) phase III trial. Presented at: 2020 ASCO Virtual Scientific Program; May 28, 2020. LBA3.  Skarzynski et al., Carfilzomib Triplet Fails to Induce Superior PFS in Newly	Der Verweis auf Carfilzomib-Schemata wurde nicht ergänzt. Stattdessen wurde verdeutlicht, dass Carfilzomib nicht für die Erstlinientherapie zugelassen ist.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
				Diagnosed Multiple Myeloma, Oncology (Williston Park, N.Y.) Publisher: UBM Medica, LLC Publication Date: 7/15/2020 Volume: 34 Issue: 7 Pages: 258 PMID: 32674212		
21	133	In der vor kurzem veröffentlichten ALCYONE-Studie konnte gezeigt werden, dass die Hinzunahme von Daratumumab zu VMP zu einem signifikant besseren Ansprechen und längerem PFS (nach 18 Monaten) führt (HR für Progress oder Tod 0,50; [95% CI, 0,38 - 0,65]; p<0.001) (Mateos, Dimopoulos et al. 2018).	...vor kurzem... bitte streichen. DVMP wurde in 09/2018 zugelassen  Auf Grundlage der ALCYONE Studie wurde im September 2018 das Regime Daratumumab-VMP zugelassen. Die Hinzunahme von Daratumumab zu VMP führte zu einem signifikant besseren Ansprechen und sowohl längerem PFS als auch Gesamtüber-	Aktuelle Daten und Vollpublikation  Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial  Maria-Victoria Mateos,et. Al, Lancet 2020 Jan 11;395(10218):132-141. doi: 10.1016/S0140-6736(19)32956-3. Epub 2019 Dec 10.	Änderungsvorschlag wurde im Hintergrundtext übernommen.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)



Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
			<p>leben. Nach einem medianen follow-up von 40,1 Monaten betrug die HR für das Versterben in der D-VMP-Gruppe im Vergleich zur VMP-Gruppe 0,60 (95% CI 0,46–0,80; <math>p = 0,0003</math>). Die Kaplan-Meier-Schätzung der Gesamtüberlebensrate nach 36 Monaten betrug 78,0 % (95 % CI 73,2–82,0) in der D-VMP-Gruppe und 67,9% (62,6–72,6) in der VMP-Gruppe. Das Progressionsfreie Überleben, der primäre Endpunkt, blieb für die D-VMP-</p>			

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
			Gruppe signifi- kant verbessert (HR 0,42 [0,34- 0,51]; p<0,0001).			
22	133	Ähnliche Daten liegen für die MAIA-Studie vor, in der Daratu- mumab/Lenalido- mid/ Dexamethason mit Lenalido- mid/Dexamethason verglichen und ebenfalls ein deutlich verbes- sertes progressi- onsfreies Überle- ben zeigte (PFS nach 30 Monaten 70,6% vs. 55,6%, HR für Progress oder Tod 0,56; [95% CI 0.43- 0.73]; p<0.001) (Facon, Kumar et al. 2019)	Ähnliche Daten streichen  Die Kombination Dara-Rd ist seit 12/2019 auf Grundlage der Phase III Maia Stu- die zugelassen.  Mit einem media- nen follow-up von 56 Monaten ist das mediane pro- gressionfreie Überleben im Da- ratumumab-Rd Arm noch nicht erreicht, im Ver- gleich zu dem Rd Arm, wo es 34.4 Monate beträgt. Die geschätzte 5- Jahres-PFS-Rate beträgt 52,5% bei	Aktuelle Daten  OVERALL SURVIVAL RESULTS WITH DA- RATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE VERSUS LENALIDO- MIDE AND DEXAMETHASONE IN TRANSPLANT-INELIGIBLE NEWLY DIAG- NOSED MULTIPLE MYELOMA: PHASE 3 MAIA STUDY  EHA Library. Facon T. 06/12/21; 330171; LB1901	Daten wurden aktuali- siert.	Neue Veröffentlichungen mit längeren Überlebenszeiten verfügbar.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
			<p>D-Rd und 28,7% bei Rd, HR, 0.53; 95% CI, 0.43-0.66; P &lt;0.0001.</p> <p>Diese Daten liefern einen neuen PFS Maßstab bei Patienten mit neu diagnostiziertem Myelom, die für eine Transplantation nicht geeignet sind</p> <p>Weiterhin zeigt die Maia Studie einen signifikanten OS-Vorteil von D-Rd gegenüber Rd. Die geschätzte 5-Jahres-OS-Rate beträgt 66,3% bei D-Rd und 53,1% bei Rd, HR, 0.68; 95% CI, 0.53-0.86; P = 0.0013, was wahrscheinlich zu einer erheblichen</p>			

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
			Verbesserung des medianen OS in dieser Patientenpopulation führen wird. Diese PFS- und OS-Ergebnisse wurden in einer Studienpopulation mit 44 % der Patienten im Alter von 75 bis 90 Jahren erreicht.			
23	134	Tabelle 16	Bei den aufgeführten Kombinationen kenntlich machen, welche für transplantationsgeeignete Patienten zugelassen sind und, welche für Patienten, die nicht für eine Transplantation geeignet sind, zugelassen sind		Änderungsvorschlag wurde im Hintergrundtext übernommen.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
24	134	Daratumumab/Bortezomib/Thalidomid/Dexamethason (noch nicht zugelassen, Stand 06/2020)	Dara-VTd durchgängig gleich schreiben  Dara-VTd ist seit dem 01.2020 in Deutschland zugelassen.	Fachinformation Daratumumab iv / sc	Änderungsvorschlag wurde übernommen.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)
25	134	Bortezomib	VMP fehlt	Fachinformation Bortezomib	Änderungsvorschlag wurde übernommen.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)
26	134	Daratumumab/Bortezomib/Thalidomid/Dexamethason (noch nicht zugelassen, stand 02/2020)	Dara-VTd ist seit dem 01.2020 in Deutschland zugelassen.	Fachinformation Daratumumab iv / sc	Änderungsvorschlag wurde übernommen.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)
27	134	Infusionsreaktionen (vor allem während der ersten Gaben), lange Infusionszeit, Infektanfälligkeit	Subkutane Applikationsform seit 06/2020 zugelassen	Fachinformation Daratumumab sc	Änderungsvorschlag wurde übernommen.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
28	135	Carfilzomib	Worauf beruht die Empfehlung? Studie zur KRd konnte keinen Vorteil gegenüber VRD zeigen.	Skarzynski et al., Carfilzomib Triplet Fails to Induce Superior PFS in Newly Diagnosed Multiple Myeloma, Oncology (Williston Park, N.Y.) Publisher: UBM Medica, LLC Publication Date: 7/15/2020 Volume: 34 Issue: 7 Pages: 258 PMID: 32674212	Hintergrundtext wurde überarbeitet und verdeutlicht, dass Carfilzomib nicht für die Erstlinientherapie zugelassen ist.	Aktueller Zulassungsstatus wurde überprüft (Stand 09 2021)
29	140/141	Der Nutzen einer Konsolidierung, wenn eine Lenalidomid-basierte Erhaltungstherapie geplant ist, ist daher nicht belegt. Eine Ausnahme bildet das Daratumumab-VTD (Bortezomib, Thalidomid, Dexamethason) - Schema, das in der CASSIOPEIA-Studie neben der Induktionstherapie auch als Konsolidierung nach Hochdosistherapie eingesetzt	In der Cassiopeia Studie wurde eine Verbesserung des Ansprechens nach der Konsolidierungstherapie im Vergleich zum Zeitpunkt nach autologer Stammzelltransplantation gezeigt.  Dara-VTd durchgängig gleich schreiben	Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study Philippe Moreau et al  Lancet. 2019 Jul 6;394(10192):29-38. doi: 10.1016/S0140-6736(19)31240-1.	Keine Änderung	Vorgeschlagene Änderung war nicht Gegenstand der randomisierten Untersuchung.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierte Ent- scheidung	Begründung der Entschei- dung																														
		<p>wurde (Moreau, Attal et al. 2019). Im Falle der Zulassung wird die Konsolidierung mit Dara-VTD dem zugelassenen Anwendungsgebiet entsprechen. Da aber in dieser Studie der Stellenwert der Zugabe von Daratumumab zu VTD und nicht der Stellenwert der Konsolidierung nach autologer Stammzelltransplantation untersucht wurde, ist auf Grundlage dieser Studie keine Aussage zum Nutzen einer Konsolidierungstherapie möglich.</p>		<p><b>A</b></p> <table border="1"> <caption>Data from Figure A: Proportion of patients (%)</caption> <thead> <tr> <th>Time Point</th> <th>Stable disease, progressive disease, or not evaluable (%)</th> <th>Partial response (%)</th> <th>Very good partial response (%)</th> <th>Very good partial response (%)</th> </tr> </thead> <tbody> <tr> <td>After induction</td> <td>7.4</td> <td>27.8</td> <td>50.5</td> <td>7.4</td> </tr> <tr> <td>After ASCT</td> <td>7.7</td> <td>15.5</td> <td>54.1</td> <td>9.2</td> </tr> <tr> <td>100 days after ASCT</td> <td>7.4</td> <td>9.2</td> <td>44.6</td> <td>9.9</td> </tr> <tr> <td>Best response*</td> <td>5.3</td> <td>9.2</td> <td>31.7</td> <td>10.5</td> </tr> <tr> <td>After induction (repeated)</td> <td>10.2</td> <td>33.8</td> <td>47.2</td> <td>6.5</td> </tr> </tbody> </table>	Time Point	Stable disease, progressive disease, or not evaluable (%)	Partial response (%)	Very good partial response (%)	Very good partial response (%)	After induction	7.4	27.8	50.5	7.4	After ASCT	7.7	15.5	54.1	9.2	100 days after ASCT	7.4	9.2	44.6	9.9	Best response*	5.3	9.2	31.7	10.5	After induction (repeated)	10.2	33.8	47.2	6.5		
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30	147	Daratumumab zu VMP bei nicht transplantationsfähigen Patienten und Fortführung als Daratumumab-Erhaltungstherapie einen deutlichen Vorteil hinsichtlich des progressionsfreien Überlebens	<p>...Fortführung als Daratumumab-Erhaltungstherapie einen deutlichen Vorteil hinsichtlich des progressionsfreien Überlebens und des Gesamtüberlebens.</p> <p>Die Hinzunahme von Daratumumab zu VMP führte zu einem signifikant besseren Ansprechen und sowohl längerem PFS als auch Gesamtüberleben. Nach einem medianen follow-up von 40,1 Monaten betrug die HR für das Versterben in der D-VMP-Gruppe im Vergleich zur VMP-</p>	<p>Aktuelle Daten und Vollpublikation</p> <p>Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial</p> <p>Maria-Victoria Mateos, et. al, Lancet 2020 Jan 11;395(10218):132-141. doi: 10.1016/S0140-6736(19)32956-3. Epub 2019 Dec 10.</p>	Der Hintergrundtext wurde entsprechend ergänzt.	Die Anregung ist nachvollziehbar und sinnvoll.



Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
			Gruppe 0,60 (95% CI 0,46–0,80; p = 0,0003). Die Kaplan-Meier-Schätzung der Gesamtüberlebensrate nach 36 Monaten betrug 78,0 % (95 % CI 73,2–82,0) in der D-VMP-Gruppe und 67,9% (62,6–72,6) in der VMP-Gruppe. Das Progressionsfreie Überleben, der primäre Endpunkt, blieb für die D-VMP-Gruppe signifikant verbessert (HR 0,42 [0,34–0,51]; p<0,0001).			
31	154	In Anhang II ist eine exemplarische Übersicht der medikamentö-	Anhang 2 einfügen		Anhang I und II wurde kombiniert und eingefügt	Übersicht fehlte in der während der Konsultation öffentlich zugänglichen Version.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
		sen Rezidivtherapie-Optionen, in Abhängigkeit des Ansprechens auf das jeweilige Induktionsregime bzw. die vorausgegangene Therapielinie, dargestellt (Chim, Kumar et al. 2018).				
32	154	Eine Übersicht der für die Behandlung des Myeloms verwendeten Arzneistoffe mit Haupt-Nebenwirkungen, inkl. der für die Rezidivtherapie zugelassenen Wirkstoffkombinationen, ist im Anhang I dieser Leitlinie aufgeführt.	Anhang 1 einfügen		Anhang I und II wurde kombiniert und eingefügt	Übersicht fehlte in der während der Konsultation öffentlich zugänglichen Version.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
33	160	In der Phase 2-Studie mit Daratumumab als Monotherapie wurden Patienten mit im Median fünf Vortherapien (2-14) behandelt. Das Gesamtansprechen lag bei 29%. Das mediane Gesamtüberleben lag bei 17,5 Monaten (Lonial, Weiss et al. 2016). Es sollte die Möglichkeit geprüft werden, Daratumumab in Kombination mit anderen aktiven Substanzen (Lenalidomid, Bortezomib) gemäß der Zulassung zu verabreichen, um das Ansprechen potenzi-	In den zur Zulassung führenden Phase II Studien GEN501 & SIRIUS konnte bei Patienten mit im median 5 (Interquartilabstand; IQR 4-7) Vortherapien nach einem medianen follow-up von 36.6 Monaten (IQR 34.5-38.2) ein Gesamtansprechen von 30.4% (95% CI 23.1-38.5), 6.5-14.7) und ein medianes Gesamtüberleben von 20.5 Monaten (95% CI 16.6-28.1) gezeigt werden.	Aktuelle Daten und Vollpublikation  Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: final results from the phase 2 GEN501 and SIRIUS trials  Saad Z Usmani, Lancet Haematol. 2020 Jun;7(6):e447-e455. doi: 10.1016/S2352-3026(20)30081-8.	Der Hintergrundtext wurde aktualisiert	Die Anregung ist nachvollziehbar und sinnvoll.

Nr.	Kapitel/ Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literatur-angaben)	Konsentierete Ent- scheidung	Begründung der Entschei- dung
		ell noch zu ver- bessern (siehe Ka- pitel 14.3).				

## 8. Unabhängigkeit und Umgang mit Interessenkonflikten

Die Deutsche Krebshilfe stellte über das Leitlinienprogramm Onkologie (OL) die finanziellen Mittel zur Verfügung. Diese Mittel wurden eingesetzt für die Projektkoordination, Personalkosten, Büromaterial, Literaturbeschaffung und -aufbereitung, anfallende Reisekosten und die Konsensuskonferenzen (Technik, Moderatorenhonorare, Catering). Die Erarbeitung der Leitlinie erfolgte in redaktioneller Unabhängigkeit von der finanzierenden Organisation. An dieser Stelle möchten wir allen Fachexperten für ihre ausschließlich ehrenamtliche Mitarbeit an dem Projekt danken.

Interessenkonflikte aller an der Leitlinie Beteiligten (Kordinator, Mandatsträger, Steuergruppenmitglieder, Autoren) wurden schriftlich mittels des Formblattes der AWMF abgefragt (Version 2.5, Zugriff 21.03.2018) und dokumentiert und sind im Kapitel 12.1 tabellarisch, nach Maßgabe des AWMF-Regelwerks vollständig dargestellt. Der Umgang mit Interessenkonflikten wurde wie folgt festgelegt (Tabelle 11).

**Tabelle 11: Einstufung der Interessenkonflikte**

Tätigkeit	Betrag	Bewertung
Berater/Gutachtertätigkeit	Unabhängig vom Betrag	Moderat
Wissenschaftlicher Beirat	Unabhängig vom Betrag	Moderat
Honorar für Vorträge, honorierte Autorenschaft	Unabhängig vom Betrag	Niedrig
Forschungsvorhaben	Unabhängig vom Betrag	Moderat
Patente /Eigentümerinteressen	Unabhängig vom Betrag	Hoch

Die Interessenkonflikte wurden von zwei Vertreterinnen des Leitliniensekretariats (Prof. Dr. Nicole Skoetz, Vanessa Piechotta) zunächst auf thematischen Bezug zur Leitlinie gesichtet und gemäß den AWMF-Kriterien als keine, gering, moderat oder hoch bezüglich der individuellen Empfehlung eingestuft. Hiernach wurde die jeweilige Konsequenz nach dem Schema in Tabelle 12 festgelegt.

**Tabelle 12: Konsequenz der Einstufung der Interessenkonflikte**

Einstufung des Interessenkonflikts	Konsequenz
Niedrig	Sollte keine leitende Funktion bezüglich des Themas übernehmen, ODER einen interessenkonfliktfreien Ko-AG-Leiter haben.
Moderat	Enthaltung zu Empfehlungen, die in Zusammenhang mit den potentiellen Interessenkonflikten stehen.
Hoch	Ausschluss von der Diskussion zu Empfehlungen, die in Zusammenhang mit den potentiellen Interessenkonflikten stehen.

Bei Interessenkonflikten der Mandatsträger wurde der thematische Bezug zur Leitlinie hergestellt und beispielsweise bei moderaten Interessenkonflikten (Mitglied im Advisory Board, Gutachtertätigkeit, Drittmitteleinnahme zur klinischen Forschung der diskutierten Substanz) eine Enthaltung bei der Abstimmung relevanter Empfehlungen beschlossen (siehe Kapitel 8412.1). Empfehlungen mit Enthaltungen wurden den Mandatsträgern vorab kommuniziert. Vorab wurde kommuniziert, dass sich die Berechnung der Konsentierung und Konsensstärke ausschließlich auf die Stimmen ohne Enthaltungen bezieht.

Die mögliche unangemessene Beeinflussung durch Interessenskonflikte wurde dadurch reduziert, dass die Recherche, Auswahl, Auswertung und Bewertung der Literatur durch Methodiker der Abteilung Evidence-Based Oncology erfolgte, die sämtlich keine Interessenkonflikte aufwiesen. Die formale Konsensbildung mit externer, unabhängiger Moderation, die interdisziplinäre Erstellung der Leitlinie und die öffentliche Begutachtung der Leitlinie bilden weitere Aspekte zur Reduktion von Verzerrungen und unangemessener Einflussnahme.

## 9. Verbreitung und Implementierung

Die Leitlinie wird in den in Kapitel 1 genannten und näher dargestellten Formaten in deutscher und englischer Sprache publiziert:

- Kurzfassung
- Langfassung
- Patientenleitlinie
- Leitlinienreport

Alle genannten Formate der Leitlinie sollen über die Internetseiten der folgenden Gesellschaften und Organisationen verfügbar sein:

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (<http://www.awmf.org/leitlinien/aktuelle-leitlinien.html>)
- Leitlinienprogramm Onkologie <https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom/>
- Guidelines International Network ([www.g-i-n.net](http://www.g-i-n.net))

Es ist explizit gewünscht, die Leitlinie in die Anwendung in der Versorgung zu überführen. Dieses kann z.B. durch Verwendung der Algorithmen in lokalen Behandlungspfaden, als Kitteltaschenformat oder durch die Einbindung in Praxis- bzw. Klinikinformationssysteme erfolgen. Intensive Öffentlichkeitsarbeit mittels Beiträgen in Fachzeitschriften (Deutsche Ärzteblatt ist in Planung), Buchbeiträgen, Vorträgen auf Kongressen, Symposien, Schulungen und Fortbildungen kann die Verbreitung und Implementierung der Leitlinie ebenfalls unterstützen.

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## 12. Anlagen

### 12.1. Ergebnisse der Interessenkonflikterklärungen

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaftlichen Beirat <sup>2</sup>	Honorierte Vortrags-/Schulungstätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autorenschaft <sup>4</sup>	Forschungsvorhaben/ Durchführung klinischer Studien <sup>5</sup>	Eigentümerinteressen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
Matthias Hellberg-Naegele	Janssen Advisory Board, Novartis, Takeda	Janssen	Celgene, Novartis	Nein	Nein	Nein	Universitätsklinikum Freiburg Klinik für Hämatologie, Onkologie und Stammzelltransplantation	Enthaltung bei Empfehlungen mit thematischem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Karin Hohloch	Roche	Janssen, Roche	Nein	Nein	Spectrum	Nein	Kantonsspital Graubünden, Medizinische Onkologie, Chur	Enthaltung bei Empfehlungen mit thematischem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Markus Munder	Nein	Janssen, Takeda, Amgen, Celgene, BMS, TEVA	Takeda, Janssen	Takeda	BMS	nein	3. medizinische Klinik, Universitätsmedizin Mainz	Enthaltung bei Empfehlungen mit thematischem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Daniela Trog	Nein	Nein	Nein	Nein	Nein	Nein	Lukaskrankenhaus Neuss	-	
Heinrich Recken	Nein	Nein	Nein	Nein	Nein	Nein	Hamburger Fern-Hochschule	-	
Ulrike Holtkamp	Nein	Nein	Nein	Nein	Nein	Nein	DLH e.V. DLH-Stiftung e.V.	-	



Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaft-lichen Beirat <sup>2</sup>	Honorierte Vortrags-/ Schulungs-tätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autoren-schaft <sup>4</sup>	Forschungs-vor-haben/ Durch-führung klini-scher Studien <sup>5</sup>	Ei-gentüme-r-inter-essen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
Lana Harder	Nein	Nein	Nein	Nein	Nein	Nein	Institut für Tumor-genetik Nord	-	
Thorsten Derlin	Nein	Nein	Nein	Nein	Nein	Nein	Medizinische Hoch-schule Hannover, Klinik für Nuklear-medizin	-	
Stefan Delorme	Nein	Nein	Nein	Nein	Nein	Nein	Uniklinik Heidel-berg	-	
Steffen Simon	Nein	Nein	DKG/DKH (Leitlini-enprogramm), For-um für medizini-sche Fortbildung, Krankenhäuser (Abtl. Für Onkolo-gie, Palliativmedi-zin, Neurologie, etc.)	Nein	Teva GmbH, Otsuka GmbH, Dt. Krebshilfe, BMBF	Nein	UK Köln	Keine themati-sche Relevanz	
Mario Schubert	Nein	Nein	Nein	Fleishman Hilard Ger-many GmbH	Nein	nein	Hamm Kliniken GmbH & Co. KG	Keine themati-sche Relevanz	
Herrmann Einsele	Janssen, Celgene, BMS, Novartis, Takeda	Janssen, Celgene, BMS, No-vartis, Takeda	Janssen, Celgene, BMS, Novartis, Takeda	Nein	Nein	Nein	Universitätsklini-kum Würzburg, Me-dizinische Klinik und Poliklinik II	Enthaltung bei Empfehlungen mit themati-schem Bezug	7.1.7 7.4.4 7.4.5 7.6.2 7.6.3 8.2.4 8.3.2
Falko Fend	Nein	Nein	Roche	Nein	Nein	nein	UK Tübingen	Keine themati-sche Relevanz	
Walter Baumann	BNHO e.V.	Nein	Ev. Akad.	Nein	BMG, Zi	Nein	Früher: WINHO GmbH Köln	Keine themati-sche Relevanz	

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Börge Schmidt	Nein	Nein	Nein	Nein	Nein	Nein	UK Essen, Institut für medizinische Informatik, Biometrie und Epidemiologie	-	
Bianca Senf	Nein	Nein	Nein	Nein	Hector Stiftung	Nein	Universitätsklinikum Frankfurt am Main, Universitäres Centrum für Tumorerkrankungen	Keine thematische Relevanz	
Valentin Goede	Nein	Roche, Janssen, Gilead, AbbVie	Roche, Janssen, Gilead	Roche	Nein	Nein	St. Marien Hospital	Enthaltung bei Empfehlungen mit thematischem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Peter Eichhorn	Nein	Nein	Nein	Nein	Nein	Nein	Institut für Laboratoriumsmedizin  Klinikum der Universität München	-	
Torsten Kluba	Depuy	ZFOU	Nein	Nein?	PROOF	Verbesserung der Zielbindungskapazität von Stammzellen mit einem kationischen Wirkstoff  The cationic agent, preferably a linear cationic	Städtisches Klinikum Dresden	Keine thematische Relevanz	

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaft-lichen Beirat <sup>2</sup>	Honorierte Vortrags-/ Schulungs-tätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autoren-schaft <sup>4</sup>	Forschungs-vor-haben/ Durch-führung klini-scher Studien <sup>5</sup>	Ei-gentüme-r-inter-essen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
						polymer, preferably a polyethylene-imine is useful for improving the targeting capacity of stem cells, preferably mesenchymal stem cells and/or hematopoietic stem cells (all claimed).			
Hartmut Goldschmidt	Wilhelm Sander Stiftung, Insitut National du Cancer, Springer Verlag, Taylor Francis Group, Kose Carreras Stiftung	Molecular Partners AG Zürich, Celgene International, Millenium Pharmaceuticals, BMS CCompany, Janssen, Adaptive Biotechnologies, Sanofi-Aventis, Studio E.R Congressi	Onko Internetportal dkg-web GmbH, I-med Institute GmbH, STIL Foschungs GmbH, Westpfalz Klinikum, Institut für versorgungsforschung in der Onkologie GbR, Janssen, Amgen, KML, Agentur Hoff Robinson Germany, Johanniter, Bristol-Myers-Squibb, UK Frankfurt, Celgene, Chop, FomF, Helbling Consulting and Research AG, Novartis, art	Zuckerschwerdt Verlag, Thieme Verlag, Springer Medizin	Uk Tübingen, Molecular Partners AG, Millenium Pharmaceuticals, Celgene, UK Heidelberg, BMS, CHugai, MSD, Janssen, Amgen. Gesellschaft für medizinische Innovation-Hämatologie und Onkologie mbH, Onyx Therapeutics, Bristol-Myers Squibb,	nein	UK Heidelberg und Nationales centrum für Tumorerkrankungen	Enthaltung bei Empfehlungen mit thematischem Bezug	7.1.7 7.4.4 7.4.5 7.6.2 7.6.3 8.2.4 8.3.2

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaftlichen Beirat <sup>2</sup>	Honorierte Vortrags-/Schulungstätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autoren-schaft <sup>4</sup>	Forschungs-vorhaben/ Durchführung klinischer Studien <sup>5</sup>	Eigentümer-interessen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
			Tempi communications, Congress Culture Concept, Klinikum Oldenburg, Chugai Pharma, NCCCR, UK Gießen, Takeda, Medical Communication, Nocartis						
Christof Scheid	UKK Management GmbH	Novartis, Amgen, Janssen, Celgene, Bristol Myers Squibb, Takeda	Novartis, Amgen, Janssen, Celgene, Bristol Myers Quibb, Takeda	Janssen, Celgene	Nein	Nein	UK Köln	Enthaltung bei Empfehlungen mit thematischem Bezug	7.1.7 7.4.4 7.4.5 7.6.2 7.6.3 8.2.4 8.3.2
Thomas Benzing	Nein	Otsuka	Otsuka, Hexal, Amgen	Nein	Nein	Nein	UK Köln	Keine thematische Relevanz	
Robert Semrau	Nein	Nein	Astellas Pharma GmbH	Merck Serono	Nein	Nein	BRS	Keine thematische Relevanz	
Chiara Bänsch	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln, Abteilung I für Innere Medizin, Evidenzbasierte Onkologie	-	
Jens Hillengas	Nein	Takeda, Amgen, Janssen	Amgen, janssen, Xian Janssen	Nein	Celgene; Thalidormid, Lanalidormid, Pomalidomid	Nein	Roswell Park Comprehensive Cancer Center	Ko-Autor ohne Mandat	
Bettina Beuthien-Baumann	Nein	Nein	Bracco Roche	Springer Verlag, CME Artikel zum Thema PET/MR –kein Bezug	Nein	Nein	Deutsches Krebsforschungszentrum Heidelberg	Keine thematische Relevanz	
Reiner Caspari	Nein	Nein	Nein	Nein	Nein	Nein	Sonnenberg Klinik	-	

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaft-lichen Beirat <sup>2</sup>	Honorierte Vortrags-/ Schulungs-tätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autoren-schaft <sup>4</sup>	Forschungs-vor-haben/ Durch-führung klini-scher Studien <sup>5</sup>	Ei-gentüme-r-inter-essen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
Elias Mai	Janssen Taheda	Celgene Taheda	Janssen Taheda	Nein	Nein	Nein	Universitätsklini-kum Heidelber	Ko-Autor ohne Mandat	
Monika Engelhardt	Nein	Amgen, Celgnen, Janssen	Nein	Celgen, Janssen	Nein	Nein	Universitätsklini-kum Freiburg	Enthaltung bei Empfehlungen mit themati-schem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Sebastian Fetscher	Nein	Nein	Nein	Nein	Nein	Nein	Sana Kliniken Lübeck	-	
Markus Follmann	Nein	Nein	AWMF zertifizier-ter Leitlinienbera-ter; Honorare als Selbstständiger von Fachgesell-schaften / LL Gruppen	Nein	Nein	Nein	Deutsche Krebsge-sellschaft	Keine themati-sche Relevanz	
Christina Gerlach	Nein	Nein	Interdisziplinäre Gesellschaft für Palliativmedizin	Nein	Rheinische Hos-pizstiftung Mainzer Pallia-tivstiftung	Nein	Universitätsmedizin Johannes Guten-berg Universität	Keine themati-sche Relevanz	
Valentin Goede	Nein	Roche, Janssen, Abbive, Gilead	Roche, Janssen, Gilead	Roche	Nein	Nein	St.Marien Hospital	Enthaltung bei Empfehlungen mit themati-schem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Marius Goldkuhle	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklini-kum Köln, Abtei-lung I für Innere Medizin, Evidenz-basierte Onkologie	-	

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaft-lichen Beirat <sup>2</sup>	Honorierte Vortrags-/ Schulungs-tätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autoren-schaft <sup>4</sup>	Forschungs-vor-haben/ Durch-führung klini-scher Studien <sup>5</sup>	Ei-gentüme-r-inter-essen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
Marco Herling	Nein	Nein	Nein	Nein	Nein	Nein	Uniklinik Köln, In-nerne Medizin	-	
Axel Heyll	Gutachten für GKV	Nein	Weiterbildung für MDK Ärzte	Nein	Nein	Nein	MDK Nordrhein	Keine the-matische Rele-vanz	
Eva Hilgenfeld	MDK	Nein	MDK	Nein	Nein	Nein	MDK Nordrhein	-	
Maximilian Holler	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklini-kum Freiburg	-	
Michael Hundemer	Nein	Nein	Celgene	Nein	Nein	Nein	Universitätsklini-kum Heidelberg	Ko-Autor ohne Mandat	
Georg Jacobs	Sozialgerichts-barkeit des Saarlandes	Roche, Janssen, BMS	Für örtliche Ärzte-verbände, interne Qualitätszirkel und Ärztekammer	Nein	Phase II-III, ins-gesamt 25 Pro-jekte in häm und solid Tumoren	Nein	Praxis für Hämato-logie und Onkolo-gie Jacobs Duas Zwick	Enthaltung bei Empfehlungen mit themati-schem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Johannes Jung	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklini-kum Freiburg	-	
Wolfgang Knauf	Nein	DKG	Amgen, BMS, Jans-sen, Celgene, Mundipharma, Ta-keda	Viele	Janssen, Mundipharma	Nein	Selbstständig	Enthaltung bei Empfehlungen mit themati-schem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Katharina Kriegs-mann	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Heidelberg	-	
Nicolaus Martin Krö-ger	Sozialgerichte	Novartis, Alexion, Neovii, Jazz, Sanofi, AMGEN	Novartis, Celgene, Neovii	Nein	Neovii, Riemsser, Pierre Fabre, No-vartis, Celgene	Nein	UKE, Onkologisches Zentrum	Enthaltung bei Empfehlungen mit themati-schem Bezug	7.1.7 7.4.5 7.6.3 8.2.4

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaftlichen Beirat <sup>2</sup>	Honorierte Vortrags-/Schulungstätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autorenschaft <sup>4</sup>	Forschungsvorhaben/ Durchführung klinischer Studien <sup>5</sup>	Eigentümerinteressen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
									8.3.2
Constantin Lapa	Nein	Nein	Nein	Nein	Wilhelm Sander Stiftung	Nein	Universitätsklinikum Würzburg	Keine thematische Relevanz	
Jan Lüneberg	Nein	Nein	Nein	Nein	Nein	Nein	Ruhestand	-	
Maximilian Merz	Nein	AMGEN	Nein	Nein	Takeda	Nein	Universitätsklinikum Heidelberg	Ko-Autor ohne Mandat	
Claas Philip Nähle	Nein	Nein	Nein	Nein	Nein	Nein	Uniklinik Köln	-	
Marc Steffen Raab	Nein	Celgene, Novartis, AMGEN, Takeda	Nein	AMGEN	AMGEN, Sanofi, Novartis, Array	Nein	Universitätsklinikum Heidelberg	Enthaltung bei Empfehlungen mit thematischem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Christina Ramsenthaler	Nein	Nein	Nein	Nein	St Christophers Hospice, London	Nein	Albert Ludwig Universität Freiburg	Keine thematische Relevanz	
Heike Reinhardt	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Freiburg	-	
Andreas Rosenwald	MorphoSys AG	Celgene, Roche, Roche	Nein	Nein	MorphoSys AG	Nein	Universität Würzburg	Enthaltung bei Empfehlungen mit thematischem Bezug	7.1.7 7.4.5 7.6.3 8.2.4 8.3.2
Benjamin Scheckel	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln, Abteilung I für Innere Medizin, Evidenzbasierte Onkologie	-	

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaft-lichen Beirat <sup>2</sup>	Honorierte Vortrags-/ Schulungs-tätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autoren-schaft <sup>4</sup>	Forschungs-vor-haben/ Durch-führung klini-scher Studien <sup>5</sup>	Ei-gentüme-r-inter-essen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
Sophia Scheubeck	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinik Freiburg	-	
Börge Schmidt	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Essen	-	
Katja Schöller	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinik Freiburg	-	
Nicole Skoetz	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln, Abteilung I für Innere Medizin, Evidenz-basierte Onkologie	-	
Aynur Temur	Nein	Nein	Nein	Nein	Nein	Nein	Uniklinik Köln	-	
Tim Weber	Bayer AG	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Heidelberg	Keine thematische Relevanz	
Matthias Weiß	Nein	Nein	Referent beim KKS-Netzwerk		Nein	Nein	Universitätsklinikum Freiburg	Keine thematische Relevanz	
Sandra Maria Woerner	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Freiburg	-	
Dirk Lang	Nein	Nein	Weiterbildung physio-soziale Onkologie	Klinik für Psychiatrie Uniklinik Ulm	Uniklinik Köln / Uniklinik Leipzig	Nein	Universitätsklinikum Ulm	Keine thematische Relevanz	
Lukas John	Nein	Nein	Nein	Nein	Boehringer-Ingelheim Foundation	Nein	Universitätsklinikum Heidelberg	Keine thematische Relevanz	
Giulia Graziani	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Freiburg	-	
Lara Mossakowski	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln, Abteilung I für Innere Medizin, Evidenz-basierte Onkologie	-	



Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaft-lichen Beirat <sup>2</sup>	Honorierte Vortrags-/ Schulungs-tätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autoren-schaft <sup>4</sup>	Forschungs-vor-haben/ Durch-führung klini-scher Studien <sup>5</sup>	Ei-gentüme-r-inter-essen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
Stefanie Huhn	Nein	Nein	Nein	Celgene, Sanofi-Aven-sis Deutschland GmbH  Bone Marrow Trans-plant, Spektrum der Hä-matologie, Janssen-Cilag GmbH, Journal Onkolo-gie, Onkologie heute, BMC Cancer	nein		Universitätsklini-kum Heidelberg	Beteiligte Exper-tin ohne Mandat	
Veronika Riebl	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklini-kum Freiburg	-	
Selin Altindis	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklini-kum Köln	-	
Burcu Besiroglu	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklini-kum Köln	-	
Susanne Blödt	Nein	Nein	CIEE-Non-profit or-ganization	Nein	Nein	Nein	AWMF-Institut für MedizinischesWis-sensmanagement	Keine themati-sche Relevanz	
Vanessa Piechotta	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklini-kum Köln, Abtei-lung I für Innere Medizin, Evidenz-basierte Onkologie	-	
Udo Holtick	Amgen, BMS/Cel-gene, GSK, Jans-sen, Novartis, Pfi-zer, Sanofi-Aven-tis, Takeda	Amgen, BMS/Celgene, GSK, Janssen, Novartis, Pfi-zer, Sanofi-Aventis, Takeda	Amgen, BMS/Cel-gene, GSK, Jans-sen, Kite/Gilead, Novartis, Pfizer, Sanofi-Aventis, Ta-keda	Nein	Nein	Nein	Universitätsklini-kum Köln, Abtei-lung I für Innere Medizin	Enthaltung bei Empfehlungen mit themati-schem Bezug	7.1.7 7.4.4 7.4.5 7.6.2 7.6.3 8.2.4 8.3.2
Klaus Werner Mahlfeld	Nein	Nein	Nein	Nein	Nein	Nein	Ruhestand	-	
Anna Jauch	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklini-kum Heidelberg,	-	

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaftlichen Beirat <sup>2</sup>	Honorierte Vortrags-/Schulungstätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autorenschaft <sup>4</sup>	Forschungsvorhaben/ Durchführung klinischer Studien <sup>5</sup>	Eigentümerinteressen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
							Institut für Human-genetik		
Niels Weinhold	Nein	Nein	Sanofi	Nein	Nein	Nein	Universitätsklinikum Heidelberg, Sektion Multiples Myelom	Keine thematische Relevanz	
Katja Weisel	Nein	Janssen, Karyopharm, Takeda	AbbVie, Adaptive Biotech, Amgen, GSK, Celgene/BMS, Karyopharm, Roche, Takeda, Sanofi	Nein	Amgen, Celgene, Janssen, Sanofi	Nein	Universitätsklinikum Hamburg Eppendorf, II. Medizinische Klinik, Onkologie, Hämatologie, KMT mit Abt. Pneumologie	Beteiligte Expertin ohne Mandat	
Ralph Wäsch	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Freiburg	-	
Maximilian Schinke	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Freiburg	-	
Patrick Marschner	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Freiburg	-	
Angela Aldin	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln, Abteilung I für Innere Medizin, Evidenzbasierte Onkologie	-	
Lisa Umlauff	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln, Abteilung I für Innere Medizin, Evidenzbasierte Onkologie	-	
Thomas Langer	Nein	Nein	AWMF e.V.	Nein	Nein	Nein	Deutsche Krebsgesellschaft	-	
Ina Monsef	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln, Abteilung I für Innere	-	

Name, Vorname, Titel	Berater-/Gutachter-tätigkeit <sup>1</sup>	Mitarbeit in einem wissenschaftlichen Beirat <sup>2</sup>	Honorierte Vortrags-/Schulungstätigkeit <sup>3</sup>	Honorierte Autoren-/Co-Autorenschaft <sup>4</sup>	Forschungsvorhaben/ Durchführung klinischer Studien <sup>5</sup>	Eigentümerinteressen <sup>6</sup>	Arbeitgeber	Relevanz	Enthaltungen <sup>7</sup>
							Medizin, Evidenzbasierte Onkologie		
Simone Wesselmann	Nein	Nein	Nein	Nein	Nein	Nein	Deutsche Krebsgesellschaft e. V.	-	

- 1 = Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung
- 2 = Bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung
- 3 = Honorare für Vortrags- und Schulungstätigkeiten im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung
- 4 = Bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung
- 5 = Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung
- 6 = Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz), oder Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft
- 7 = Nummerierung der Empfehlungen vor Konsensuskonferenz

## 12.2. Suchstrategien

Im Nachfolgenden werden die verwendeten Suchstrategien mit den korrespondierenden Trefferzahlen sowie die Anzahl der eingeschlossenen Treffer aufgeführt.

### Suche nach RCTs für alle therapeutischen Fragestellungen

Suche vom 07.06.2018; insgesamt 3317 Treffer in MEDLINE und 4852 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 1553 Publikationen zu RCTs identifiziert werden.

MEDLINE/Ovid (bis 07.06.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	randomi?ed.ab.
15	placebo.ab.
16	clinical trials as topic.sh.
17	randomly.ab.
18	trial.ti.
19	or/12-18
20	exp ANIMALS/ not HUMANS/
21	19 not 20
22	11 and 21

3317 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 07.06.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myelom*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	#11 in Trials

4852 Treffer in Central

### Suche für alle therapeutischen Fragestellungen

Suche vom 11.06.2018; insgesamt 983 Treffer in MEDLINE. Es wurde nur die Datenbank MEDLINE (über OVID) zur Identifikation der Primärpublikationen durchsucht. Es konnten 145 systematische Übersichtsarbeiten identifiziert werden.

MEDLINE/Ovid (bis 11.06.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp Plasmacytoma/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	(MEDLINE or systematic review).tw. or meta analysis.pt.
13	11 and 12
14	limit 11 to systematic reviews

#	Searches
15	13 or 14
16	from 15 keep 1-818

983 Treffer in Medline

### Suche für alle Fragestellungen zum PET-CT (Kapitel 4.1.2.7.4 PET/CT)

Suche vom 24.08.2018; insgesamt 794 Treffer in MEDLINE und 352 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 113 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 24.08.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myeloma.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	exp POSITRON-EMISSION TOMOGRAPHY/
13	(pet\$ or petscan\$ or fdg-pet\$).tw,kf,ot.
14	(emission adj3 tomograph\$).tw,kf,ot.
15	(positron adj4 tomograph\$).tw,kf,ot.
16	FLUORODEOXYGLUCOSE F18/ (deoxyglucose\$ or desoxyglucose\$ or deoxy-glucose\$ or desoxy-glucose\$ or deoxy-d-glucose\$ or desoxy-d-glucose\$ or 2deoxyglucose\$ or 2deoxy-d-glucose\$ or
17	fluorodeoxyglucose\$ or fluorodesoxyglucose\$ or fludeoxyglucose\$ or fluorodeoxyglucose\$ or fluordesoxyglucose\$ or 18fluorodeoxyglucose\$ or 18fluorodesoxyglucose\$ or 18fluorodeoxyglucose\$ or fdg\$ or 18fdg\$ or 18f-dg\$ or de-oxyglucose\$).tw.
18	((fluoro\$ adj3 deoxy\$) or fluorodeoxy\$ or fludeoxy\$ or fluorine\$ or 18flu\$).tw.

#	Searches
19	or/12-18
20	11 and 19
21	ANIMALS/ not HUMANS/
22	20 not 21

794 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 24.08.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myeloma*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MeSH descriptor: [Positron-Emission Tomography] explode all trees
13	(pet* or petscan* or fdg-pet*)
14	(emission near/3 tomograph*)
15	(positron near/4 tomograph*)
16	MeSH descriptor: [Fluorodeoxyglucose F18] explode all trees
17	(deoxyglucose* or desoxyglucose* or deoxy-glucose* or desoxy-glucose* or deoxy-d-glucose* or desoxy-d-glucose* or 2deoxyglucose* or 2deoxy-d-glucose* or fluorodeoxyglucose* or fluorodesoxyglucose* or fludeoxyglucose* or fluorodeoxyglucose* or fluordesoxyglucose* or 18fluorodeoxyglucose* or 18fluordesoxyglucose* or 18fluorodeoxyglucose* or fdg* or 18fdg* or 18f-dg* or de-oxyglucose*)
18	((fluoro* near/3 deoxy*) or fluorodeoxy* or fludeoxy* or fluorine* or 18flu*)
19	#12 or #13 or #14 or #15 or #16 or #17 or #18
20	#11 and #19 in Trials

352 Treffer in Central

**Suche für alle Fragestellungen zur minimalen Resterkrankung (Kapitel 4.3 Verlaufsdiagnostik)**

Suche vom 25.09.2018; insgesamt 500 Treffer in MEDLINE und 170 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 52 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 25.09.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myeloma.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	NEOPLASM, RESIDUAL/
13	(residual* adj3 (cancer* or neoplasm* or tumour* or tumor*)).tw,kf,ot.
14	(residual adj1 disease*).tw,kf,ot.
15	minimal*.tw,kf,ot.
16	14 and 15
17	12 or 13 or 16
18	11 and 17
19	ANIMALS/ not HUMANS/
20	18 not 19

500 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 25.09.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myeloma*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*



#	Searches
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MeSH descriptor: [Neoplasm, Residual] explode all trees
13	(residual* near/3 (cancer* or neoplasm* or tumour* or tumor*))
14	(residual near/1 disease*)
15	minimal*
16	#14 and #15
17	#12 or #13 or #16
18	#11 and #18 in Trials

170 Treffer in Central

### Suche für Fragestellung zum Stellenwert chirurgischer Verfahren zur der symptomatischen Schmerzbehandlung (Kapitel 6.2 Skelettkomplikationen)

Suche vom 28.11.2018; insgesamt 3526 Treffer in MEDLINE und 484 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 215 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 28.11.2018)

#	Searches
1	*NEOPLASM METASTASIS/
2	*BONE NEOPLASMS/
3	(bone adj3 (cancer or neoplasm* or metastas*)).tw,kf,ot.
4	"BONE AND BONES"/
5	or/1-4
6	exp MULTIPLE MYELOMA/
7	myeloma.tw,kf,ot.
8	exp PLASMACYTOMA/
9	plasm?cytom*.tw,kf,ot.
10	plasmozytom*.tw,kf,ot.
11	plasm* cell myelom*.tw,kf,ot.
12	myelomatosis.tw,kf,ot.

## 12.2.Suchstrategien

#	Searches
13	LEUKEMIA, PLASMA CELL/
14	(plasma* adj3 neoplas*).tw,kf,ot.
15	kahler*.tw,kf,ot.
16	or/6-15
17	SURGICAL PROCEDURES, OPERATIVE/
18	surg*.hw.
19	(surgical* adj2 (therap* or treatment* or intervention* or resection*)).tw,kf,ot.
20	(surger* or surgical*).tw,kf,ot.
21	(operation or operative*).tw,kf,ot.
22	(pathologic* adj1 fracture*).tw,kf,ot.
23	17 or 18 or 20 or 21 or 22
24	randomized controlled trial.pt.
25	controlled clinical trial.pt.
26	randomi?ed.ab.
27	placebo.ab.
28	drug therapy.fs.
29	randomly.ab.
30	trial.ab.
31	groups.ab.
32	or/24-31
33	exp ANIMALS/ not HUMANS/
34	32 not 33
35	meta analysis.mp.
36	meta analysis.pt.
37	review.pt.
38	search*.tw.
39	or/35-38
40	exp COHORT STUDIES/
41	cohort*.tw.
42	controlled clinical trial.pt.
43	EPIDEMIOLOGIC METHODS/
44	limit 43 to yr=1971-1988
45	40 or 41 or 42 or 44

#	Searches
46	16 and 23 and (34 or 39 or 45)
47	5 and (19 or 22) and (34 or 39 or 45)
48	46 or 47

3526 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 28.11.2018)

#	Searches
1	MeSH descriptor: [Neoplasm Metastasis] this term only
2	MeSH descriptor: [Bone Neoplasms] this term only
3	(bone near/3 (cancer or neoplasm* or metastas*))
4	MeSH descriptor: [Bone and Bones] this term only
5	#1 or #2 or #3 or #4
6	MeSH descriptor: [Multiple Myeloma] explode all trees
7	myeloma*
8	MeSH descriptor: [Plasmacytoma] explode all trees
9	plasm?cytom*
10	plasmozytom*
11	plasm* cell myelom*
12	myelomatosis
13	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
14	(plasma* near/3 neoplas*)
15	kahler*
16	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
17	MeSH descriptor: [Surgical Procedures, Operative] this term only
18	(surgical* near/2 (therap* or treatment* or intervention* or resection*))
19	(surger* or surgical*)
20	(operation or operative*)
21	(pathologic* near/1 fracture*)
22	#17 or #18 or #19 or #20 or #21
23	#16 and #22 in Trials
24	#5 and (#18 or #21) in Trials
25	#23 or #24

484 Treffer in Central

### Suche für alle Fragestellungen zur Strahlentherapie (Kapitel 6.2 Skelettkomplikationen und Kapitel 7.3 Indikation zur Strahlentherapie)

Suche vom 26.09.2018; insgesamt 1606 Treffer in MEDLINE und 213 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 53 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 26.09.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	exp RADIOTHERAPY/
13	rt.fs.
14	radiotherapy.mp.
15	irradiat\$.mp.
16	radiat\$.mp.
17	radiac\$.tw,kf,ot.
18	RADIATION ONCOLOGY/mt, st, is [Methods, Standards, Instrumentation]
19	(external\$ adj3 beam\$).tw,kf,ot.
20	XRT.ti,ab.
21	or/12-20
22	11 and 21
23	randomized controlled trial.pt.
24	controlled clinical trial.pt.
25	randomi?ed.ab.
26	placebo.ab.
27	drug therapy.fs.

#	Searches
28	randomly.ab.
29	trial.ab.
30	groups.ab.
31	or/23-30
32	exp ANIMALS/ not HUMANS/
33	31 not 32
34	meta analysis.pt.
35	meta analysis.mp.
36	review.pt.
37	search*.tw.
38	or/34-37
39	22 and (33 or 38)

1606 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 26.09.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myeloma*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MeSH descriptor: [Radiotherapy] explode all trees
13	radiotherapy
14	irradiat*
15	radiat*
16	radiac*
17	MeSH descriptor: [Radiation Oncology] explode all trees and with qualifier(s): [methods - MT, standards - ST, instrumentation - IS]

#	Searches
18	(external* near/3 beam*)
19	XRT
20	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21	#11 and #20
22	#21 in Trials

213 Treffer in Central

### Suche für alle Fragestellungen zur Indikation für die Hochdosistherapie + autologe Stammzelltransplantation (Kapitel 7.4 Induktionstherapie)

Suche vom 16.10.2018; insgesamt 1204 Treffer in MEDLINE und 344 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 15 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 16.10.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	highdose.tw,kf,ot.
13	high-dose.tw,kf,ot.
14	(high adj5 dose).tw,kf,ot.
15	tbi.tw,kf,ot.
16	hdct.tw,kf,ot.
17	(dose adj2 (intensif* or intensiv* or intensification*)).tw,kf,ot.
18	dose density.tw,kf,ot.
19	or/12-18

## 12.2.Suchstrategien

#	Searches
20	BONE MARROW TRANSPLANTATION/
21	(bone marrow adj3 (graft* or transplant*).tw,kf,ot.
22	abmt.tw.
23	or/20-22
24	exp TRANSPLANTATION, AUTOLOGOUS/
25	AUTOGRAFTS/
26	(autolog* adj4 (transplant* or graft*).tw,kf,ot.
27	asct.tw.
28	(autograft* or auto-graft*).tw,kf,ot.
29	(autotransplant* or auto-transplant*).tw,kf,ot.
30	((tandem* or double*) adj3 (transplant* or graft*).tw,kf,ot.
31	or/24-30
32	TRANSPLANTATION CONDITIONING/
33	myeloablativ\$.tw,kf,ot.
34	11 and 19 and (23 or 31 or 34)

1204 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 16.10.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myeloma*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	highdose
13	high-dose
14	(high near/5 dose)
15	tbi

#	Searches
16	hdct
17	(dose near/2 (intensif* or intensiv* or intensification*))
18	dose density
19	#12 or #13 or #14 or #15 or #16 or #17 or #18
20	MeSH descriptor: [Bone Marrow Transplantation] this term only
21	(bone marrow near/3 (graft* or transplant*))
22	abmt
23	#20 or #21 or #22
24	MeSH descriptor: [Transplantation, Autologous] explode all trees
25	MeSH descriptor: [Autografts] explode all trees
26	(autolog*near/4 (transplant* or graft*))
27	asct
28	(autograft* or auto-graft*)
29	(autotransplant* or auto-transplant*)
30	((tandem* or double*) near/3 (transplant* or graft*))
31	#24 or #25 or #26 or #27 or #28 or #29 or #30
32	MeSH descriptor: [Transplantation Conditioning] explode all trees
33	myeloablativ*
34	#32 or #33
35	#23 or #31 or #34
36	#11 and #19 and #35
37	#36 in Trials

344 Treffer in Central

### Suche für alle Fragestellungen zur Rezidivtherapie (Kapitel Wahl der Rezidivtherapie)

Suche vom 17.10.2018; insgesamt 5721 Treffer in MEDLINE. Zur Identifikation der Primärpublikationen wurde die Datenbank MEDLINE (über OVID) durchsucht. Es konnten 40 nRCTs identifiziert werden.

MEDLINE/Ovid (bis 17.10.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.



## 12.2.Suchstrategien

#	Searches
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	exp RECURRENCE/
13	recurrence.tw,kf,ot.
14	recrudescence*.tw,kf,ot.
15	rezidiv*.tw,kf,ot.
16	relapse*.tw,kf,ot.
17	refractor*.tw,kf,ot.
18	(pregredient* or progredient*).tw,kf,ot.
19	progressiv*.tw,kf,ot.
20	previous* treat*.tw,kf,ot.
21	(pretreat* or pre treat*).tw,kf,ot.
22	fail*.tw,kf,ot.
23	subsequent.tw,kf,ot.
24	salvage.tw,kf,ot.
25	or/12-24
26	(second line or 2nd line).tw,kf,ot.
27	(third line or 3rd line).tw,kf,ot.
28	(fourth line or 4th line).tw,kf,ot.
29	or/26-28
30	RRMM.tw.
31	25 or 29 or 30
32	11 and 31
33	exp COHORT STUDIES/
34	cohort*.tw.
35	controlled clinical trial.pt.
36	EPIDEMIOLOGIC METHODS/
37	limit 36 to yr=1966-1989
38	exp CASE-CONTROL STUDIES/

#	Searches
39	(case* and control*).tw.
40	(case* and series).tw.
41	case reports.pt.
42	(case* adj2 report*).tw.
43	(case* adj2 stud*).tw.
44	33 or 34 or 35 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45	11 and 31 and 44
46	("clinical trial, phase i" or "clinical trial, phase ii").pt. or Clinical Trials, Phase I As Topic/ or CLINICAL TRIALS, PHASE II AS TOPIC/
47	11 and 31 and 46
48	45 or 47

5721 Treffer in Medline

### Suche für Fragestellungen zu Sport, Physio- & Ergotherapie (Kapitel Rehabilitation)

Suche vom 03.08.2018; insgesamt 585 Treffer in MEDLINE und 377 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 22 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 03.08.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myeloma.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	REHABILITATION/
13	OCCUPATIONAL THERAPY/
14	RECREATION THERAPY/

#	Searches
15	PHYSICAL THERAPY MODALITIES/
16	EXERCISE MOVEMENT TECHNIQUES/
17	EXERCISE THERAPY/
18	SPORTS/
19	EXERCISE/
20	PHYSICAL FITNESS/
21	(occupation* adj5 (therap* or rehabl*)).tw,kf,ot.
22	(recover* adj5 function*).tw,kf,ot.
23	(rehabilitat* or exercis* or physiotherap* or training or mobili*).tw,kf,ot.
24	(physical* adj3 (fit or fitness or train* or activit* or strength* or aerobic*)).tw,kf,ot.
25	(aerobic* adj3 exercise*).tw,kf,ot.
26	(exercise* adj3 train*).tw,kf,ot.
27	rehabilitation.fs.
28	ergotherap*.tw,kf,ot.
29	or/12-28
30	exp EXERCISE/
31	exp exercise movement techniques/
32	exp EXERCISE THERAPY/
33	exp PHYSICAL FITNESS/
34	exp SPORTS/
35	sport\$.tw,kf,ot.
36	exp WALKING/
37	walking\$.tw,kf,ot.
38	exp JOGGING/
39	jogging\$.tw,kf,ot.
40	exp SWIMMING/
41	swimming\$.tw,kf,ot.
42	exp BICYCLING/
43	(bicycling\$ or cycling\$).tw,kf,ot.
44	exp GYMNASTICS/
45	gymnastic\$.tw,kf,ot.
46	(calisthenic\$ or callisthenic\$).tw,kf,ot.
47	(resistan\$ adj2 (training\$ or exercise\$)).tw,kf,ot.

## 12.2.Suchstrategien

#	Searches
48	(pilates\$ adj5 exercise\$).tw,kf,ot.
49	(resistanc\$ adj2 (training\$ or exercise\$)).tw,kf,ot.
50	((aerobic\$ or isometric\$) adj2 exercise\$).tw,kf,ot.
51	(muscular\$ adj fitness\$).tw,kf,ot.
52	exertion\$.tw,kf,ot.
53	pilates\$.tw,kf,ot.
54	(physical\$ adj (activit\$ or fitness\$ or exercise\$)).tw,kf,ot.
55	(physical\$ adj (conditioning\$ or effort\$)).tw,kf,ot.
56	or/30-55
57	(review or review,tutorial or review, academic).pt.
58	(medline or medlars or embase or pubmed or cochrane).tw,sh.
59	(scisearch or psycinfo or psycinfo).tw,sh.
60	(psychlit or psyclit).tw,sh.
61	cinahl.tw,sh.
62	((hand adj2 search\$) or (manual\$ adj2 search\$)).tw,sh.
63	(electronic database\$ or bibliographic database\$ or computeri?ed database\$ or online database\$).tw,sh.
64	(pooling or pooled or mantel haenszel).tw,sh.
65	(peto or dersimonian or der simonian or fixed effect).tw,sh.
66	(retraction of publication or retracted publication).pt.
67	or/58-66
68	57 and 67
69	meta-analysis.pt.
70	meta-analysis.sh.
71	(meta-analys\$ or meta analys\$ or metaanalys\$).tw,sh.
72	(systematic\$ adj5 review\$).tw,sh.
73	(systematic\$ adj5 overview\$).tw,sh.
74	(quantitativ\$ adj5 review\$).tw,sh.
75	(quantitativ\$ adj5 overview\$).tw,sh.
76	(quantitativ\$ adj5 synthesis\$).tw,sh.
77	(methodologic\$ adj5 review\$).tw,sh.
78	(methodologic\$ adj5 overview\$).tw,sh.
79	(integrative research review\$ or research integration).tw.
80	or/69-79

#	Searches
81	68 or 80
82	randomized controlled trial.pt.
83	controlled clinical trial.pt.
84	randomi?ed.ab.
85	placebo.ab.
86	drug therapy.fs.
87	randomly.ab.
88	trial.ab.
89	groups.ab.
90	or/82-89
91	exp ANIMALS/ not HUMANS/
92	90 not 91
93	11 and (30 or 56) and (81 or 92)
94	11 and 56
95	11 and (29 or 56) and (81 or 92)

585 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 03.08.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myeloma
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MeSH descriptor: [Rehabilitation] explode all trees
13	MeSH descriptor: [Occupational Therapy] explode all trees
14	MeSH descriptor: [Recreation Therapy] explode all trees
15	MeSH descriptor: [Physical Therapy Modalities] explode all trees

## 12.2.Suchstrategien

#	Searches
16	MeSH descriptor: [Exercise Movement Techniques] explode all trees
17	MeSH descriptor: [Exercise Therapy] explode all trees
18	MeSH descriptor: [Sports] explode all trees
19	MeSH descriptor: [Exercise] explode all trees
20	physical fitness
21	(occupation* near/5 (therap* or rehabl*))
22	(recover* near/5 function*)
23	(rehabilitat* or exercis* or physiotherap* or training or mobili*)
24	(physical* near/3 (fit or fitness or train* or activit* or strength* or aerobic*))
25	(aerobic* near/3 exercise*)
26	(exercise* near/3 train*)
27	rehabilitation.fs.
28	ergotherap*
29	sport*
30	MeSH descriptor: [Walking] explode all trees
31	walking*
32	MeSH descriptor: [Jogging] explode all trees
33	jogging*
34	MeSH descriptor: [Swimming] explode all trees
35	swimming*
36	MeSH descriptor: [Bicycling] explode all trees
37	(bicycling* or cycling*)
38	MeSH descriptor: [Gymnastics] explode all trees
39	gymnastic*
40	(calisthenic* or callisthenic*)
41	(resistan* near/2 (training* or exercise*))
42	(pilates* near/5 exercise*)
43	(resistanc* near/2 (training* or exercise*))
44	((aerobic* or isometric*) near/2 exercise*)
45	(muscular* near fitness*)
46	exertion*
47	(physical* near (activit* or fitness* or exercise*))
48	(physical* near (conditioning* or effort*))

#	Searches
49	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48
50	#11 and #49 in Trials

377 Treffer in Central

### Suche für alle Fragestellungen zu Ergotherapie (Kapitel Rehabilitation)

Suche vom 02.08.2018; insgesamt 127 Treffer in MEDLINE und 272 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 55 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 02.08.2018)

#	Searches
1	exp NEOPLASMS BY HISTOLOGIC TYPE/
2	exp NEOPLASMS BY SITE/
3	neoplas\$.tw,kf,ot.
4	tumo?r\$.tw,kf,ot.
5	(krebs or cancer\$).tw,kf,ot.
6	malignan\$.tw,kf,ot.
7	(carcino\$ or karzino\$).tw,kf,ot.
8	karzinom\$.tw,kf,ot.
9	sarcom\$.tw,kf,ot.
10	leuk#?m\$.tw,kf,ot.
11	lymphom\$.tw,kf,ot.
12	melano\$.tw,kf,ot.
13	metastas\$.tw,kf,ot.
14	(mesothelio\$ or mesotelio\$).tw,kf,ot.
15	carcinomatos\$.tw,kf,ot.
16	(gliom\$ or glioblastom\$).tw,kf,ot.
17	osteo?sarcom\$.tw,kf,ot.
18	(blastom\$ or neuroblastom\$).tw,kf,ot.
19	or/1-18
20	OCCUPATIONAL THERAPY/
21	RECREATION THERAPY/
22	(occupation* adj5 (therap* or rehabil*)).tw,kf,ot.

#	Searches
23	ergotherap*.tw,kf,ot.
24	ERGOMETRY/
25	or/20-24
26	19 and 25
27	(review or review,tutorial or review, academic).pt.
28	(medline or medlars or embase or pubmed or cochrane).tw,sh.
29	(scisearch or psychinfo or psycinfo).tw,sh.
30	(psychlit or psyclit).tw,sh.
31	cinahl.tw,sh.
32	((hand adj2 search\$) or (manual\$ adj2 search\$)).tw,sh.
33	(electronic database\$ or bibliographic database\$ or computeri?ed database\$ or online database\$).tw,sh.
34	(pooling or pooled or mantel haenszel).tw,sh.
35	(peto or dersimonian or der simonian or fixed effect).tw,sh.
36	(retraction of publication or retracted publication).pt.
37	or/28-36
38	27 and 37
39	meta-analysis.pt.
40	meta-analysis.sh.
41	(meta-analys\$ or meta analys\$ or metaanalys\$).tw,sh.
42	(systematic\$ adj5 review\$).tw,sh.
43	(systematic\$ adj5 overview\$).tw,sh.
44	(quantitativ\$ adj5 review\$).tw,sh.
45	(quantitativ\$ adj5 overview\$).tw,sh.
46	(quantitativ\$ adj5 synthesis\$).tw,sh.
47	(methodologic\$ adj5 review\$).tw,sh.
48	(methodologic\$ adj5 overview\$).tw,sh.
49	(integrative research review\$ or research integration).tw.
50	or/39-49
51	38 or 50
52	randomized controlled trial.pt.
53	controlled clinical trial.pt.
54	randomi?ed.ab.
55	placebo.ab.



#	Searches
56	drug therapy.fs.
57	randomly.ab.
58	trial.ab.
59	groups.ab.
60	or/52-59
61	exp ANIMALS/ not HUMANS/
62	60 not 61
63	19 and 25 and (51 or 62)

172 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 02.08.2018)

#	Searches
1	MeSH descriptor: [Neoplasms by Histologic Type] explode all trees
2	MeSH descriptor: [Neoplasms by Site] explode all trees
3	neoplas*
4	tumor* or tumour*
5	Krebs or cancer*
6	malignan*
7	(carcino* or karzino*)
8	karzinom*
9	sarcom*
10	leukaem* or leukem* or leucem*
11	lymphom*
12	melano*
13	metastas*
14	mesothelio* or mesotelio*
15	carcinomatos*
16	(gliom* or glioblastom*)
17	osteosarcom*
18	(blastom* or neuroblastom*)
19	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
20	MeSH descriptor: [Occupational Therapy] explode all trees
21	MeSH descriptor: [Recreation Therapy] explode all trees

#	Searches
22	(occupation* near/5 (therap* or rehabl*))
23	ergotherap*
24	MeSH descriptor: [Ergometry] explode all trees
25	#20 or #21 or #22 or #23 or #24
26	#19 and #25
27	#26 in Trials

272 Treffer in Central

### Suche für Fragestellung nach dem Stellenwert von Ergotherapie bei Polyneuropathie (Kapitel Rehabilitation)

Suche vom 23.08.2018; insgesamt 511 Treffer in MEDLINE und 139 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 38 Treffer identifiziert werden.

MEDLINE/Ovid (bis 23.08.2018)

#	Searches
1	exp NEOPLASMS BY HISTOLOGIC TYPE/
2	exp NEOPLASMS BY SITE/
3	neoplas\$.tw,kf,ot.
4	tumo?r\$.tw,kf,ot.
5	(Krebs\$ or cancer\$).tw,kf,ot.
6	malignan\$.tw,kf,ot.
7	(carcino\$ or karzino\$).tw,kf,ot.
8	karzinom\$.tw,kf,ot.
9	sarcom\$.tw,kf,ot.
10	leuk#?m\$.tw,kf,ot.
11	lymphom\$.tw,kf,ot.
12	melano\$.tw,kf,ot.
13	metastas\$.tw,kf,ot.
14	(mesothelio\$ or mesotelio\$).tw,kf,ot.
15	carcinomatos\$.tw,kf,ot.
16	(gliom\$ or glioblastom\$).tw,kf,ot.
17	osteo?sarcom\$.tw,kf,ot.
18	(blastom\$ or neuroblastom\$).tw,kf,ot.
19	exp MULTIPLE MYELOMA/

#	Searches
20	myeloma.tw,kf,ot.
21	or/1-20
22	POLYNEUROPATHIES/
23	polyneuropath*.tw,kf,ot.
24	neuropath*.tw,kf,ot.
25	or/22-24
26	REHABILITATION/
27	OCCUPATIONAL THERAPY/
28	RECREATION THERAPY/
29	PHYSICAL THERAPY MODALITIES/
30	EXERCISE MOVEMENT TECHNIQUES/
31	EXERCISE THERAPY/
32	PHYSICAL EXERTION/
33	EXERCISE/
34	PHYSICAL FITNESS/
35	(occupation* adj5 (therap* or rehabil*)).tw,kf,ot.
36	(recover* adj5 function*).tw,kf,ot.
37	(rehabilitat* or exercis* or physiotherap* or training or mobili*).tw,kf,ot.
38	(physical* adj3 (fit or fitness or train* or activit* or strength* or aerobic*)).tw,kf,ot.
39	(aerobic* adj3 exercise*).tw,kf,ot.
40	(exercise* adj3 train*).tw,kf,ot.
41	rehabilitation.fs.
42	ergotherap*.tw,kf,ot.
43	or/26-42
44	21 and 25 and 43

511 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 23.08.2018)

#	Searches
1	MeSH descriptor: [Neoplasms by Histologic Type] explode all trees
2	MeSH descriptor: [Neoplasms by Site] explode all trees
3	neoplas*
4	tumour* or tumor*

#	Searches
5	(krebs* or cancer*)
6	malignan*
7	(carcino* or karzino*)
8	karzinom*
9	sarcom*
10	leukem* or leukaem*
11	lymphom*
12	melano*
13	metastas*
14	(mesothelio* or mesotelio*)
15	carcinomatos*
16	(gliom* or glioblastom*)
17	osteo*sarcom*
18	(blastom* or neuroblastom*)
19	MeSH descriptor: [Multiple Myeloma] explode all trees
20	myeloma
21	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
22	MeSH descriptor: [Polyneuropathies] explode all trees
23	polyneuropath*
24	neuropath*
25	#22 or #23 or #24
26	MeSH descriptor: [Rehabilitation] explode all trees
27	MeSH descriptor: [Occupational Therapy] explode all trees
28	MeSH descriptor: [Recreation Therapy] explode all trees
29	MeSH descriptor: [Physical Therapy Modalities] explode all trees
30	MeSH descriptor: [Exercise Movement Techniques] explode all trees
31	MeSH descriptor: [Exercise Therapy] explode all trees
32	MeSH descriptor: [Physical Exertion] explode all trees
33	MeSH descriptor: [Exercise] explode all trees
34	MeSH descriptor: [Physical Fitness] explode all trees
35	(occupation* near/5 (therap* or rehabl*))
36	(recover* near/5 function*)
37	(rehabilitat* or exercis* or physiotherap* or training or mobili*)

#	Searches
38	(physical* near/3 (fit or fitness or train* or activit* or strength* or aerobic*))
39	(aerobic* near/3 exercise*)
40	(exercise* near/3 train*)
41	ergotherap*
42	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
43	#21 and #25 and #42 in Trials

139 Treffer in Central

### Suche für alle Fragestellungen zu Lymphdrainage (Kapitel Rehabilitation)

Suche vom 27.08.2018; insgesamt 118 Treffer in MEDLINE und 1 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 2 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 27.08.2018)

#	Searches
1	*LYMPHOMA/
2	exp HODGKIN DISEASE/
3	Germinoblastom\$.tw,kf,ot.
4	Reticulolymphosarcom\$.tw,kf,ot.
5	Hodgkin\$.tw,kf,ot.
6	(malignan\$ adj2 (lymphogranulom\$ or granulom\$)).tw,kf,ot.
7	or/1-6
8	exp MULTIPLE MYELOMA/
9	myeloma.tw,kf,ot.
10	exp PLASMACYTOMA/
11	plasm?cytom\$.tw,kf,ot.
12	plasmozytom\$.tw,kf,ot.
13	plasm\$ cell myelom\$.tw,kf,ot.
14	myelomatosis.tw,kf,ot.
15	LEUKEMIA, PLASMA CELL/
16	(plasma\$ adj3 neoplas\$).tw,kf,ot.
17	kahler*.tw,kf,ot.
18	or/8-17
19	exp LYMPHEDEMA/

#	Searches
20	lymphedema.mp.
21	lymphoedema.mp.
22	exp EDEMA/ and exp ARM/
23	(arm adj2 edema).mp.
24	(arm adj2 oedema).mp.
25	upper extremity edema.mp.
26	upper extremity oedema.mp.
27	lymphedemic.mp.
28	lymphoedemic.mp.
29	(lymph* adj3 drainag*).tw,kf,ot.
30	or/19-29
31	(7 or 18) and 30

118 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 27.08.2018)

#	Searches
1	MeSH descriptor: [Lymphoma] this term only
2	MeSH descriptor: [Hodgkin Disease] explode all trees
3	Germinoblastom*
4	Reticulolymphosarcom*
5	hodgkin*
6	(malignan* near/2 (lymphogranulom* or granulom*))
7	#1 or #2 or #3 or #4 or #5 or #6
8	MeSH descriptor: [Multiple Myeloma] explode all trees
9	myeloma
10	MeSH descriptor: [Plasmacytoma] explode all trees
11	plasm*cytom*
12	plasmozytom*
13	plasm* cell myelom*
14	myelomatosis
15	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
16	(plasma* near/3 neoplas*)
17	kahler*

#	Searches
18	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
19	MeSH descriptor: [Lymphedema] explode all trees
20	lymphedema
21	lymphoedema
22	MeSH descriptor: [Edema] explode all trees
23	MeSH descriptor: [Arm] explode all trees
24	#22 and #23
25	(arm near/2 edema)
26	(arm near/2 oedema)
27	upper extremity edema
28	upper extremity oedema
29	lymphedemic
30	lymphoedemic
31	(lymph* near/3 drainag*)
32	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
33	(#7 or #18) and #32

1 Treffer in Central

### Suche für alle Fragestellungen zum Stellenwert von Calcium & Vitamin D in der antiresorptiven Therapie (Kapitel 10.1 Antiresorptive Therapie)

Suche vom 06.09.2018; insgesamt 511 Treffer in MEDLINE und 135 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 7 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 06.09.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	Leukemia, Plasma Cell/

## 12.2.Suchstrategien

#	Searches
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	Kahler\$.tw,kf,ot.
11	or/1-10
12	VITAMIN D/
13	vitamin d.tw,kf,ot,nm.
14	or/12-13
15	exp CALCIUM/
16	calcium*.tw,kf,ot,nm.
17	or/15-16
18	11 and (14 or 17)
19	randomized controlled trial.pt.
20	controlled clinical trial.pt.
21	randomi?ed.ab.
22	placebo.ab.
23	drug therapy.fs.
24	randomly.ab.
25	trial.ab.
26	groups.ab.
27	or/19-26
28	exp ANIMALS/ not HUMANS/
29	27 not 28
30	meta analysis.pt.
31	meta analysis.mp.
32	META-ANALYSIS/
33	review.pt.
34	search*.tw.
35	or/30-34
36	11 and (14 or 17) and (27 or 35)

511 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 06.09.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees



#	Searches
2	myelom*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MeSH descriptor: [Vitamin D] explode all trees
13	vitamin d
14	#12 or #13
15	MeSH descriptor: [Calcium] explode all trees
16	calcium*
17	#15 or #16
18	#11 and (#14 or #17) in Trials

135 Treffer in Central

### Suche für alle Fragestellungen zur Anwendung von Bisphosphonaten bei skelettalen Komplikationen (Kapitel 10.1 Antiresorptive Therapie)

Suche vom 06.09.2018; insgesamt 1280 Treffer in MEDLINE und 270 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 73 RCTs und 8 systematische Übersichtsarbeiten identifiziert werden.

MEDLINE/Ovid (bis 06.09.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.

## 12.2.Suchstrategien

#	Searches
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler\$.tw,kf,ot.
11	or/1-10
12	exp DIPHOSPHONATES/
13	(diphosphonate\$ or diphosph#nate\$).tw,kf,ot,nm.
14	(bisphosph#nate\$ or biphosph#nate\$).tw,kf,ot,nm.
15	or/12-14
16	ALENDRONATE/
17	(alendronat\$ or aledronic\$).tw,kf,ot,nm.
18	(fosamax\$ or binosto\$ or adronat\$ or alendros\$ or onclast\$).tw,kf,ot,nm.
19	or/16-18
20	CLODRONIC ACID/
21	(clodronic\$ or clodronat\$).tw,kf,ot,nm.
22	(bonefos\$ or clasteon\$ or difosfonal\$ or ossiten\$ or mebonat\$ or loron\$).tw,kf,ot,nm.
23	Cl2MDP.tw,kf,ot,nm.
24	or/20-23
25	ETIDRONIC ACID/
26	(etidronic\$ or etidronat\$).tw,kf,ot,nm.
27	(didroneI\$ or xidifon\$ or dicalcium or xidiphon\$).tw,kf,ot.
28	(HEDP or EHDP).tw,kf,ot.
29	or/25-28
30	TECHNETIUM TC 99M MEDRONATE/
31	(medronat\$ or medronic\$).tw,kf,ot,nm.
32	(Technetium adj2 Tc 99m adj2 Medronat\$).tw,kf,ot,nm.
33	or/30-32
34	(pamidronat\$ or pamidronic\$ or amidronat\$).tw,kf,ot,nm.
35	(aredia\$ or ADP sodium\$ or aminomux\$).tw,kf,ot,nm.
36	(GCP23339A or GCP-23339A).tw,kf,ot,nm.
37	or/34-36
38	(zoledronic\$ or zoledronat\$).tw,kf,ot,nm.
39	(zometa\$ or zomera\$ or aclasta\$ or reclast\$ or aredia\$).tw,kf,ot,nm.
40	(m05BA08 or CGP-42446\$ or CGP42446\$ or zol-446 or zol446).tw,kf,ot,nm.

## 12.2.Suchstrategien

#	Searches
41	or/38-40
42	(ibandronic\$ or ibandrovic\$ or ibandronat\$).tw,kf,ot,nm.
43	(bon?iva\$ or bondronat\$ or adronil\$).tw,kf,ot,nm.
44	(RPR102289A or RPR-102289A).tw,kf,ot,nm.
45	(BM210955 or BM-210955).tw,kf,ot,nm.
46	or/42-45
47	RISEDRONATE SODIUM/
48	(risedronic\$ or risedronat\$).tw,kf,ot,nm.
49	(actonel\$ or atelvia\$ or benet\$).tw,kf,ot,nm.
50	(NE58095 or NE-58095).tw,kf,ot,nm.
51	or/47-50
52	(neridronat\$ or neridronic\$).tw,kf,ot,nm.
53	(AHHexBP or 6AHHDP or 6-AHHDP).tw,kf,ot,nm.
54	or/52-53
55	(tiludronat\$ or tiludronic\$).tw,kf,ot,nm.
56	(Incadronat\$ or YM175).tw,kf,ot,nm.
57	(olpadronat\$ or olpadronic\$).tw,kf,ot,nm.
58	or/55-57
59	RANK LIGAND/
60	(rank\$ adj3 ligand\$).tw,kf,ot,nm.
61	RANK ligand inhibitor\$.tw,kf,ot,nm.
62	(protein\$ adj2 (RANKL or TRANCE)).tw,kf,ot,nm.
63	Tumor Necrosis Factor-Related Activation-Induced Cytokin\$.tw,kf,ot,nm.
64	(CD254 or CD-254).tw,kf,ot,nm.
65	or/59-64
66	DENOSUMAB/
67	denosumab\$.tw,kf,ot,nm.
68	(xgeva\$ or prolia\$).tw,kf,ot,nm.
69	(AMG162 or AMG-162).tw,kf,ot,nm.
70	or/66-69
71	15 or 19 or 24 or 29 or 33 or 37 or 41 or 46 or 51 or 54 or 58 or 65 or 70
72	11 and 71
73	randomized controlled trial.pt.

#	Searches
74	controlled clinical trial.pt.
75	randomi?ed.ab.
76	placebo.ab.
77	drug therapy.fs.
78	randomly.ab.
79	trial.ab.
80	groups.ab.
81	or/73-80
82	exp ANIMALS/ not HUMANS/
83	81 not 82
84	meta analysis.pt.
85	meta analysis.mp.
86	META-ANALYSIS/
87	review.pt.
88	search*.tw.
89	or/84-88
90	11 and 71 and (83 or 89)

1280 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 06.09.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myelom*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MeSH descriptor: [Diphosphonates] explode all trees

## 12.2.Suchstrategien

#	Searches
13	(diphosphonate* or diphosph?nate*)
14	(bisphosph?nate* or biphosph?nate*)
15	#12 or #13 or #14
16	MeSH descriptor: [Alendronate] explode all trees
17	(alendronat* or aledronic*)
18	(fosamax* or binosto* or adronat* or alendros* or onclast*)
19	#16 or #17 or #18
20	MeSH descriptor: [Clodronic Acid] explode all trees
21	(clodronic* or clodronat*)
22	(bonefos* or clasteon* or difosfonal* or ossiten* or mebonat* or loron*)
23	Cl2MDP
24	#20 or #21 or #22 or #23
25	MeSH descriptor: [Etidronic Acid] explode all trees
26	(etidronic* or etidronat*)
27	(didronel* or xidifon* or dicalcium or xidiphon*)
28	(HEDP or EHDP)
29	#25 or #26 or #27 or #28
30	MeSH descriptor: [Technetium Tc 99m Medronate] explode all trees
31	(medronat* or medronic*)
32	(Technetium near/2 Tc 99m near/2 Medronat*)
33	#30 or #31 or #32
34	(pamidronat* or pamidronic* or amidronat*)
35	(aredia* or ADP sodium* or aminomux*)
36	(GCP23339A or GCP-23339A)
37	#34 or #35 or #36
38	(zoledronic* or zoledronat*)
39	(zometa* or zomera* or aclasta* or reclast* or aredia*)
40	(m05BA08 or CGP-42446* or CGP42446* or zol-446 or zol446)
41	#38 or #39 or #40
42	(ibandronic* or ibandrovic* or ibandronat*)
43	(bon?iva* or bondronat* or adronil*)
44	(RPR102289A or RPR-102289A)
45	(BM210955 or BM-210955)

#	Searches
46	#42 or #43 or #44 or #45
47	MeSH descriptor: [Risedronate Sodium] explode all trees
48	(risedronic* or risedronat*)
49	(actonel* or atelvia* or benet*)
50	(NE58095 or NE-58095)
51	#47 or #48 or #49 or #50
52	(neridronat* or neridronic*)
53	("AHHexBP" or "6AHHDP" or "6-AHHDP")
54	#52 or #53
55	(tiludronat* or tiludronic*)
56	(Incadronat* or YM175)
57	(olpadronat* or olpadronic*)
58	#55 or #56 or #57
59	MeSH descriptor: [RANK Ligand] explode all trees
60	(rank* near/3 ligand*)
61	RANK ligand inhibitor*
62	(protein* near/2 (RANKL or TRANCE))
63	Tumor Necrosis Factor-Related Activation-Induced Cytokin*
64	#59 or #60 or #61 or #62 or #63
65	MeSH descriptor: [Denosumab] explode all trees
66	denosumab*
67	(xgeva* or prolia*)
68	(AMG162 or AMG-162)
69	#65 or #66 or #67 or #68
70	#15 or #19 or #24 or #29 or #33 or #37 or #41 or #46 or #51 or #54 or #58 or #64 or #69
71	#11 and #70 in Trials
72	#11 and #70

270 Treffer in Central

### Suche für alle Fragestellungen zur Verabreichung von Immunglobulinen (Kapitel 10.2 Infektionsprophylaxe)

Suche vom 05.09.2018; insgesamt 240 Treffer in MEDLINE und 18 Treffer in CENTRAL). Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive

CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Es konnten 9 relevante Treffer identifiziert werden.

MEDLINE/Ovid (bis 05.09.2018)

#	Searches
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler*.tw,kf,ot.
11	or/1-10
12	IMMUNOGLOBULINS, INTRAVENOUS/
13	GAMMA-GLOBULINS/
14	(gamma globulin\$ or gammaglobulin\$).tw,kf,ot.
15	immunoglobulin*.tw,kf,ot,nm.
16	((immune\$ globulin\$ or immunoglobulins\$ or immunoglobulins\$ or antibodies) adj3 intravenous\$).tw,kf,ot.
17	omrigam\$.tw,kf,ot.
18	sandoglobulin\$.tw,kf,ot.
19	ivig.tw,kf,ot,nm.
20	hyperimmune\$.tw,kf,ot.
21	alphaglobin\$.tw,kf,ot.
22	endobulin\$.tw,kf,ot.
23	(gamimune or gamimmune or gamimune N or gamimmune N).tw,kf,ot.
24	venimmune\$.tw,kf,ot.
25	(venoglobulin-I or venoglobulinI or venoglobulin).tw,kf,ot.
26	iveegam\$.tw,kf,ot.
27	intraglobin\$.tw,kf,ot.
28	gammagard\$.tw,kf,ot.
29	gammonativ\$.tw,kf,ot.
30	(globulin-N or globulinN).tw,kf,ot.

#	Searches
31	or/12-30
32	randomized controlled trial.pt.
33	controlled clinical trial.pt.
34	randomi?ed.ab.
35	placebo.ab.
36	drug therapy.fs.
37	randomly.ab.
38	trial.ab.
39	groups.ab.
40	or/32-39
41	exp ANIMALS/ not HUMANS/
42	40 not 41
43	meta analysis.pt.
44	meta analysis.mp.
45	META-ANALYSIS/
46	review.pt.
47	search*.tw.
48	or/43-47
49	11 and 31 and (42 or 48)

240 Treffer in Medline

Cochrane Central Register of Controlled Trials (bis 05.09.2018)

#	Searches
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myelom*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*



#	Searches
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MeSH descriptor: [Immunoglobulins, Intravenous] explode all trees
13	MeSH descriptor: [gamma-Globulins] explode all trees
14	gamma globulin* or gammaglobulin*
15	immunoglobulin*
16	((immune* globulin* or immunoglobulins* or immunoglobulins* or antibodies) near/3 intravenous*)
17	omrigam*
18	sandoglobulin*
19	ivig
20	hyperimmune*
21	alphaglobin*
22	endobulin*
23	(gamimune or gamimmune or gamimune N or gamimmune N)
24	venimmune*
25	(venoglobulin-I or venoglobulinI or venoglobulin)
26	iveegam*
27	intraglobin*
28	gammagard*
29	gammonativ*
30	(globulin-N or globulinN)
31	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
32	#11 and #31 in Trials

18 Treffer in Central

## 12.3. Recherche nach internationalen Qualitätsindikatoren

### 12.3.1. Rechercheauftrag

Die Recherche wurde vom Bereich Infoplattform (Steffi Derenz und Jessica Lobitz) zwischen dem 20.07.2020 und 29.07.2020 durchgeführt.

Als Recherchevokabular wurden folgende Begriffe verwendet:

**Population:**

Erwachsene Patienten mit Multiplem Myelom in allen Versorgungssettings (ambulant/stationär).

MeSH Terms: "multiple myeloma"; "plasmacytoma"; "leukemia, plasma cell"

Freitextbegriffe: myelom\*; plasmacytom\*; plasmocytom\*; plasm\* cell myelom\*; kahler\* disease; myelomatosis; myelomatoses

Websuche (zusätzlich): haematological cancer\*  
de: Knochenmarkkrebs, Plasmazytom

#### **Intervention:**

MeSH Terms: "Quality Indicators, Health Care"

Freitextbegriffe: quality/performance; indicator/indicators/measure/measures

Websuche (zusätzlich): de: qualitätsindikator\*

#### **Limits:**

Bei der Suche erfolgte eine Einschränkung des Suchzeitraums (2010 bis 07.2020).

Weitere Einschränkungen bezüglich spezifischer Subgruppen innerhalb der Zielpopulation erfolgten nicht.

#### **Die Suche wurde in folgenden Quellen durchgeführt:**

- Literaturdatenbanken:  
PubMed: <https://pubmed.ncbi.nlm.nih.gov/advanced>  
Cochrane: <https://www.cochranelibrary.com/advanced-search>
- Webseiten nationaler Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Webseiten internationaler Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Internetrecherche via [www.google.de](http://www.google.de)

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle. Sie wurden entsprechend modifiziert und unter Punkt 2: Recherchestrategien dargelegt.

## 12.3.2. Recherchestrategien

### 12.3.2.1. Bibliographische Datenbanken

#### 12.3.2.1.1. PubMed

Recherche erfolgte am: 20.07.2020

Search	Query	Items found
#1	"multiple myeloma"[MeSH Terms]	41.074
#2	myelom*[tiab]	64.680
#3	plasmacytoma"[MeSH Terms]	8.605
#4	plasmacytom*[tiab]	6.662
#5	plasmocytom*[tiab]	1.491
#6	plasm*[tiab] AND cell[tiab] AND myelom*[tiab]	9.491
#7	"leukemia, plasma cell"[MeSH Terms]	990
#8	kahler*[tiab] AND disease[tiab]	233
#9	myelomatosis[tiab] OR myelomatoses[tiab]	768
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	78.906
#11	Quality Indicators, Health Care [MeSH Terms]Search	21.386
#12	(quality[tiab] OR performance[tiab]) AND (indicator[tiab] OR indicators[tiab] OR measure[tiab] OR measures[tiab])	275.326
#13	#11 OR #12	288.593
#14	#10 AND #13	324
#15	#14 Filters: in the last 10 years, English, German	219
#16	#15 NOT "The Cochrane database of systematic reviews"[Journal]	218

#### 12.3.2.1.2. Cochrane

Recherche erfolgte am: 20.07.2020

Search	Query	Items found
#1	MeSH descriptor: [Multiple Myeloma] explode all trees	1569
#2	myelom*:ti,ab,kw (Word variations have been searched)	5715
#3	MeSH descriptor: [Plasmacytoma] explode all trees	87
#4	plasmacytom*:ti,ab,kw (Word variations have been searched)	254
#5	plasmocytom*:ti,ab,kw (Word variations have been searched)	8

Search	Query	Items found
#6	<b>(plasm* cell myelom*):ti,ab,kw</b> (Word variations have been searched)	969
#7	<b>MeSH descriptor: [Leukemia, Plasma Cell]</b> explode all trees	3
#8	<b>plasma* near/3 neoplas*):ti,ab,kw</b> (Word variations have been searched)	633
#9	<b>(kahler* next disease):ti,ab,kw</b> (Word variations have been searched)	7
#10	<b>(myelomatosis or myelomatoses):ti,ab,kw</b> (Word variations have been searched)	38
#11	<b>#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10</b>	5877
#12	<b>MeSH descriptor: [Quality Indicators, Health Care]</b> explode all trees	490
#13	Search <b>((quality OR performance):ti,ab,kw) AND ((indicator OR indicators OR measure OR measures):ti,ab,kw)</b>	56868
#14	Search <b>(#12 OR #13)</b>	57106
#15	Search <b>(#11 AND #14)</b>	130
#16	<b>(#15)</b> with Cochrane Library publication date from Jul 2010 to Jul 2020, in Cochrane Reviews, Cochrane Protocols, Trials, Clinical Answers and Special collections <b>NOT Editorial</b>	121
	Cochrane Reviews: 2 / Trials: 119 with Publication Year from 2010 to 2020, in Trials =102 Trials (102) NOT Studienregister (24 ICTRP/CZ.gov - und - 1 Dissertation) 102-25=77 [Embase (67), PubMed (19), CINAHL (1) - 10 Dubletten]	
	Gesamt: 2 Reviews + 77 Trials	<b>79</b>

Anzahl der Treffer in Cochrane nach Duplikatecheck: 79

Anzahl der Treffer in Cochrane nach Dublikatecheck mit PubMed: 59

Anzahl der Treffer insgesamt (PubMed und Cochrane): 277

### 12.3.2.2. Nationale Qualitätsindikatorenprojekte/-programme

Recherche erfolgte am: 24.07.2020

Institution	Quelle	Treffer
<b>aQua-Institut</b> (Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen)	SQG (Sektorenübergreifende Qualität im Gesundheitswesen) <a href="https://sqq.de/front_content.php">https://sqq.de/front_content.php</a>	0
	QISA (Qualitätsindikatorensystem für die ambulante Versorgung) <a href="https://www.aok-gesundheitspartner.de/bund/qisa/themen/index_04881.html">https://www.aok-gesundheitspartner.de/bund/qisa/themen/index_04881.html</a>	0
<b>IQTiG</b> (Institut für Qualitätssicherung und Transparenz im Gesundheitswesen)	<a href="https://iqtiq.org">https://iqtiq.org</a> <a href="https://iqtiq.org/qs-instrumente/qualitaetsindikatoren">https://iqtiq.org/qs-instrumente/qualitaetsindikatoren</a>	0

### 12.3.2.3. Internationale Qualitätsindikatorenprojekte/-programme

Recherche erfolgte am: 24.07.2020 bis JCAHO und am 27.07.2020 ab NHS

Institution	Quelle	Treffer
<b>AHRQ</b> (Agency for Health Research and Quality)	<a href="http://www.qualityindicators.ahrq.gov">http://www.qualityindicators.ahrq.gov</a> <a href="https://www.ahrq.gov/gam/summaries/index.html">https://www.ahrq.gov/gam/summaries/index.html</a> <a href="https://www.qualityindicators.ahrq.gov/Modules/all_resources.aspx">https://www.qualityindicators.ahrq.gov/Modules/all_resources.aspx</a>	0
<b>CMS</b> (Centers for Medicare & Medicaid Services)	<a href="https://cmit.cms.gov/CMIT_public/ListMeasures">https://cmit.cms.gov/CMIT_public/ListMeasures</a>	1
<b>ASCO</b> (American Society of Clinical Oncology) Quality Oncology Practice Initiative	QOPI (Quality Oncology Practice Initiative) <a href="http://qopi.asco.org/index.html">http://qopi.asco.org/index.html</a> <a href="https://practice.asco.org/quality-improvement/quality-programs/quality-oncology-practice-initiative/qopi-related-measures">https://practice.asco.org/quality-improvement/quality-programs/quality-oncology-practice-initiative/qopi-related-measures</a> <a href="https://practice.asco.org/quality-improvement/quality-programs/qopi-reporting-registry">https://practice.asco.org/quality-improvement/quality-programs/qopi-reporting-registry</a>	1
<b>CIHI</b> (Canadian Institute for Health Information)	Health Indicators <a href="https://www.cihi.ca/en/health-indicators">https://www.cihi.ca/en/health-indicators</a>	0
<b>CQCO</b> (Cancer Quality Council of Ontario)	Cancer System Quality Index – set of indicators <a href="https://www.csqi.on.ca/2019/indicators">https://www.csqi.on.ca/2019/indicators</a>	Kein Zugang!

Institution	Quelle	Treffer
ISD (Scotland Health Indicators)	<a href="http://www.isdscotland.org/Health-Topics/Cancer">http://www.isdscotland.org/Health-Topics/Cancer</a> <a href="http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis/quality_performance_indicators.aspx">http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis/quality_performance_indicators.aspx</a> <a href="https://www.isdscotland.org/Health-Topics/Quality-Indicators/Cancer-QPI">https://www.isdscotland.org/Health-Topics/Quality-Indicators/Cancer-QPI</a>	0
JCAHO (Joint Commission on Accreditation of Health-care Organizations)	<a href="http://www.jointcommission.org/accountability_measures.aspx">http://www.jointcommission.org/accountability_measures.aspx</a>	0
NHS (National Health Services)	Indicators for Quality Improvement <a href="https://digital.nhs.uk">https://digital.nhs.uk</a> <a href="https://digital.nhs.uk/data-and-information">https://digital.nhs.uk/data-and-information</a>	0
NQF (National Quality Forum)	Performance Measures <a href="http://www.qualityforum.org/QPS">http://www.qualityforum.org/QPS</a> <a href="http://www.qualityforum.org/Home.aspx">http://www.qualityforum.org/Home.aspx</a>	1
OECD (Health Care Quality Indicators)	<a href="http://www.oecd.org/health/health-systems/hcqi-cancer-care.htm">http://www.oecd.org/health/health-systems/hcqi-cancer-care.htm</a>	0
RAND (Corporation Quality of Care Assessment Tools)	QA Tools <a href="http://www.rand.org/health/surveys_tools/qatools.html">http://www.rand.org/health/surveys_tools/qatools.html</a> <a href="https://www.rand.org/pubs/monograph_reports/MR1281.html">https://www.rand.org/pubs/monograph_reports/MR1281.html</a>	0
Oncoline (Niederlande)	<a href="http://oncoline.nl/index.php">http://oncoline.nl/index.php</a>	0
KCE (Belgian Health Care Knowledge Centre)	<a href="https://kce.fgov.be">https://kce.fgov.be</a> <a href="https://kce.fgov.be/en/all-reports">https://kce.fgov.be/en/all-reports</a>	0

Zusätzlich würden folgende Webseiten durchsucht. Auf diese sind wir beim TiAb-Screening in den Abstracts gestoßen. Die Suche hat keine Treffer ergeben.

[www.rarecarenet.eu](http://www.rarecarenet.eu); [www.haemacare.eu](http://www.haemacare.eu); <https://www.myeloma.org>

#### 12.3.2.4. Suchmaschine

Recherche erfolgte am: 27.07.2020 mit deutschem und englischem Suchvokabular.

Suchmaschine: [www.google.de](http://www.google.de) (Google Scholar)

Suchbegriffe:

Suche deutsch:

Myelom/Plasmozytom/Knochenmarkkrebs/Kahler AND Qualitätsindikator: 0 Treffer

Suche englisch:

myeloma/plasmacytoma/"haematological cancer"/kahler AND (quality/measure AND indicator): 3 Treffer

Anzahl der Treffer gesamt: 3

### 12.3.3. Rechercheergebnisse

**Ausschlussgründe:**

- A1: Doppelpublikation
- A2: andere Entität
- A3: kein Qualitätsindikator
- A4: Publikationsart (z.B.: Letter, Editorial)
- A5: Volltext nicht verfügbar

#### 12.3.3.1. Bibliographische Datenbanken

Anzahl der Treffer nach Titel- und Abstract-Sichtung (PubMed/Cochrane): 0

Treffer nach Volltextsichtung: 0

#### 12.3.3.2. Nationale Qualitätsindikatoren

Recherchedatum: 24.07.2020

Treffer: 0

#### 12.3.3.3. Internationale Qualitätsindikatoren

Recherchedatum: 24.07 – 27.07.2020

Treffer: 3 (zum selben Qualitätsindikator)

(Centers for Medicare & Medicaid Services (CMS) 2020), (American Society of Clinical Oncology (ASCO)), (National Quality Forum (NQF) 2017)

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
<p><i>Centers for Medicare &amp; Medicaid Services (CMS) (Centers for Medicare &amp; Medicaid Services (CMS) 2020)</i></p> <p><i>American Society of Clinical Oncology (ASCO) (American Society of Clinical Oncology (ASCO))</i></p> <p><i>National Quality Forum (NQF) (National Quality Forum (NQF) 2017)</i></p>	Nein	<p>Ja.</p> <p>Vgl. QI 85 bzw. Empfehlung 10.1.1.3: „Bei Patienten mit Multiplem Myelom und Osteolysen <b>sollen</b> Bisphosphonate oder RANK-L Inhibitoren zur Prophylaxe skelettaler Ereignisse angewandt werden.“</p>

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
<p><b>Hematology: Multiple Myeloma: Treatment with Bisphosphonates</b>  <b>Numerator:</b> Patients who were prescribed or received intravenous bisphosphonate therapy within the 12 month reporting period  <b>Denominator:</b> All patients aged 18 years and older with a diagnosis of multiple myeloma, not in remission  <b>(Exclusions: Denominator Exceptions:</b> Documentation of medical reason(s) for not prescribing bisphosphonates (e.g., patients who do not have bone disease, patients with dental disease, patients with renal insufficiency) Documentation of patient reason(s) for not prescribing bisphosphonates)</p>		

#### 12.3.3.4. Suchmaschine

Recherchedatum: 28.07.2020

Anzahl der Treffer: 3 (davon 2 zum selben Qualitätsindikator, siehe auch 3.3)

**(Quality Payment Program (QPP) 2019), (American Society of Hematology (ASH) 2018), (The National Institute for Health and Care Excellence (NICE) 2017)**

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
<p><i>Quality Payment Program (QPP) (Quality Payment Program (QPP) 2019)</i>  <i>American Society of Hematology (ASH) (American Society of Hematology (ASH) 2018)</i>  <b>Hematology: Multiple Myeloma: Treatment with Bisphosphonates</b>  <b>Numerator:</b> Patients who were prescribed or received intravenous bisphosphonate therapy within the 12 month reporting period  <b>Denominator:</b> All patients aged 18 years and older with a diagnosis of multiple myeloma, not in remission</p>	Nein	Ja, s.o.
<p><i>The National Institute for Health and Care Excellence (NICE) (The National Institute for Health and Care Excellence (NICE) 2017)</i></p>	Nein	Nein.



Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
<p><b>Quality statement 4b: End-of-treatment summary plan</b>  <b>Numerator:</b> the number in the denominator who have a discussion about their end-of-treatment summary plan.  <b>Denominator:</b> the number of young people and adults who have completed their treatment for myeloma.</p>		<p>Definition “Young people and adults” = 16 Jahre und älter</p> <p>Definition “End-of-treatment summary plan”:</p> <p>“Includes personal and general risk factors, such as late effects related to lymphoma subtype, myeloma and/or its treatment as follows:</p> <ul style="list-style-type: none"> <li>• heart damage</li> <li>• peripheral neuropathy</li> <li>• cognitive disorders</li> <li>• second cancers</li> <li>• infertility</li> <li>• endocrine (hormonal) problems</li> <li>• bone and joint damage</li> <li>• chronic tiredness</li> <li>• lifestyle factors - exercise, diet and smoking</li> <li>• inability to do day-to-day tasks.”</li> </ul>

## 12.4. Evidenztabellen

### 12.4.1. Abkürzungsverzeichnis der Evidenztabellen

Abkürzung	Erläuterung
AE	Adverse events
ASCT	Autologous haemopoietic stem cell transplantation
BPs	Bisphosphonates
c	Continuous
C	Cyclophosphamide
CI	Confidence interval
CR	Complete response
CT	Clinical trial
CT	Computertomografie
D	Dexamethasone
EMP	Extramedullary plasmocytoma
FDG	2-Fluor-2-desoxy-D-glucose
FL	Focal lesions
HR	Hazard ratio
HRD	High-risk disease
i.v.	Intravenous
i.v.	Intravenous
iChT	Intravenous chemotherapy
Ig	Immunoglobulin
ISS	International Staging System
ITT	Intention to treat
M	Melphalan
MM	Multiple myeloma
MRD	Minimal residual disease
MRI	Magnet resonance imaging
n/a	Not applicable
n/r	Not reported
NDMM	Newly diagnosed Multiple myeloma
NE	Not estimable
ns	Not significant.
OS	Overall survival
P	prednisone
PET	Positronenemissionstomografie
PFS	Progression-free survival
QoL	Quality of Life
R	Lenalidomide
RCT	Randomized controlled trial
RR	Risk Ratio
RVD	Lenalidomid-Bortezomib-Dexametason
s.c.	Subcutaneous

<b>Abkürzung</b>	<b>Erläuterung</b>
SAE	Serious adverse events
SCT	Stem cell transplantation
SRD	Standard-risk disease
SRE	skeletal-related events
SUV	Standard uptake value
T	Thalidomide
V	Bortezomib
vs	Versus
WB	Whole body

## 12.4.2. patholBildgebende Verfahren

12.4.2.1. Bei Patienten mit solitärem skelettalem Plasmozytom soll eine Bildgebung mittels Ganzkörper-MRT oder FDG-PET/CT\* eingesetzt werden, um weitere Manifestationen eines MM zu identifizieren.

### 12.4.2.1.1. Evidenztabellen

#### 12.4.2.1.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(Lu, Chen et al. 2012)	<ul style="list-style-type: none"> <li>Search limited to human subjects, analysis limited to articles in English</li> <li>Search dates not reported</li> <li>MEDLINE and EBM Review search engines</li> <li>Studies that (1) evaluated MM for staging and/or recurrence,</li> </ul>	<ul style="list-style-type: none"> <li>Diagnostic performance of FDG-PET or FDG-PET/CT in the detection of intramedullary or extramedullary lesions of MM</li> <li>Reference standard was follow-up or pathology</li> </ul>	<ol style="list-style-type: none"> <li>Sensitivity</li> <li>Specificity</li> </ol> <p>Positive and negative likelihood ratio (LR+ and LR-)</p>	<ul style="list-style-type: none"> <li>14 studies</li> <li>395 patients (median age not reported)</li> <li>6 studies performed FDG-PET, 7 studies performed FDG-PET/CT and 1 study performed either; no significant difference (<math>P=0.7458</math>)</li> <li>3 studies evaluated diagnostic performance for intramedullary lesions, 4 studies for extramedullary lesions and 7 studies for both</li> <li>Detection of extramedullary lesions by FDG-PET or PET-CT: sensitivity 96.0% (79.6 to 99.9) specificity 77.8% (40.0 to 97.2)</li> </ul>	<ul style="list-style-type: none"> <li>Small studies (6 to 67 patients)</li> <li>Only half of the included studies were analysed due to incomplete data</li> <li>Assessment of methodological quality of the included studies (Cochrane criteria)</li> </ul>	<p>(Durie 2002) (Jadvar 2002) (Schirmeister 2002) (Hung 2005) (Bredella 2005) (Breyer 2006) (Zamagni 2007) (Nanni 2007) (Nanni 2008) (Salaun 2008) (Hur 2008) (Shortt 2009) (Kim 2009) (Elliott 2011)</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	(2) used FDG-PET or FDG- PET/CT for diagnosis, (3) pro- vided suffi- cient data for 2x2 ta- bles			LR+ 3.28 (1.29 to 8.32) LR- 0.12 (0.03 to 0.42) <ul style="list-style-type: none"> <li>• Detection of intramedullary lesions by FDG-PET or PET-CT: sensitivity 61.1% (43.5 to 76.9) specificity 94.1% (71.3 to 99.9) LR+ 5.73 (1.53 to 21.40) LR- 0.43 (0.28 to 0.65)</li> </ul>		
(Regelink, Minnema et al. 2013)	<ul style="list-style-type: none"> <li>• Search re-stricted to English language</li> <li>• Search up to May 2012</li> <li>• MEDLINE, EMBASE and Cochrane Central</li> <li>• <b>Inclusion criteria:</b> studies that assessed the diag-</li> </ul>	<ul style="list-style-type: none"> <li>• CT, MRI, FDG-PET or FDG-PET-CT vs. WBXR</li> <li>• FDG-PET or MRI vs. CT</li> </ul>	1. Sensi- tivity 2. Speci- ficity	<ul style="list-style-type: none"> <li>• 32 studies</li> <li>• Total no. of patients not reported, ranges 6 to 611 patients (median age not reported)</li> <li>• Results reported per patient and without preselection based on bone disease, if not indicated otherwise</li> <li>• <b>Sensitivity (index test):</b> CT vs. WBXR: 0.947 to 1.00 PET-CT vs. WBXR: 0.667 to 1.00 PET vs. WBXR: 0.953 (0.369 to 0.999) per region: 0.938 MRI vs. WBXR: 0.916 (0.883 to 0.940)</li> </ul>	<ul style="list-style-type: none"> <li>• Large variations in sample size of the included studies</li> <li>• Assessment of methodological quality of the included studies (QUADAS criteria)</li> <li>• Majority of studies did not report blinding (availability of results from reference test during interpretation of index test and vice versa)</li> </ul>	(Spira 2012) (Gleeson 2009) (Dinter 2009) (Nanni 2008) (Baur-Melnyk 2008) (Adam 2007) (Hur 2007) (Walker 2007) (Zamagni 2007) (Breyer 2006) (Ghanem 2006) (Nanni 2006) (Hung 2005) (Bredella 2005) (Schirrmeister 2003)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	nostic accuracy of CT, MRI, FDG-PET or FDG-PET-CT (index tests) for identification of bone disease using WBXR or CT as reference standard			<p>per region: 0.957 to 1.00            PET vs. CT, per region: 0.824            MRI vs. CT: 0.800 to 1.00            per region: 0.931</p> <ul style="list-style-type: none"> <li>• <b>Specificity (index test):</b>            CT vs. WBXR: 0.467 to 0.500            preselection based on bone disease: 0.957            PET-CT vs. WBXR: 0.286 to 0.500            PET vs. WBXR: 0.217 (0.178 to 0.679)            per region: 0.000            preselection based on bone disease: 0.842 to 1.000            MRI vs. WBXR: 0.412 (0.261 to 0.582)            per region: 0.596 to 0.873            preselection based on bone disease: 0.478 to 0.811            PET vs. CT, per region: 1.00            MRI vs. CT: 0.782 to 0.789            per region: 1.00</li> <li>• <b>Detection rate:</b>            CT vs. WBXR: 1.10 to 1.33            preselection based on bone disease: 1.04            PET-CT vs. WBXR: 1.27 to 1.45</li> </ul>		(Durie 2002) (Baur 2002) (Mahnken 2002) (Schirrmeister 2002) (Lecouvet 1999) (Mariette 1999) (Agren 1998) (Kusumoto 1997) (Van de Berg 1997) (Laroche 1996) (Tertti 1995) (Moulopoulos 1995) (Moulopoulos 1993) (Dimopoulos 1993) (Fruehwald 1988) (Ludwig 1987) (Schreiman 1985)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
(van Lammeren- Venema, Regelink et al. 2012)	<ul style="list-style-type: none"> <li>Language restriction to English</li> <li>Search up to December 2010</li> <li>MEDLINE and EMBASE, additionally cross-referencing</li> <li><b>Inclusion criteria:</b> primary studies that (1) included MM or</li> </ul>	<ul style="list-style-type: none"> <li>FDG-PET or FDG-PET-CT vs. WBXR and, if performed, MRI of the spine and pelvis at staging, during and after treatment</li> </ul>	<ol style="list-style-type: none"> <li>Accuracy</li> <li></li> <li>Value for response assessment (after first-line treatment) and follow-up</li> </ol>	<ul style="list-style-type: none"> <li>18 studies</li> <li>798 patients (median age not reported, range 23 to 85 years)</li> <li>No meta-analysis, results presented per study; see table 5 of original article below</li> </ul>	<ul style="list-style-type: none"> <li>Large variations in sample size of the included studies</li> <li>Assessment of methodological quality of the included studies (QUADAS criteria)</li> <li>Variations in definition of PET positivity between studies</li> <li>Poor description of reference test in most studies</li> <li>Lack of information regarding</li> </ul>	<p>(Durie 2002) (Jadvar 2002) (Schirrmeister 2002) Schirrmeister 2003) (Mileshkin 2004) (Bredella 2005) (Hung 2005) (Breyer 2006) (Adam 2007) (Fonti 2007) (Hur 2007) (Zamagni 2007) (Hur 2008) (Salaun 2008) (Bartel 2009) (Shortt 2009)</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen																																																
	<p>plasmacytoma (Salmon-Durie criteria) and (2) used a dedicated FDG-PET scan complementary to standard diagnostic tools</p> <ul style="list-style-type: none"> <li><b>Exclusion criteria:</b> use of radiopharmaceuticals other than FDG, animal studies, other types of studies (abstracts, reviews, case reports, editorials, comments)</li> </ul>			<p>Table 5. Concordance</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Study Design</th> <th>Diagnosis (No. of Pat)</th> </tr> </thead> <tbody> <tr> <td>Brewer, 2006</td> <td>Retrospective</td> <td>MM (15)</td> </tr> <tr> <td>Fors, 2007</td> <td>Prospective</td> <td>MM untreated</td> </tr> <tr> <td>Zamagni, 2007</td> <td>Prospective</td> <td>MM untreated</td> </tr> <tr> <td>Strauss, 2008</td> <td>Prospective</td> <td>Plasmacytoma</td> </tr> <tr> <td>Durie, 2002</td> <td>Retrospective</td> <td>MM (52), MM<sub>1</sub> (16), MM<sub>2</sub> (4), MM<sub>3</sub> (4)</td> </tr> <tr> <td>Jadlov, 2002</td> <td>Prospective</td> <td>MM (25), MM<sub>1</sub> or MM<sub>2</sub> (2)</td> </tr> <tr> <td>Schremler, 2002</td> <td>Prospective</td> <td>MM (26), MM<sub>1</sub> (15)</td> </tr> <tr> <td>Schremler, 2003</td> <td>Prospective</td> <td>Plasmacytoma (11)</td> </tr> <tr> <td>Misra, 2004</td> <td>Retrospective</td> <td>MM (20), MM<sub>1</sub> (10), MM<sub>2</sub> (10)</td> </tr> <tr> <td>Bridoux, 2005</td> <td>Retrospective</td> <td>MM (4), MM<sub>1</sub> (2), MM<sub>2</sub> (2)</td> </tr> <tr> <td>Hung, 2005</td> <td>Prospective</td> <td>MM (12)</td> </tr> <tr> <td>Adam, 2007</td> <td>Retrospective</td> <td>MM (20), MM<sub>1</sub> (10), MM<sub>2</sub> (10)</td> </tr> <tr> <td>Hu, 2007</td> <td>Retrospective</td> <td>MM (10), MM<sub>1</sub> (5), MM<sub>2</sub> (5)</td> </tr> <tr> <td>Hu, 2008</td> <td>Retrospective</td> <td>MM untreated</td> </tr> <tr> <td>Short, 2009</td> <td>Prospective</td> <td>MM (24)</td> </tr> </tbody> </table> <p>CT, computed tomography; FDG, <sup>18</sup>F-fluorodeoxyglucose; MM, multiple myeloma; MM<sub>1</sub>, monoclonal gammopathy of undetermined significance; WBXR, whole-body X-ray.</p>	Study	Study Design	Diagnosis (No. of Pat)	Brewer, 2006	Retrospective	MM (15)	Fors, 2007	Prospective	MM untreated	Zamagni, 2007	Prospective	MM untreated	Strauss, 2008	Prospective	Plasmacytoma	Durie, 2002	Retrospective	MM (52), MM <sub>1</sub> (16), MM <sub>2</sub> (4), MM <sub>3</sub> (4)	Jadlov, 2002	Prospective	MM (25), MM <sub>1</sub> or MM <sub>2</sub> (2)	Schremler, 2002	Prospective	MM (26), MM <sub>1</sub> (15)	Schremler, 2003	Prospective	Plasmacytoma (11)	Misra, 2004	Retrospective	MM (20), MM <sub>1</sub> (10), MM <sub>2</sub> (10)	Bridoux, 2005	Retrospective	MM (4), MM <sub>1</sub> (2), MM <sub>2</sub> (2)	Hung, 2005	Prospective	MM (12)	Adam, 2007	Retrospective	MM (20), MM <sub>1</sub> (10), MM <sub>2</sub> (10)	Hu, 2007	Retrospective	MM (10), MM <sub>1</sub> (5), MM <sub>2</sub> (5)	Hu, 2008	Retrospective	MM untreated	Short, 2009	Prospective	MM (24)	blinding of clinicians	(Dimitrakopoulou-Strauss 2009) (Castellani 2010)
Study	Study Design	Diagnosis (No. of Pat)																																																				
Brewer, 2006	Retrospective	MM (15)																																																				
Fors, 2007	Prospective	MM untreated																																																				
Zamagni, 2007	Prospective	MM untreated																																																				
Strauss, 2008	Prospective	Plasmacytoma																																																				
Durie, 2002	Retrospective	MM (52), MM <sub>1</sub> (16), MM <sub>2</sub> (4), MM <sub>3</sub> (4)																																																				
Jadlov, 2002	Prospective	MM (25), MM <sub>1</sub> or MM <sub>2</sub> (2)																																																				
Schremler, 2002	Prospective	MM (26), MM <sub>1</sub> (15)																																																				
Schremler, 2003	Prospective	Plasmacytoma (11)																																																				
Misra, 2004	Retrospective	MM (20), MM <sub>1</sub> (10), MM <sub>2</sub> (10)																																																				
Bridoux, 2005	Retrospective	MM (4), MM <sub>1</sub> (2), MM <sub>2</sub> (2)																																																				
Hung, 2005	Prospective	MM (12)																																																				
Adam, 2007	Retrospective	MM (20), MM <sub>1</sub> (10), MM <sub>2</sub> (10)																																																				
Hu, 2007	Retrospective	MM (10), MM <sub>1</sub> (5), MM <sub>2</sub> (5)																																																				
Hu, 2008	Retrospective	MM untreated																																																				
Short, 2009	Prospective	MM (24)																																																				
				<ul style="list-style-type: none"> <li>Authors' conclusions: "In general, FDG-PET has a higher sensitivity for myeloma bone lesions compared with WBXR, although head-to-head comparisons suggest that MRI may surpass PET." "Response monitoring with the use of FDG-PET-CT during treatment is promising, allowing more precise pre-</li> </ul>																																																		




Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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diction if prognosis com-  
pared with the standard re-  
sponse monitoring.”

12.4.2.1.3. Ergänzende Einzelstudien

Referenz/ Stu- dientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenzklasse
(Zhang, Zhang et al. 2018) Retrospective single center cohort study	<p><b>n =</b></p> <p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• biopsy of tissue confirmed lesions with neoplastic-appearing plasma cells</li> <li>• conventional imaging had no evidence of diffused bone involvement</li> <li>• bone marrow biopsy ensured plasma cell infiltration not exceeding 5% of all nucleated cells;</li> <li>• absence of hypercalcaemia, significant cytopenia, renal dysfunction, prior treatment for plasma cell neoplasm, or second malignancy; and</li> <li>• low serum monoclonal protein (M-protein) concentration</li> </ul>	<p><b>Index Test:</b> PET/CT</p>	<p><b>Reference standard:</b> CT, MRI</p>	<ul style="list-style-type: none"> <li>• Change of management</li> <li>• Detection of new lesions</li> <li>• Prognostic value</li> </ul>	<ul style="list-style-type: none"> <li>• <b>OS:</b> n/r</li> <li>• <b>PFS:</b> In univariate analysis (detailed in Table 3), tumour size &gt; 4 cm (Fig. 3) and PR after treatment (Fig. 4) were significant prognostic factors for PFS (p = 0.020 and 0.040). The other factor, such as age, gender, tumour number, and SUVmax were not significant predictors for PFS.</li> <li>• <b>AE:</b> n/r</li> <li>• <b>QoL:</b> n/r</li> <li>• <b>Other: Detection of new lesions:</b> PET/CT detected new lesions in 38.1% (8/21) of patients with 17 lesions, and lymph nodes were the most common site, accounting for 70.6% (12/17) of all lesions, followed by bone (n = 2), and less frequently, breast (n = 1), lung (n = 1), and stomach (n = 1)</li> </ul> <p><b>Change of management:</b> findings resulted in treatment changes in 7 patients with EMP. Among these, 4 patients had major treatment changes and 3 patients had minor changes</p>	<ul style="list-style-type: none"> <li>• <b>Study Duration:</b> n/r</li> <li>• <b>Follow-up:</b> 22-76 months</li> <li>• <b>ITT:</b> n/a</li> <li>• <b>Randomisation:</b> n/a</li> <li>• <b>Blinding:</b> physicians blinded for other image information</li> <li>• <b>Funding</b> Youth Foundation of Guangzhou Medical University (No.2016A24) and Guangzhou key medical discipline construction project.</li> </ul> <p><b>Other limitations:</b></p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>history of malignancy</li> <li>already accepted any treatment</li> </ul> <p><b>Baseline characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: 51.1 ± 15.3 years</li> <li>Stage: n/r</li> </ul> <p><b>Recurrence status:</b> n/r</p>					
(Fouquet, Guidez et al. 2014) Retrospective cohort study	<p><b>n = 43</b></p> <p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>Patients with solitary plasmacytoma (SP) from three French centers (Lille, Caen, Rennes) of the IFM (Intergroupe Francophone du Myélome), diagnosed between 2002 and 2013</li> <li>Clinical evidence of SP, either extramedullary plasmacytoma (EMP) or solitary bone plasmacytoma (SBP), confirmed by histology</li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>Evidence of MM</li> </ul> <p><b>Baseline characteristics:</b></p>	<b>Index Test:</b> 18F-FDG PET-CT and MRI of the spine and pelvis at baseline diagnosis and at completion of therapy	n/a	<ul style="list-style-type: none"> <li>Time-to-progression to active MM (TTMM)</li> <li>Prognostic factor(s) at diagnosis predicting progression to active MM</li> </ul>	<ul style="list-style-type: none"> <li><b>OS:</b> median not reached, 6-year OS 79.4%</li> <li><b>PFS:</b> n/r</li> <li><b>AE:</b> n/r</li> <li><b>QoL:</b> n/r</li> <li><b>TTMM:</b> median 71 months (95% CI: 59 to 101)</li> <li><b>Multivariate analysis:</b> risk model for progression with two variables and three categories (risk groups); see table 3 of original article below</li> </ul>  <ul style="list-style-type: none"> <li><b>Other:</b> n/a</li> </ul>	<ul style="list-style-type: none"> <li><b>Study Duration:</b> 2002 to 2013</li> <li><b>Follow-up:</b> median 50 months</li> <li><b>ITT:</b> n/a</li> <li><b>Randomisation:</b> n/a</li> <li><b>Blinding:</b> n/r</li> <li><b>Funding:</b> n/r</li> <li><b>Other limitations:</b> none</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<ul style="list-style-type: none"> <li>• <b>Age:</b> median 57.5 years</li> <li>• <b>Stage:</b> n/r</li> </ul> <p><b>Recurrence status:</b> n/r</p>					
(Albano, Bosio et al. 2018) Retrospective cohort study	<p><b>n = 62</b></p> <p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Patients with histologically confirmed solitary plasmacytoma (SP)</li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Evidence of MM</li> </ul> <p><b>Baseline characteristics:</b></p> <ul style="list-style-type: none"> <li>• <b>Age:</b> mean 64 years (range 40 to 87)</li> <li>• <b>Stage:</b> n/r</li> </ul> <p><b>Recurrence status:</b> n/r</p>	<b>Index Test:</b> 18F-FDG PET-CT at diagnosis	n/a	<ul style="list-style-type: none"> <li>• Time-to-progression to active MM (TTMM)</li> <li>• Prognostic value of PET/CT at diagnosis for predicting progression to active MM</li> </ul>	<ul style="list-style-type: none"> <li>• <b>OS:</b> n/r</li> <li>• <b>PFS:</b> n/r</li> <li>• <b>AE:</b> n/r</li> <li>• <b>QoL:</b> n/r</li> <li>• <b>TTMM:</b> average 18.3 months (ranges 6 to 41 months)</li> <li>• <b>Uni-/Multivariate analysis: mean TTMM (95% CI)</b> FDG-avidity: 16.7 months (14.4 to 21.5) FDG-non-avidity: 32.6 months (16.6 to 48.6) p=0.004</li> <li>• <b>Other:</b> n/a</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Study Duration:</b> 2005 to 2016</li> <li>• <b>Follow-up:</b> average 47 months (ranges 12 to 129)</li> <li>• <b>ITT:</b> n/a</li> <li>• <b>Randomisation:</b> n/a</li> <li>• <b>Blinding:</b> not blinded</li> <li>• <b>Funding:</b> n/r</li> <li>• <b>Other limitations:</b> uni-/multivariate analysis Unclear due to poor reporting of methods and results</li> </ul>

12.4.2.1.4. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA, retrospective studies	Sensitivität	-1	-	-	-	-1	⊕⊕⊕⊕ Low

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA, retrospective studies	Spezifität	-1	-	-	-	-1	⊕⊕⊕⊕ Low

Verzerrungsrisiko: Moderates-Hohes Verzerrungsrisiko eingeschlossener Studien

Weitere Überlegungen: Hohes Risiko für Publikationsbias

### 12.4.3. Verlaufsdagnostik

#### 12.4.3.1. Die routinemäßige Bestimmung des MRD-Status kann nicht empfohlen werden. Aktuell ist der Einsatz der MRD-Bestimmung im Kontext klinischer Studien zu sehen.

##### 12.4.3.1.1. Evidenztabellen

##### 12.4.3.1.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(Munshi, Avet-Loiseau et al. 2017)	<ul style="list-style-type: none"> <li>RCTs, CTs, and cohort studies reporting MRD status and PFS or OS in NDMM patients after first-line</li> </ul>	<ul style="list-style-type: none"> <li>n/a</li> </ul>	<ol style="list-style-type: none"> <li>prognostic value of MRD status in terms of PFS</li> </ol>	<p>21 studies included in MA</p> <ol style="list-style-type: none"> <li>Prognostic value of PFS: 14 studies, 1273 patients included in MA; PFS of MRD negative vs MRD positive: Overall HR: 0.41 (95% CI: 0.36-0.48), P &lt; .001; (<math>\chi^2 = 42.1, 13df; P &lt; 0.001</math>)</li> </ol>	<ul style="list-style-type: none"> <li><i>“For a pooled analysis of all studies reporting survival data, PFS and OS curves were generated. This method adjusts for the different</i></li> </ul>	<p>Rawstron et al, 2002 San Miguel et al, 2002 Ferrero et al, 2014 Bakkus et al, 2004 Dal Bó et al, 2013 Paiva et al, 2011</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<ul style="list-style-type: none"> <li>Included therapies: any type of treatment, except allogeneic SCT</li> <li>All MRD measurement techniques included, with a minimum detection of 0.01% or lower</li> </ul>		<ol style="list-style-type: none"> <li>prognostic value of MRD status in terms of OS</li> <li>Superiority of MRD vs. conventional CR to predict survival</li> </ol>	<ol style="list-style-type: none"> <li>Prognostic value of OS: 12 studies, 1100 patients included in MA; OS of MRD negative vs. MRD positive: Overall HR: 0.57 (95% CI: 0.46-0.71), <math>P &lt; .001</math>; <math>\chi^2 = 8.81</math>, 11 df; <math>P = 0.64</math>)</li> <li>A) PFS of MRD negative vs. MRD positive in patients with CR: Overall HR: 0.44 (95%-CI, 0.34-0.56), <math>P &lt; .001</math> B) OS of MRD negative vs. MRD positive in patients with CR: Overall HR: 0.47 (95% CI: 0.33-0.67), <math>P &lt; .001</math></li> </ol>	<p><i>proportions of MRD positivity and negativity in each study, thereby avoiding inappropriate bias potentially generated by studies with high or low proportions of MRD positivity."</i></p>	<p>Paiva et al, 2008 Korthals et al, 2012 Korthals et al, 2013 Swedin et al, 1998 Rawstron et al, 2013 Roussel et al, 2014 Fukumoto et al, 2016 Sarasquete et al, 2005 Ludwig et al, 2015</p>
(Landgren, Devlin et al. 2016)	<ul style="list-style-type: none"> <li>CTs or RCTs with MRD assessment in NDMM</li> <li>Allogeneic SCT patients excluded</li> </ul>		<ol style="list-style-type: none"> <li>prognostic value of MRD status in terms of PFS</li> <li>prognostic value of MRD status in terms of OS</li> </ol>	<p>4 studies included in MA</p> <ol style="list-style-type: none"> <li>PFS of MRD negative vs MRD positive: HR: 0.35 (95% CI: 0.27-0.46), <math>P &lt; 0.001</math></li> <li>OS of MRD negative vs. MRD positive: HR: 0.48 (95% CI 0.33-0.70), <math>P &lt; 0.001</math></li> </ol>	<ul style="list-style-type: none"> <li>Study qualities or confidence in estimates not assessed</li> <li>"meta-analysis was conducted using a random effects model, which weighted studies using the inverse-variance method"</li> </ul>	<p>Korde 2015 Mateos 2014 Paiva 2008 Silvennoinen 2013</p>

12.4.3.1.3. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA	MRD negativity as prognostic factor for OS	-1	-1	-	-	-	⊕⊕⊕⊖ Moderate
	SR/MA	MRD negativity as prognostic factor for PFS	-1	-	-	-	-	⊕⊕⊕⊖ Low

Verzerrungsrisiko: Verzerrungsrisiko in keiner der SRs für die eingeschlossenen Studien untersucht

PFS: statistisch signifikante Heterogenität:  $\chi^2 = 42.1, 13df; P < 0.001$ )

## 12.4.4. Skelettkomplikationen

12.4.4.1. Bei spinaler Kompression soll - interdisziplinär abgestimmt und abhängig von Grad und der klinischen Dynamik der Kompression sowie Grad der knöchernen Instabilität - eine Strahlentherapie und/oder ein chirurgischer Eingriff erfolgen.

### 12.4.4.1.1. Evidenztabellen

#### 12.4.4.1.2. Einzelstudien

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Patchell, Tibbs et al. 2005) Randomized-controlled trial	<b>N=101</b>  Patient characteristics: 1. Patients with spinal cord compressions caused by metastatic cancer 2. at least one neurological sign or symptom (including pain) and not have been totally paraplegic for longer than 48 h before study entry 3. median age: 60 years in both groups 4. male/female: 33/17 (Intervention), 37/14 (control) 5. amount of MM patients not given	Surgery followed by radiotherapy (n=50)	Radiotherapy alone (n=51)	1. Mortality 2. Morbidity 3. Harms 4. QoL	1. Mortality 1.1 Survival time: 126 days vs. 100 days; RR: 1.67 (95%CI: 1.04 to 2.63) 1.2 30-day mortality rates: 6% vs. 14%, p=0.32  2. 2.1 Retainment of ability to walk: for a median duration of 122 days vs. 13 days, p=0.003, less patients could walk in control group at study entry: 94% vs. 74%, p=0.024, Subgroup analysis: OR: 1.82 (95%CI: 1.08 to 3.12) 2.2 Maintenance of continence: 156 days vs. 17 days; RR: 2.13 (95%CI: 1.15 to 4.0) 2.3 Muscle strength/Maintenance	Prospective study  Randomisation within strata by permuted blocks  Non-blinded  patients were stratified according to treating institution, tumour type, ambulatory status, and relative stability of the spine  COI: declared that authors have no COIs  Funding: supported by grants from the National Cancer Institute (RO1 CA55256) and the National In-

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Fehlings, Nater et al. 2016)  Prospective single-arm study	<p><b>N= 142 patients</b></p> <p><b>Patient characteristics</b></p> <ol style="list-style-type: none"> <li>1. Patients with a single symptomatic metastatic epidural spinal cord compression (MESCC) lesion who were treated surgically</li> <li>2. 59 women, 83 men</li> <li>3. Mean age: 59.4 years</li> <li>4. Amount of MM patients not stated</li> </ol>	<p>Patients with MESCC treated with surgery for intractable pain, neurologic deficits, and imminent or overt spinal stability</p> <p>The type and extent of the surgery and postoperative radiation therapy (RT) protocol were at the discretion of the clinical team.</p>	Not applicable	<ol style="list-style-type: none"> <li>1. Mortality</li> <li>2. Morbidity</li> <li>3. Harms</li> <li>4. QoL</li> </ol>	<ol style="list-style-type: none"> <li>1. Mortality: During follow-up, 88 patients died and 54 patients were censored; median survival time: 230.5 days</li> <li>2. Morbidity                             <ol style="list-style-type: none"> <li>a. Ability to walk 4 steps independently (mean post-op score): 72.2% at 6 weeks, 77.3% at 3 months, 74.6% at 6 months, 74.2% at 12 months</li> <li>b. International Standards for</li> </ol> </li> </ol>	<p>stitute for Neurological Disorders and Stroke (K24 NS502180). The sponsor had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.</p> <p>Prospective observational trial</p> <p>Supported by the Halbert Chair in Neural Repair and Regeneration and the DeZwirek Foundation</p> <p>Authors declared COIs</p>



Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
					<p>Neurological Classification of Spinal Cord Injury (ISNCSCI) total motor score (mean post-op score): 95.80 (SD: 10.77) at 6 weeks, 97.69 (SD: 8.48) at 3 months, 9.23 (SD: 3.15) at 6 months, 99.91 (SD: 0.43) at 12 months</p> <p>c. Brief Pain Inventory (BPI) pain severity (mean post-op score): 4.39 (SD: 2.38) at 6 weeks, 4.07(SD: 2.47) at 3 months, 4.32 (SD: 2.68) at 6 months, 3.06 (SD: 1.97) at 12 months</p> <p>3. Surgical complications: n=42 (29.6%) patients experienced a total of 96 complications within 30 days after surgery</p> <p>a. n=3 patients with cerebrospinal</p>	

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Rades, Conde-Moreno et al. 2016)  Retrospective analysis	<b>N = 237</b>  <b>Inclusion criteria:</b> 1. patients with motor deficits of the lower extremities in consequence of spinal cord compression (SCC) from vertebral body myeloma  <b>Exclusion criteria:</b> Not reported	Radiotherapy  target volumes included the vertebrae affected by SCC plus on additional vertebra on either side.  RT was administered without upfront neurosurgery and performed either as short-course RT (1 x 8Gy, 5 x 4Gy) or longer-course RT (10 x 3Gy, 15 x 2.5Gy, 20 x 2Gy).	Not applicable	1. Mortality 2. Morbidity a. Local control of SCC (defined as freedom from symptomatic in-field recurrence of SCC)	fluid (CSF) leakage b. n=20 patients with infections 4. QoL measured with EQ-5D (mean post-op score): 0.57 (SD: 0.24) at 6 weeks, 0.67 (SD: 0.20 at 3 months, 0.74 (SD: 0.15) at 6 months, 0.68 (SD: 0.22) at 12 months	Retrospective study  COI: n.a. Funding: n.a.

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
				b. The effect of RT on motor function (improvement, no further progression, deterioration) 3. Harms 4. QoL	ambulatory patients 44 patients (64%) regained the ability to walk 3. Harms: not reported 4. QoL: not reported	

12.4.4.1.3. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT, prospective single-arm	Mortality	-1	-	-1	-1	-	⊕⊕⊕⊕ very low

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT, prospective single-arm, retrospektive	Morbidity	-1	-	-1	-1	-	⊕⊕⊕⊕ very low
	prospective single-arm	Harms	-1	-	-1	-1	-	⊕⊕⊕⊕ very low
	prospective single-arm	QoL	-1	-	-1	-1	-	⊕⊕⊕⊕ very low

Verzerrungsrisiko, hohes Risiko da RCT nicht verblindet, und einarmige Studien (retro- und prospektiv)

Impräzise, da Kriterium der optimalen Informationsgröße nicht erfüllt.

Indirekte Evidenz, da Krebspatienten untersucht, nicht speziell Patienten mit Myelom

**12.4.4.2. Bei pathologischen Frakturen oder drohender Fraktur gewichtstragender Skelettanteile sollte primär eine stabilisierende chirurgische Intervention erwogen werden. Dieser sollte sich - unter Berücksichtigung der systemischen Therapie - eine Radiotherapie der betroffenen Skelettanteile anschließen.**

**12.4.4.2.1. Evidenztabellen**

*12.4.4.2.2. Einzelstudien*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
(Sadeghi-Naini, Aarabi et al. 2018)	<p><b>Type of study:</b> Randomized controlled trials and prospective nonrandomized controlled clinical trials</p> <p><b>Databases:</b> MEDLINE, EMBASE, PubMed, and CENTRAL</p> <p><b>Inclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1. Randomized controlled trials and prospective nonrandomized controlled clinical trials assessing VP or KP for the treatment of pain following metastatic spinal lesion (MSL) without spinal cord compression</li> </ol> <p><b>Exclusion criteria:</b> Not reported</p>	<p>Vertebroplasty</p> <p>Kyphoplasty</p>	<p><b>Primary outcomes:</b></p> <ol style="list-style-type: none"> <li>1. Pain, measured by standard scoring [visual analog scale (VAS)]</li> <li>2. Functional assessments by standard scoring [Oswestry disability index (ODI), Roland Morris Disability Questionnaire (RMDQ), or Karnofsky performance score (KPS)]</li> </ol>	<p><b>Number of studies:</b> 9</p> <p><b>N = 622</b></p> <p><b>Effects of interventions</b></p> <p><b>VP+chemotherapy vs. chemotherapy</b></p> <ol style="list-style-type: none"> <li>1. Pain relief: MD: -3.01 (95%CI: -3.21 to -2.80), n=166, low certainty in the evidence</li> <li>2. Disability/function assessed by means of KPS: MD: 14.28 (95%CI: 4.22-24.34), n=166, very low certainty in the evidence</li> <li>3. SAEs: over 5 years: VP+chemotherapy group: n=1 (pathologic vertebral compression fracture); chemotherapy group: n=2 (paraplegia); RR: 0.50; 95%CI: 0.05-5.28)</li> </ol>	<p><b>Design:</b> 9 studies were included in qualitative synthesis and 7 studies were included in quantitative synthesis (meta-analysis)</p> <p><b>Random allocation:</b> n.r.</p> <p><b>Allocation concealment:</b> n.r.</p> <p><b>Intention-to-treat analysis:</b> yes</p>	<p>Basile 2012</p> <p>Berenson 2011</p> <p>Cai 2005</p> <p>li 2009</p> <p>Panagiotis 2014</p> <p>Xie 2009</p> <p>Yang 2005</p> <p>Yang 2009</p> <p>Yang 2012</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) In- terventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkun- gen / Evi- denzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
			<p>3. Serious ad-verse events were grouped into 2 main categories: procedure-re-lated and general com-plexions</p> <p><b>Secondary outco- mes:</b></p> <p>4. Bone cement leakage and its location</p> <p>5. Therapeutic cost</p> <p>6. Duration of hospital stay</p> <p>7. Vertebral height</p> <p>8. Use of post-operative opi-oids or other analgesics</p> <p>9. HRQoL meas-ured by 36-item Short Form (SF-36)</p>	<p>4. Bone cement leakage: reported by 1 study: 21 incidents of bone cement leakage in 38 patients treated by VP+chemo-therapy</p> <p>7. Vertebral height: reported by 1 study: no significant differences between groups</p> <p>5.,6.,8.,9., not reported for this compari-son</p> <p><b>KP versus nonsurgical management (NSM):</b></p> <p>1. Pain relief: MD: -2.61 (95%CI: -2.79 to -2.43)</p> <p>2. Functional outcomes: by means of KPS (12 months follow-up): MD: 15.5 (95%CI: 14.64-16-36), by RMDQ score (1 months follow-up): MD -8.20 (95%CI: -8.47 to -7.93), RMDQ score (at 1 year): no signifi-cant difference</p> <p>3. SAE: over 1 months: n=37 (events) in KP group (n=70 patients), n=8 (events) in NSM group (n=26 patients), n=18 in crossover group (n=38 patients); RR (KP vs NSM): 1.66; 95%CI:0.90-3.03)</p>	<p><b>Blinding:</b> n.r.</p> <p><b>Heterogeneity (95% CI):</b> Chi<sup>2</sup> = 0.62, df = 1 (P = 0.43); I<sup>2</sup> = 0%</p> <p><b>Test for over-all effect (95% CI):</b> Z = 28.91 (P &lt; 0.00001)</p> <p><b>Publication bias:</b> n.r.</p> <p><b>Length of fol-low-up:</b> ranged from 1 month to 5 years</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) In- terventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkun- gen / Evi- denzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
				<p>4. Bone cement leakage: 1 patient with cement leakage in KP group had adjacent fracture</p> <p>5.,6., not reported</p> <p>7. Vertebral height: significant midthoracic height restoration for KP vs. NSM: midpoint of VB: P=0.015, posterior of VP: P=0.034 and transition zone vertebrae: P&lt;0.0001</p> <p>8. use of analgesic: fewer KP patients used analgesics for pain relief than NSM patients at 1 month follow-up (P=0.0018)</p> <p>9. HRQoL: KP improved more than NSM by means of SF-36 at 1 month follow-up: MD: 9.50 (95%CI: 9.069.94)</p> <p><b>VP+Iodine-125 vs. VP:</b></p> <p>1. Pain relief: at 1y follow-up: MD: -3 (95%CI: -3.20 to -2.80)</p> <p>2. Functional outcomes: at 1y follow-up: MD: 7.08 (95%CI: 4.92-9.24)</p> <p>3. SAE: not reported</p> <p>4. Bone cement leakage: not significant 6 vs. 7 (40 patients in each group)</p>		

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				<p>5., 6.,7.,8.,9. Not reported</p> <p><b>KP vs. Kiva implant:</b> no significant differences in improving pain and functional scores after 1 month follow-up compared to baseline. Vertebral height increased postoperatively, insignificantly in both groups</p> <p><b>VP+Dexamethasone vs. VP:</b> VP+D had some, insignificant advantages in pain relief at 3 months after intervention</p> <p><b>VP+radiochemotherapy vs. Radiochemotherapy:</b></p> <p>1. Pain relief: MD: -5.90 (95%CI: -6.92 to -4.88)</p> <p>2.-8. Not reported</p> <p>9. HRQoL: MD: 10.3 (95%CI: 2.9-17.6)</p> <p><b>Surgical Versus NSM:</b></p> <p>1. Pain relief: MD: -2.66 (95%CI: -3.65 to -1.67), n=205, low-quality evidence</p> <p>2. Functional outcomes by means of KPS: MD: 15.49 (95%CI: 14.71-16,27), n=278, low-quality evidence</p> <p>3. SAE: RR: 1.50 (95%CI: 0.84-2.68) n=210</p>		



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				<p>4.-8. Not reported 9. HRQoL: MD: 9.50 (95%CI: 9.06-9.94), n=163, low-quality evidence</p> <p><b>Patient characteristics:</b> patients with metastatic spinal lesions mean age of participants was 58</p>		
<p>(Health Quality 2016) Health Technol- ogy Assessment</p>	<p><b>Type of included studies:</b> randomized controlled trials (RCTs), systematic reviews, metaanalyses, and observational studies including case reports</p> <p><b>Databases:</b> Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and EBM Reviews, for studies published from January 1, 2000, to October 2014</p> <p><b>Inclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1. English-language full-text publications</li> <li>2. Studies published between January 1, 2000, and October 2014</li> </ol>	<p>Vertebroplasty Kyphoplasty</p>	<ol style="list-style-type: none"> <li>1. Patient satisfaction</li> <li>2. Pain intensity reduction, time course, and durability</li> <li>3. Fatigue, sleep disturbances, depression, anxiety</li> <li>4. Neurological symptoms or neurological status</li> </ol>	<p><b>Number of studies:</b> 150 <b>N = 4,235</b></p> <p><b>Effectiveness of Vertebroplasty:</b></p> <ol style="list-style-type: none"> <li>1. <b>Patient satisfaction:</b> Trumm et al reported satisfaction levels (satisfied, unsatisfied) for patients with multiple myeloma (64% [18/39] satisfied)</li> <li>2. <b>Pain intensity:</b> baseline mean VAS values were in the high pain intensity levels (VAS ≥ 7.0); Post-procedurally the mean VAS values were in mild pain intensity levels (VAS &lt; 4.0), representing both statistically and clinically significant reductions</li> <li>8. <b>Analgesic use:</b> In multiple myeloma groups, 3 studies reported on patients discontinuing pain medications after vertebral augmentation: 51% (54/106), 36% (10/29), and 64% (7/11)</li> </ol>	<p><b>Design:</b> 14 SR, 6 RCTs, 80 observational cohorts, 50 case reports</p> <p><b>No meta-analysis</b> due to high heterogeneity between studies</p> <p><b>Quality of evidence:</b> assessed with GRADE (for vertebroplasty and kyphoplasty; not separately graded for myeloma patients)</p>	<p>Included studies = 150</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) In- terventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkun- gen / Evi- denzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
	<p>3. Reports including randomized controlled trials (RCTs), systematic reviews, metaanalyses, and observational studies including case reports</p> <p>4. Reports involving vertebral augmentation techniques such as vertebroplasty or kyphoplasty for cancer-related vertebral compression fractures</p> <p><b>Exclusion criteria:</b></p> <p>1. Experimental or animal studies involving evaluations of technology performance</p> <p>2. Clinical reports not involving technical or clinical outcomes</p> <p>3. Studies involving vertebral augmentation techniques not performed percutaneously under imaging guidance</p> <p>4. Clinical studies mainly involving patients with osteoporotic or traumatic vertebral compression fracture etiologies</p>		<p>5. Safety, including procedural and post-procedural complications</p> <p>6. Degree of vertebral height restoration or kyphosis correction</p> <p>7. Mobility, activities of daily living, and self-care</p> <p>8. Analgesic drug use</p> <p>9. Disability related to back pain</p> <p>10. Health-related quality of life</p>	<p>After vertebroplasty, a discontinuation of opioid use, a decreased dose, or a change from intravenous or transdermal delivery from baseline use was reported for 89% (53/59), 43% (3/7), 64% (36/56), and 88% (22/25)</p> <p><b>9. Pain-related disability and physical performance:</b> For patients with multiple myeloma, 2 studies reported this outcome.</p> <p>Anselmetti et al reported the median Oswestry Disability Index score for 106 patients was significantly reduced from baseline to post-vertebroplasty (82% to 7%, <math>P &lt; .001</math>)</p> <p>McDonald et al reported the median Roland Morris Disability Questionnaire (RMDQ) score improvement for 66 patients was 11 points (95% confidence interval [CI] 7.7–14.3), with improvement persisting at the 1-year follow-up</p> <p><b>10. Health-related quality of life and patient satisfaction:</b> 1 study with multiple myeloma patients reported Health-related quality of life. The mean physical component summary score of the survey improved from 22.1 (range 20–25) at baseline to 41.8 (range 38–45), with scores remaining improved at the 1-year follow-up</p>		

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	<p>5. Studies involving vertebral augmentation techniques performed simultaneously with spinal surgical interventions</p> <p>6. Narrative reviews and opinions or commentaries</p>			<p><b>Endpoints 3-7 were not reported for this group</b></p> <p><b>Vertebroplasty and adjunctive systemic therapy:</b></p> <p>2. <b>Pain intensity:</b> Yang et al with multiple myeloma patients reported, mean pain intensity (<math>3.0 \pm 0.62</math> vs. <math>6.0 \pm 0.40</math>, <math>P = .032</math>) and physical performance (KPS scores <math>89.4 \pm 6.3</math> vs. <math>80.3 \pm 7.2</math>, <math>P = .002</math>) worsened in the chemotherapy-only group. Of interest, the height of the vertebral body was reported to be increased after vertebroplasty in the anterior position (<math>15.71 \pm 0.70</math> to <math>16.61 \pm 0.67</math> mm, <math>P = .002</math>) and the midline (<math>13.65 \pm 0.59</math> to <math>14.52 \pm 0.85</math> mm, <math>P = .001</math>), but not in the posterior position (<math>15.71 \pm 0.70</math> to <math>16.61 \pm 0.67</math> mm, <math>P = .002</math>)</p> <p><b>No other endpoint was reported for this group</b></p> <p><b>Vertebroplasty and adjunctive radiofrequency ablation:</b></p> <p>Orgera et al with multiple myeloma patients was the only RCT comparing vertebroplasty and radiofrequency ablation to vertebroplasty.</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) In- terventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkun- gen / Evi- denzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
				<p><b>Pain intensity</b> (endpoint 2), <b>analgesic use</b> (Endpoint 8), and <b>pain-related disability</b> (Endpoint 9) were improved in both groups, but differences between the groups were not significant at 24 hours or at 6 weeks</p> <p><b>Effectiveness of Kyphoplasty:</b></p> <p><b>1. Patient satisfaction:</b> One study, involving multiple myeloma patients, reported on patient satisfaction with kyphoplasty treatment.<sup>93</sup> In that study, at 1 year patients rated their overall satisfaction with their treatment as being excellent (65%, 13/20), good (25%, 5/20), and fair (10%, 2/20)</p> <p><b>2. Pain intensity:</b> 2 studies involving kyphoplasty for multiple myeloma patients reported VAS pain scores, and these involved significant reductions in pain intensity over baseline at follow-up</p> <p><b>9. Pain related disability:</b> For the patients with multiple myeloma, the mean Oswestry Disability Index scores at baseline were all in the severe (49%) or very severe (63%, 72%) levels of disability. Mean values were significantly reduced (<math>P &lt; .01</math>) to moderate levels at 24 hours (37%) and at 3 months (33%, 28%) and 24 months (30%)</p>		

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				<p>(⊕⊕⊕ Moderate certainty of the evi- dence for 18 observational trials, ⊕⊕⊕⊕ High certainty of the evidence for 1 RCT)</p> <p><b>10. Health-related quality of life</b> Dudeney et al included multiple mye- loma patients and mean survey scores for bodily pain, physical functioning, vi- tality, and social functioning were signif- icantly improved at the 7-month follow- up (⊕⊕ Low certainty of the evidence for 3 observational trials, ⊕⊕⊕ Moderate certainty of the evi- dence for 1 RCT)</p> <p><b>No other endpoint was reported for this group</b></p> <p><b>Kyphoplasty and radiotherapy:</b> <b>2. Pain intensity:</b> Kasperk et al reported pain intensity levels at 1 month follow- ing treatment for multiple myeloma were reduced to similar levels in the groups treated with either kyphoplasty or pallia- tive external beam radiotherapy</p> <p><b>9. Pain related disability:</b> Kasperk et al reported the Oswestry Disability Index was significantly improved from baseline</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) In- terventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkun- gen / Evi- denzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
				<p>at the 1-year follow-up in both the kyphoplasty group (53% ± 3.8% to 30% ± 4.5%) and the external beam radiotherapy group (43% ± 7.3% to 35% ± 5.6%), but not the systemic therapy-only group (36% ± 4.8% to 30% ± 5.2%)</p> <p><b>No other endpoint was reported for this group</b></p> <p><b>Patient characteristics:</b></p> <ol style="list-style-type: none"> <li>patients with mixed primary spinal metastatic cancers, multiple myeloma, or hemangiomas</li> </ol>		

12.4.4.2.3. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungs- risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	HTA/SR	Mortality	-	-	-	-	-	Not reported
	HTA/SR	Morbidity	-	-	-1	-	-	⊕⊕⊕⊖ moderate
	SR	Harms	-	-	-1	-	-	⊕⊕⊕⊖

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
								moderate
	HTA (1 retrospektive Studie mit MM Patienten eingeschlossen und bewertet)	QoL	-	-	-	-	-	⊕⊕⊕⊖ low

Indirekte Evidenz, da Krebspatienten untersucht, nicht speziell Patienten mit Myelom

**12.4.4.3. Eine lokale Radiotherapie mit dem Ziel der Analgesie kann in Fraktionierungen von 1 x 8Gy, 5 x 4Gy, 10 x 3Gy 15 x 2,5Gy oder 20 x 2 Gy appliziert werden.**

**12.4.4.3.1. Evidenztabellen**

*12.4.4.3.2. Systematische Übersichtsarbeiten (Chirurgische Interventionen)*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
(Sadeghi-Naini, Aarabi et al. 2018)	<b>Type of study:</b> Randomized controlled trials and prospective nonrandomized controlled clinical trials	Vertebroplasty  Kyphoplasty	<b>Primary outcomes:</b> 1. Pain, measured by standard scoring [visual	<b>Number of studies:</b> 9  <b>N = 622</b>  <b>Effects of interventions</b>	<b>Design:</b> 9 studies were included in qualitative synthesis and 7 studies	Basile 2012 Berenson 2011 Cai 2005 li 2009 Panagiotis 2014

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Inter- ventionen/ (ggf. Dosierung)	untersuchte End- punkte	Ergebnisse	methodische Be- merkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
	<p><b>Databases:</b> MEDLINE, EM-BASE, PubMed, and CENTRAL</p> <p><b>Inclusion criteria:</b></p> <p>3. Randomized controlled trials and prospective nonrandomized controlled clinical trials assessing VP or KP for the treatment of pain following MSL without spinal cord compression</p> <p><b>Exclusion criteria:</b> Not reported</p>		<p>analog scale (VAS)]</p> <p>2. Functional assessments by standard scoring [Oswestry disability index (ODI), Roland Morris Disability Questionnaire (RMDQ), or Karnofsky performance score (KPS)]</p> <p>3. Serious adverse events were grouped into 2 main categories: procedure-related and general complications</p> <p><b>Secondary outcomes:</b></p> <p>4. Bone cement leakage and its location</p> <p>5. Therapeutic cost</p> <p>6. Duration of hospital stay</p>	<p><b>VP+chemotherapy vs. chemotherapy</b></p> <p>1. Pain relief: MD: -3.01 (95%CI: -3.21 to -2.80), n=166, low certainty in the evidence</p> <p>2. Disability/function assessed by means of KPS: MD: 14.28 (95%CI: 4.22-24.34), n=166, very low certainty in the evidence</p> <p>3. SAEs: over 5 years: VP+chemotherapy group: n=1 (pathologic vertebral compression fracture); chemotherapy group: n=2 (paraplegia); RR: 0.50; 95%CI: 0.05-5.28)</p> <p>4. Bone cement leakage: reported by 1 study: 21 incidents of bone cement leakage in 38 patients treated by VP+chemotherapy</p> <p>7. Vertebral height: reported by 1 study: no significant differences between groups</p> <p>5.,6.,8.,9., not reported for this comparison</p> <p><b>KP versus NSM:</b></p> <p>1. Pain relief: MD: -2.61 (95%CI: -2.79 to -2.43)</p>	<p>were included in quantitative synthesis (meta-analysis)</p> <p><b>Random allocation:</b> n.r.</p> <p><b>Allocation concealment:</b> n.r.</p> <p><b>Intention-to-treat analysis:</b> yes</p> <p><b>Blinding:</b> n.r.</p> <p><b>Heterogeneity (95% CI):</b> Chi<sup>2</sup> = 0.62, df = 1 (P = 0.43); I<sup>2</sup> = 0%</p> <p><b>Test for overall effect (95% CI):</b> Z = 28.91 (P &lt; 0.00001)</p> <p><b>Publication bias:</b> n.r.</p> <p><b>Length of follow-up:</b> ranged</p>	<p>Xie 2009</p> <p>Yang 2005</p> <p>Yang 2009</p> <p>Yang 2012</p>



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			<p>7. Vertebral height</p> <p>8. Use of postoperative opioids or other analgesics</p> <p>9. HRQoL measured by 36-item Short Form (SF-36)</p>	<p>2. Functional outcomes: by means of KPS (12 months follow-up): MD: 15.5 (95%CI: 14.64-16.36), by RMDQ score (1 months follow-up): MD -8.20 (95%CI: -8.47 to -7.93), RMDQ score (at 1 year): no significant difference</p> <p>3. SAE: over 1 months: n=37 (events) in KP group (n=70 patients), n=8 (events) in NSM group (n=26 patients), n=18 in crossover group (n=38 patients); RR (KP vs NSM): 1.66; 95%CI:0.90-3.03)</p> <p>4. Bone cement leakage: 1 patient with cement leakage in KP group had adjacent fracture</p> <p>5.,6., not reported</p> <p>7. Vertebral height: significant midthoracic height restoration for KP vs. NSM: midpoint of VB: P=0.015, posterior of VP: P=0.034 and transition zone vertebrae: P&lt;0.0001</p> <p>8. use of analgesic: fewer KP patients used analgesics for pain relief than NSM patients at 1 month follow-up (P=0.0018)</p> <p>9. HRQoL: KP improved more than NSM by means of SF-36 at 1 month follow-up: MD: 9.50 (95%CI: 9.069.94)</p>	<p>from 1 month to 5 years</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Inter- ventionen/ (ggf. Dosierung)	untersuchte End- punkte	Ergebnisse	methodische Be- merkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
				<p><b>VP+Iodine-125 vs. VP:</b></p> <p>1. Pain relief: at 1y follow-up: MD: -3 (95%CI: -3.20 to -2.80)</p> <p>2. Functional outcomes: at 1y follow-up: MD: 7.08 (95%CI: 4.92-9.24)</p> <p>3. SAE: not reported</p> <p>4. Bone cement leakage: not significant 6 vs. 7 (40 patients in each group)</p> <p>5., 6.,7.,8.,9. Not reported</p> <p><b>KP vs. Kiva implant:</b> no significant differences in improving pain and functional scores after 1 month follow-up compared to baseline. VB height increased postoperatively, insignificantly in both groups</p> <p><b>VP+Dexamethasone vs. VP:</b> VP+D had some, insignificant advantages in pain relief at 3 months after intervention</p> <p><b>VP+radiochemotherapy vs. Radiochemotherapy:</b></p> <p>1. Pain relief: MD: -5.90 (95%CI: -6.92 to -4.88)</p> <p>2.-8. Not reported</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Inter- ventionen/ (ggf. Dosierung)	untersuchte End- punkte	Ergebnisse	methodische Be- merkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
				<p>9. HRQoL: MD: 10.3 (95%CI: 2.9-17.6)</p> <p><b>Surgical Versus NSM:</b></p> <p>1. Pain relief: MD: -2.66 (95%CI: -3.65 to -1.67), n=205, low-quality evidence</p> <p>2. Functional outcomes by means of KPS: MD: 15.49 (95%CI: 14.71-16,27), n=278, low-quality evidence</p> <p>3. SAE: RR: 1.50 (95%CI: 0.84-2.68) n=210</p> <p>4.-8. Not reported</p> <p>9. HRQoL: MD: 9.50 (95%CI: 9.06-9.94), n=163, low-quality evidence</p> <p><b>Patient characteristics:</b> patients with metastatic spinal lesions mean age of participants was 58</p>		
(Health Quality 2016) Health Technol- ogy Assessment	<p><b>Type of included studies:</b> randomized controlled trials (RCTs), systematic reviews, metaanalyses, and observational studies including case reports</p> <p><b>Databases:</b> Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and EBM Reviews, for studies</p>	Vertebroplasty  Kyphoplasty	<ol style="list-style-type: none"> <li>Patient satisfaction</li> <li>Pain intensity reduction, time course, and durability</li> <li>Fatigue, sleep disturbances, depression, anxiety</li> </ol>	<p><b>Number of studies:</b> 150</p> <p><b>N = 4,235</b></p> <p><b>Effectiveness of Vertebroplasty:</b></p> <p><b>1. Patient satisfaction:</b> Trumm et al reported satisfaction levels (satisfied, unsatisfied) for patients with multiple myeloma (64% [18/39] satisfied)</p> <p><b>2. Pain intensity:</b> baseline mean VAS values were in the high pain intensity levels (VAS ≥ 7.0); Post-procedurally</p>	<p><b>Design:</b> 14 SR, 6 RCTs, 80 observational cohorts, 50 case reports</p> <p><b>No meta-analysis</b> due to high heterogeneity between studies</p> <p><b>Quality of evidence:</b> assessed</p>	Included studies = 150

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Inter- ventionen/ (ggf. Dosierung)	untersuchte End- punkte	Ergebnisse	methodische Be- merkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
	<p>published from January 1, 2000, to October 2014</p> <p><b>Inclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1 English-language full-text publications</li> <li>2 Studies published between January 1, 2000, and October 2014</li> <li>3 Reports including randomized controlled trials (RCTs), systematic reviews, metaanalyses, and observational studies including case reports</li> <li>4 Reports involving vertebral augmentation techniques such as vertebroplasty or kyphoplasty for cancer-related vertebral compression fractures</li> </ol> <p><b>Exclusion criteria:</b></p> <ol style="list-style-type: none"> <li>7. Experimental or animal studies involving evaluations of technology performance</li> <li>8. Clinical reports not involving technical or clinical outcomes</li> </ol>		<ol style="list-style-type: none"> <li>4. Neurological symptoms or neurological status</li> <li>5. Safety, including procedural and post-procedural complications</li> <li>6. Degree of vertebral height restoration or kyphosis correction</li> <li>7. Mobility, activities of daily living, and self-care</li> <li>8. Analgesic drug use</li> <li>9. Disability related to back pain</li> </ol>	<p>the mean VAS values were in mild pain intensity levels (VAS &lt; 4.0), representing both statistically and clinically significant reductions</p> <p><b>8. Analgesic use:</b> In multiple myeloma groups, 3 studies reported on patients discontinuing pain medications after vertebral augmentation: 51% (54/106), 36% (10/29), and 64% (7/11)</p> <p>After vertebroplasty, a discontinuation of opioid use, a decreased dose, or a change from intravenous or transdermal delivery from baseline use was reported for 89% (53/59), 43% (3/7), 64% (36/56), and 88% (22/25)</p> <p><b>9. Pain-related disability and physical performance:</b> For patients with multiple myeloma, 2 studies reported this outcome.</p> <p>Anselmetti et al reported the median Oswestry Disability Index score for 106 patients was significantly reduced from baseline to post-vertebroplasty (82% to 7%, <math>P &lt; .001</math>)</p> <p>McDonald et al reported the median Roland Morris Disability Questionnaire (RMDQ) score improvement for 66 patients was 11 points (95% confidence interval [CI] 7.7-14.3), with improvement persisting at the 1-year follow-up</p>	<p>with GRADE (for vertebroplasty and kyphoplasty; not separately graded for myeloma patients)</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Inter- ventionen/ (ggf. Dosierung)	untersuchte End- punkte	Ergebnisse	methodische Be- merkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
	<p>9. Studies involving vertebral augmentation techniques not performed percutaneously under imaging guidance</p> <p>10. Clinical studies mainly involving patients with osteoporotic or traumatic vertebral compression fracture etiologies</p> <p>11. Studies involving vertebral augmentation techniques performed simultaneously with spinal surgical interventions</p> <p>12. Narrative reviews and opinions or commentaries</p>		<p>10. Health-related quality of life</p>	<p><b>10. Health-related quality of life and patient satisfaction:</b> 1 study with multiple myeloma patients reported Health-related quality of life. The mean physical component summary score of the survey improved from 22.1 (range 20–25) at baseline to 41.8 (range 38–45), with scores remaining improved at the 1-year follow-up</p> <p><b>Endpoints 3-7 were not reported for this group</b></p> <p><b>Vertebroplasty and adjunctive systemic therapy:</b></p> <p>10. <b>Pain intensity:</b> Yang et al with multiple myeloma patients reported, mean pain intensity (<math>3.0 \pm 0.62</math> vs. <math>6.0 \pm 0.40</math>, <math>P = .032</math>) and physical performance (KPS scores <math>89.4 \pm 6.3</math> vs. <math>80.3 \pm 7.2</math>, <math>P = .002</math>) worsened in the chemotherapy-only group. Of interest, the height of the vertebral body was reported to be increased after vertebroplasty in the anterior position (<math>15.71 \pm 0.70</math> to <math>16.61 \pm 0.67</math> mm, <math>P = .002</math>) and the midline (<math>13.65 \pm 0.59</math> to <math>14.52 \pm 0.85</math> mm, <math>P = .001</math>), but not in the posterior position (<math>15.71 \pm 0.70</math> to <math>16.61 \pm 0.67</math> mm, <math>P = .002</math>)</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Inter- ventionen/ (ggf. Dosierung)	untersuchte End- punkte	Ergebnisse	methodische Be- merkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
				<p><b>No other endpoint was reported for this group</b></p> <p><b>Vertebroplasty and adjunctive radiofrequency ablation:</b> Orgera et al with multiple myeloma patients was the only RCT comparing vertebroplasty and radiofrequency ablation to vertebroplasty.</p> <p><b>Pain intensity</b> (endpoint 2), <b>analgesic use</b> (Endpoint 8), and <b>pain-related disability</b> (Endpoint 9) were improved in both groups, but differences between the groups were not significant at 24 hours or at 6 weeks</p> <p><b>Effectiveness of Kyphoplasty:</b></p> <p><b>1. Patient satisfaction:</b> One study, involving multiple myeloma patients, reported on patient satisfaction with kyphoplasty treatment.<sup>93</sup> In that study, at 1 year patients rated their overall satisfaction with their treatment as being excellent (65%, 13/20), good (25%, 5/20), and fair (10%, 2/20)</p> <p><b>2. Pain intensity:</b> 2 studies involving kyphoplasty for multiple myeloma patients reported VAS pain scores, and these involved significant reductions in pain intensity over baseline at follow-up</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Inter- ventionen/ (ggf. Dosierung)	untersuchte End- punkte	Ergebnisse	methodische Be- merkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
				<p><b>9. Pain related disability:</b> For the patients with multiple myeloma, the mean Oswestry Disability Index scores at baseline were all in the severe (49%) or very severe (63%, 72%) levels of disability. Mean values were significantly reduced (<math>P &lt; .01</math>) to moderate levels at 24 hours (37%) and at 3 months (33%, 28%) and 24 months (30%)            (⊕⊕⊕ Moderate certainty of the evidence for 18 observational trials,            ⊕⊕⊕⊕ High certainty of the evidence for 1 RCT)</p> <p><b>10. Health-related quality of life</b>            Dudeney et al included multiple myeloma patients and mean survey scores for bodily pain, physical functioning, vitality, and social functioning were significantly improved at the 7-month follow-up            (⊕⊕ Low certainty of the evidence for 3 observational trials,            ⊕⊕⊕ Moderate certainty of the evidence for 1 RCT)</p> <p><b>No other endpoint was reported for this group</b></p> <p><b>Kyphoplasty and radiotherapy:</b>  <b>2. Pain intensity:</b> Kasperk et al reported pain intensity levels at 1 month</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Inter- ventionen/ (ggf. Dosierung)	untersuchte End- punkte	Ergebnisse	methodische Be- merkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbe- lege/ eingeschlos- sene Publikati- onen
				<p>following treatment for multiple myeloma were reduced to similar levels in the groups treated with either kyphoplasty or palliative external beam radiotherapy</p> <p><b>9. Pain related disability:</b> Kasperk et al reported the Oswestry Disability Index was significantly improved from baseline at the 1-year follow-up in both the kyphoplasty group (53% ± 3.8% to 30% ± 4.5%) and the external beam radiotherapy group (43% ± 7.3% to 35% ± 5.6%), but not the systemic therapy-only group (36% ± 4.8% to 30% ± 5.2%)</p> <p><b>No other endpoint was reported for this group</b></p> <p><b>Patient characteristics:</b></p> <p>2. patients with mixed primary spinal metastatic cancers, multiple myeloma, or hemangiomas</p>		



## 12.4.4.3.3. Ergänzende Einzelstudien (Vergleich Strahlentherapie vs. Chirurgie)

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Audat, Hajyousef et al. 2016)  Randomized-controlled trial	<b>N = 27</b>  <b>Patient Characteristics:</b> 1. Patients with multiple myeloma (histological diagnosis with none marrow biopsy) 2. mean age: 58.15 (Group I), 58.86 (Group II) 3. all patients had back pain without neurological deficits  <b>Exclusion Criteria:</b> Not reported	Conventional therapy + vertebral augmentation (KP and VP) (Group II) (n=14)	Conventional therapy: chemotherapy and radiotherapy (Group I) (n=13)	1. Mortality 2. Back pain improvement 3. ODI 4. SS SINS	<b>1. Mortality:</b> Group I: n=4 patient died (3 due to advanced disease, 1 due to acute pneumonia), Group II: n=4 patients died (1 due to acute lung embolism, 3 due to advanced disease and severe pneumonia) <b>2. Back pain improvement:</b> Group I: Six patients improved partially Group II: All patients improved after Vertebroplasty with three of them had episodes of pain  <b>3. ODI:</b> ODI of group I was 31.9 (63.8%) with SD = 8.34 and of group II was 33.2 (66.4%) with SD = 5.98 (p = 0.418)  At 1 year follow up: ODI value for group I was 28.4 (56.8%) with SD = 8.79 and for group II was 21.4 (42.8%) with SD = 9.24 (p = 0.874)  At 2 years follow up: ODI for group I was 28.42 (56.85%) with SD 8.79 and for group II was 21.43 (42.65%) with SD 9.24 (p = 0.874)  At 3 years follow up: ODI for group I was 29.17	Prospective study  Patients were randomly categorized into two groups  Mean follow up: 36 months (Group I and II) COI: authors declare that they have no competing interests  Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. IRB (Institutional Research Committee) of Jordan University of Science & Technology agreement number 218-2014 was obtained.

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
					<p>(58.34%) with SD = 9.37 and for group II was 21.43 (42.86%) with SD 9.931 (p = 0.840)</p> <p><b>4. SS:</b>  SS of group I was 4.3 (SD = 2.6) and of group II was 4.6 (SD = 2.9) (p = 0.309)</p> <p>At 1 year follow up:  SS value for group I was 5.28 with SD 2.88 and for group II was 7.52 with SD 1.48 (p = 0.012)</p> <p>At 2 years follow up:  SS for group I was 5.40 with SD 2.83 and for group II was 7.68 with SD 1.56 (p = 0.047)</p> <p>At 3 years follow up:  SS mean value for group I was 5.27 with SD 2.94 and for group II was 7.83 with SD 1.64 (p = 0.040)</p> <p><b>5. SINS:</b>  SINS of group I was 13.8 (SD = 2.9) and of group II was 12.8 (SD = 2.9) (p = 0.482)</p> <p>At 1 year follow up:  SINS value for group I was 12.85 with SD 2.88 and for group II was 7.23 with SD 3.37 (p = 0.526)</p>	

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Bornemann, Roessler et al. 2017)  Clinical controlled trial	<p><b>N = 86</b></p> <p><b>Recruiting period:</b> Not reported</p> <p><b>Patient characteristics:</b> 1. Mean age: 65.05±9.35 in RFK group, 63.3±9.57 in RT group</p> <p><b>Inclusion criteria:</b> 1. MM patients with 1 to 6 vertebral compression fractures 2. at least 18 years of age</p> <p><b>Exclusion criteria:</b></p>	Group I (RFK group): Radiofrequency kyphoplasty (RFK) followed by radiation therapy (RT)	Group II (RT group): Radiation therapy (RT) followed by radiofrequency kyphoplasty (RFK)	<ol style="list-style-type: none"> <li>1. Mean vertebral height</li> <li>2. Patient reported pain</li> <li>3. Functional impairment</li> <li>4. Adverse events (cement leakage, additional fractures)</li> </ol>	<p>At 2 years follow up: SINS value for group I was 12.75 with SD 2.67 and for group II was 7.31 with SD 3.43 (p =0.278)</p> <p>At 3 years follow up: SINS mean value for group I was 12.58 with SD 2.75 and for group II was 7.36 with SD = 3.72 a (p = 0.121)</p> <p>At the end of the study (3 years) ODI and SINS showed significant difference between two groups (p = 0.047 and p = 0.002) with less significant difference by using SS (p = 0.180)</p> <p><b>1. Mean vertebral height:</b> In RFK group, the improvement was significant: from baseline 24.86±1.85 mm to postoperative 24.91±1.82 mm (p=0.06)</p> <p>In RT group, the improvement was not significant: from baseline 25.38±1.84 mm to 25.4±1.81 mm</p> <p><b>2. Mean VAS for patient reported pain:</b> At 3 months of follow up, in RFK group, there was VAS reduction: 21.86±10.08 (p&lt;0.001), in RT group, there</p>	Prospective study

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<p>1. additional spinal surgeries or comparable treatments (endoscopic facetectomy, facet joint ablation, etc.) were required during the course of the study</p> <p>2. patients required high-dose steroids (<math>\geq 100</math> mg prednisone or 20 mg dexamethasone per day)</p> <p>3. patients required intravenous (i.v.) pain medication or nerve blocks</p>				<p>was an improvement: <math>21.48 \pm 8.64</math> (<math>p &lt; 0.001</math>)</p> <p>At 6 months of follow up, in RFK group: it worsened with the value of <math>22.2 \pm 10.35</math> (<math>p = 0.06</math>), in RT group: it was constant with the value of <math>21.48 \pm 9.49</math> (<math>p = 1.000</math>)</p> <p><b>3. ODI for functional impairment:</b></p> <p>Improvement was noted during the follow-up period</p> <p>At 3 months of follow up, in RFK group: <math>34.47 \pm 8.1</math> (<math>p &lt; 0.001</math>), in RT group: <math>45.74 \pm 11.94</math> (<math>p &lt; 0.001</math>)</p> <p>At 6 months of follow up, in RFK group: <math>31.49 \pm 8.35</math> (<math>p &lt; 0.001</math>), in RT group: <math>33.3 \pm 4.21</math> (<math>p = 0.01</math>)</p> <p><b>4. Adverse Events:</b></p> <p>Cement leakage within 6 months: 10 cases (16.9%) in RFK group and 6 cases (22.2%) in RT group</p> <p>Additional fractures within 6 months: 5 cases (8.5%) in RFK group and 4 cases (14.8%) in RT group</p>	

## 12.4.4.3.4. Ergänzende Einzelstudien (Strahlentherapie)

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Lang, König et al. 2017)  Retrospective analysis	<b>N = 130</b>  <b>Recruiting period:</b> March 2003-May 2016  <b>Patient characteristics:</b> 1. Multiple myeloma patients 2. 91% of patients had stage III disease 3. median age: 58 years 4. karnofsky performance score $\geq 60$ 5. male (90) + female (40) 6. 92% of patients were treated with additional bisphosphonates  <b>Inclusion criteria:</b> 1. multiple myeloma and osteolytic lesions of the vertebral column  <b>Exclusion criteria:</b> not reported	3-dimensional conformal RT (97% of patients) or Intensity-modulated RT (IMRT)  Patients received a median single dose of 3 Gy (range, 2-3 Gy) and a median total dose of 30 Gy (range, 20-40 Gy)  The dose was applied in 5 fractions per week	n.a.	1. Bone density 2. RT-related AEs 3. Median overall survival	1. <b>Bone density</b> significantly increased at 3 and 6 months after RT compared with BD before RT: $\Delta$ mean(HU) of -16.7 (P= 0.0015) and -40.4 (P < 0.0001), respectively. 2. Acute <b>RT-related</b> grade 1&2 <b>AEs</b> detected in 34% of patients: 21% pulmonary, 29% gastrointestinal, 6% bone marrow, 24% constitutional symptoms, 28% dermatology or skin problems, 2& cardiac problems; late side effects in 23% of patients; no Grade 3-4 AEs (acute or late) 3. <b>Median overall survival:</b> 9.1 years for all patients; 3.4 years for patients with a KPS of $\leq 70\%$ and 9.1 years for patients with a KPS of $\geq 80\%$  The 2-year overall survival rate was 79% for patients with stable lesions and 73% for patients with unstable lesions	Retrospective analysis  Median follow-up period: 12.9 years
(Lee and Lee 2016)	<b>N = 51</b>  <b>Recruiting period:</b> January 2006 - July 2014	Local radiotherapy (LRT)	Not applicable	1. Symptom relief (pain,	<b>1. Symptom relief:</b> Symptom relief was achieved for 85 of 87 lesions (97.7%)	Retrospective study  Median follow-up time of 66.7 weeks

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<p><b>Inclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1. histopathologically confirmed MM with subjective symptoms related to the radiographic findings (from computed tomography or magnetic resonance imaging [MRI]) of an osteolytic lesion, pathologic fracture, and/or a soft tissue-like mass involving the bone and bone marrow</li> <li>2. no prior radiotherapy</li> </ol> <p><b>Exclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1. patients who received radiation treatment to an extraskelletal site</li> <li>2. patients with remnant lesions after tumor resection</li> <li>3. patients with a history of other malignancies</li> </ol>	LRT was delivered at a median total dose of 21 Gy (range, 12 to 40 Gy) in a median of 7 fractions (range, 4 to 20 fractions)		<ol style="list-style-type: none"> <li>1. neurologic impairment)</li> <li>2. Toxicities</li> <li>3. In-field failure-free survival</li> <li>4. Partial response (PR) and complete response (CR)</li> </ol>	<p>Median time to symptom relief : 7 days from the start of LRT (range, 1 to 67 days)</p> <p><b>2. Toxicities:</b> For all patients, most acute and chronic toxicities were mild to moderate. There were no cases of grade 3 or higher complications caused by LRT</p> <p><b>3. In-field failure-free survival:</b> 11 of 85 lesions exhibited in-field failure. The duration of in-field failure-free survival ranged from 1.1 to 450.9 weeks (median, 66.7 weeks). Radiation dose or use of previous and concurrent chemotherapy was not significantly associated with in-field failure for LRT (<math>p = 0.354</math>, <math>0.758</math>, and <math>0.758</math>, respectively)</p> <p><b>4. Partial response (PR) and complete response (CR):</b> In cases of the lesion size &lt;5 cm, PR accounted for 65.2% (<math>n = 15</math>) and CR was 34.8% (<math>n = 8</math>). In cases of the lesion size <math>\geq 5</math> cm, the ratios of PR and CR were 82.8% (<math>n = 24</math>) and 17.2% (<math>n = 5</math>)</p>	<p>COI: no potential conflict of interest relevant to this article was reported</p> <p>Funding: This research was supported by Kyungpook National University Research Fund in 2012</p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Matuschek, Ochtrop et al. 2015)  Retrospective analysis	<p><b>N</b> = 107 patients received radiotherapy (46 patients received also underwent surgery)</p> <p><b>Recruiting period:</b> 1989-2013</p> <p><b>Inclusion criteria:</b> patients with the diagnosis of multiple myeloma</p> <p><b>Exclusion criteria:</b> 1. documentation lacked accurate information 2. suffered from another acutely life threatening neoplasm</p> <p>Indications for radiation: osseous pain, pathologic fractures, neurological symptoms related to osteolytic lesions</p>	Radiotherapy (Total radiation doses varied between 8Gy to 50Gy; median dose 25Gy in 2.5 Gy fractions, 5 times a week)	Not applicable	<ol style="list-style-type: none"> <li>1. Analgesia</li> <li>2. Recalcification</li> <li>3. Toxicities</li> <li>4. Median overall survival</li> </ol>	<p><b>1. Analgesia:</b> 85% of treated patients achieved analgesic effect by irradiation of painful areas. Patients reported complete local pain relief in 31% and partial local Pain relief in 54%.</p> <p>Uivariate analysis: higher total radiation doses (<math>p = 0.023</math>) and higher age (<math>p = 0.014</math>) at the time of radiotherapy were significantly associated with a higher likelihood of pain relief, whereas no significant association was detected for concurrent systemic treatment, type and stage of myeloma and location of bone lesions. The same variables were independent predictors for pain relief in the multivariate analysis</p> <p><b>2. Recalcification</b> Observed in 48% of irradiated bone lesions.</p> <p>Uni- and multivariate analysis: higher radiation doses were significantly associated (<math>p = 0.048</math>) with an increased likelihood of recalcification</p> <p><b>3. Toxicities</b></p>	<p>Retrospective study</p> <p>Patients were followed until 2013</p> <p>COI: authors declare that they have no competing interests</p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Rades, Conde-Moreno et al. 2016)  Retrospective analysis	<p><b>N = 237</b></p> <p><b>Inclusion criteria:</b> 2. patients with motor deficits of the lower extremities in consequence of SCC from vertebral body myeloma</p> <p><b>Exclusion criteria:</b> Not reported</p>	<p>Radiotherapy</p> <p>target volumes included the vertebrae affected by SCC plus on additional vertebra on either side.</p> <p>RT was administered without upfront neurosurgery and performed either as short-course RT (1 x</p>	Not applicable	<p>1. Local control of SCC (defined as freedom from symptomatic in-field recurrence of SCC)</p> <p>2. The effect of</p>	<p>40 of 107 patients (37%) suffered from side effects related to radiotherapy. Of these, 50% showed grade 1, and 47.2% grade 2 side effects. One patient suffered from dysphagia (grade 3 adverse event). No case of radiation induced myelopathy was observed clinically</p> <p><b>4. Median overall survival</b> was 89.1 months for the whole cohort</p> <p><b>5. Local control:</b> The overall response rate at one month was 97% (230 of 237 patients); 53% of patients (n = 126) showed improvement and 44% (n = 104) no further progression; Local control rates at 1, 2 and 3 years were 93%, 82% and 82%, respectively</p> <p><b>6. Motor function</b> Following RT, 88% of the patients were able to walk</p> <p>Of the 69 non-ambulatory patients 44 patients (64%) regained the ability to walk</p>	<p>Retrospective study</p> <p>COI: n.a.</p> <p>Funding: n.a.</p>



Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Rudzianskiene, Inciura et al. 2017)  Randomized controlled trial	N = 101  <b>Recruitment period:</b> 2010-2015  <b>Inclusion criteria:</b> 1. age over 18 years 2. diagnosis of MM according to the International Myeloma Working Group's Criteria 3. presence of painful bone destructions or impending fracture verified by radiographs 4. Karnofsky index (KI) above 40% 5. written informed consent  <b>Exclusion criteria:</b> 1. presence of bone metastases from solid tumours 2. solitary plasmacytoma	8Gy, 5 x 4Gy) or longer-course RT (10 x 3Gy, 15 x 2.5Gy, 20 x 2Gy).  Palliative radiotherapy treatment with 8Gy x 1 fraction  (n=43 patients)	  Palliative radiotherapy treatment with 3 Gy x 10 fractions  (n=58 patients)	RT on motor function (improvement, no further progression, deterioration)  1. Pain relief 2. Use of analgesics 3. Recalcification 4. Quality of life 5. Acute toxicity	  <b>1. Pain relief</b> was obtained in 81/101 patients (80.2%): complete response in 56 (69%) and partial in 25 patients (30.9%) Control Group: median VAS before treatment: 8 (range 2-10), 4 weeks after treatment: 4 (range 0-10), after 12 and 24 weeks: 0 Experimental Group: median VAS before treatment: 8 (range 2-10), 4 weeks after treatment: 3 (range 0-10), after 12 and 24 weeks: 0 Differences not significant  <b>2. Use of analgesics</b> Median MED before RT: 60 (range 10-260) in control group,	Randomised prospective clinical trial  Random sequence generation: n.r.  Blinding: n.r.  ITT: n.r.  Follow-up period: 12 weeks  COI: authors declared that they have no competing interests  Funding: n.r.

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<ul style="list-style-type: none"> <li>3. prior irradiation at the same site</li> <li>4. inability to complete the QoL questionnaires</li> <li>5. patients that could not be monitored</li> </ul>				<p>60 (range 10-210) in experimental group  Median MED 4 weeks post-RT:  10 (range 0-190) in control group, 25 (range 0-270) in experimental group  Median MED 12 and 24 weeks post-RT: 0 in both groups  Differences not significant</p> <p><b>3. Recalcification</b>  found in 32/101 patients (33.7%): complete in 17 (53.2%) and partial in 15 (46.2%)</p> <p><b>4. QoL</b>  Control Group:  QLQ-C30 global health scale: median before RT: 16.7 (0-83.3), after RT: 16.7 (0-83.3); p=0.004  QLQ-C30 symptom scales: before RT: 33.3 (6.8-87.7), after RT: 24.4 (14.2-81.5), p=0.003  QLQ-C30 functional scales: before RT: 75.5 (10-133), after RT: 87.3 (9-133) p=0.017  QLQ-MY20 symptom scales: before RT: 33.3 (15-80), after RT: 33.3 (7.2-76.7), p=0.034  QLQ-MY20 functional scales: before RT: 66.7 (0-133.3), after RT: 77.8 (0-133), p=0.3</p> <p>Experimental group:</p>	

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
					<p>QLQ-C30 global health scale: median before RT: 16.7 (0-75), after RT: 16.7 (0-75); p=0.606</p> <p>QLQ-C30 symptom scales: before RT: 50 (18.5-92.6), after RT: 39.5 (23.5-92.6), p=0.181</p> <p>QLQ-C30 functional scales: before RT: 49.3 (0-133), after RT: 50.3 (0-133) p=0.854</p> <p>QLQ-MY20 symptom scales: before RT: 41.7 (15-95), after RT: 47.2 (24.4-98.3), p=0.94</p> <p>QLQ-MY20 functional scales: before RT: 61.1 (0-133.3), after RT: 61.1 (0-133), p=0.987</p> <p><b>5. Toxicity</b> Evaluated in the first 4 weeks after RT. Side effects were uncommon, low grade and reversible; no significant differences between groups</p>	
(Talamo, Dimaio et al. 2015)  Retrospective analysis	<p><b>N = 149</b></p> <p><b>Recruitment period:</b> 2010-2012</p> <p><b>Patient characteristics:</b> 1. MM patients 2. mean age: 62.3</p> <p><b>Exclusion criteria:</b> Not reported</p>	Radiation therapy	Not applicable	<p>1. Complete and partial pain relief</p> <p>2. OS</p>	<p><b>1. Pain relief</b> Of the 55 patients evaluable for pain relief, complete and partial responses were obtained in 76.4 and 7.2%, respectively The median biological effective edose was 37.5, 36, and 39Gy in patients With complete response, partial response, and stable pain level, Respectively.</p>	<p>Retrospective study</p> <p>median follow-up was 28 months</p> <p>COI: n.r.</p> <p>Funding: n.r.</p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
					<b>2. Median OS</b> 85months (95% CI 49-98)	

12.4.4.3.5. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	Mortality	-	-	-	-2	-	⊕⊕⊕⊖ low
	HTA/SR/RCT, retrospective trials	Morbidity	-	-	-1	-	-1	⊕⊕⊕⊖ moderate
	HTA/SR/RCT, retrospective trials	Harms	-	-	-1	-	-1	⊕⊕⊕⊖ moderate
	RCT	QoL	-1	-	-	-	-	⊕⊕⊕⊖ moderate

Mortality: sehr unpräzise, da Kriterium der optimalen Informationsgröße nicht erfüllt.

Morbidity/Harms: Indirekt, da auch andere Krebspatienten eingeschlossen, verschiedene Studiendesigns

QoL: Verzerrungsrisiko unklar

### 12.4.5. Indikation zur Strahlentherapie (kurativ, symptomatisch)

### 12.4.6. Singulärer Befall (kurativ)

Schlüsselfrage: Wie soll bei lokalem Befall bestrahlt werden (Dosis, Zielvolumen)?

#### 12.4.6.1. Empfehlungen:

„Es **sollte** eine Dosis zwischen 40 – 50 Gy appliziert werden.“

„Eine Behandlung mit einer geringeren Dosis als 40 Gy **soll**, wegen der deutlich geringeren lokalen Kontrollrate, **nicht** durchgeführt werden.“

#### 12.4.6.1.1. Evidenztabellen

##### 12.4.6.1.2. Einzelstudien (Bestrahlungsdosis als prognostischer Faktor)

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenz- klasse
(Barzenje, Kolstad et al. 2018) Retrospective analysis	N= 77 patients (N= 49 patients with SBP N=28 patients with SEP)  Identified from the Oslo University Hospital lymphoma registry  Treated with radiotherapy from 1980 until 2010  field photon beam radiotherapy with a curative intent and with 2 Gy/fraction	Median RT dose of 45.5 Gy	Median RT dose of 40 Gy	1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>Prognostic factor analysis respectively comparing 45.5 Gy vs. 40Gy</li> <li>OS <ul style="list-style-type: none"> <li>HR for SBP: 2.96 (95%-CI: 1.02-8.57)</li> <li>HR for SEP: not significant</li> </ul> </li> <li>PFS <ul style="list-style-type: none"> <li>HR for SBP: not significant</li> <li>HR for SEP: not significant</li> </ul> </li> <li>MM free survival <ul style="list-style-type: none"> <li>HR for SBP: not significant</li> </ul> </li> </ul>	Retrospective analysis  Results from <b>multivariate survival analysis</b>  The authors declared to have no competing intertests

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
	The planning treatment volume included the radiologically visible macrotumour with a sufficient margin, ie, for vertebral SBPs, the 2 adjacent vertebrae were included				<ul style="list-style-type: none"> <li>○ HR for SEP: not significant</li> <li>2. <b>LC:</b> differences between radiation doses not analysed</li> <li>3. <b>Progression to MM:</b> differences between radiation doses not analysed</li> <li>4. <b>Toxicity:</b> differences between radiation doses not analysed</li> </ul>	
(Goyal, Bartley et al. 2018) Retrospective analysis	N= 2816 patients included in analysis Median age: 62 years SBP: 70% SEP: 30%  Patients diagnosed with plasmacytoma from 2000 to 2011	RT < 40 Gy N=703 patients (N=572 with SBP, N=131 with SEP)	RT ≥40 Gy N=2113 patients (N=1476 with SBP, N=637 with SEP)	1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>• OS (≥40 Gy vs. &lt;40 Gy): <ul style="list-style-type: none"> <li>○ HR for total cohort: 0.62 (95%CI: 0.54-0.72)</li> <li>○ HR for SBP: 0.66 (95%CI: 0.56-0.77)</li> <li>○ HR for SEP: 0.49 (95%CI: 0.35-0.67)</li> </ul> </li> <li>2. <b>LC:</b> differences between radiation doses not analysed</li> <li>3. <b>Progression to MM:</b> differences between radiation doses not analysed</li> <li>4. <b>Toxicity:</b> differences between radiation doses not analysed</li> </ul>	Retrospective analysis  Results from <b>multivariate survival analysis</b>  COI : authors declared potential COIs  Funding : This research was funded by the Mayo Clinic Division of Hematology and Oncology Outcomes Research (HONOR) Group. This publication was also supported by the National Cancer Institute of the National Institutes of Health under Award Number K23CA218742.

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
(Jyothirmayi, Gangadharan et al. 1997) Retrospective analysis	N= 23 patients with SPB  Patients treated between 1983 and 1993 at the regional cancer centre, Trivandrum  Mean age: 52 years	RT ≤ 45Gy N=9 patients	RT > 45Gy N= 14 patients	1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>• PFS: <ul style="list-style-type: none"> <li>○ 5-year PFS for ≤ 45Gy: 55%</li> <li>○ 5-year PFS for &gt; 45Gy: 56%</li> <li>○ HR: 1.3; p=0.7</li> </ul> </li> </ul> <b>2. LC:</b> differences between radiation doses not <b>3. Progression to MM:</b> differences between radiation doses not analysed <b>4. Toxicity:</b> differences between radiation doses not analysed	Retrospective analysis Cox proportional hazards model was used to test the independent significance of prognostic factors  COI : no information provided Funding : no information provided
(Kilciksiz, Celik et al. 2008) Retrospective analysis	N= 80 patients with SP included in analysis (n=57 patients with SBP, n=23 patients with SEP) Patients treated between 1991 and 2007  Median age of 54 years	RT ≥ 50 Gy	RT < 50Gy	1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>• <b>10-year OS:</b> 89% for ≥50Gy; median of 7.6 years for &lt;50Gy; p=0.2078</li> <li>• <b>Median PFS:</b> 7.7 years for ≥50Gy, 2.7 for &lt;50Gy; p=0.0299</li> <li>• <b>10-year LRFS:</b> 90% in both groups; p=0.0998</li> <li>• <b>Median MMFS:</b> 7.7 years for ≥50Gy; 3.2 years for &lt;50Gy; p=0.1084</li> </ul> <b>2. LC:</b> differences between radiation doses not <b>3. Progression to MM:</b> differences between radiation doses not analysed <b>4. Toxicity:</b> differences between radiation doses not analysed	Retrospective analysis  Univariate analysis of prognostic factors  COI : no information provided Funding : no information provided

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
(Ozsahin, Tsang et al. 2006) and (Knobel, Zouhair et al. 2006)  Retrospective analysis	N= 258 patients (n=206 with SBP; n= 52 patients with SEP)  Patients treated between 1977 and 2001 Median age: 60 years (range: 18-95)  Additional treatments in SBP patients: <ul style="list-style-type: none"> <li>33% (n=69) of patients received surgical treatment</li> <li>16% (n=32) of patients received chemotherapy</li> </ul> Additional treatments in SEP patients: <ul style="list-style-type: none"> <li>48% (n=25) of patients received surgical treatment</li> </ul> a patient was considered to have a bone SP if there was a biopsy-proven solitary bone lesion; <10% plasma cells in the bone-marrow biopsy; no additional pathological lesions in the skeletal diagnostic work-up; no anemia; and normal blood chemistry.	RT ≥ 50 Gy: n=75 patients (n=56 patients with SBP)  RT ≥ 40 Gy and <50Gy: n=76 patients (n= 65 patients with SBP)  RT ≥ 30 Gy and <40 Gy: n= 70 patients (n=55 patients with SBP)  RT <30 Gy: n= 27 patients (n=25 patients with SBP)  No RT: n=10 patients (n=5 patients with SBP)		1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>10-year OS: <ul style="list-style-type: none"> <li>RT ≥ 50 Gy: 53% (95%CI: 36-70) (SBP: 47% (95%CI: 28-66))</li> <li>RT ≥ 40 Gy and &lt;50Gy: 57% (95% CI: 39-75) (SBP: 55% (95%CI:34-76))</li> <li>RT ≥ 30 Gy and &lt;40 Gy: 53% (95%CI: 38-68) (SBP: 46% (95%CI: 28-46))</li> <li>RT &lt;30 Gy: 38% (95%CI: 14-62) (SBP:37% (95%CI: 13-61))</li> <li>No RT: 40% (95%CI: 0-96) (SBP: 0%)</li> </ul> </li> <li>10-year DFS: <ul style="list-style-type: none"> <li>RT ≥ 50 Gy: 32% (95%CI: 18-46) (SBP: 26% (95%CI: 10-42))</li> <li>RT ≥ 40 Gy and &lt;50Gy: 31% (95%CI: 13-49) (SBP: 25% (95%CI:6-44))</li> <li>RT ≥ 30 Gy and &lt;40 Gy: 37% (95%CI: 22-52) (SBP: 32% (95%CI: 16-48))</li> <li>RT &lt;30 Gy: 37% (95%CI: 14-51) (SBP: 17% (95%CI: 0-43))</li> <li>No RT: 0% (SBP: 0%)</li> </ul> </li> </ul>	Retrospective analysis SBP patients were separately reported in (Knobel, Zouhair et al. 2006)  Univariate analysis of prognostic factors  COI: The author(s) declared that they have no competing interests.  Funding : no information provided



Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
					<p><b>2. LC (10-year LC):</b></p> <ul style="list-style-type: none"> <li>• RT ≥ 50 Gy: 71% (95%CI: 59-89) (SBP: 82% (95%CI: 68-96))</li> <li>• RT ≥ 40 Gy and &lt;50Gy: 73% (95%CI: 51-95) (SBP: 67% (95%CI:40-94))</li> <li>• RT ≥ 30 Gy and &lt;40 Gy: 90% (95%CI: 83-97) (SBP: 90% (95%CI: 81-99))</li> <li>• RT &lt;30 Gy: 96% (95%CI: 89-100) (SBP: 96% (95%CI: 88-100))</li> <li>• No RT: 36 (95%CI: 4-68) (SBP: 0%)</li> </ul> <p><b>3. Progression to MM (10-year pro- gression to MM):</b></p> <ul style="list-style-type: none"> <li>• RT ≥ 50 Gy: 63% (95%CI: 49-77) (SBP:71% (95%CI: 5-87))</li> <li>• RT ≥ 40 Gy and &lt;50Gy: 69% (95%CI: 50-88) (SBP: 78% (95%CI:59-97))</li> <li>• RT ≥ 30 Gy and &lt;40 Gy: 58% (95%CI: 43-73) (SBP: 63% (95%CI: 47-79))</li> <li>• RT &lt;30 Gy: 60% (95%CI: 36-84) (SBP: 81% (95%CI: 53-100))</li> <li>• No RT: 100% (SBP: 33% (95%CI: 0-86))</li> </ul> <p><b>4. Toxicity:</b> differences between radia- tion doses not analysed</p>	
(Sasaki, Yasuda et al. 2012)	N=67 patients with SEP in the head and neck regions	RT ≤ 40Gy (n=13) vs.		1. Survival 2. LC	<p><b>1. Survival (OS):</b></p> <ul style="list-style-type: none"> <li>• RT ≤ 40Gy vs. &gt;40.1 Gy: p=0.82</li> <li>• RT ≤45Gy vs. &gt;45.1 Gy: p=0.73</li> </ul>	Retrospective analysis

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
Retrospective analysis	Diagnosed between 1983 and 2008 at 23 Japanese institutions  Median age: 64 years (range: 12-83)	>40.1 Gy (n=54)  RT ≤45Gy (n=17) vs. >45.1 Gy (n=50)  RT ≤ 50 Gy (n=56) vs. >50.1 Gy (n=11)		3. Progres- sion to MM 4. Toxicity	<ul style="list-style-type: none"> <li>• RT ≤ 50 Gy vs. &gt;50.1 Gy: p=0.72</li> </ul> 2. <b>LC:</b> differences between radiation doses not 3. <b>Progression to MM:</b> differences between radiation doses not analysed 4. <b>Toxicity:</b> differences between radiation doses not analysed	Not described how prognostic factor analysis was conducted COI: not declared Funding: no information provided
(Shih, Dunn et al. 1995)	n=22 patients with SBP	RT >40 Gy vs. <40Gy		1. Sur- vival	<b>1. Survival:</b>	Retrospective analysis
Retrospective analysis	patients diagnosed between 1978 and 1993 in Taiwan  SP were defined as: (1) having a radiologically solitary lytic bone lesion or soft-tissue mass which was histologically proven to be a plasmacytoma, (2) less than 5% plasma cells in the bone marrow at diagnosis and (3) no anaemia, hypercalcaemia or impairment of renal function. Patients with M-protein in the serum or urine at	RT ≥45 Gy vs. < 45Gy  RT ≥ 50 Gy vs. <50 Gy		2. LC 3. Progres- sion to MM 4. Tox- icity	<ul style="list-style-type: none"> <li>• OS:               <ul style="list-style-type: none"> <li>○ RT &gt;40 Gy vs. &lt;40Gy: p=0.50</li> <li>○ RT ≥45 Gy vs. &lt; 45Gy: p=0.99</li> <li>○ RT ≥ 50 Gy vs. &lt;50 Gy: p=0.74</li> </ul> </li> <li>• DFS:               <ul style="list-style-type: none"> <li>○ RT &gt;40 Gy vs. &lt;40Gy: p=0.24</li> <li>○ RT ≥45 Gy vs. &lt; 45Gy: p=0.26</li> <li>○ RT ≥ 50 Gy vs. &lt;50 Gy: p=0.26</li> </ul> </li> </ul> <b>2. LC (Radiation dose as prognostic factor for relapse):</b> <ul style="list-style-type: none"> <li>• RT &gt;40 Gy vs. &lt;40Gy: p=0.55</li> <li>• RT ≥45 Gy vs. &lt; 45Gy: p=0.25</li> <li>• RT ≥ 50 Gy vs. &lt;50 Gy: p=0.59</li> </ul>	Not described how prognostic factor analysis was conducted COI: not declared Funding: no information provided

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
	presentation were not ex- cluded from the study if they met the above criteria.				<p>3. <b>Progression to MM:</b> differ- ences between radiation doses not analysed</p> <p>4. <b>Toxicity:</b> differences between radiation doses not analysed</p>	
(Tournier- Rangeard, Lapeyre et al. 2006)  Retrospective analysis	<p>N=17 patients with SEP in the head and neck</p> <p>Average age: 62,4 years (range: 39-80)</p> <p>Patients were treated be- tween 1979 and 2003 in France</p>	<p>RT ≥ 40 Gy (n=12 pa- tients) vs. &lt; 40 Gy (n=5 patients)</p> <p>RT ≥ 45 Gy (n=9 pa- tients) vs. &lt; 45 Gy (n=8 patients )</p>		<p>1. Survival</p> <p>2. LC</p> <p>3. Progres- sion to MM</p> <p>4. Toxicity</p>	<p>1. <b>Survival:</b></p> <ul style="list-style-type: none"> <li>• 5-year DFS: <ul style="list-style-type: none"> <li>○ 71.4% for patients treated with RT ≥ 40 Gy vs. 40% for patients treated with &lt; 40 Gy; p=0.18</li> <li>○ 87.5% for patients treated with RT ≥ 45 Gy vs. 37.5% for patients treated with &lt; 45 Gy; p=0.056</li> </ul> </li> <li>• 10-year DFS: 65.6% for patients treated with RT ≥ 45 Gy vs. 37.5% for patients treated with &lt; 45 Gy; p=0.056</li> </ul> <p>2. <b>LC (5-year LC):</b></p> <ul style="list-style-type: none"> <li>• 90% for patients treated with RT ≥ 40 Gy vs. 40% for patients treated with &lt; 40 Gy; p=0.031</li> <li>• 100% for patients treated with RT ≥ 45 Gy vs. 50% for patients treated with &lt; 45 Gy; p=0.034</li> </ul>	<p>Retrospective analysis</p> <p>Prognostic factors were an- alyzed with the log- rank test and Fisher's exact test</p> <p>COI: not declared Funding: no information pro- vided</p>

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
(Wilder, Ha et al. 2002) Retrospective analysis	N= 60 patients with SBP  Median age: 54 years (range: 29-77)  Patients treated between 1965 and 2000  75% of patients had a myeloma protein in blood and/or urine	Arm 1: RT 50.0-70.1 Gy (n= 28 patients)	Arm 2: RT 30.0-49.9 Gy (n=32 patients)	1. Survival 2. LC 3. Progression to MM 4. Toxicity	<ul style="list-style-type: none"> <li>No statistically difference was seen for local control for patient who received a dose <math>\geq 40</math> Gy vs. a dose <math>\geq 45</math> Gy (p=0.39).</li> </ul> 3. <b>Progression to MM:</b> differences between radiation doses not analysed 4. <b>Toxicity:</b> differences between radiation doses not analysed	Retrospective analysis  Univariate analysis of prognostic factors  COI: not declared Funding: no information provided

## 12.4.6.1.3. Einzelstudien (prospektive Studien)

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Aviles, Huerta-Guzman et al. 1996)  RCT	N = 56 patients with SBP  Patients diagnosed between 1982 and 1989  In all patients treatment was delivered at a rate of 200 cGy per fraction, per 5-day week  Criteria for diagnosis of SBP: (a) radiologic solitary bone lesion with histological confirmation of plasmacytomata; (b) absence of myeloma cells in bone marrow; (c) absence of anaemia, hypercalcaemia and renal involvement; (d) less than 2.0 g/dl M-protein in the serum	RT+MP: Local RT with dose ranging from 40-50 Gy + followed by MP every 6 weeks 3 years  N= 25 patients  MP treatment: 6 mg/m <sup>2</sup> PO Melphalan, daily, days 1 to 4 and prednisone 40 mg/m <sup>2</sup> PO days 1 to 4	RT only: Local RT with dose ranging from 40-50 Gy  N=28 patients	1. Survival 2. LC 3. progression to MM 4. Toxicity	<b>1. Survival:</b> • <b>DFS:</b> ○ Median not reached ○ 22 patients remain alive in RT+MP arm vs. 13 patients in RT only arm (p<0.01)  <b>2. LC:</b> not reported <b>3. progression to MM:</b> • 12% of patients in RT+MP vs. 54% of patients in RT only <b>4. Toxicity:</b> • RT was well tolerated; no local or systemic toxicities were evident after median follow-up of 98 months • MP was well tolerated; no evidence of secondary neoplasms or acute leukaemia has been observed	Randomization : by envelope assignment  Blinding : not described  Median follow-up : 8.9 years (range : 6.0-14.8) No patients lost to follow-up  COI: not declared Funding: no information provided
(Wiazane, Chargari et al. 2013)  Prospective trial	N= 6 patients with SP  Median age: 59,5 years (range: 50-74)  Patients were treated between 2009 and 2011	Helical tomotherapy (40Gy in 20 fractions) concomitantly with systemic tar-		1. Acute toxicity profile 2. Reponse rates 3. Symptom relief	<b>1. Toxicity</b> No acute or delayed toxicity more than grade 1 was reported at 6 wk, 4 mo, and 12 mo after treatment.  <b>2. Response rates</b>	Clinical, biological and radiological follow-ups at 6 weeks, 4 months, and 12 months after initial therapy  COI: not declared

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
		<p>geted treatment (n=4 patients received RD out of which 2 received additional zoledronic acid; n=2 patients received VD)</p>			<ul style="list-style-type: none"> <li>• Four patients experienced complete radiological response and four had partial response on PET/scan.</li> <li>• With a median follow-up of 18 mo (range, 11-22), five of the six patients were free of clinical, radiological, or biological progression.</li> <li>• Four patients had achieved a radiological response and five patients had a complete relief of symptoms 4 mo after <ul style="list-style-type: none"> <li>• treatment.</li> </ul> </li> </ul> <p><b>3. Symptom relief</b></p> <ul style="list-style-type: none"> <li>• Five patients had a complete relief of symptoms 4 mo after treatment.</li> <li>• Of five patients who initially suffered from pain, three experienced a complete relief of symptoms 6 wk after treatment and all of them were relieved after 4 mo.</li> </ul>	<p>Funding: no information provided</p>

## 12.4.6.1.4. Einzelstudien (median radiation &lt;40Gy)

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Tsang, Gospodarowicz et al. 2001)	N= 46 patients with SP (n=32 with SBP, n= 14 with SEP)	All patients were treated with RT.		1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>8-year actuarial survival rate: 65%</li> <li>8-year actuarial DFS rate: 44%</li> </ul> <b>2. LC:</b> <ul style="list-style-type: none"> <li>Eventual local control rate was 40/46 (crude rate: 87%)</li> <li>8-year actuarial local-disease free rate: 83%</li> <li>Radiation dose was not associated with local failure (8-year local disease-free rates: 100% for <math>\leq 30</math> Gy, 81% for 35 Gy, and 80% for <math>\geq 40</math> Gy, <math>p= 0.50</math>) or progression to myeloma</li> <li>Bulky tumors (<math>\geq 5</math> cm) had a much lower local control rate than the smaller tumors</li> </ul> <b>3. Progression to MM:</b> <ul style="list-style-type: none"> <li>8-year actuarial MFR: 50%</li> </ul> <b>4. Toxicity:</b> not reported	Retrospective analysis  COI: not declared Funding: no information provided
Retrospective analysis	A patient was considered to have SP if the following criteria were satisfied at presentation: a histologically-confirmed single lesion, normal bone marrow biopsy (, 10% plasma cells), negative skeletal survey, no anemia, and normal calcium and renal function.	Patients were treated once daily, 5 days a week, with a median dose per fraction of 2.33 Gy (range 1.75–4). The most frequent regimens were 35 Gy in 15–20 daily fractions over a period of 3–4 weeks  N=41 patients received RT alone, and n=5 received combined modality therapy (MP)				

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
		in 4, and $\alpha$ -interferon in 1)				

#### 12.4.6.1.5. Einzelstudien (median radiation 40Gy-50Gy)

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Le Ray, Belin et al. 2018)  Retrospective analysis	N= 28 patients with SBP (Patients were treated with IMRT (n=26) or 2D-RT (n=2))  Patients treated between 2003 and 2013  All patients had a diagnosis of histologically proven SBP obtained by a surgical biopsy without bone marrow involvement as defined by bone marrow plasma cell count less than 5%.  Absence of additional bone lesions at diagnosis was assessed by whole-body skeletal X-ray associated with more sensitive techniques such as MRI and either CT or PET-CT.	Group 1 : N=15 patients were treated by 40Gy of normofractionated RT	Group 2: N=13 patients were treated with IMRT (40Gy) and concomitant short-course IMiD or PI therapy	1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>OS at 4 years: 95% (95%CI: 58.7-100); not different between groups</li> <li>PFS at 48 months: 50.3% (95%CI: 29.8-84.6) in Group 1 vs. 80% (95%CI: 58.7-100) in Group 2; p=0.032</li> </ul> <b>2. LC:</b> <ul style="list-style-type: none"> <li>All patients achieved local control of the plasmacytoma</li> <li>no local relapse was observed in either group</li> <li>Group 1: 10 patients (66%) had a relapse of the plasma cell malignancy and five patients developed another SBP during follow-up</li> <li>Group 2: 2 patients (13%) had relapse and one patient developed another SBP during follow-up</li> </ul> <b>3. Progression to MM:</b> <ul style="list-style-type: none"> <li>Group 1: five patients (33%) developed MM</li> </ul>	Retrospective analysis  median Follow-up : 52 months (range : 7-99)  COI : Disclosure forms provided by the authors are available online at <a href="https://doi.org/10.1080/10428194.2017.1393667">https://doi.org/10.1080/10428194.2017.1393667</a> .  Funding : no information provided.



Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	Patients presented no CRAB and/or myeloma defining events				<ul style="list-style-type: none"> <li>Group 2: one patient developed MM</li> </ul> <p><b>4. Toxicity:</b></p> <ul style="list-style-type: none"> <li>Increased hematological toxicity was observed in Group 2 compared to Group 1.</li> <li>Most events were grade 1-2</li> <li>four patients in Group 2 presented grade 3 hematological toxicity (neutropenia, lymphopenia)</li> <li>one patient with grade 3 lymphopenia in Group 1.</li> <li>No grade 4 toxicities occurred</li> <li>One patient experienced deep vein thrombosis with Lenalidomide despite aspirin prophylaxis</li> <li>one patient discontinued lenalidomide after three cycles because of superficial hematomas while receiving enoxaparin prophylaxis.</li> </ul>	
(Gagliardi, Losa et al. 2013)  Retrospective analysis	N= 4 patients with clival SP  Mean age at diagnosis: 57 years (range: 50-68)  Patients treated between 1989 and 2012	Surgical resection of the tumor followed by adjuvant RT  Median RT dose: 45 Gy  Median dose per fraction: 1.8 Gy		<ol style="list-style-type: none"> <li>survival</li> <li>LC</li> <li>progression to MM</li> <li>Toxicity</li> </ol>	<p><b>1. Survival:</b></p> <ul style="list-style-type: none"> <li>3 patients were still alive at last follow-up</li> <li>Mean OS: 54 months (range: 9-165)</li> <li>Mean PFS after surgery: 51.7 months (range: 13-165)</li> </ul> <p><b>2. LC: not reported</b></p> <p><b>3. Progression to MM:</b></p> <ul style="list-style-type: none"> <li>One patient developed MM 13 months after surgery and underwent systemic chemotherapy</li> </ul>	Retrospective analysis  Average follow-up: 54 months (range: 9-165 months)  The authors declared to have no conflicts of interest

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
					with cyclophosphamide-vincristine-doxorubicin-methylprednisolone and subsequent bone marrow transplantation <ul style="list-style-type: none"> <li>The patient died 22 months after surgery</li> </ul> 4. <b>Toxicity:</b> not reported	Funding: no information provided
(Suh, Suh et al. 2012)  Retrospective analysis	N=38 patients with SP (22 patients with SBP; 16 patients with SEP)  Median age: 55 years (range: 15-82)  Patients were diagnosed between 1996 and 2010	All patients received RT (35 patients received definitive RT; 3 patients received RT post-surgery)  Median RT dose: 45 Gy (range: 30-54Gy)  Median dose per fraction: 1.8 Gy (range: 1.8-3)  13 patients were additionally treated with chemotherapy (8 pa-		1. Survival 2. LC 3. Progression to MM 4. toxicity	1. <b>survival:</b> <ul style="list-style-type: none"> <li>OS:                             <ul style="list-style-type: none"> <li>5-year OS: 78% (SEP: 87.1% vs. SBP: 70%)</li> <li>10-year OS: 54% (SEP: 87.1% vs. SBP: 33.3%)</li> <li>Differences between SEP and SBP were not statistically significant (p=0.11)</li> </ul> </li> <li>MMFS:                             <ul style="list-style-type: none"> <li>5-year MMFS: 51.9% (SEP: 71.2% vs. SBP: 36.4%)</li> <li>10-year MMFS: 35.4% (SEP: 71.2% vs. SBP: 0%)</li> <li>SBP progressed more frequently to MM compared to SEP (p=0.02)</li> <li>Median time of MMS: 36 months for SBP; not determined for SEP due to low progression rate</li> </ul> </li> <li>PFS:                             <ul style="list-style-type: none"> <li>5-year PFS: 43%</li> <li>10-year PFS: 25%</li> </ul> </li> </ul>	Retrospective analysis  Median follow-up: 50 months (range: 8-142)  COI: All authors have no conflict of interest to declare.  Funding: no information provided

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
		tients received MP, 5 patients received VAD )			<ul style="list-style-type: none"> <li>○ Patients with SPB demonstrated worse PFS rates compared with SEP; difference was not statistically significant (p=0.16)</li> </ul> <p>2. <b>LC:</b></p> <ul style="list-style-type: none"> <li>• 31 patients (82%) achieved CR, 7 patients (18%) PR</li> <li>• 5- and 10-year LC: 81%; no statistically significant differences between SEP and SBP (p=0.59)</li> <li>• Dose-response relationship was observed for SBP patients: 10-year LC of 100% for RT &gt;40Gy vs. 60% for RT &lt;40Gy; p=0.04</li> </ul> <p>3. <b>Progression to MM:</b></p> <ul style="list-style-type: none"> <li>• Median time to MM progression <ul style="list-style-type: none"> <li>○ 45 months (range: 8-142) for SEP</li> <li>○ 25 months (range: 4-108) for SBP</li> </ul> </li> </ul> <p>4. <b>Toxicity:</b></p> <ul style="list-style-type: none"> <li>○ Mild conjunctivitis (Grade 1) occurred in 2 patients with tumors in the paranasal sinus.</li> <li>○ Mucositis was observed in 8 patients: 2 patients had Grade 1 mucositis, while 6 patients had Grade 2 mucositis.</li> <li>○ Radiation dermatitis occurred in 28 patients</li> <li>○ all patients experienced mild erythema or dry desquamation</li> </ul>	

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Reed, Shah et al. 2011)	N= 84 patients with SP (59 with SBP and 25 with SEP)	All patients received definitive megavoltage radiation, which was delivered as 3-D conformal radiation or IMRT		1. survival 2. LC 3. Progression to MM 4. Toxicity	<p>that did not require medical intervention</p> <ul style="list-style-type: none"> <li>Two patients with tumors in the abdominal cavity experienced mild abdominal pain.</li> <li>1 patient with SBP in the lumbar vertebrae (L1) presented with pancreatic cancer 6 years after completion of RT</li> </ul>	
Retrospective analysis	<p>Median age: 56 years (range: 19-92)</p> <p>Patients were diagnosed between 1988 and 2008</p> <p>Diagnosis was based on the following criteria:                      1) biopsy-proven plasma cell neoplasm                      2) monoclonality of plasma cells determined by immunohistochemical staining for kappa and lambda light chains                      3) a bone marrow aspirate smear with &lt;10% plasma cells and a bone marrow biopsy specimen with no evidence of plasma cell nodules</p>	<p>median RT dose: 45 Gy (range: 36-53.4)</p> <p>given in 1.8 to 2.0 Gy fractions</p> <p>Adding 3-cm margins around the GTV inside</p>			<p><b>1. Survival:</b></p> <ul style="list-style-type: none"> <li>5-year OS: 78% (76% for SBP vs. 85% for SEP; p=0.274)</li> </ul> <p><b>2. LC:</b></p> <ul style="list-style-type: none"> <li>7 patients had local progressive disease</li> <li>5-year LC rate: 92%</li> </ul> <p><b>3. Progression to MM:</b></p> <ul style="list-style-type: none"> <li>38 patients (45%) developed MM</li> <li>5-year probability of MM occurrence: 47% (56% for SBP vs. 30% for SEP; p=0.021)</li> <li>5-year probability of MM occurrence of 60% for patients who had serum myeloma protein detected at diagnosis vs. 39% for patients without serum myeloma protein (p=0.016)</li> </ul> <p><b>4. Toxicity:</b></p> <ul style="list-style-type: none"> <li>Xerostomia was common in patients who received RT to the head and neck.</li> <li>No patient experienced grade 4 or 5 late radiation toxicity according to the Radiation Therapy</li> </ul>	<p>Retrospective analysis</p> <p>Median follow-up from start of RT: 64 months (range: 4-208)</p> <p>COI. The authors made no disclosures</p> <p>Funding: no specific funding was disclosed</p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	4) normal findings on skeletal survey  The presence of a monoclonal band on serum protein electrophoresis, Bence-Jones protein in urine, or radiologic evidence of local bone destruction as a result of direct extension of tumor mass did not exclude any patient from this analysis	the bone or 2-cm margins around the GTV in the soft tissue created clinical tumor volumes.			Oncology group/European Organization for Research and Treatment of Cancer late-effects scoring system.	
(Krause, Hillengass et al. 2011)  Retrospective analysis	N=18 patients with SP (10 patients with SBP, 8 patients with SEP)  Median age: 60.9 years (range: 35-81)  Patients were treated between 1995 and 2008  Inclusion criteria were: one solitary lesion confirmed by histology (fine-needle or open biopsy), verification of localized disease by whole-body MRI or CT or plain film skeletal survey, normal serum calcium, blood count and renal function, <10% plasma cells in	All patients were treated with RT (10 received definitive RT, 8 post-surgery)  Median RT dose: 45 Gy (range: 30-50.4)  Applied in single fractions ranging from 1.8-2.5 Gy		1. Survival 2. LC 3. Progression to MM 4. Toxicity	1. <b>Survival:</b> ○ 4 patients died during follow-up ○ 2-year OS: 87.5% ○ 5- and 10-year OS: 77.8%, respectively ○ No statistically significant differences between SBP and SEP (p=0.234) 2. <b>LC:</b> ○ One patient experienced local relapse 7 years after development of MM and 8 years after initial RT 3. <b>Progression to MM:</b> ○ Nine patients (50%) progressed to MM ○ Median time to progression: 34.3 months (range: 2-154) ○ Progression occurred in the majority of cases (6 patients) within one year of first diagnosis	Retrospective analysis  Median follow-up: 47 months (range: 6-67)  COI: not declared  Funding: no information provided

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	bone marrow biopsy, normal serum protein electrophoresis, and no prior treatment for plasmacytoma.				<ul style="list-style-type: none"> <li>2- and 5-year MMFS: 59.1%, respectively</li> <li>10-year MMFS: 49.2%</li> <li>25% of SEP progressed to MM vs. 70% of SBP (p=0.015)</li> </ul> <p><b>4. Toxicity:</b></p> <ul style="list-style-type: none"> <li>local radiotherapy was tolerated very well</li> <li>No grade III-IV toxicity occurred</li> <li>Patients with irradiation of the head and neck mainly suffered from mild acute mucositis and skin erythema.</li> <li>Patients treated for bone lesions reported no side effects</li> <li>None of the patients developed secondary malignancies</li> </ul>	
(Dagan, Morris et al. 2009)  Retrospective analysis	<p>N=32 patients with SP (22 with SBP; 10 with SEP)</p> <p>Patients were treated between 1963 and 2006</p> <p>Diagnosis of SP defined as: (1) a single biopsy-confirmed lesion of neoplastic-appearing plasma cells (2) no clinical or radiographic evidence secondary sites of disease; either a skeletal survey or bone scan were required for the radiographic evaluation</p>	<p>All patients received RT (25 as definitive treatment; 7 post-surgery)</p> <p>Median RT dose: 42.7 Gy (range: 15-54)</p> <p>Once daily fractions over a median of 25</p>		<ol style="list-style-type: none"> <li>Survival</li> <li>LCI</li> <li>Progression to MM</li> <li>Toxicity</li> </ol>	<p><b>1. Survival:</b></p> <ul style="list-style-type: none"> <li>10 patients were alive at the time of analysis</li> <li>5-year actuarial OS: 87%</li> <li>10-year actuarial OS: 65% (SBP: 55% vs. SEP: 80%; p=0.018)</li> <li>5-year cause specific survival: 90%</li> <li>10-year cause specific survival: 77% (SBP: 65% vs. SEP: 100%; p=0.006)</li> </ul> <p><b>2. LC:</b></p> <ul style="list-style-type: none"> <li>LC was observed in 28 patients (88%)</li> <li>5- and 10-year actuarial LC: 87%, respectively (SBP vs. SEP, p=0.167)</li> </ul>	<p>Retrospective analysis</p> <p>Median follow-up: 10.1 years (range: 1-33)</p> <p>COI: The authors have no conflicts of interest to declare</p> <p>Funding: no information provided</p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<p>(3) bone marrow biopsy with less than 10% plasma cells; and (4) absence of hypercalcemia, significant cytopenia, renal dysfunction, prior treatment for plasma cell neoplasm, or second malignancy.</p> <p>Patients with elevated immunoglobulin levels, abnormal serum protein electrophoresis, or urine protein electrophoresis were not excluded.</p>	fractions (range: 1-32)			<p><b>3. Progression to MM:</b></p> <ul style="list-style-type: none"> <li>17 patients (53%) progressed to MM</li> <li>5-year actuarial MMFS: 58%</li> <li>10-year actuarial MMFS: 50% (SBP: 30% vs. SEP: 90%; p=0.009)</li> <li>15 SBP-patients (68%) progressed to MM vs. 2 SEP-patients (20%); p=0.01</li> </ul> <p><b>4. Toxicity:</b></p> <ul style="list-style-type: none"> <li>Treatment was tolerated with few complications.</li> <li>One patient with SEP involving the nasopharynx experienced severe mucositis requiring a brief treatment break on the 13th day of RT.</li> <li>One patient with SEP of the maxillary sinus experienced serous otitis media requiring placement of a myringotomy tube.</li> <li>One patient experienced a deep vein thrombosis while receiving treatment.</li> <li>One patient experienced radiation-induced fibrosis resulting in limited upper-extremity range of motion.</li> <li>2 Patients with SEP experienced radiation induced retinopathy.</li> <li>with conventional RT fields.</li> <li>There were 2 cases of secondary malignancies that may have been treatment related. One patient was diagnosed with acute myeloid</li> </ul>	

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Coskun, Er et al. 2005)	N=23 patients with SP (18 with SBP, 5 with SEP)	Surgical resection followed by 45Gy RT in average.			leukemia approximately 5 years after treatment with a dose of 45 Gy. He underwent a stem cell transplant and died of treatment-related complications. A second patient developed diffuse large B-cell lymphoma in the cervical lymph nodes at the margin of the previous treatment field 10-years after treatment to 45 Gy with Co-60 for a maxillary sinus SEP.	
Retrospective analysis	Median age: 58 years (range: 46-72)  Diagnosed between 1990 and 2002	MP or VAD were used in the treatment of patients who had changed into MM.		1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>8 patients died during follow-up</li> <li>3-year OS: 54%</li> <li>5-year OS: 27%</li> <li>Median OS: 49 ± 17.36 months</li> <li>3-year PFS: 45.6%</li> <li>5-year PFS: 22.8%</li> <li>Median PFS: 18 ± 6.55 months</li> </ul> <b>2. LC:</b> <ul style="list-style-type: none"> <li>Local relapse occurred in 1 patient</li> </ul> <b>3. Progression to MM:</b> <ul style="list-style-type: none"> <li>8 patients progressed to MM (6 SBP patients, 2 SEP patients)</li> </ul> <b>4. Toxicity:</b>	Retrospective analysis  Median follow-up: not stated  COI: not disclosed  Funding: no information provided
(Chao, Gibbs et al. 2005)	N= 16 patients with SEP	All patients were treated with local RT, with two patients also receiving				
Retrospective analysis	Median age: 59.1 years (range: 34-82)			1. Survival 2. LC	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>At the time of data analysis, eight patients (50%) were alive and eight (50%) had died.</li> <li>10-year OS: 54%</li> <li>10-year MMFS: 75%</li> </ul>	Retrospective analysis  Median follow-up: 66 months (12-211)



Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Liebross, Ha et al. 1999)	<p>Patients were treated between 1980 and 1999</p> <p>Inclusion criteria:</p> <p>(i) histological confirmation of clonal plasma cells involving a single extramedullary site with or without lymph node involvement</p> <p>(ii) no histological evidence of bone marrow involvement</p> <p>(iii) no evidence of distant bone lesion on radiographic skeletal survey (bone erosions adjacent to the primary thought to be due to contiguous involvement were permitted)</p> <p>(iv) no anaemia, hypercalcaemia or renal impairment due to plasma cell dyscrasia</p>	<p>chemotherapy</p> <p>median RT dose: 45 Gy (range: 40-50.4)</p> <p>delivered at 1.8-2 Gy fractions per day</p>		<p>3. Progression to MM</p> <p>4. Toxicity</p>	<p>2. <b>LC:</b></p> <ul style="list-style-type: none"> <li>LC was achieved in all patients</li> <li>2 patients developed regional recurrences outside the radiation field</li> </ul> <p>3. <b>Progression to MM:</b></p> <ul style="list-style-type: none"> <li>Five of 13 patients with non-secretory disease progressed to MM, while all three patients with an initial M protein remained free of MM (p =0.91)</li> <li>Time to progression: after a mean of 21 months following RT (range: 7-41 months)</li> </ul> <p>4. <b>Toxicity:</b> not reported</p>	<p>- Funding: None</p> <p>- Potential conflicts of interest: None</p>
	N=22 patients with SEP	RT alone was given to 18 patients		<p>1. Survival</p> <p>2. LC</p>	<p>1. <b>Survival:</b></p> <ul style="list-style-type: none"> <li>median survival from diagnosis: 9.5 years</li> </ul>	Retrospective analysis

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
Retrospective analysis	<p>Median age: 55 years (range: 31-80)</p> <p>Patients were diagnosed between 1963 and 1996</p> <p>The diagnosis was based on histologic confirmation of a single extramedullary mass of plasma cells with no evidence of MM on bone survey or of marrow plasmacytosis of more than 5%. Additional pretreatment evaluations consisted of electrophoreses of serum and urine concentrates, including immunoelectrophoresis, immunofixation and immunoglobulin quantitations as these procedures became available</p>	<p>2 patients received surgery plus adjuvant RT</p> <p>2 patients received surgery alone</p> <p>Median RT dose: 50Gy (range: 40-60)</p> <p>Median fraction size: 200 cGy</p>		<p>3. Progression to MM</p> <p>4. Toxicity</p>	<ul style="list-style-type: none"> <li>5-year actuarial OS: 78%</li> <li>10-year actuarial OS: 68%</li> </ul> <p><b>2. LC:</b></p> <ul style="list-style-type: none"> <li>LC was achieved in 21 patients (95%)</li> <li>One patient had local recurrence 16 months after resection of cervical lymph node plasmaytoma.</li> <li>No patient developed recurrence in a regional node following RT</li> </ul> <p><b>3. Progression to MM:</b></p> <ul style="list-style-type: none"> <li>MM developed in 7 patients (32%)</li> <li>Median time to MM progression: 22 months (range: 6-52) after start of local treatment</li> <li>five of 17 patients with non-secretory disease and two of five patients with myeloma protein observed at initial presentation developed MM</li> <li>There was no relationship between radiation dose and the later occurrence of multiple myeloma; while four of 15 patients who received 50±60 Gy developed MM, one of five patients who received 40±49 Gy had progressive disease.</li> <li>5-year actuarial rate of freedom from progression to MM: 56%</li> </ul> <p><b>4. Toxicity:</b></p> <p>No significant acute or late radiation toxicity was observed</p>	<p>Median follow-up for living patients: 44 months (range: 11-218)</p> <p>COI: not declared</p> <p>Funding: no information provided</p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Liebross, Ha et al. 1998)  Retrospective analysis	N= 57 patients with SBP  Median age: 53 years (range: 29-77)  Patients were diagnosed between 1965-1996  The diagnosis was based on histologic confirmation with no evidence of other bone destruction on bone survey or of marrow plasmacytosis >5%. Additional diagnostic evaluation consisted of electrophoreses of serum and urine concentrates, including immunoelectrophoresis, immunofixation, and immunoglobulin quantitations as these procedures became available. In recent years, five patients were excluded when magnetic resonance imaging of the thoracic and lumbar spine showed an intramedullary defect that had not been recognized on bone survey	RT was given to all but one patient, whose rib lesion was excised  Median RT dose: 50Gy (range: 30-70) Median fraction size: 2Gy (1.3-5.0)		<ol style="list-style-type: none"> <li>1. Survival</li> <li>2. LC</li> <li>3. Progression to MM</li> <li>4. Toxicity</li> </ol>	<ol style="list-style-type: none"> <li>1. <b>Survival:</b> <ul style="list-style-type: none"> <li>• Median survival from RT: 11.0 years</li> </ul> </li> <li>2. <b>LC:</b> <ul style="list-style-type: none"> <li>• LC was achieved in 55 patients (96%)</li> <li>• One patient had radiographic progression of rib lesion 1 year after 50Gy in 25 fractions</li> <li>• One patient showed recurrence of a thoracic spine tumor 4 years after 41 Gy in 23 fractions and subsequently had a resection</li> </ul> </li> <li>3. <b>Progression to MM:</b> <ul style="list-style-type: none"> <li>• MM developed in 29 patients (53%) and after a median of 1.8 years</li> </ul> </li> <li>4. <b>Toxicity:</b> <ul style="list-style-type: none"> <li>• No patient had acute or late radiation toxicity</li> </ul> </li> </ol>	Retrospective analysis  Median follow-up: not reported  COI: not declared  Funding: no information provided

## 12.4.6.1.6. Einzelstudien (median radiation &gt;50Gy)

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Creach, Foote et al. 2009)  Retrospective analysis	N= 18 patients with EMPHN  Patients were treated with RT between 1976 and 2006  N=16 patients were primarily treated with RT; n=2 patients received salvage RT after recurrence following surgical resection	Median dose: 50Gy (range: 34-56) Median dose/fraction: 2.0 Gy (1.8-2.06) Median no. of fractions: 28 (17-31) Median overall treatment time: 40 days (22-75) Elective lymph node treatment: 7 Therapeutic lymph node treatment: 3		1. Survival 2. LC 3. Progression to MM 4. Toxicity	<b>1. Survival:</b> <ul style="list-style-type: none"> <li>OS rates from the date of initial diagnosis: <ul style="list-style-type: none"> <li>Median survival: 12.5 years</li> <li>5-year survival: 88%</li> <li>10-year survival: 55%</li> </ul> </li> <li>OS rates from the date of first RT: <ul style="list-style-type: none"> <li>Median survival: 12.5 years</li> <li>5-year survival: 80%</li> <li>10-year survival: 54%</li> </ul> </li> </ul> <b>2. LC:</b> <ul style="list-style-type: none"> <li>All but two patients achieved complete response (1 patient terminated RT prematurely and died 10 days after RT-termination; in 1 patient the tumor did not regress during RT and was surgically removed)</li> <li>1 patient developed a recurrence just outside the margin of the treatment volume in the adjacent nasal cavity. The patient had received 50.4 Gy and underwent salvage radiotherapy consisting of 45 Gy in 25 fractions of 1.8 Gy each with CR and local tumor control at last follow-up</li> </ul>	Retrospective analysis  Authors declared to have no conflicts of interest  Funding: no information provided

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Skora, Pudelek et al. 2017)  Retrospective analysis	N=17 patients with EMPHN  Patients were treated between 1976 and 2009 at the Krakow oncology center	Median dose: 56 Gy (range: 45-70) given in 2-2.5 Gy fractions		1. Survival 2. LC	<ul style="list-style-type: none"> <li>No patient developed recurrent plasmacytoma within therapeutically irradiated cervical lymph nodes.</li> <li>No patient developed a new plasmacytoma in electively irradiated cervical lymph nodes.</li> </ul> <p><b>3. Progression to MM or distant disease:</b></p> <ul style="list-style-type: none"> <li>2 patients progressed to MM and 4 others developed another plasmacytoma or multiple plasmacytomas</li> </ul> <p><b>4. Toxicity (Late effects of RT):</b></p> <ul style="list-style-type: none"> <li>Xerostomia on 10 patients</li> <li>Nasal dryness and epistaxis in 5 patients</li> <li>Nasal obstruction and dysphagia in 2 patients each</li> <li>Laryngeal edema, lacrimal duct dysfunction, hypothyroidism, sinus tenderness, thick secretions, and the Lhermitte's sign in 1 patient each</li> <li>One patient developed dry eyes with blurred vision</li> </ul>	Retrospective analysis Median follow-up: 103 months

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
		<p>4 patients received adjuvant MP due to partial response after RT</p> <p>RT was directed to the involved site in n=9 patients; for n=8 patients, the regional lymph nodes were included</p>		<p>3. Progression to MM</p> <p>4. Toxicity</p>	<ul style="list-style-type: none"> <li>5- and 10-year MMFS: 63% and 55%, respectively</li> </ul> <p><b>2. LC:</b></p> <ul style="list-style-type: none"> <li>All patients achieved a complete response, including 13 patients (75.5%) after RT alone and the remaining 4 (23.5%) with partial response after RT followed by adjuvant chemotherapy</li> <li>No in-field local recurrence was observed</li> <li>A local failure outside the treatment field occurred in one case, 77 months after the initial treatment</li> </ul> <p><b>3. Progression to MM:</b></p> <ul style="list-style-type: none"> <li>During the follow-up, progression into MM was observed in five patients (29.4%).</li> <li>Generalized disease was diagnosed from 8 to 37 months after radiotherapy (mean 24 months).</li> <li>In all cases, systemic treatment was implemented.</li> </ul> <p><b>4. Toxicity:</b></p> <ul style="list-style-type: none"> <li>Radiotherapy was well tolerated. No grades 4 and 5 acute and late toxicity were noticed according to RTOG/EORTC scale</li> <li>Radiation induced mucositis and skin erythema were observed in all patients, mainly in grades of 1 and 2</li> </ul>	<p>The authors declared to have no conflicts of interest</p> <p>Funding: no information provided</p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
					<ul style="list-style-type: none"> <li>During the follow-up, the late effects of radiotherapy in grades of 1 and 2 were presented in 13 and 4 patients, respectively. These patients had a slight mucosa atrophy and xerostomia.</li> </ul>	

**12.4.6.1.7. GRADE Bewertung**

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Retrospektive analyses	Gesamtüberleben	-	-	-	-	-	⊕⊕⊕⊖ low
	Retrospektive analyses	Progressionsfreies Überleben	-	-	-	-1	-	⊕⊖⊖⊖ Very low
	Retrospektive analyses	Lokale Kontrolle	-	-	-	-1	-	⊕⊖⊖⊖ Very low
	Retrospektive analyses	Harms	-	-	-	-	-	⊕⊖⊖⊖ Very low
	Not reported	Lebensqualität	-	-	-	-	-	Not reported

Progressionsfreies Überleben/ Lokale Kontrolle: unpräzise, multivariate Analysen finden keine statistisch signifikanten Unterschiede im Progressionsfreien Überleben und der lokalen Kontrolle

## 12.4.7. Multipler Befall

### 12.4.7.1. Aufgrund der zu erwartenden Einschränkung der Knochenmarksreserve soll das Radiotherapievolumen so gering wie möglich gewählt werden.

#### 12.4.7.1.1. Evidenztabellen

##### 12.4.7.1.2. Einzelstudien

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenz- klasse
(Resende Salgado, Wang et al. 2019)	<ul style="list-style-type: none"> <li>- Retrospective study</li> <li>- Data collected from 2007 to 2017</li> <li>- 130 MM patients (279 treatment sites) included</li> <li>- RT+biologic agents: 91 patients (172 different sites)</li> <li>- RT only: 39 patients (107 different sites)</li> <li>- Patients required to be receiving a biological agent at least within 1 month before starting and up to 1 month after RT</li> </ul>	RT + biologic agents (42% Bortezomib, 23% Carfilzomib, 15% Daratumumab, 20% other)	RT only	<ol style="list-style-type: none"> <li>1. OS</li> <li>2. PFS</li> <li>3. Harms</li> <li>4. QoL</li> </ol>	<p>median dose was 20 Gy (range, 2-40 Gy)</p> <ol style="list-style-type: none"> <li>1. OS</li> <li>- Not reported</li> <li>2. PFS</li> <li>- Not reported</li> <li>3. Harms</li> <li>- No grade <math>\geq 3</math> toxicity was noted in the entire cohort</li> <li>- Acute fatigue: 17 patients (RT+BA) vs. 12 (RT only)</li> <li>- Acute erythema: 4 patients (RT+BA) vs. 0 (RT only)</li> <li>- Subacute fatigue: 5 patients (RT+BA) vs. 5 patients (RT only)</li> <li>- Subacute pain: 4 (RT+BA) vs. 1 patient (RT only)</li> </ol>	<ul style="list-style-type: none"> <li>- Retrospective study</li> <li>- Not randomized</li> <li>- Not blinded</li> <li>- No inclusion and exclusion criteria given</li> <li>- No conflicts of interest listed</li> </ul>



Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
	<ul style="list-style-type: none"> <li>- Dosing was based on standard parameters as opposed to RT</li> <li>- Toxicities rated according to Common Terminology Criteria for AEs</li> </ul>				<ul style="list-style-type: none"> <li>- Total number of toxicities by drug combination:               <ul style="list-style-type: none"> <li>•                   <ul style="list-style-type: none"> <li>○ RT+bortezomib: 48 patients (17% acute and 6% subacute)</li> <li>○ RT+carfizomib: 24 patients (42% acute and 4% subacute)</li> <li>○ RT+daratumumab: 18 patients (50% acute and 22% subacute)</li> <li>○ RT+other: 23 patients (22% acute and 26% subacute)</li> <li>○ RT only: 69 patients (19 patients acute and 11 patients subacute)</li> </ul> </li> </ul> </li> </ul>	

Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
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Table 4. Prevalence ratios for side effects and hematological events

Toxicity event by RT	Prevalence ratios (95% CI)	P value	
<b>Acute side effects (N = 157)</b>			
RT alone	20/21	36%	
RT + SA	33/115	1.03 [0.58-1.82]	>.050
<b>Subacute side effects (N = 121)</b>			
RT alone	14/12	46%	
RT + SA	26/78	0.62 [0.33-1.17]	>.050
<b>Anemia (N = 124)</b>			
RT alone	4/28	6%	
RT + SA	14/105	1.04 [0.48-2.26]	>.050
<b>White blood cells (N = 125)</b>			
RT alone	11/21	49%	
RT + SA	26/112	1.34 [0.67-2.67]	>.050
<b>Neutropenic events (N = 125)</b>			
RT alone	4/21	19%	
RT + SA	24/115	1.55 [0.74-3.24]	>.050

Abbreviations: SA = Subacute agent; CI = confidence interval; RT = radiation therapy.

4. QoL

- Not reported

Median follow-up: 14 months

(Shin, Chouake et al. 2014)	- 39 patients with MM (66 different sites were treated) (4 patients were unable to conclude their course of RT)	RT + systematic therapy (ST) (cytotoxic chemotherapy (CTx) and novel agents (NAs))	RT alone	<ol style="list-style-type: none"> <li>OS</li> <li>PFS</li> <li>Harms</li> <li>QoL</li> </ol>	<ol style="list-style-type: none"> <li>OS</li> <li>Not reported</li> <li>PFS</li> <li>Not reported</li> <li>Harms</li> </ol>	<ul style="list-style-type: none"> <li>Very small amount of patients</li> <li>Intention-to-treat analysis</li> </ul>
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Referenz/ Studientyp	Untersuchte Popula- tion	Interven- tion	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenz- klasse
	<ul style="list-style-type: none"> <li>- RT+ST: 21 patients (16 patients with NAs and 5 patients with CTx)</li> <li>- RT alone: 18 patients</li> <li>- 2007 to 2012</li> </ul>				<ul style="list-style-type: none"> <li>- Grade 3 hematological toxicity: 50% (RT+NAs) vs. 23% (RT+CTx) vs. 50% (RT alone)</li> <li>- Grade 4 hematological toxicity: 0% (RT+NAs) vs. 11% (RT+CTx) vs. 0% (RT alone)</li> <li>- Esophagitis: 5% (RT+NAs) vs. 0% (RT+CTx) vs. 0% (RT alone)</li> <li>- Dermatitis: 5% (RT+NAs) vs. 20% (RT+CTx) vs. 4% (RT alone)</li> <li>- Fatigue: 0% (RT+NAs) vs. 20% (RT+CTx) vs. 10% (RT alone)</li> <li>- Diarrhea: 11% (RT+NAs) vs. 0% (RT+CTx) vs. 4% (RT alone)</li> <li>- Mucositis: 5% (RT+NAs) vs. 0% (RT+CTx) vs. 4% (RT alone)</li> <li>- In the RT+ST group 19 of 21 patients completed treatment safely without significant hematologic and nonhematologic toxicity</li> </ul> <p>4. QoL</p> <ul style="list-style-type: none"> <li>- Not reported</li> </ul> <p>5. Median follow-up: 6 months</p>	<ul style="list-style-type: none"> <li>- Authors stated that they have no conflicts of interest</li> <li>- No inclusion and exclusion criteria given</li> </ul>

12.4.7.1.3. GRADE Bewertung

Schlüsselfrage	Design		Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Retrospektive analyses		Gesamtüberleben	-	-	-	-	-	Not reported
	Retrospektive analyses		Progressionsfreies Überleben	-	-	-	-	-	Not reported
	Retrospektive analyses		Harms	-	-	-1	-1	-	⊕⊖⊖⊖ Very low
	Retrospektive analyses		Lebensqualität	-	-	-	-	-	Not reported

Indirekt, da verschiedene Bestrahlungsdosen nicht untersucht.

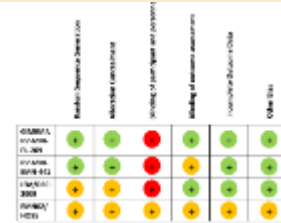
Impräzise, da Kriterium für die optimale Informationsgröße nicht erfüllt.

## 12.4.8. Induktionstherapie

12.4.8.1. Patienten, die für eine Hochdosistherapie in Frage kommen, sollen eine Induktions-therapie im Rahmen eines Hochdosis-konzepts erhalten.

12.4.8.1.1. Evidenztabellen

12.4.8.1.2. Einzelstudien

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(Dhakal, Szabo et al. 2018)	<ul style="list-style-type: none"> <li>- Phase 3 randomized clinical trials</li> <li>- January 2000 to April 2017 (systematic literature) &amp; January 2014 to December 2016 (relevant annual meeting abstracts)</li> <li>- Cochrane Central,</li> </ul>	<b>HDT/ASCT compared to standard-dose-therapy (SDT) using novel agents</b>	<ol style="list-style-type: none"> <li>1. OS</li> <li>2. PFS</li> <li>3. Harms</li> <li>4. QoL</li> </ol>	<ul style="list-style-type: none"> <li>- 4 RCTs for conventional meta-analysis</li> <li>- 2421 patients (conventional meta-analysis)</li> <li>- Included studies: 4 RCTs</li> </ul> <p>Results:</p> <ol style="list-style-type: none"> <li>1. OS                             <ul style="list-style-type: none"> <li>- HR 0.76 (95% CI, 0.42-1.36; P = .20) (benefit with HDT/ASCT)</li> <li>- OR: 0.76 (0.42 to 1.37; P=0.36) favors HDT/ASCT</li> </ul> </li> <li>2. PFS:                             <ul style="list-style-type: none"> <li>- HR 0.55 (95% CI, 0.41-0.74; P=.004) (benefit with HDT/ASCT)</li> <li>- OR: 0.55 (95% CI 0.41 to 0.74) P&lt;0.001 (favors HDT/ASCT)</li> </ul> </li> </ol>	<p><b>Search strategy given?</b></p> <ul style="list-style-type: none"> <li>- Briefly described in methods-section, but not given</li> </ul> <p><b>Risk of bias or other form of qualitative judgement by the authors:</b></p> <ul style="list-style-type: none"> <li>- Done by the authors</li> </ul> 	<p>(Palumbo, Cavallo et al. 2014)</p> <p>(Gay, Oliva et al. 2015)</p> <p>(Attal, Lauwers-Cances et al. 2017)</p> <p>Cavo et al, 2016, Blood</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	<p>MEDLINE, Scopus</p> <ul style="list-style-type: none"> <li>- Only stu- dies in Eng- lish in- cluded</li> </ul> <p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>- use of phase 3 RCT design</li> <li>- enrolled and re- ported out- comes for patients with newly diagnosed MM under- going HDT/ASCT</li> <li>- directly compared combina- tion chemo- therapy with novel agents fol- lowed by</li> </ul>			<p>-</p> <p>Follow up/time point of measurement</p> <p>3. Harms</p> <ul style="list-style-type: none"> <li>- not analysed in review</li> </ul> <p>4. QoL</p> <ul style="list-style-type: none"> <li>- not analysed in review</li> </ul> <p>follow up: minimum of 2 years</p> <p>medium follow-up ranged from 26 to 52 months</p>	<p><b>Inconsistency (I<sup>2</sup>, Cochran's-Q):</b></p> <ul style="list-style-type: none"> <li>- 1. OS: I<sup>2</sup> 78.7%</li> <li>- 2. PFS: I<sup>2</sup> 77.2%, Q=11.28</li> </ul> <p>- Inconsistency was evaluated by fitting an extended model including design-by- treatment interaction via a random effect and comparing the models by a likeli- hood-ratio test.</p> <p>•</p> <p><b>Indirectness (PICO fits review question):</b></p> <ul style="list-style-type: none"> <li>- No limitations</li> </ul> <p><b>Imprecision (number of events and patients in- cluded): low</b></p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	<p>consolidation with HDT/ASCT vs SDT alone</p> <ul style="list-style-type: none"> <li>- directly compared HDT1 vs HDT2 (for network meta-analysis only).</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>- Small-scale studies (sample size &lt;100 patients)</li> </ul>				<p><b>Other</b></p> <ul style="list-style-type: none"> <li>- Intention-to-treat analysis</li> <li>- Limitations: <ul style="list-style-type: none"> <li>o Limited number of studies</li> <li>o Heterogeneous treatments delivered</li> <li>o Unreported outcomes (eg. OS in Cavo et al. and HRs in STaMINA)</li> </ul> </li> <li>- While we found that the trial characteristics explained some of the heterogeneity, we were not able to explore the functional form of the effect of modifiers or fully adjust for them owing to the low number of trials</li> </ul>	

**12.4.8.1.3. GRADE Bewertung**

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA	Gesamtüberleben	-	-1	-	-	-	⊕⊕⊕⊖ moderate
	SR/MA	Progressionsfreies Überleben	-1	-1	-	-1	-	⊕⊕⊖⊖ low
	Not reported	Harms	-	-	-	-	-	Not reported
	Not reported	Lebensqualität	-	-	-	-	-	Not reported

Hohes Verzerrungsrisiko für subjektive Endpunkte (PFS), da 3 von 4 Studien unverblindet

Inkonsistenz: OS: I<sup>2</sup>= 78.7%; PFS: I<sup>2</sup>= 77.2%

**12.4.8.2. Die Induktionstherapie soll einen Proteasominhibitor enthalten.**

**12.4.8.2.1. Summary of findings Tabelle Cochrane Review (Scott, Hayden et al. 2016)**

Summary of findings for the main comparison

**Bortezomib versus no bortezomib for the treatment of multiple myeloma**

Patient or population: All patients with a diagnosis of multiple myeloma

Settings: International multicentre studies

Intervention: Bortezomib

Comparison: Bortezomib versus no bortezomib (same or different background therapy or other agents)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk without bortezomib	Risk with bortezomib				



Bortezomib versus no bortezomib for the treatment of multiple myeloma						
Overall survival	215 per 1.000	166 per 1.000 (148 to 185)	Peto OR 0.77 (0.69 to 0.86)	4118 (9 RCTs)	++++ high	
Progression-free survival	523 per 1.000	350 per 1.000 (319 to 377)	Peto OR 0.67 (0.61 to 0.72)	4344 (9 RCTS)	+++ low <sup>1,2</sup>	
Peripheral Neuropathy	44 per 1.000	145 per 1.000 (118 to 176)	OR 3.71 (2.92 to 4.70)	4636 (10 RCTs)	+++ moderate <sup>3</sup>	
Health related Quality of Life	See comment	See comment	See comment	717 (4RCTs)	See comment	Each trial used the same validated quality of life instrument (European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), whereas the time points of administration of the questionnaire

Bortezomib versus no bortezomib for the treatment of multiple myeloma						
						varied between the four trials.
<p>* The basis for the assumed risks (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)</p> <p>CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference.</p>						
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>						
<p>1: Downgraded one level because TTP was analysed instead of PFS in one trial.</p> <p>2: Downgraded one level due to heterogeneity 56%.</p> <p>3: Downgraded one level due to low number of events, wide CI.</p>						

### 12.4.8.3. Patienten ohne schwerwiegende Komorbiditäten, die potentiell transplantationsfähig sind, sollen eine Dreifachtherapie erhalten.

### 12.4.8.4. Evidenztabellen

#### 12.4.8.4.1. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(Huang, Zhou et al. 2014) SR with MA	<ul style="list-style-type: none"> <li>- 1765 patients included</li> <li>- Medline, Embase, Cochrane Library until April 2014</li> <li>- 5 studies met the prespecified inclusion criteria</li> </ul> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>- Phase 3 RCT</li> </ul>	Tripple (VT-based) vs. double drug (V- or T-based) combinations as induction treatment	<ol style="list-style-type: none"> <li>1. OS</li> <li>2. PFS</li> <li>3. Harms</li> <li>4. QoL</li> </ol>	<ol style="list-style-type: none"> <li>1. OS: HR 1.04 (95% CI 0.91 to 1.19), 4 studies included</li> <li>2. PFS: HR 0.69 (95% CI 0.54 to 0.88), 5 studies included in MA</li> <li>3. Harms: <ol style="list-style-type: none"> <li>a. grade 3 or higher peripheral neuropathy: OR 1.64 (95% CI 0.77 to 3.46)</li> <li>b. grade 3 or higher deep venous thrombosis: OR 1.26 (95% CI 0.73 to 2.16)</li> <li>c. SAEs: OR 1.15 (95% CI 0.81 to 1.64)</li> </ol> </li> <li>4. QoL: not reported</li> </ol> <p>Median follow-up: 21.8–47.2 months</p>	<ul style="list-style-type: none"> <li>- Intention-to-treat analysis</li> <li>- COI assessment not reported</li> <li>- Study quality not formally assessed</li> <li>- Search strategy only described in 3 keywords</li> <li>- Indirectness: no limitations</li> <li>- Considerable Heterogeneity for two outcomes: PFS (<math>I^2=63\%</math>), severe polyneuropathies (<math>I^2=73\%</math>)</li> <li>- Authors declare to have no COIs</li> <li>- Funding: National Natural Science</li> </ul>	<p>Cavo 2010</p> <p>Moreau 2011</p> <p>Niesvizky 2011</p> <p>Palumbo 2010</p> <p>Rosinol 2012</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	- Induction treatment for NDMM -				Foundation of China (Grant No. 81172248), Shanghai Committee of Foundation for Outstanding Leaders in Science (11XD1406600), Yangtze River Delta Unit Breakthroughs Project, and Shanghai Leading Scientists Foundation	

#### 12.4.8.4.2. Ergänzende Einzelstudien

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Moreau, Attal et al. 2019)	n = 1085 <b>Inclusion Criteria:</b> - Transplant eligible NDMM - 18-65 years of age - Eastern Cooperative Oncology Group performance status of 0-2, Absolute neutrophil	Dara-VTD (543)	VTD (n=542)	<ul style="list-style-type: none"> <li>OS</li> <li>PFS</li> <li>Harms</li> <li>QoL</li> </ul>	<ul style="list-style-type: none"> <li>• OS: HR 0.43, 95% CI 0.23-0.80</li> <li>• PFS: HR 0.47, 95% CI 0.33-0.67</li> <li>• AE: overall number of affected patients not reported</li> <li>• QoL: n/r</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Study Duration:</b> part 2 ongoing</li> <li>• <b>Follow-up:</b> 18.8 months (0.0-32.2)</li> <li>• <b>ITT:</b> yes</li> <li>• <b>Randomisation:</b> 1:1</li> <li>• <b>Blinding:</b> open-label</li> <li>• <b>Funding:</b> Intergroupe Francophone du Myélome and Dutch-Belgian</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<p>count of <math>1 \times 10^9</math> per L or more</p> <ul style="list-style-type: none"> <li>- Haemoglobin concentration of 7.5 g/dL or more</li> <li>- platelet count of <math>70 \times 10^9</math> per L or more (if &lt;50% of bone marrow nucleated cells were plasma cells, otherwise platelet count <math>&gt;50 \times 10^9</math> per L)</li> <li>- calculated creatinine clearance of 40 mL/min or more,</li> <li>- corrected serum calcium level of 14 mg/dL or less (&lt;3.5 mmol/L)</li> <li>- adequate liver function</li> </ul> <p><b><u>Exclusion Criteria:</u></b></p> <ul style="list-style-type: none"> <li>- previous systemic therapy or stem-cell transplantation for any plasma cell dyscrasia</li> <li>- grade 2 or higher peripheral neuropathy or neuropathic pain</li> </ul> <p><b><u>Baseline characteristics:</u></b></p>					<p>Cooperative Trial Group for Hematology Oncology</p> <ul style="list-style-type: none"> <li>• COI: fully disclosed</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
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- **Age:** 58y (range 22-65)

12.4.8.4.3. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA, RCT	Gesamtüberleben	-	-	-	-	-	⊕⊕⊕⊖ moderate
	SR/MA, RCT	Progressionsfreies Überleben	-1	-1	-	-	-	⊕⊕⊖⊖ low
	SR/MA, RCT	Harms	-1	-1	-	-	-	⊕⊕⊖⊖ low
	Not reported	Lebensqualität	-	-	-	-	-	Not reported

Hohes Verzerrungsrisiko da für subjektive Endpunkte (PFS, AEs), da Studien unverblindet

Inkonsistent, da hohe Heterogenität

### 12.4.8.5. Nicht transplantationsfähige Patienten ohne schwerwiegende Komorbiditäten sollten mit einer 3- oder 4-fach Kombination behandelt werden.

#### 12.4.8.5.1. Evidenztabellen

#### 12.4.8.5.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(Piechotta, Jakob et al. 2019)	<ul style="list-style-type: none"> <li>RCTs comparing treatment regimens for non-transplant NDMM</li> <li>Searches run in MEDLINE and CENTRAL until February 2019</li> <li>Search started in 1999</li> <li>First-line therapy of interest only; maintenance- or RRMM-studies excluded</li> <li>Symptomatic MM only;</li> </ul>	<ul style="list-style-type: none"> <li>MP, MPc, RCD, RCPC, RD, RDc, RMP, RMPc, TCD, TDc, TMP, TMPc, VD, VDc, VMP, VMPC, VRD, VRDc, VTDC, VTMPc, VTpc were compared to each other in a network-meta analysis</li> <li>Treatments were differentiated between fixed duration and continuous (c) therapy (until plateau in response was reached, continuous first-line treatment,</li> </ul>	<ol style="list-style-type: none"> <li>OS</li> <li>PFS</li> <li>QoL</li> <li>SAEs</li> <li>Grade 3 and 4 AEs</li> <li>Withdrawals due to AEs</li> <li>Anemia</li> <li>Infections</li> <li>Neutropenia</li> <li>Polyneuropathy</li> <li>Thrombocytopenia</li> </ol>	<p>25 included studies including 11403 patients</p> <p><b>NMA-OS:</b></p> <ul style="list-style-type: none"> <li>continuous therapies do not appear superior compared to fixed duration of therapy</li> <li>please refer to table 1 for all network comparisons</li> </ul> <p><b>NMA-PFS:</b></p> <ul style="list-style-type: none"> <li>evidence suggests a superiority of continuous therapies compared to fixed duration of therapy</li> <li>please refer to table 2 for all network comparisons</li> </ul> <p><b>QoL:</b></p> <ul style="list-style-type: none"> <li>NMA not possible for this outcome</li> </ul> <p><b>NMA-SAE:</b></p> <ul style="list-style-type: none"> <li>Evidence suggests an increased risk for SAEs for patients treated with continuous therapies compared to fixed duration of therapy</li> </ul>	<ul style="list-style-type: none"> <li>Risk of Bias assessed for each included study, cf. RoB Graph</li> <li>GRADE approach applied</li> <li>higher P score indicates a greater chance of being the best treatment</li> </ul>	<ul style="list-style-type: none"> <li>Included Studies:</li> <li>Myeloma XI (Pawlyn, 2017)</li> <li>EMN01 (Maga-roto, 2016)</li> <li>FIRST (Bahlis, 2017)</li> <li>ECOG E1A06 (Stewart, 2014)</li> <li>MM-015 (Palumbo, 2012)</li> <li>HOVON 87</li> </ul>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Smouldering MM excluded</p> <ul style="list-style-type: none"> <li>Non-transplant only; induction therapy prior to transplant excluded</li> </ul>	first-line followed by maintenance)	15. Thromboembolism	<ul style="list-style-type: none"> <li>please refer to table 3 for all network comparisons</li> </ul> <p><b>Grade 3 and 4 AEs:</b></p> <ul style="list-style-type: none"> <li>NMA not possible for this outcome</li> </ul> <p><b>Withdrawals due to AEs:</b></p> <ul style="list-style-type: none"> <li>continuous therapies do not appear inferior compared to fixed duration of therapy</li> <li>please refer to table 4 for all network comparisons</li> </ul> <p><b>Anemia:</b></p> <ul style="list-style-type: none"> <li>continuous therapies do not appear inferior compared to fixed duration of therapy</li> <li>please refer to table 5 for all network comparisons</li> </ul> <p><b>Infections:</b></p> <ul style="list-style-type: none"> <li>evidence suggests a lower risk for infections for fixed duration of therapy compared to continuous therapies</li> <li>please refer to table 6 for all network comparisons</li> </ul> <p><b>Neutropenia:</b></p> <ul style="list-style-type: none"> <li>evidence suggests a lower risk for neutropenia for fixed duration of therapy compared to continuous therapies</li> <li>please refer to table 7 for all network comparisons</li> </ul> <p><b>Polyneuropathy:</b></p>		<p>(Zweegman, 2016)</p> <ul style="list-style-type: none"> <li>Myeloma IX (Morgan, 2011)</li> <li>GBRAM002 (Hungria, 2016)</li> <li>Kim, 2007</li> <li>Ludwig, 2009</li> <li>TMSG (Beksac, 2011)</li> <li>HOVON 49 (Wijermans, 2010)</li> <li>IFM 99-06 (Facon, 2007)</li> <li>GISMM2001-A (Paumbo, 2006)</li> </ul>



Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<ul style="list-style-type: none"> <li>continuous therapies do not appear inferior compared to fixed duration of therapy</li> <li>please refer to table 8 for all network comparisons</li> </ul> <p><b>Thrombocytopenia:</b></p> <ul style="list-style-type: none"> <li>continuous therapies do not appear inferior compared to fixed duration of therapy</li> <li>please refer to table 9 for all network comparisons</li> </ul> <p><b>Thromboembolism:</b></p> <ul style="list-style-type: none"> <li>evidence suggests a lower risk for thromboembolism for fixed duration of therapy compared to continuous therapies</li> <li>please refer to table 10 for all network comparisons</li> </ul>		<ul style="list-style-type: none"> <li>MM03 (Sacchi, 2011)</li> <li>IFM 01/01 (Hulin, 2009)</li> <li>NMSG #12 (Waage, 2010)</li> <li>Katsuoka, 2013</li> <li>UPFRONT (Niesvizky, 2015)</li> <li>VISTA (San Miguel, 2008)</li> <li>GEM2005 (Mateos, 2014)</li> <li>Mookerje, 2017</li> <li>SWOG S0777 (Durie, 2017)</li> </ul>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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- E1A05 (Ja-  
cobus,  
2016)
- GIMEMA-  
MM-03-05  
(Palumbo,  
2014)

12.4.8.5.3. Einzelstudien

Referenz/ Stu- dientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemer- kungen/ Evidenzklasse
(Mateos, Dimopoulos et al. 2018)	<ul style="list-style-type: none"> <li>- Randomized, open-label phase 3 trial</li> <li>- Enrolled patients between February 2015 and July 2016</li> <li>- Randomly assigned by means of an interactive Web-response system in a 1:1 ratio</li> <li>- Randomization stratified according to International Staging System disease stage</li> <li>- 706 enrolled patients</li> </ul>	<p>Induction therapy with daratumumab</p> <p>(bortezomib + melphalan + prednisone + daratumumab)</p>	<p>Induction therapy without daratumumab</p> <p>(bortezomib + melphalan + prednisone)</p>	<ol style="list-style-type: none"> <li>1. OS</li> <li>2. PFS</li> <li>3. Harms</li> <li>4. QoL</li> </ol>	<ol style="list-style-type: none"> <li>1. OS</li> <li>2. PFS</li> </ol> <ul style="list-style-type: none"> <li>- Median overall survival was not reached in either group</li> <li>- 18 months-PFS: 71.6% (with daratumumab; 95% CI 65.5 to 76.8) vs. 50.2% (without daratumumab; 95% CI 43.2 to 56.7)</li> <li>- HR for disease progression or death: 0.50 (95% CI 0.38 to 0.65, P&lt;0.001), benefits daratumumab group</li> <li>- Median PFS: 18.1 months (daratumumab; 95% CI 16.5 to 19.9;</li> </ul>	<ul style="list-style-type: none"> <li>- Conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation-Good Clinical Practice guidelines</li> <li>- Janssen Research and Development sponsored the trial and designed it with the academic authors</li> <li>- Data compiled and maintained by the sponsor</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<ul style="list-style-type: none"> <li>- In the daratumumab group:               <ul style="list-style-type: none"> <li>o 350 assigned</li> <li>o 346 received intervention</li> <li>o 276 patients (79.8%) completed all nine cycles</li> </ul> </li> <li>- In the control group:               <ul style="list-style-type: none"> <li>o 356 assigned</li> <li>o 354 received intervention</li> <li>o 220 patients (62.1%) completed all nine cycles</li> </ul> </li> </ul> <p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>- Newly diagnosed MM</li> <li>- Ineligible for high-dose chemotherapy with stem-cell transplantation owing to coexisting conditions or an age of 65 years or older</li> <li>- Hemoglobin level <math>\geq 7.5</math>g/dL</li> </ul>				<p>P&lt;0.001) vs. Not reached (control group; 95% CI could not be estimated)</p> <p>3. Harms</p> <ul style="list-style-type: none"> <li>- Grade 3 or 4 neutropenia (39.9% daratumumab vs. 38.7% control group)</li> <li>- Grade 3 or 4 thrombocytopenia (34.4% daratumumab vs. 37.6% control group)</li> <li>- Grade 3 or 4 anemia (15.9% daratumumab vs. 19.8% control group)</li> <li>- Grade 3 or 4 infections (23.1% daratumumab vs. 14.7% control group)</li> <li>- Pneumonia (most common grade 3 or 4 infection) (11.3% daratumumab vs. 4.0% control group)</li> </ul> <p>4. QoL</p> <ul style="list-style-type: none"> <li>- Not reported</li> </ul> <p>Median follow-up: 16.5 months Median duration of treatment: 14.7 months (daratumumab) vs. 12.0 months (control group)</p>	<ul style="list-style-type: none"> <li>- Professional medical writers who prepared the manuscript were funded by the sponsor</li> <li>- Treatment assignments were not blinded</li> <li>- Intention-to-treat analysis</li> <li>- Flowchart is missing</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<ul style="list-style-type: none"> <li>- Absolute neutrophil count <math>\geq 1.0 \times 10^9/L</math></li> <li>- aspartate aminotransferase and alanine aminotransferase levels of 2.5 or fewer times the upper limit of the normal range</li> <li>- total bilirubin level of 1.5 or fewer times the upper limit of the normal range</li> <li>- creatinine clearance of <math>\geq 40</math>ml/minute</li> <li>- corrected serum calcium level of 14 mg or less per deciliter (<math>\leq 3.5</math> mmol per liter)</li> <li>- platelet count of <math>70 \times 10^9</math> or more per liter (if <math>&lt; 50\%</math> of bone marrow nucleated cells were plasma cells; otherwise, platelet count of <math>&gt; 50 \times 10^9</math> per liter)</li> <li>- Eastern Cooperative Oncology Group performance status of 0 to 2 (on a 5-point scale, with higher numbers</li> </ul>					

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<p>indicating greater disability)</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>- Primary amyloidosis</li> <li>- Monoclonal gammopathy of undetermined significance</li> <li>- Smoldering MM</li> <li>- Waldenström's macroglobulinemia (or other conditions in which IgM paraprotein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions)</li> <li>- Previous systemic therapy or stem-cell transplantation</li> <li>- Cancer within 3 years before randomization (exceptions were squamous-cell and basal-cell carcinomas of the skin, carcinoma in situ of the cervix and any cancer that was considered to be cured with</li> </ul>					

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	minimal risk of recurrence within 3 years) - Peripheral neuropathy - Grade 2 or higher neuropathic pain (as defined by the National Cancer Institute Common Terminology Criteria for AE)					

12.4.8.5.4. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	NMA/RCT	Gesamtüberleben	-	-1	-	-	-	⊕⊕⊕⊖ moderate
	NMA/RCT	Progressionsfreies Überleben	-1	-1	-	-	-	⊕⊕⊖⊖ low
	NMA/RCT	Harms	-1	-	-	-	-	⊕⊕⊕⊖ moderate
	NMA/RCT	Lebensqualität	-	-	-	-	-	Not reported

Hohes Verzerrungsrisiko, da die meisten Studien unverblindet

Inkonsistenz in NMA: OS I<sup>2</sup>=53.9%; PFS I<sup>2</sup>=55.3%

## 12.4.9. Therapiefortführung

### 12.4.9.1. Empfehlungen

„Hochrisikopatienten (Hochrisikozytogenetik oder Stadium R-ISS III) kann eine Tandemtransplantation angeboten werden.“

„Patienten, die nach der ersten Hochdosistherapie keine fast komplette Remission, aber eine Verbesserung des Ansprechens erreicht haben, kann eine Tandemtransplantation angeboten werden.“

#### 12.4.9.1.1. Evidenztabellen

##### 12.4.9.1.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
IQWiG 2011 (Gesundheits- wesen 2011) HTA	N=5 Studien identifiziert (davon 2 Studien eingeschlossen, da bei 3 der Volltext noch nicht publiziert war)	Mehrfach autologe vs. einfach autologe Stammzelltransplan- tation	Subgruppenana- lysen  Gesamtüberleg- en  Ereignisfreies/ Rezidivfreies Überleben  Therapiebezoge- ne Mortalität	Die Unsicherheiten in der Einschätzung der Vergleichbarkeit beider Studien (nur 1 Studie verwendete eine Ganzkörperbestrahlung) ließen eine meta-analytische Aggregation bzgl. des Gesamtüberlebens als nicht sinnvoll erscheinen.  Einschlusskriterium in beiden Studien: NDMM < 60 Jahre; normale Leber- und Herzfunktion wurde vorausgesetzt	Verzerrungspotential auf Studien- und Endpunktebene bewertet:  Randomisierung: ja, beide  Concealment: ja, beide  Verblindung: unklar, beide  Ergebnisunabhängige Berichterstattung: ja, beide (bis auf unerwünschte	Cavo 2007  Attal 2003

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Suche: bis 17.01.2011</p> <p>Datenbanken: MEDLINE, EMBASE, CENTRAL, Database of Abstracts of Reviews of Effects, HTA Database, Studienregister, Unterlagen des GBA</p> <p>Einschlusskriterie n:</p> <p>-Studien mit mindestens 80% MM Patienten</p> <p>-RCTs</p>			<p>Subgruppenanalysen:</p> <p>Cavo 2007: prognostische Faktoren einer multivariaten Analyse, die das Gesamtüberleben signifikant beeinflussten, wurden zwar berichtet, allerdings ohne die hier interessierende Interaktion mit der Behandlung zu untersuchen.</p> <p>Attal 2003: Gesamtüberleben nach 2-x- versus 1-x-Auto-Transplantation in verschiedenen Subgruppen wurde untersucht</p> <p>Subgruppen wurden mit einem Effekt zugunsten der 2-x-Auto-Transplantation (ohne Angabe von Punktschätzern, Konfidenzintervallen oder p-Werten).</p> <p>Diese waren: Patienten mit <math>\beta_2</math>-Mikroglobulin <math>\leq 3</math> mg/l und <math>&gt; 3</math> mg/l, LDH <math>\leq 330</math> IU bzw. <math>&gt; 330</math> IU, Durie-Salmon-Stadium I oder II und III, Alter <math>\leq 50</math> Jahre und <math>&gt; 50</math> Jahre. Da jeweils alle Subgruppen einen Vorteil zugunsten der 2-x-Auto-Transplantation zeigten, konnte aus diesen Angaben keine (zumindest qualitative) Interaktion abgeleitet werden.</p>	<p>Ereignisse bei Cavo 2007: es wurden nur die häufigsten unerwünschten Ereignisse WHO Grad 3-4 berichtet)</p> <p>Kein sonstiges Verzerrungspotential: ja, beide (bis auf RFS bei Attal 2003: Sowohl beim OS als auch beim EFS zeigten sich in den Langzeitdaten von Attal 2003 im Gegensatz zur Hauptpublikation mit einem kürzeren Nachbeobachtungszeitraum keine statistisch signifikanten Ergebnisse mehr. Da für das RFS keine Langzeitdaten vorlagen, sind die Daten für den kürzeren Beobachtungszeitraum möglicherweise relevant verzerrt im Hinblick auf die langfristige Aussage)</p>	



Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				Eine Untersuchung möglicher differenzieller Therapieeffekte in den Subgruppen, z. B. durch einen Interaktionstest, wurde nicht berichtet.	Gesamtbewertung: niedriges Verzerrungspotential	
				<p>Gesamtüberleben:</p> <p>das Gesamtüberleben sowohl bei Cavo 2007 als auch bei Attal 2003 zeigte keinen statistisch signifikanten Unterschied zwischen den Behandlungsgruppen</p> <p>Bei Cavo 2007 betrug das mediane Überleben 71 versus 65 Monate zugunsten der 2-x-Auto-Transplantation, p-Wert des Log-Rank-Tests = 0,90, bei Attal 2003 54 versus 48 Monate zugunsten der 2-x-Auto-Transplantation (p-Wert des Log-Rank-Tests = 0,08).</p> <p>Überleben nach 7 Jahren (2-x-Auto vs. 1-x-Auto):</p> <p>Cavo 2007: 43 % vs. 46 % (2-x-Auto vs. 1-x-Auto)</p> <p>Attal 2003: 38 % vs. 28 %.</p> <p>Überleben nach 10 Jahren (2-x-Auto vs. 1-x-Auto):</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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Attal 2003: 31% vs. 21%

Insgesamt lagen in beiden Studien keine statistisch signifikanten Effekte vor. Für den Bericht wurden die Daten der Langzeitauswertung von Attal 2003 mit einer medianen Nachbeobachtungszeit von 11,5 Jahren berücksichtigt. Anzumerken ist hier, dass sich die Schätzer der ersten Auswertung mit einer medianen Nachbeobachtungszeit von 6 Jahren deutlich von denen der Langzeitauswertung unterschieden und sich gegenläufig entwickelten (7-Jahresraten bei einer medianen Nachbeobachtungszeit von 6 bzw. 11,5 Jahren: 42 / 21 % bzw. 38 / 28 % (I / K), p-Werte des Log-Rank-Tests: 0,01 bzw. 0,08).

Von Bedeutung ist auch, dass in Attal 2003 ein heute nicht mehr empfohlenes Therapieprotokoll [7] eingesetzt wurde. Die beiden differierenden Therapieprotokolle von Cavo 2007 und Attal 2003 wurden bezüglich des Kontrollarms (1-x-Auto-Transplantation) in 1 randomisierten Studie head-to-head verglichen wurden [97]. Dabei wurde ein signifikanter Vorteil in einer relevanten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<p>Größenordnung zugunsten der heute üblichen Therapieempfehlung gefunden.</p> <p>Ereignisfreies/rezidivfreies Überleben:</p> <p>Cavo 2003: medianes EFS 35 Monate (95 %-KI [30; 40]) vs. 23 Monate (95 %-KI [20; 26]), 5-Jahres Rate EFS 29 % vs. 17 %, Log-Rank-Test: p-Wert = 0,001</p> <p>Attal 2003: mediane EFS betrug 31 vs. 26 Monate (kein Konfidenzintervall berichtet), die 10-Jahres-Rate für EFS 13 vs. 6 % (Log-Rank-Test: p = 0,06).</p> <p>Bei einer vergleichbaren Nachbeobachtungszeit von ca. 75 Monaten zeigte sich in beiden Studien eine statistisch signifikante Überlegenheit der zweifachen autologen Stammzelltransplantation für die Zielgröße RFS.</p> <p>TRM:</p> <p>Cavo 2007: (Todesfälle innerhalb der ersten 90 Tage nach der Transplantation) 4% vs 3% (2-x- bzw. 1-x-Auto-Gruppe.) p=0.70</p> <p>Attal 2003: Die therapiebezogenen Todesfälle unterschieden sich nicht statistisch signifikant (p-Wert = 0,40)</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				und betrug 6 % respektive 4 % für die 2-x- bzw. 1-x-Auto-Gruppe.		

12.4.9.1.3. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungs- risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegun- gen	Gesamtqualität
	IQWIG Nut- zendossier	Gesamtüber- leben	-	-	-1	-1	-1	⊕⊕⊕⊕ Very low
	IQWIG Nut- zendossier	Progressi- onsfreies Überleben	-	-	-	-	-	Not reported
	IQWIG Nutzen- dossier	Harms	-	-	-	-	-	Not reported
	IQWIG Nut- zendossier	Lebensquali- tät	-	-	-	-	-	Not reported

Indirekt, da Ergebnisse aus prognostic factor Analyse

Impräzise, da Kriterium die optimale Informationsgröße nicht erfüllt.

Weitere Überlegungen: Subgruppen wurden mit einem Effekt zugunsten der 2-x-Auto-Transplantation (ohne Angabe von Punktschätzern, Konfidenzintervallen oder p-Werten)

## 12.4.9.2. Nicht transplantierbare Patienten sollen eine kontinuierliche Therapie erhalten.

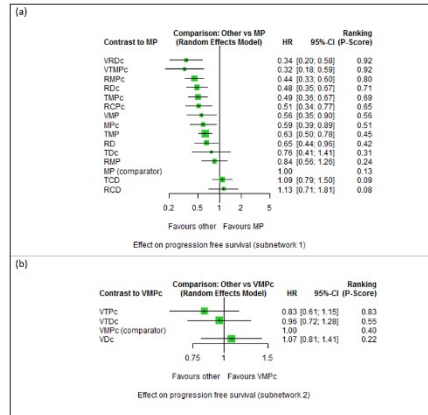
### 12.4.9.2.1. Evidenztabelle

#### 12.4.9.2.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(Piechotta, Jakob et al. 2019)  Network Metaanalysis	RCTs comparing treatment regimes for non-transplant NDMM  Searches run in MEDLINE and CENTRAL until February 2019  Search started in 1999  First-line therapy of interest only; maintenance- or RRMM- studies excluded	MP, MPc, RCD, RCPC, RD, RDC, RMP, RMPc, TCD, TDc, TMP, TMPc, VD, VDC, VMP, VMPc, VRD, VRDc, VTDC, VTMPc, VTPc were compared to each other in a network-meta analysis  Treatments were differentiated between fixed duration and continuous (c) therapy (until	OS PFS QoL SAEs Grade 3 and 4 AEs Withdrawals due to AEs Anemia Infections Neutropenia Polyneuropathy Thrombocytopenia	25 included studies including 11403 patients  NMA-OS:  continuous therapies do not appear superior compared to fixed duration of therapy	Risk of Bias assessed for each included study, cf. RoB Graph  GRADE approach applied  higher P score indicates a greater chance of being the best treatment	Included Studies:  Myeloma XI (Pawlyn, 2017)  EMN01 (Magra-rotto, 2016)  FIRST (Bahlis, 2017)  ECOG E1A06 (Stewart, 2014)  MM-015 (Pallam, 2012)  HOVON 87 (Zweegman, 2016)  Myeloma IX (Morgan, 2011)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen																																																																																				
	Symptomatic MM only; Smouldering MM excluded  Non-transplant only; induc- tion therapy prior to trans- plant excluded	plateau in re- sponse was reached, contin- uous first-line treatment, first- line followed by maintenance)	Thromboem- bolism	<p>(a)</p> <table border="1"> <thead> <tr> <th>Contrast to MP</th> <th>HR</th> <th>95% CI</th> <th>Ranking (P-Score)</th> </tr> </thead> <tbody> <tr><td>VTDc</td><td>0.48</td><td>(0.28, 0.82)</td><td>0.88</td></tr> <tr><td>VTMPc</td><td>0.49</td><td>(0.28, 0.83)</td><td>0.89</td></tr> <tr><td>RD</td><td>0.63</td><td>(0.40, 0.99)</td><td>0.78</td></tr> <tr><td>RDC</td><td>0.69</td><td>(0.47, 1.03)</td><td>0.69</td></tr> <tr><td>WMP</td><td>0.70</td><td>(0.45, 1.07)</td><td>0.87</td></tr> <tr><td>RCPc</td><td>0.74</td><td>(0.44, 1.23)</td><td>0.62</td></tr> <tr><td>TMP</td><td>0.75</td><td>(0.50, 0.97)</td><td>0.62</td></tr> <tr><td>MPc</td><td>0.83</td><td>(0.58, 1.19)</td><td>0.51</td></tr> <tr><td>TMPc</td><td>0.93</td><td>(0.64, 1.35)</td><td>0.38</td></tr> <tr><td>MPc (comparator)</td><td>1.00</td><td>(0.61, 1.67)</td><td>0.31</td></tr> <tr><td>TDC</td><td>1.01</td><td>(0.69, 1.46)</td><td>0.30</td></tr> <tr><td>MP</td><td>1.00</td><td>(0.63, 1.62)</td><td>0.29</td></tr> <tr><td>RDC</td><td>1.10</td><td>(0.87, 1.39)</td><td>0.25</td></tr> <tr><td>RMP</td><td>1.13</td><td>(0.87, 1.49)</td><td>0.22</td></tr> <tr><td>TDC</td><td>1.57</td><td>(0.75, 3.27)</td><td>0.07</td></tr> </tbody> </table> <p>Effect on overall survival (subnetwork 1)</p> <p>(b)</p> <table border="1"> <thead> <tr> <th>Contrast to VMPc</th> <th>HR</th> <th>95% CI</th> <th>Ranking (P-Score)</th> </tr> </thead> <tbody> <tr><td>VMPc (comparator)</td><td>1.00</td><td>(0.78, 1.54)</td><td>0.81</td></tr> <tr><td>VTDc</td><td>1.09</td><td>(0.78, 1.54)</td><td>0.59</td></tr> <tr><td>VDC</td><td>1.12</td><td>(0.80, 1.57)</td><td>0.53</td></tr> <tr><td>VTPc</td><td>1.49</td><td>(1.10, 2.03)</td><td>0.07</td></tr> </tbody> </table> <p>Effect on overall survival (subnetwork 2)</p> <p>NMA-PFS: evidence suggests a superiority of continuous therapies compared to fixed duration of therapy</p>	Contrast to MP	HR	95% CI	Ranking (P-Score)	VTDc	0.48	(0.28, 0.82)	0.88	VTMPc	0.49	(0.28, 0.83)	0.89	RD	0.63	(0.40, 0.99)	0.78	RDC	0.69	(0.47, 1.03)	0.69	WMP	0.70	(0.45, 1.07)	0.87	RCPc	0.74	(0.44, 1.23)	0.62	TMP	0.75	(0.50, 0.97)	0.62	MPc	0.83	(0.58, 1.19)	0.51	TMPc	0.93	(0.64, 1.35)	0.38	MPc (comparator)	1.00	(0.61, 1.67)	0.31	TDC	1.01	(0.69, 1.46)	0.30	MP	1.00	(0.63, 1.62)	0.29	RDC	1.10	(0.87, 1.39)	0.25	RMP	1.13	(0.87, 1.49)	0.22	TDC	1.57	(0.75, 3.27)	0.07	Contrast to VMPc	HR	95% CI	Ranking (P-Score)	VMPc (comparator)	1.00	(0.78, 1.54)	0.81	VTDc	1.09	(0.78, 1.54)	0.59	VDC	1.12	(0.80, 1.57)	0.53	VTPc	1.49	(1.10, 2.03)	0.07		<p>GBRAM0002 (Hungria, 2016)</p> <p>Kim, 2007</p> <p>Ludwig, 2009</p> <p>TMSG (Beksac, 2011)</p> <p>HOVON 49 (Wijer- mans, 2010)</p> <p>IFM 99-06 (Facon, 2007)</p> <p>GISMM2001-A (Paumbo, 2006)</p> <p>MM03 (Sacchi, 2011)</p> <p>IFM 01/01 (Hulin, 2009)</p> <p>NMSG #12 (Waage, 2010)</p> <p>Katsuoka, 2013</p> <p>UPFRONT (Nies- vizky, 2015)</p> <p>VISTA (San Mi- guel, 2008)</p> <p>GEM2005 (Mateos, 2014)</p> <p>Mookerje, 2017</p>
Contrast to MP	HR	95% CI	Ranking (P-Score)																																																																																							
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Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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SWOG S0777 (Durie, 2017)  
E1A05 (Jacobus, 2016)  
GIMEMA-MM-03-05 (Palumbo, 2014)

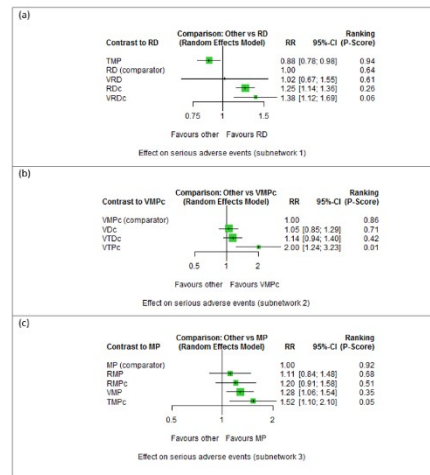
**QoL:**

From baseline until completion of cycle, 10 health-related QoL scores increased steadily for RMPc (+ 12.2 (standard deviation (SD):25.4), P < 0.001), RMP (+ 8.8 (SD; 24.7), P < 0.001), and MP (+ 6.2 (SD:24.6), P < 0.05) and the difference was statistically significant for all groups (Palumbo 2012). The largest increase in global health scores was reported for RMPc (baseline score: 49.6 (SD: 23.5)). However, the baseline score was lower in this group compared to RMP (base-line score: 53.2 (SD: 23.5)) and MP (baseline score: 52.8 (SD: 22.8)), respectively.

**NMA-SAE:**

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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Evidence suggests an increased risk for SAEs for patients treated with continuous therapies compared to fixed duration of therapy



Grade 3 and 4 AEs:

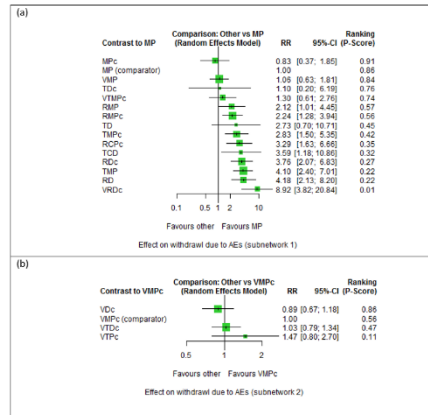
NMA not possible for this outcome

Withdrawals due to AEs:

continuous therapies do not appear inferior compared to fixed duration of therapy



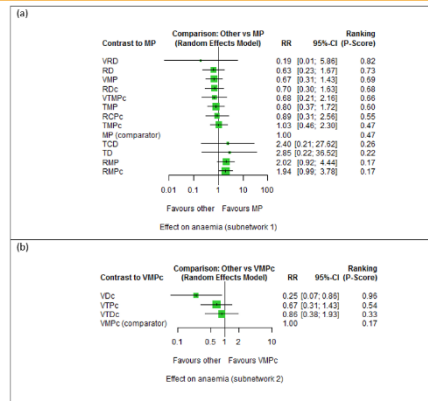
Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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Anemia:

continuous therapies do not appear inferior compared to fixed duration of therapy

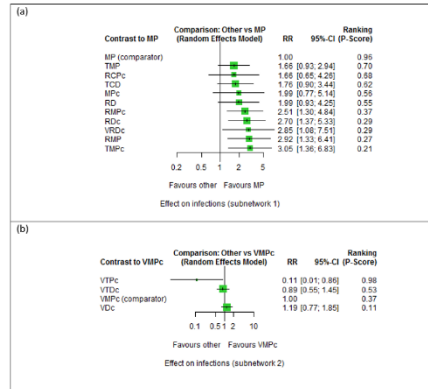
Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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Infections:

evidence suggests a lower risk for infections for fixed duration of therapy compared to continuous therapies

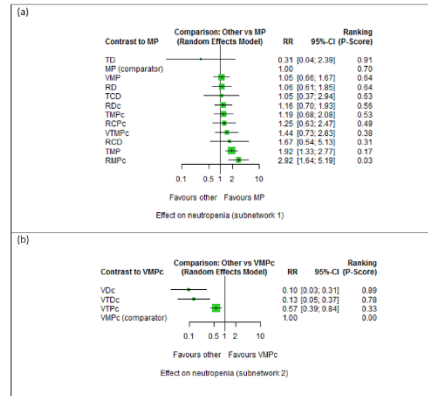
Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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Neutropenia:

evidence suggests a lower risk for neutropenia for fixed duration of therapy compared to continuous therapies

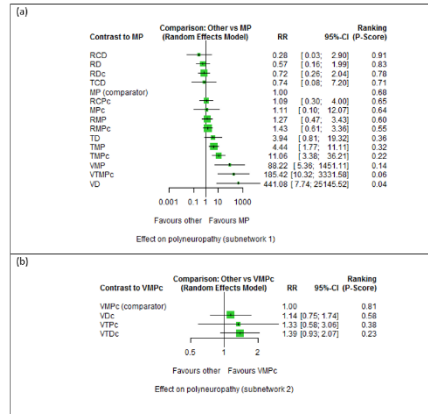
Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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Polyneuropathy:

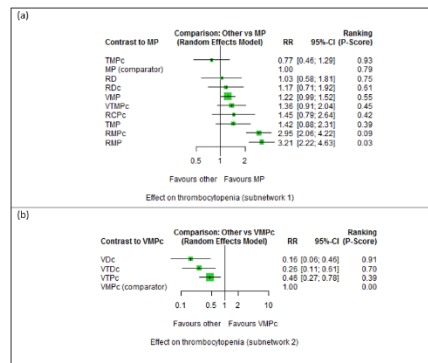
continuous therapies do not appear inferior compared to fixed duration of therapy

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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Thrombocytopenia:

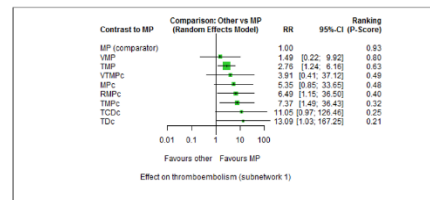
continuous therapies do not appear inferior compared to fixed duration of therapy



Thromboembolism:

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
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evidence suggests a lower risk for thromboembolism for fixed duration of therapy compared to continuous therapies



12.4.9.2.3. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungs- risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegun- gen	Gesamtqualität
	NMA	Gesamtüber- leben	-	-1	-	-	-	⊕⊕⊕⊖ moderate
	NMA	Progressi- onsfreies Überleben	-1	-1	-	-	-	⊕⊕⊖⊖ low
	NMA	Harms	-1	-	-	-	-	⊕⊕⊕⊖ moderate

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	NMA	Lebensqualität	-	-	-1	-1	-	⊕⊕⊕⊖ low

Inkonsistenz: OS: I<sup>2</sup> =53.9%; PFS: I<sup>2</sup>=55.3%

Verzerrungsrisiko: hohes Verzerrungsrisiko für subjective Endpunkte (PFS, AEs) wegen großteils unverblindeten Studiendesigns

Lebensqualität: Ergebnisse Indirekt, da nur eine Studie, die kontinuierliche Therapie mit RMP mit fixer RMP-Therapie verglich, Lebensqualität berichtete. Keine Daten über weitere Therapieregime vorhanden. Ergebnisse unpräzise, da Kriterium die optimale Informationsgröße nicht erfüllt.

## 12.4.10. Erhaltungstherapie

### 12.4.10.1. Allen Patienten soll eine Erhaltungstherapie angeboten werden.

#### 12.4.10.1.1. Evidenztabellen

##### 12.4.10.1.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(McCarthy, Holstein et al. 2017)	- 1208 patients included (605	Maintenance vs. Placebo or observation	5. OS 6. PFS	5. OS - Median OS: has not been reached (maintenance) vs. 86.0 months	- Intention-to-treat analysis	Attal, Lauwers-Cances et al. 2012

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
Meta-analysis	<p>mainte- nance and 603 pla- cebo or ob- servation</p> <ul style="list-style-type: none"> <li>- PubMed</li> <li>- 3 studies met the prespeci- fied inclu- sion criteria</li> </ul> <p>Inclusion crite- ria:</p> <ul style="list-style-type: none"> <li>- RCT in pa- tients with newly diag- nosed MM receiving post-ASCT lenalido- mide before progression</li> <li>- Mainte- nance com- paring a le- nalidomide arm to a placebo or</li> </ul>		<p>7. Harms</p> <p>8. QoL</p>	<p>(placebo/observation), HR 0.75, 95% CI, 0.63 to 0.90, P=0.001</p> <ul style="list-style-type: none"> <li>- 7-year OS: 62% (maintenance) vs. 50% (placebo/observation)</li> <li>- With extended follow-up (88.8 months) the median OS time was: 111.0 months (maintenance) vs. 86.9 months (placebo/observation)</li> </ul> <p>6. PFS</p> <ul style="list-style-type: none"> <li>- Median PFS: 52.8 months (mainte- nance) vs. 23.5 months (pla- cebo/observation), HR 0.48, 95% CI 0.41 to 0.55</li> </ul> <p>7. Harms</p> <ul style="list-style-type: none"> <li>- Blood and lymphatic system disor- ders: 4.3% (maintenance) vs. 2.1% (placebo/observation)</li> <li>- General disorders and administra- tion site conditions: 4.7% (mainte- nance) vs. 1.5% (placebo/observa- tion)</li> <li>- Neoplasms: 4.3% (maintenance) vs. 1% (placebo/observation)</li> </ul>	<ul style="list-style-type: none"> <li>- Some conflicts of in- terest reported</li> <li>- Only one database searched</li> <li>- Search strategy only described in 3 key- words</li> <li>- Did not report the period of time for their search</li> <li>- Indirectness: no limi- tations</li> <li>- Heterogeneity: <ul style="list-style-type: none"> <li>o Pignon heteroge- neity test indi- cated a signifi- cant difference in quantitative treatment effect across studies (P=0.047)</li> <li>o No qualitative heterogeneity in OS was found using the Gail-Si- mon test (P=0.75)</li> </ul> </li> </ul>	Palumbo, Cavallo et al. 2014



Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	<ul style="list-style-type: none"> <li>observation arm</li> <li>- achieved database lock for the primary efficacy analysis</li> <li>- primary-source patient-level data or available documentation</li> </ul>			<ul style="list-style-type: none"> <li>- Skin and subcutaneous tissue disorders: 3.4% (maintenance) vs. 1.9% (placebo/observation)</li> <li>- Nervous system disorders: 3.4% (maintenance) vs. 1.7% (placebo/observation)</li> <li>- Gastrointestinal disorders: 3.4% (maintenance) vs. 0.2% (placebo/observation)</li> </ul> <p>8. QoL</p> <ul style="list-style-type: none"> <li>- Not reported</li> </ul> <p>Median follow-up: 79.5 months (range 0.0 to 114.3 months)</p>	<ul style="list-style-type: none"> <li>o The heterogeneity observed is driven by the difference in magnitude of the treatment effect among the studies.</li> <li>o Heterogeneity in OS was mainly a result of differences between the GALGB and IFM studies (P=0.015 for treatment by study interaction)</li> <li>o No significant heterogeneity between GALGB and GIMEMA (P=0.525 for treatment by study interaction)</li> </ul>	

## 12.4.10.1.3. Ergänzende Einzelstudien

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Be- merkungen/ Evi- denzklasse
	<p>Phase 3, multi-center, open-label, randomized FIRST (Frontline Investigation of Revlimid and Dexamethasone Versus Standard Thalidomide) trial</p> <p>Randomisation in a 1:1:1 ratio</p> <p>Inclusion criteria:</p> <p>Newly diagnosed MM</p> <p>aged <math>\geq 65</math> years or <math>&lt; 65</math> years</p> <p>ineligible for stem cell transplant</p> <p>previously untreated, symptomatic and measurable MM as</p>	<p>RD continuous</p> <p>lenalidomide plus low-dose dexamethasone until disease progression</p>	<p>72-weeks</p> <p>RD18</p> <ul style="list-style-type: none"> <li>lenalidomide plus low-dose dexamethasone until disease progression</li> </ul> <p>MPT</p> <ul style="list-style-type: none"> <li>melphalan, prednisone and thalidomide for 12 cycles</li> </ul>	<ol style="list-style-type: none"> <li>OS</li> <li>PFS</li> <li>Harms</li> <li>QoL</li> </ol>	<ol style="list-style-type: none"> <li>OS <ul style="list-style-type: none"> <li>Rd continuous improved survival in all subgroups of responders compared with MPT</li> <li>RDC vs. RD18: HR: 1.02 (95%CI: 0.86 to 1.2)</li> <li>RDC vs. TMP: HR: 0.78 (95%CI: 0.67 to 0.92)</li> </ul> </li> <li>PFS <ul style="list-style-type: none"> <li>Rd continuous treatment prolonged PFS in responding patients with MPT and Rd18, with a reduction in the risk of progression or death by 35% and 38%</li> <li>RDC vs. RD18: HR: 0.7 (95%CI: 0.6 to 0.81)</li> <li>RDC vs. TMP: HR: 0.69 (95%CI: 0.59 to 0.79)</li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>Some conflicts of interest reported</li> <li>Sponsor was also included in analysis and interpretation of the data</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Be- merkungen/ Evi- denzklasse
	<p>defined by International Myeloma Working Group criteria</p> <p>Eastern Cooperative Oncology Group performance status score of 0-2</p> <p>Exclusion criteria:</p> <p>Patients who had received any prior antimyeloma treatment (with the exception of radiotherapy, bisphosphonates or short-term steroids)</p> <p>Patients with laboratory abnormalities including absolute neutrophil count <math>&lt;1.0 \times 10^9/l</math></p>				<p>-</p> <p>3. Harms</p> <p>4. QoL</p> <p>1. Median follow-up: 45.5 months</p>	

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Be- merkungen/ Evi- denzklasse
	<p>untransfused platelet count <math>&lt;50 \times 10^9/l</math></p> <p>aspartate aminotransferase or alanine aminotransferase <math>43.0 \times</math> the upper limit of normal</p> <p>renal failure requiring dialysis</p> <p>peripheral neuropathy <math>\geq</math> grade 2</p> <p>history of malignancies, other than multiple myeloma, within the last 3 or fewer years</p>					
	<p>Open-label, randomised, phase 3, adaptive design trial</p> <p>3 randomisation stages</p> <p>Randomisation from January</p>	Maintenance (lenalidomide)	observation	<ol style="list-style-type: none"> <li>1. OS</li> <li>2. PFS</li> <li>3. Harms</li> <li>5. QoL</li> </ol>	<ol style="list-style-type: none"> <li>1. OS</li> </ol> <ul style="list-style-type: none"> <li>- Median OS: not reached in both groups</li> <li>- 3-year OS: 78.6% (maintenance, 95% CI 75.6 to 81.6) vs. 75.8% (observation,</li> </ul>	<ul style="list-style-type: none"> <li>- Intention-to-treat analysis</li> <li>- Funders of the study had no role in study design, data collection, data analysis, data interpretation or</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Be- merkungen/ Evi- denzklasse
	<p>2011 to August 2017</p> <p>1:1 ratio (January 2011 to June 2013) and 2:1 ratio (June 2013 to August 2017)</p> <p>1917 patients recruited</p> <p>Maintenance group:</p> <ul style="list-style-type: none"> <li>- 1137 patients assigned</li> <li>- 1097 received allocated intervention</li> <li>- 456 PFS-events and 234 OS-events</li> <li>- 671 patients alive and progression free</li> </ul> <p>Observation group:</p>				<p>95% CI 72.4 to 79.2), HR 0.87 (95% CI 0.73 to 1.05)</p> <ul style="list-style-type: none"> <li>- 5-year OS: 61.3% (maintenance, 95% CI 56.6 to 66.1) vs. 56.5% (observation, 95% CI 51.5 to 61.7)</li> <li>- No difference was detected between maintenance and observation group (HR 0.87, 95% CI 0.73 to 1.05, p=0.15)</li> </ul> <p>2. PFS</p> <ul style="list-style-type: none"> <li>- Median PFS: 39 months (maintenance, 95% CI 36 to 42) vs. 20 months (observation, 95% CI 18 to 22), HR 0.46 (95% CI 0.41 to 0.53, p&lt;0.0001)</li> </ul> <p>3. Harms</p> <ul style="list-style-type: none"> <li>- Grade 3 or 4 neutropenia: 33% (maintenance) vs.</li> </ul>	<p>writing of the report</p> <ul style="list-style-type: none"> <li>- Heterogeneity statistic: <math>I^2=54.6</math> → potential moderate heterogeneity</li> <li>- No analysis of risk of bias was undertaken</li> <li>- Some conflicts of interest reported</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Be- merkungen/ Evi- denzklasse
	<ul style="list-style-type: none"> <li>- 834 patients assigned</li> <li>- 834 received allocated intervention</li> <li>- 533 PFS-events and 226 OS-events</li> <li>- 294 patients alive and progression free</li> </ul> <p>At the time of analysis, median duration of lenalidomide maintenance therapy was 18 cycles (IQR 6-30)</p> <p>Inclusion criteria:</p> <p>18 years or older</p> <p>Symptomatic or non-secretory MM based on</p>				<ul style="list-style-type: none"> <li>- Grade 3 or 4 thrombocytopenia: 7% (maintenance) vs.</li> <li>- Grade 3 or 4 anaemia: 4% (maintenance) vs.</li> <li>4. QoL</li> <li>- Not reported</li> <li>5. Median follow up: 31 months</li> </ul>	

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Be- merkungen/ Evi- denzklasse
	<p>bone marrow clonal plasma cells, organ or tissue impairment considered by the clinician to be myeloma related</p> <p>Paraprotein (M-protein) in serum or urine</p> <p>Patients who had completed their assigned induction therapy as per protocol and had achieved at least a minimal response to protocol treatment, including lenalidomide</p> <p>Exclusion criteria: Previous or concurrent malignancies, includ-</p>					

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Be- merkungen/ Evi- denzklasse
	<p>ing myelodys- plastic syn- dromes</p> <p>Previous treat- ment for mye- loma (except lo- cal radiotherapy, bisphosphonates and corticoster- oids)</p> <p>Grade 2 or worse peripheral neu- ropathy</p> <p>Acute renal fail- ure (unrespon- sive to up to 72h of rehydration, characterised by creatinine &gt;500 µmol/L or urine output &lt;400mL per day, or re- quiring dialysis)</p> <p>Active or previ- ous hepatitis C infection</p>					



12.3.9.1.1 GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA, RCTs	Gesamtüberleben	-	-	-	-	-	⊕⊕⊕⊕ high
	SR/MA, RCTs	Progressionsfreies Überleben	-1	-	-	-	-	⊕⊕⊕⊖ moderate
	SR/MA, RCTs	Harms	-1	-	-	-	-	⊕⊕⊕⊖ moderate
	SR/MA, RCTs	Lebensqualität	-	-	-	-	-	Not reported

Hohes Verzerrungsrisiko für subjektive Endpunkte (PFS, Harms), da eingeschlossene Studien unverblindet

12.4.11. Wahl der Rezidivtherapie (1.-3. Rezidiv)

12.4.11.1. Fitte Patienten mit frühem Rezidiv nach autologer Stammzelltransplantation, kann eine allogene Stammzelltransplantation angeboten werden. Wenn möglich, sollte dies im Rahmen einer klinischen Studien erfolgen.

12.4.11.1.1. Evidenztabellen

12.4.11.1.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
(Yin, Tang et al. 2018) SR+MA	Inclusion criteria:		1. OS 2. PFS	Total of 61 citations with n=8698 eligible patients included	Quality assessment: 5 items used to evaluate study quality: conditioning regimens, stem cell	N=61 studies (please refer to report for details)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen / Evidenz- klasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	<ul style="list-style-type: none"> <li>- Studies involving patient with MM</li> <li>- Treatment with allo-SCT</li> <li>- Sample-size <math>\geq</math> 5</li> <li>- Date of publication 01.2007-05.2017</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>- Use of cord blood as stem</li> </ul>		<ul style="list-style-type: none"> <li>3. AEs</li> <li>4. HRQoL</li> </ul>	<p>Sample size varied from 7-1667 patients</p> <p>Follow-up ranged from 1-217.2 months</p> <p>Patients age ranged from 21-77 years</p> <p>Quality assessment: 29 studies of good quality, 25 studies of moderate quality, 7 studies of low quality</p> <ol style="list-style-type: none"> <li>1. <b>OS:</b> OS benefit for patients who underwent planned auto-SCT before allo-SCT compared to allo-SCT directly (RR: 1.28; 95%CI: 1.11-1.49); auto-allo vs. tandem-auto (RR: 0.91; 95%CI: 0.77-1.06); reduced-intensity conditioning vs. myeloablative conditioning (RR:0.88; 95%CI: 0.74-1.05), high-cytogenic risk patients vs. standard risk (RR: 0.83; 95%CI: 0.67-1.03); PBSC vs. BM (HR: 1.02; 95%CI: 0.53-1.96); allo-SCT as first-line vs. allo-SCT as salvage-therapy (RR: 1.42; 95%CI: 1.14-1.78)</li> <li>2. <b>PFS:</b> auto-allo-SCT vs. tandem-auto (RR:1.27; 95%CI: 0.84-1.93), auto-SCT before allo-SCT vs. allo-SCT directly (RR: 1.46; 95%CI: 1.19-1.80), allo-SCT as salvage vs. younger patients or patients receiving allo-SCT</li> </ol>	<p>source, donor, GvHD prophylaxis regimen, and disease status before allo-SCT. When articles provided one corresponding item, 1 was given to the study or otherwise 0. Only studies received 5 scores were deemed as good quality, 4 scores were moderate quality and 3 scores were low quality.</p> <p>Publication bias: Egger test find substantial publication bias' evidence in 5-year PFS, 5-year OS and exGVHD (<math>p = 0.046</math>, <math>p = 0.036</math>, <math>p = 0.013</math>, respectively)</p> <p>COI: Authors declared no competing interests</p> <p>Funding: supported by Grants of National Natural Science Foundation of China</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen / Evidenz- klasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	<ul style="list-style-type: none"> <li>cell source</li> <li>- Patients with various haematological malignancies without myeloma-subgroup reporting</li> <li>- Use of wide variety of transplant strategies</li> </ul>			<p>as first-line (RR: 0.36; 95%CI: 0.25-0.51)</p> <p>3. <b>AEs:</b> acute Grade 2-4 GvHD incidence rate: 2.3-69.9%; extensive chronic GvHD incidence rate: 5.1-46.3%</p> <p>4. <b>HRQoL</b> not reported</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	- Lack of outcome data					

#### 12.4.11.1.3. Ergänzende Einzelstudien

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Bashir, Khan et al. 2013) Phase II RCT	N = 50 Recruiting period: 04.2002-04.2011 Patient characteristics: - All but two had received at least one auto-HCT and 80% of patients had experienced at least one relapse prior to allo-HCT. - Significantly more FM100 patients had MSD allo-HCT vs FM140 patients. Inclusion criteria: - NDMM or RRMM - age ≤ 70 years	FM100 followed by allo-HCT (n=23): fludarabine + melphalan 100 mg/m <sup>2</sup>	FM140 followed by allo-HCT (n=27): fludarabine + melphalan 140 mg/m <sup>2</sup>	5. OS 6. PFS 7. AEs 8. HRQoL Additional endpoints: 9. one-year TRM 10. TTPE 11. GVHD 12. ORR	1. <b>Median OS:</b> FM100: 35.1 months vs. FM140: 19.7 months (p=0.38) 2. <b>Median PFS:</b> FM100: 11.7 months vs. FM140: 8.4 months (p=0.12) 3. <b>AEs:</b> FM100: in 19 patients (82%) vs. FM140: in 23 patients (85%) (p=1.0) 4. <b>HRQoL:</b> not reported 5. <b>1y-TRM:</b> FM100: 13% vs. FM140: 15% (p=1.0) 6. <b>TTPE:</b> FM100: 12.5 days vs. FM140: 13 days (p=0.27) 7. <b>GVHD:</b> acute: Grade 1: 8 vs. 12 patients, Grade 2: 5 vs. 6 patients, Grade 3-4: 1 vs. 6 patients; chronic: 11 vs. 8 patients (respectively FM100 vs FM 140)	randomization : using Pocock-Simon dynamic allocation method - blinding not described - small sample size - no flowchart available, response rates assessed for all participants, GVHD-data only for 48 available - no COIs - Financial Disclosure: None

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	- ...				8. <b>ORR:</b> 83% vs. 82%, <b>CR:</b> 26% vs. 26%, <b>VGPR:</b> 22% vs. 26%, <b>PR:</b> 35% vs. 30% (respectively FM100 vs. FM140)	

12.4.11.1.4. *Evidenz der NICE-Leitlinie: Übernommen aus Appendix G (S. 226-232) und Tabelle 30-35.*

Study	Population	Intervention	Comparator	Results	Additional comment																																									
<p>Björkstrand et al., 2011</p> <p>Prospective study Multi-centre</p> <p>Europe</p>	<p>newly diagnosed</p> <p>357 patients with myeloma up to age 69 years were enrolled from 2001 to 2005. Patients with an HLA-identical sibling donor were allocated to the auto-allo arm (n=108) and patients without a matched sibling donor were allocated to the auto arm (n=249).</p> <p>Median time of follow-up after inclusion (i.e., the first ASCT) was 61 months (range, 21 to 91 months) for patients alive at last follow-up.</p>	<p>Of the 108 patients allocated to the auto-allo arm, 91 received an RIC alloSCT</p> <p>Median time between autograft and allograft was 4.2 months (range, 1.3 to 22.2 months)</p> <p>65 male, 43 female Median age 54 (34-66)</p>	<p>Patients without a matched sibling donor received either no further treatment (n=145) or, at the discretion of the centre, a second ASCT as part of a tandem transplantation program (n=104).</p> <p>146 male, 103 female Median age 57 (31-69)</p>	<p>Cytogenetic analysis with respect to chromosome 13 deletion was performed in 214 patients by FISH.</p> <table border="1"> <thead> <tr> <th></th> <th>allo</th> <th>2<sup>nd</sup> auto</th> </tr> </thead> <tbody> <tr> <td>Del(13)</td> <td>29</td> <td>63</td> </tr> <tr> <td>no Del(13)</td> <td>34</td> <td>88</td> </tr> </tbody> </table> <p><b>Del(13)</b></p> <table border="1"> <thead> <tr> <th></th> <th>PFS at 60 months (95% CI)</th> <th>OS at 60 months (95% CI)</th> <th>relapse/ progression risk</th> </tr> </thead> <tbody> <tr> <td>allo</td> <td>31% (18% - 53%)</td> <td>69% (54% - 88%)</td> <td>55% (39% - 77%)</td> </tr> <tr> <td>2<sup>nd</sup> auto</td> <td>11% (5% - 22%)</td> <td>55% (44% - 69%)</td> <td>86% (78% - 96%)</td> </tr> <tr> <td></td> <td>P=.002</td> <td>P=.003</td> <td>P=.004</td> </tr> </tbody> </table> <p><b>no Del(13)</b></p> <table border="1"> <thead> <tr> <th></th> <th>PFS at 60 months (95% CI)</th> <th>OS at 60 months (95% CI)</th> <th>relapse/ progression risk</th> </tr> </thead> <tbody> <tr> <td>allo</td> <td>44% (30% - 64%)</td> <td>70% (56% - 88%)</td> <td>39% (25% - 60%)</td> </tr> <tr> <td>2<sup>nd</sup> auto</td> <td>20% (12% - 32%)</td> <td>61% (51% - 73%)</td> <td>76% (67% - 87%)</td> </tr> <tr> <td></td> <td>P=.017</td> <td>P = .363</td> <td>P=.005</td> </tr> </tbody> </table>		allo	2 <sup>nd</sup> auto	Del(13)	29	63	no Del(13)	34	88		PFS at 60 months (95% CI)	OS at 60 months (95% CI)	relapse/ progression risk	allo	31% (18% - 53%)	69% (54% - 88%)	55% (39% - 77%)	2 <sup>nd</sup> auto	11% (5% - 22%)	55% (44% - 69%)	86% (78% - 96%)		P=.002	P=.003	P=.004		PFS at 60 months (95% CI)	OS at 60 months (95% CI)	relapse/ progression risk	allo	44% (30% - 64%)	70% (56% - 88%)	39% (25% - 60%)	2 <sup>nd</sup> auto	20% (12% - 32%)	61% (51% - 73%)	76% (67% - 87%)		P=.017	P = .363	P=.005	<p>Although del(13) is an optimal prognostic marker for outcome, at the time the study was being done this was the only chromosomal aberration that could be adequately analyzed across most centres.</p> <p>It is still of some value since it is often associated with new better prognostic chromosomal markers which indicate poor prognosis (del(17p), t(14;16), t(14;20)).</p> <p>For update at 96 months see Gahrton et al., 2012</p>
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<p>Bruno et al., 2007</p> <p>Prospective Multicentre</p> <p>Italy</p>	<p>newly diagnosed</p> <p>The study enrolled 245 consecutive patients 65 years of age or younger with stage II or III myeloma at five Italian centres.</p> <p>Of these 245 patients, 199 had siblings, and 162 of the patients who had siblings</p>	<p>Auto-allo transplant (nonmyeloablative)</p> <p>N=58</p> <p>30 male, 28 female</p> <p>Mean age 55 years (34-65)</p>	<p>Tandem auto transplant</p> <p>N=46</p> <p>27 male, 19 female</p> <p>Mean age 55 years (33-63)</p>	<p>The availability of an HLA-identical sibling and, therefore, the possibility of receiving an allograft were significantly associated with longer overall survival (HR 0.35; 95% CI, 0.19- 0.64; P = 0.001) and event-free survival (HR, 0.54; 95% CI, 0.35-0.81; P = 0.003).</p> <p>In a stratified analysis that classified patients with high <math>\beta</math>2-microglobulin levels or with chromosome 13 abnormalities as being at high risk, the adjusted hazard ratios were 0.34 (95% CI, 0.10 to 1.18) for overall survival and 0.52 (95% CI, 0.22 to 1.21) for event-free survival.</p>																																										

Study	Population	Intervention	Comparator	Results	Additional comments
	<p>underwent HLA typing to determine whether they had potential HLA-identical donors.</p> <p>median follow-up 45 months (range: 21 to 90)</p>				
<p>Efebera et al., 2010</p> <p>Retrospective analysis Single-centre</p> <p>USA</p>	<p>Relapsed</p> <p>51 patients with heavily pre-treated relapsed myeloma</p> <p>27 males, 24 females Median age 51 years (32-65)</p> <p>Median follow-up in surviving patients was 27 months (3–98).</p>	<p>RIC allo STC</p> <p>Median time from diagnosis to allo HCT was 34 months</p>	n/a	<p>Multivariate Factors affecting OS and PFS:</p> <p>Age, Immunoglobulin subtype (IG), serum lactate dehydrogenase (LDH), serum albumin, stem cell source, donor type, use of DLI, interval between diagnosis and allo SCT or interval between auto and allo SCT did not emerge as statistically significant predictors of outcome.</p>	<p>Non-comparative/si intervention study b included as study re predictive factors.</p>
<p>Freytes et al., 2014</p> <p>Retrospective analysis of a multicentre database</p> <p>USA</p>	<p>Relapsed</p> <p>The study population comprised of myeloma patients &lt;65 years who had relapsed/progressed after prior autologous transplant and subsequently received NST/RIC allogeneic transplant or a 2nd autotransplant between 1995 and 2008</p> <p>Median follow-up of NST/RIC survivors is 30 months (range, 2–98 months) and 29 months for patients who underwent a 2nd autotransplant (range, 3–97 months).</p>	<p>152 subjects received NST/RIC (32 from HLA-identical siblings and 120 from HLA-matched unrelated donors</p> <p>90 male, 62 female median age 53 (32 – 65)</p>	<p>137 subjects received a 2nd autotransplant</p> <p>84 male, 53 female median age 56 years (28 – 65)</p>	<p>Durie-Salmon stage III.</p> <p>In these patients, allotransplant was associated with a higher risk relapse and treatment-failure compared to autotransplantation (HR 3.05, 95% CI, 2.20–4.22; p = 0.001).</p> <p>Patients who underwent NST/RIC from related and unrelated donors had a similar outcome.</p> <p>The 3-year OS of patients who underwent NST/RIC from related donors was 19% (95% CI: 7–33) compared to patients whose donors were unrelated, 21% (95% C: 14–28).</p> <p>The TRM was also similar irrespective of donor type (HR 1.077, 95% CI 0.75–1.54, p = 0.68).</p>	<p>Major limitations of study are the absence of cytogenetic data and paucity of other prognostic factors available in the NST/RIC cohort. 25% of the NST/RIC patients had these data available</p>



Study	Population	Intervention	Comparator	Results	Additional comment																		
<p>Gahrton et al., 2013</p> <p>Update at a median follow-up of 96 months of Björkstrand et al. that prospectively compares auto/RIC allo to auto.</p> <p>Europe.</p>	<p>newly diagnosed</p> <p>See Björkstrand et al</p> <p>Median time of follow-up after inclusion (i.e., the first ASCT) was 96 months (range, 47 to 127 months) for patients alive at last follow-up.</p>	<p>See Björkstrand et al</p>	<p>See Björkstrand et al</p>	<p><b>Del(13)</b></p> <table border="1"> <thead> <tr> <th></th> <th>PFS at 96 months (95% CI)</th> <th>OS at 96 months (95% CI)</th> </tr> </thead> <tbody> <tr> <td>allo</td> <td>21%</td> <td>47%</td> </tr> <tr> <td>2<sup>nd</sup> auto</td> <td>5%</td> <td>31%</td> </tr> </tbody> </table> <p><b>no Del(13)</b></p> <table border="1"> <thead> <tr> <th></th> <th>PFS at 96 months (95% CI)</th> <th>OS at 96 months (95% CI)</th> </tr> </thead> <tbody> <tr> <td>allo</td> <td>26%</td> <td>55%</td> </tr> <tr> <td>2<sup>nd</sup> auto</td> <td>16%</td> <td>46%</td> </tr> </tbody> </table> <p>Patients with or without the del(13) abnormality had similar outcome when treated with auto/RIC allo and better outcome than those with auto. This is in contrast to the outcome with auto, which was poorer in patients with the del(13) abnormality than in those without.</p>		PFS at 96 months (95% CI)	OS at 96 months (95% CI)	allo	21%	47%	2 <sup>nd</sup> auto	5%	31%		PFS at 96 months (95% CI)	OS at 96 months (95% CI)	allo	26%	55%	2 <sup>nd</sup> auto	16%	46%	<p>See Björkstrand et al</p>
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<p>Garban et al., 2006</p> <p>Prospective study multicentre</p> <p>France &amp; Switzerland</p>	<p>newly diagnosed 284 patients</p> <p>High risk myeloma: Patients younger than 65 years who had Durie-Salmon stage I (one bone lesion), II, or III myeloma and initial biologic features chr13 deletion (FISH analysis) and B2-microglobulin levels greater than 3 mg</p> <p>When an HLA-identical sibling donor was identified at diagnosis, the patient was offered dose-reduced allogeneic stem cell transplantation after ASCT.</p> <p>Patients who had no donor underwent tandem ASCT.</p> <p>Median follow-up time of</p>	<p>RIC-Allo SCT (n=65)</p> <p>32 male, 33 female Median age 54 (36-65)</p> <p>46 patients completed the entire program</p> <p>The median time between diagnosis and ASCT was 153 days (range, 120-226 days), and it was 73 days (range, 44-92 days) between ASCT and dose-reduced allograft.</p>	<p>Second ASCT (n=219)</p> <p>114 male, 105 female Median age 58 (28-65)</p>	<p>Combination of ASCT followed by allogeneic transplant was not superior to tandem ASCT.</p> <p>OS and EFS – no significant difference.</p> <table border="1"> <thead> <tr> <th></th> <th>EFS</th> <th>OS</th> </tr> </thead> <tbody> <tr> <td>RIC-Allo</td> <td>31.7 months</td> <td>35 months</td> </tr> <tr> <td>2<sup>nd</sup> auto</td> <td>35 months</td> <td>47.2 months</td> </tr> <tr> <td></td> <td>P=0.35</td> <td>P=0.07</td> </tr> </tbody> </table> <p>There was a trend for better OS for the patients in the tandem transplantation trial than for patients treated with the combination of ASCT followed by mini-allogeneic transplantation.</p>		EFS	OS	RIC-Allo	31.7 months	35 months	2 <sup>nd</sup> auto	35 months	47.2 months		P=0.35	P=0.07							
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Study	Population	Intervention	Comparator	Results	Additional comments																																								
	24 months.																																												
<p>Krishnan et al., 2011</p> <p>Phase 3 multicentre trial</p> <p>USA</p>	<p>newly diagnosed</p> <p>710 patients with multiple myeloma within 10 months from initiation of induction therapy were classified as standard (SRD) or high risk (HRD) disease based on cytogenetics and beta-2-microglobulin levels. (standard risk : <math>\beta</math>-2 microglobulin was &lt; 4 mg/L and no deletion of chr 13)</p> <p>Assignment to auto-allo HCT was based on availability of an HLA-matched sibling donor.</p> <p>Median follow up of the study population is 40 months (inter-quartile range 38–43 months)</p>	<p>allogeneic transplant using a non-myeloablative conditioning</p> <p>standard risk: n=156 111 male, 78 female Median age 53 (29-68)</p> <p>High risk: N=29 21 male, 16 female Median age 51 (32-66)</p>	<p>second autologous transplant</p> <p>standard risk: n=366 260 male, 176 female Median age 55 (22-70)</p> <p>High risk: n=31 27 male, 21 female Median age 57 (32-70)</p>	<p><b>Standard risk</b></p> <table border="1"> <thead> <tr> <th></th> <th>3 yr PFS</th> <th>3 yr OS</th> <th>Relapse/pr ogression at 3 yrs</th> <th>3 yr TRM</th> </tr> </thead> <tbody> <tr> <td>allo</td> <td>43% (36% - 51%)</td> <td>77% (72% - 84%)</td> <td>46% (39% - 54%)</td> <td>11% (7% - 16%)</td> </tr> <tr> <td>2<sup>nd</sup> auto</td> <td>46% (42% - 51%)</td> <td>80% (77% - 84%)</td> <td>50% (46% - 55%)</td> <td>4% (2% - 5%)</td> </tr> <tr> <td></td> <td>P=0.671</td> <td>P=0.191</td> <td>P=0.402</td> <td>P&lt;0.001</td> </tr> </tbody> </table> <p><b>High risk</b></p> <table border="1"> <thead> <tr> <th></th> <th>3 yr PFS</th> <th>3 yr OS</th> <th>Relapse/pr ogression at 3 yrs</th> <th>3 yr TRM</th> </tr> </thead> <tbody> <tr> <td>allo</td> <td>40% (47% - 60%)</td> <td>59% (45% - 78%)</td> <td>38% (22% - 54%)</td> <td>22% (8% - 35%)</td> </tr> <tr> <td>2<sup>nd</sup> auto</td> <td>33% (22% - 50%)</td> <td>67% (54% - 82%)</td> <td>57% (42% - 71%)</td> <td>11% (2% - 19%)</td> </tr> <tr> <td></td> <td>P=0.743</td> <td>P=0.460</td> <td>P=0.079</td> <td>P=0.311</td> </tr> </tbody> </table>		3 yr PFS	3 yr OS	Relapse/pr ogression at 3 yrs	3 yr TRM	allo	43% (36% - 51%)	77% (72% - 84%)	46% (39% - 54%)	11% (7% - 16%)	2 <sup>nd</sup> auto	46% (42% - 51%)	80% (77% - 84%)	50% (46% - 55%)	4% (2% - 5%)		P=0.671	P=0.191	P=0.402	P<0.001		3 yr PFS	3 yr OS	Relapse/pr ogression at 3 yrs	3 yr TRM	allo	40% (47% - 60%)	59% (45% - 78%)	38% (22% - 54%)	22% (8% - 35%)	2 <sup>nd</sup> auto	33% (22% - 50%)	67% (54% - 82%)	57% (42% - 71%)	11% (2% - 19%)		P=0.743	P=0.460	P=0.079	P=0.311	
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<p>Lokhorst et al., 2012</p> <p>Prospective multicentre study</p> <p>Netherlands</p>	<p>Newly diagnosed</p> <p>donor versus no-donor analysis of patients included in the phase 3 HOVON-50MMtrial.</p> <p>266 patients having received an autologous-SCT fulfilled the criteria to be included, 138 patients without an HLA-identical sibling donor and 122 patients with a donor</p> <p>Median follow-up of 77 months.</p>	<p>donor n=122 71 male, 51 female Median age 54 (32-65)</p> <p>99 allo-RIC 15 maintenance 8 no treatment</p> <p>Median time between auto and allo was 3.9 months</p>	<p>no donor n=138 93 male, 45 female Median age 54 (30-65)</p> <p>97 patients started with maintenance 3 high dose melphan 41 no treatment</p>	<p>ISS stage III</p> <table border="1"> <thead> <tr> <th></th> <th>5-year PFS</th> <th>5-year OS</th> </tr> </thead> <tbody> <tr> <td>Maintenance of second HDM</td> <td>41%</td> <td>65%</td> </tr> <tr> <td>Second auto n=17</td> <td>13%</td> <td>42%</td> </tr> <tr> <td></td> <td>P=0.17</td> <td>P=0.55</td> </tr> </tbody> </table> <p>B2M great than 3 mg/L</p> <table border="1"> <thead> <tr> <th></th> <th>5-year PFS</th> <th>5-year OS</th> </tr> </thead> <tbody> <tr> <td>Allo SCT n=46</td> <td>35%</td> <td>59%</td> </tr> <tr> <td>Other treatment n=47</td> <td>15%</td> <td>42%</td> </tr> <tr> <td></td> <td>P=0.13</td> <td>P=0.31</td> </tr> </tbody> </table>		5-year PFS	5-year OS	Maintenance of second HDM	41%	65%	Second auto n=17	13%	42%		P=0.17	P=0.55		5-year PFS	5-year OS	Allo SCT n=46	35%	59%	Other treatment n=47	15%	42%		P=0.13	P=0.31	<p>Among the 260 patients included in this analysis there were 224 (86%) with conventional karyotyping data available. However, 23 patients had del(13/13q), of whom only 10 received an SCT. These numbers are too small to draw any conclusion.</p>																
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Study	Population	Intervention	Comparator	Results	Additional comments
				In the subgroup of donor-patients who actually received an allo-SCT, higher age was significantly associated with worse PFS (HR = 1.04, 95% CI = 1.01-1.07, P = .02) and OS (HR = 1.05, 95% CI = 1.01-1.09, P = .01)	
Patriarca et al., 2012  Retrospective analysis multicentre  Italy	Relapsed  169 patients with myeloma who relapsed after auto-SCT underwent HLA typing and search for a donor. 75 patients found a donor (median age 55 years (34-68)) and 68 underwent allo-SCT.  Median follow-up after the beginning of salvage treatment was 19 months (range 1-97) in all patients and 29 months (range 6-88) in surviving patients.	allo-SCT	n/a	Variables considered as possible prognostic factors: <ul style="list-style-type: none"> <li>- time between diagnosis and allo-SCT (months)</li> <li>- disease status before SCT (responsive or unresponsive)</li> <li>- donor (sibling or unrelated)</li> <li>- HLA typing (HLA-matched related versus HLA-matched unrelated versus HLA-mismatched unrelated)</li> <li>- stem cell source (bone marrow or peripheral blood),</li> <li>- ATG (yes or no)</li> <li>- acute GVHD (grade 0-I or grade II-IV)</li> <li>- chronic GVHD (absent or present),</li> <li>- donor lymphocyte infusion (DLI; yes or no)</li> </ul> Prognostic factors that were significantly ( $P \leq .10$ ) associated with PFS in the univariate proportional hazards model: <ul style="list-style-type: none"> <li>• interval between diagnosis and allo-SCT (HR, 1.01; 95%CI, 1.00-1.02; P=.08)</li> <li>• progressive disease before transplant (HR, 4.27; 95%CI, 1.01-16.56; P=.04)</li> <li>• development of chronic GVHD (HR, 0.43; 95%CI, 0.18-1.04; P=.06)</li> </ul> The final survival model showed no significant prognostic factors for PFS.  The variables with a significant association with OS in univariate analysis: <ul style="list-style-type: none"> <li>• interval between auto-SCT and relapse (HR, 1.012; 95%CI, 1.00-1.04; P=.08)</li> <li>• progressive disease before transplant (HR, 3.74; 95%CI, 0.81-17.28; P=.09)</li> <li>• T cell depletion with ATG (HR, 0.52; 95%CI, 0.26-1.05; P=.07)</li> <li>• development of chronic GVHD (HR, 0.32; 95%CI, 0.10-0.95; P=.04).</li> </ul> In multivariate analysis, development of chronic GVHD maintained a protective effect on OS (HR, 0.11; 95%CI, 0.17-0.68; P=.02), whereas an increased interval between auto-SCT and relapse was associated with poor OS (HR, 1.07; 95% CI, 1.01-1.13; P=.02).	Non-comparative/si intervention study b included as study re predictive factors.
Qazilbash et al., 2006  Retrospective analysis  USA	Relapsed  patients relapsing after an autograft  In general, younger patients (up to age 65 yrs) with available human	RIC allo  N=26  15 male, 11 female median age 51 yrs (32-65)	n/a	Prognostic indicators for survival in the allogeneic transplant group:  On univariate analysis, an interval of > 1 year between the first and the salvage transplant (P = 0.02) predicted a significantly better OS.  Age, cytogenetics, disease status at the time of transplantation, type of donor,	Multivariate analysis not performed due small sample size.

Study	Population	Intervention	Comparator	Results	Additional comments																								
	leukocyte antigen-matched donors, financial clearance, better performance status, and less comorbidity were treated with an allogeneic transplant.	median interval between the first and the second transplant was 17 months  median follow-up of 30 months		tumour mass, B2 microglobulin level, serum albumin level, and chronic GVHD also were studied and were found to have no effect on survival.																									
Rosinol et al., 2008  Prospective study  Spain	Newly diagnosed  110 chemosensitive myeloma patients failing to achieve at least near complete remission (nCR) after a first ASCT were scheduled to receive a second ASCT or allo-RIC depending on HLA-identical sibling donor availability.  follow-up median 5.2 years	allo-RIC n=25 Mean age 52 + 6	2 <sup>nd</sup> auto n=85 Mean age 55 + 8	<table border="1"> <thead> <tr> <th></th> <th>CR rate</th> <th>Median PFS</th> <th>Median EFS</th> <th>Median OS</th> <th>TRM</th> </tr> </thead> <tbody> <tr> <td>allo</td> <td>40%</td> <td>Not reached</td> <td>26 months</td> <td>Not reached</td> <td>16%</td> </tr> <tr> <td>2<sup>nd</sup> auto</td> <td>11%</td> <td>31 months</td> <td>19.6 months</td> <td>58 months</td> <td>5%</td> </tr> <tr> <td></td> <td>p=0.001</td> <td>p=0.08</td> <td>P=0.4</td> <td>P=0.9</td> <td>p=0.09</td> </tr> </tbody> </table>		CR rate	Median PFS	Median EFS	Median OS	TRM	allo	40%	Not reached	26 months	Not reached	16%	2 <sup>nd</sup> auto	11%	31 months	19.6 months	58 months	5%		p=0.001	p=0.08	P=0.4	P=0.9	p=0.09	
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Sahbe  Shimoni et al., 2010  retrospective analysis  Israel and Germany	Relapsed  Retrospective analysis was conducted of allo- SCT outcomes in 50 patients who received RIC for recurrent/refractory myeloma in 2 participating centres.  Female 21, male 29 median age 53 years (32-64)  Median years from diagnosis = 3 (range 6 months – 14 years).  Median follow-up 6.4 years	RIC allo- SCT	n/a	<p>Variables considered as possible prognostic factors:</p> <ul style="list-style-type: none"> <li>- time between diagnosis and allo-SCT</li> <li>- disease status at SCT</li> <li>- donor type (sibling or unrelated)</li> <li>- donor gender</li> <li>- prior auto SCT</li> <li>- time from auto SCT</li> <li>- prior lines of therapy</li> </ul> <p>The independent factors found to be predictive of worse OS were:</p> <ul style="list-style-type: none"> <li>- refractory disease (hazard ratio [HR], 2.5; 95% CI, 1.4-4.6% [P=.003])</li> <li>- SCT from a female donor to a male recipient (HR, 5.5; 95% CI, 2.5-12.5% [P=.001]).</li> </ul> <p>The factors found to be predictive of worse PFS were:</p> <ul style="list-style-type: none"> <li>- refractory disease (HR, 3.6; 95% CI, 1.4-4.6% [P=.001])</li> <li>- SCT from a female donor to a male recipient (HR, 4.1; 95% CI, 1.7-9.6% [P=.001])</li> <li>- disease duration of &gt;5 years (HR, 2.8; 95% CI, 1.3-6.1% [P=.01])</li> </ul>	Non-comparative/s intervention study b included as study re predictive factors.																								

Study	Population	Intervention	Comparator	Results	Additional comments
	(5-7.9).			The 7-year PFS in 19 patients with none of these adverse prognostic factors was 47% (95% CI, 25-70%).  Could not assess the prognostic effect of deletion 13 accurately due to missing data (32% of patients had no genetic data).	

**Table 30: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in patients with newly diagnosed myeloma del13)?**

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
<b>PFS at 96 months</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	29	63	-	PFS at 96 months was 16% greater in the allo group compared to those in the second auto group	VERY LOW
<b>OS at 96 months</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	29	63	-	OS at 96 months was 16% greater in the allo group compared to those in the second auto group	VERY LOW

<sup>1</sup> imprecision due to small sample size

**Table 31: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in patients with newly diagnosed myeloma who have high risk disease)?**

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
<b>EFS</b>											
2	observational studies	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	123	265	-	One study: HR 0.52 (95%CI: 0.22-1.21).	LOW



Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
		limitations								Second study: mean EFS was 3 months longer in patients in the second auto group compared to those in the allo group.	
<b>OS</b>											
2	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	123	265	-	One study: HR 0.34 (95%CI: 0.10-1.18). Second study: mean OS was 12 months longer in patients in the second auto group compared to those in the allo group.	LOW
<b>3 yr PFS</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	29	31	-	3 yr PFS was 3% greater in patients in the second auto group compared to those in the allo group.	VERY LOW
<b>3 yr OS</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	29	31	-	3 yr OS was 3% greater in patients in the second auto group compared to those in the allo	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
3 yr TRM											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	29	31	-	3 yr TRM was 7% lower in patients in the second auto group compared to those in the allo group.	VERY LOW
relapse/progression at 3 yrs											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	29	31	-	Relapse/progression at 3yrs was 4% greater in patients in the second auto group compared to those in the allo group.	VERY LOW

<sup>1</sup> imprecision due to small sample size

**Table 32: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in patients with newly diagnosed myeloma who have ISS stage III)?**

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
5yr PFS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	17	17	-	5 yr PFS was 28% greater in patients in the allo group	VERY LOW



Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
5yr OS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	17	17	-	5 yr OS was 23% greater in patients in the allo group compared to those in the second auto group.	VERY LOW

<sup>1</sup> imprecision due to small sample size

**Table 33: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus other treatment in patients with newly diagnosed myeloma who have  $\beta$ 2M greater than 3mg/L)?**

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	other treatment	Relative (95% CI)	Absolute	
5yr PFS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	46	47	-	5 yr PFS was 20% greater in patients in the allo group compared to those in the second auto group.	VERY LOW
5yr OS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	46	47	-	5 yr OS was 17% greater in patients in the allo group	VERY LOW

Quality assessment							Summary of findings				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality
							Allo	other treatment	Relative (95% CI)	Absolute	
										compared to those in the second auto group.	

<sup>1</sup> imprecision due to small sample size

**Table 34: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in patients with newly diagnosed myeloma who are chemosensitive)?**

Quality assessment							Summary of findings				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality
							Allo	second auto	Relative (95% CI)	Absolute	
<b>CR rate</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	25	85	-	CR was 29% greater in patients in the allo group compared to those in the second auto group.	VERY LOW
<b>median PFS</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	25	85	-	median PFS was 31 months in the second auto group and not reached in the allo group.	VERY LOW
<b>median EFS</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	25	85	-	median EFS was 6 months greater in patients in the allo group compared to those in the second	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
auto group.											
<b>median OS</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	25	85	-	median OS was 58 months in the second auto group and not reached in the allo group	VERY LOW
<b>TRM</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious <sup>1</sup>	none	25	85	-	TRM was 11% greater in patients in the allo group compared to those in the second auto group.	VERY LOW

*1 imprecision due to small sample size*

**Table 35: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in relapsed myeloma patients with Durie-Salmon stage III myeloma)?**

Quality assessment							Summary of findings				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality
							Allo	second auto	Relative (95% CI)	Absolute	
<b>relapse</b>											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	152	137	-	Allotransplant was associated with a high risk of relapse compared to autotransplant (HR 3.05, 95% CI 2.20-4.22)	LOW

*imprecision due to small sample size*

**12.4.11.1.5. GRADE Bewertung**

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA	Gesamtüberleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	SR/MA	Progressionsfreies Überleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	SR/MA	Harms	-1	-	-1	-	-	⊕⊕⊕⊖ Low

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA	Lebensqualität	-	-	-	-	-	Not reported

Hohes Verzerrungsrisiko, da verschiedene Studientypen, mit unterschiedlicher Studienqualität in MA eingeschlossen.

Indirekt, da NDMM und RRMM eingeschlossen, Anteil an RRMM unklar.

#### 12.4.11.2. Patienten, bei denen eine allogene Stammzelltransplantation durchgeführt werden soll und bei denen kein verwandter Spender verfügbar ist, können auch von nicht verwandten HLA-identischen Fremdspendern transplantiert werden.

##### 12.4.11.2.1. Evidenztabellen

##### 12.4.11.2.2. Einzelstudien

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
El-Cheikh et al., Eur J Haematol 88, 2012	<ul style="list-style-type: none"> <li>- January 2007 to January 2011</li> <li>- 40 consecutive patients identified</li> <li>- Related donors: 23 patients</li> <li>- Unrelated donors: 17 patients</li> </ul>	Related donors in allo-transplant  (MRD)	Unrelated donors in allo-transplant  (URD)	<ol style="list-style-type: none"> <li>1. OS</li> <li>2. PFS</li> <li>3. Harms</li> <li>4. QoL</li> </ol>	<ol style="list-style-type: none"> <li>1. OS               <ul style="list-style-type: none"> <li>- 2-year OS: 67% (MRD, 95% CI 47 to 87) vs. 60% (URD, 95% CI 35 to 85), p=0.362</li> </ul> </li> <li>2. PFS               <ul style="list-style-type: none"> <li>- 2-year PFS: 53% (MRD, 95% CI 28 to 78) vs. 36% (URD, 95% CI 10-62), p=0.399</li> </ul> </li> <li>3. Harms</li> </ol>	<ul style="list-style-type: none"> <li>- No inclusion and exclusion criteria given</li> <li>- The number of patients is very small</li> <li>- Not blinded</li> <li>- URD was used only when a MRD was not available</li> <li>- Heterogeneity in age (median age of MRD)</li> </ul>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
					<ul style="list-style-type: none"> <li>- Grade 2-4 acute GvHD: 17% (MRD) vs. 47% (URD), P=0.092</li> <li>- Chronic CvHD: no significant difference</li> <li>4. QoL</li> <li>- Not reported</li> </ul> <p>Median follow-up: 22 months (1 to 49)</p>	<ul style="list-style-type: none"> <li>- much older than that of URD group), P&lt;0.0001</li> <li>- Supported by Association pour la Recherche sur le Cancer and by the Frenche Ministry of Health</li> <li>- No conflicts of interest to declare</li> </ul>
Freytes et al., Bone Marrow Transplantation, 2014	<ul style="list-style-type: none"> <li>- 1995 to 2008</li> <li>- 152 patients received NST/RIC (32 related donors and 120 unrelated donors)</li> </ul> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>- MM patients &lt;65 years who had relapsed/progressed after prior autologous transplant</li> <li>- Patients who subsequently received NST/RIC allogeneic transplant or a second autotransplant between 1995 and 2008</li> </ul> <p>Exclusion criteria:</p>	Related donors	Unrelated donors	<ol style="list-style-type: none"> <li>1. OS</li> <li>2. PFS</li> <li>3. Harms</li> <li>5. QoL</li> </ol>	<ol style="list-style-type: none"> <li>1. OS</li> <li>- 3-year OS: 19% (related donors, 95% CI 7 to 33) vs. 21% (unrelated donors, 95% CI 14 to 28, p=0.82)</li> <li>- OS of unrelated and related donors were similar at 1, 3 and 5 years</li> <li>2. PFS</li> <li>- PFS of unrelated and related donors were similar at 1, 3 and 5 years</li> <li>3. Harms</li> <li>- Not reported</li> <li>4. QoL</li> <li>5. Not reported</li> </ol>	-

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<ul style="list-style-type: none"> <li>- Recipients of planned tandem transplants</li> <li>- Patients receiving NST/RIC for graft failure</li> <li>- Second malignancies</li> <li>- Cord blood transplants</li> </ul>					

**12.4.11.2.3. GRADE Bewertung**

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Retrospektive	Gesamtüberleben	-	-	-	-1	-	⊕⊕⊕⊕ Very low
	Retrospektive	Progressionsfreies Überleben	-	-	-	-1	-	⊕⊕⊕⊕ Very low
	Retrospektive	Harms	-	-	-	-1	-	⊕⊕⊕⊕ Very low
	Retrospektive	Lebensqualität	-	-	-	-	-	Not reported

Impräzise, da Kriterium für die optimale Informationsgröße nicht erfüllt.

## 12.4.12. Rehabilitation

12.4.12.1. Ein an der individuellen Leistungsfähigkeit ausgerichtetes körperliches Training sollte den Patienten frühzeitig, ggfs. auch bereits während der Primärtherapie, angeboten werden.

### 12.4.12.2. Evidenztabellen

#### 12.4.12.2.1. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(Knips, Bergenthal et al. 2019)  Systematic review with meta-analysis (Cochrane Review)	<ul style="list-style-type: none"> <li>• RCTs</li> <li>• 1950-2018</li> <li>• Cochrane Central Register of Controlled Trials; MEDLINE; Conference proceedings of annual meetings (1990 to 2018) of the following societies for abstracts if not included in CENTRAL: American Society of Hematology (ASH) (2011 to</li> </ul>	<ul style="list-style-type: none"> <li>• The main intervention was aerobic physical exercise in addition to standard care, compared to standard care alone.</li> <li>• We only included studies that evaluated the response of the participant to aerobic exercise intending to improve the oxygen system.</li> <li>• Studies were included that chose exercise interventions</li> </ul>	<ul style="list-style-type: none"> <li>• OS</li> <li>• QoL</li> <li>• Fatigue</li> <li>• physical performance</li> <li>• anthropometric measurements (e.g. weight, body mass index)</li> <li>• AEs</li> </ul>	<p><b>18 trials</b> in 38 publications, including a total of <b>1892 participants</b> (range 18 to 711)</p> <p><b>OS:</b> no statistically significant difference between exercise and control arms (RR1.10; 95% confidence interval (CI) 0.79 to 1.52; P = 0.59; Analysis 1.2). Heterogeneity is small (<math>I^2 = 29%</math>); low certainty of the evidence</p> <p><b>QoL:</b> no evidence for a difference (standardised mean difference (SMD) 0.11, 95% CI -0.03 to 0.24; 1259 participants) small heterogeneity (<math>I^2 = 26%</math>); certainty of the evidence is low, due to a confidence interval that includes both, improvement and worsening of QoL (one point downgraded for imprecision) and unblinded outcome assessors (participants) for the participant-reported outcome (QoL questionnaires) (one point downgraded for risk of bias)</p>	<p>GRADE approach applied for rating of the certainty of the evidence (see results)</p> <p>For heterogeneity see results section</p> <p>Certainty of the evidence body judged as low to moderate for most outcomes, because of an open-label design, unblinded outcome assessment and a small number of events, leading to wide confidence intervals and imprecision of the results.</p>	<p>Alibhai. Leukemia Research 2014, Alibhai. Supportive Care in Cancer 2014, Alibhai Supportive Care in Cancer abstract 2014</p> <p>Baumann. Bone Marrow Transplantation 2010, Baumann. European Journal of Haematology 2011</p> <p>Bryant. Integrative Cancer Therapies 2018</p> <p>Chang. Journal of Pain and Symptom Management 2008</p>



Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	2017); American Society of Clinical Oncology (ASCO) (2011 to 2018); European Hematology Association (2011 to 2018). Databases of ongoing trials: for the original version of the review: ◊ meta-register of controlled trials: <a href="http://www.controlled-trials.com/mrct/">www.controlled-trials.com/mrct/</a> . ◊ for the update: we electronically searched in the database of ongoing trials up to 01 July 2018 ◊ ISRCTN; ◊ EU clinical trials register; Clinicaltrials.gov:	such as moderate cycling, walking, Nordic walking, running, swimming and other related forms of sport. <ul style="list-style-type: none"> <li>• There were also studies included that analyzed further physical exercise programmes, such as moderate strength training in addition to the aerobic exercise programme.</li> <li>• <b>Excluded trials:</b> Training programmes that were composed of yoga, tai chi chuan, qigong and similar types of exercise. We also excluded studies solely exploring the influence of</li> </ul>		<p><b>Subscale physical functioning:</b> no significant advantage for participants in the exercise arm (SMD 0.15, 95% CI -0.01 to 0.32; Analysis 1.7). Heterogeneity is moderate (<math>I^2 = 48\%</math>). Certainty of the evidence is judged to be low</p> <p><b>Subscale depression:</b> Pooled result of six trials (N = 445) for depression shows a small effect for patients exercising (SMD 0.19, 95%CI 0.0 to 0.38; <math>I^2 = 0\%</math>; certainty of the evidence for the outcome depression is low</p> <p><b>Subscale anxiety:</b> substantial heterogeneity for this analysis (<math>I^2 = 63\%</math>), but no evidence for differences between the exercise arm and the standard treatment arm (SMD 0.03, 95% CI -0.30 to 0.36, very low certainty of the evidence</p> <p><b>Fatigue:</b> Nine studies (N = 826) assessed fatigue and found a statistically significant advantage for those participants exercising (SMD 0.31, 95% CI 0.13 to 0.48; P = 0.0005; Analysis 1.15), with moderate heterogeneity (<math>I^2 = 31\%</math>), certainty of the evidence is moderate</p> <p><b>Physical performance:</b> Different scales used, so data were not pooled; no significant results for trials only including myeloma (Coleman 2003, Coleman 2012). Anthropometric measurements :</p>		<p>Coleman. <i>Cancer Nursing</i> 2003, Coleman <i>Clinical</i></p> <p>Coleman. <i>Journal of Oncology Nursing</i> 2012, Coleman. <i>JCO</i> 2006, Coleman. <i>Oncology Nursing Forum</i> 2008, Coleman. <i>Nursing Forum</i> 2012</p> <p>Courneya. <i>Cancer Causes &amp; Control</i> 2015, Courneya <i>Oncologist</i> 2008, Courneya. <i>Cancer Epidemiology, Biomarkers &amp; Prevention</i> 2009, Courneya. <i>JCO</i> 2009, Courneya <i>Cancer Epidemiology, Biomarkers &amp; Prevention</i> 2012, Courneya. <i>Medicine &amp; Science in Sports &amp; Exercise</i> 2012, Courneya. <i>Psycho-Oncology</i> 2012, Courneya. <i>Annals of Behavioral Medicine</i> 2010</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
		strength training. Additionally, we excluded studies assessing outcomes without any clinical impact.		no significant difference between exercise and control groups (MD 0.44 kg; 95% CI -1,94 to 2,82; P = 0.72; Analysis 1.19), without evidence for heterogeneity (I2 = 0%). AEs : Uncertain evidence whether exercise is related to more serious adverse events (RR 1.39; 95% CI 0.94 to 2.06; P = 0.10; I2 = 0%), without heterogeneity. The certainty of the evidence is very low		Cunningham. Journal of Parenteral and Enteral Nutrition 1986 DeFor. Biology of Blood and Marrow Transplantation 2007 Furzer. Supportive Care in Cancer 2016 Jacobsen. <i>Biology of Blood &amp; Marrow Transplantation</i> 2014 (für Jacobsen 2014/2014a/2014b) Jarden. <i>Supportive Care in Cancer</i> 2015, Jarden. <i>Haematologica</i> . 2016, Jarden <i>BMC Cancer</i> 2013, Jarden. <i>Haematologica</i> 2016 Kim. <i>European Journal of Cancer Care</i> 2006 Knols. <i>Bone Marrow Transplantation</i> 2011 Mello. <i>Bone Marrow Transplantation</i> 2003

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
						Persoon. PLOS One 2017, Persoon. Eu- ropean Journal of Cancer Care 2018, Persoon. BMC Can- cer 2010 Streckmann. Annals of Oncology 2014 Wiskemann Blood 2011, Wiskemann. International Journal of Cancer 2015

**12.4.12.2.2. GRADE Bewertung**

Summary of findings for the main comparison

Physical exercise versus no physical exercise for adults with haematological malignancies					
Patient or population: Adults with haematological malignancies					
Settings: Inpatient or outpatient					
Intervention: Physical exercise versus no physical exercise					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evi- dence (GRADE)
	Assumed risk	Corresponding risk			
	Control group without exercise	Physical exercise			

Physical exercise versus no physical exercise for adults with haematological malignancies					
Mortality	149 per 1.000	164 per 1.000 (117 to 226)	RR 1.10 (0.79 to 1.52)	1172 (6 RCTs)	++ low <sup>1,2</sup>
Quality of Life Scale from: -1 to 1 with 1 indicating best out- come		The mean QoL score in the intervention group was 0.11 higher (better) (-0.03 to 0.24 higher)	SMD 0.11 higher (-0.03 to 0.24 hig- her)	1259 (8 RCTs)	++ low <sup>2,3</sup>
Physical function- ing/QoL Scale from: -1 to 1 with 1 indicating best out- come		The mean physical functioning/QoL score in the intervention group was 0.15 higher (better) (-0.01 to 0.32 higher)	SMD 0.15 higher (-0.01 to 0.32 hig- her)	1329 (8 RCTs)	++ low <sup>2,3</sup>
Depression/QoL Scale from: -1 to 1 with 1 indicating best out- come		The mean depression/QoL score in the intervention group was 0.19 higher (better) (0.00 to 0.38 higher)	SMD 0.19 higher (0.00 to 0.38 hig- her)	445 (6 RCTs)	++ low <sup>1,3</sup>
Anxiety/QoL Scale from: -1 to 1 with 1 indicating best out- come		The mean anxiety/QoL score in the in- tervention group was 0.03 higher (better) (-0.30 to 0.36 higher)	SMD 0.03 higher (-0.30 to 0.36 hig- her)	445 (6 RCTs)	+ very low <sup>2,3,4</sup>
Fatigue Scale from: -1 to 1 with 1 indicating best out- come		The mean fatigue score in the interven- tion group was 0.31 higher (better) (0.13 to 0.48 higher)	SMD 0.31 higher (0.13 to 0.48 hig- her)	826 (9 RCTs)	+++ moderate <sup>3</sup>

## Physical exercise versus no physical exercise for adults with haematological malignancies

Serious adverse events	174 per 1.000	242 per 1.000 (164 to 359)	RR 1.39 (0.94 to 2.06)	435 (6 RCTs)	+ very low <sup>5,6</sup>
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\* The basis for the assumed risks (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference.

## GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1: Small number of participants/events leads to downgrading (1 point) for imprecision.

2: Confidence interval including clinically relevant benefits or harms leads to downgrading (1 point) for imprecision.

3: Outcome assessor (participant) not blinded in participant-reported outcome (QoL questionnaires) leads to downgrading (1 point) for risk of bias.

4: High heterogeneity leads to downgrading (1 point) due to inconsistency.

5: Baseline imbalances, especially usage of erythropoietin and thalidomide unknown in both intervention arms, leads to downgrading (1 point) due to inconsistency.

6: Very small number of participants and events, and very wide confidence interval leads to downgrading (1 point) for imprecision.

Verzerrungsrisiko, hoch, da Studie unverblindet, vorzeitig geschlossen und Endpunkte selektiv berichtet

Indirekte Evidenz, da Krebspatienten untersucht, nicht speziell Patienten mit Myelom; nur Patienten >65y eingeschlossen

Impräzision, da Anzahl eingeschlossener Patienten sehr gering

### 12.4.12.3. Bei peripherer Neuropathie sollten neben körperlichem Kraft- und Ausdauertraining auch Therapieansätze wie neuroperzeptives und/oder sensomotorisches Training, Balancetraining und Funktions- und physikalische Therapie eingesetzt werden.

#### 12.4.12.3.1. Evidenztabellen

##### 12.4.12.3.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
(Duregon, Vendramin et al. (2018))  Systematic review	<ul style="list-style-type: none"> <li>RCTs und non-RCTs</li> <li>Until 2017</li> </ul> <p>MEDLINE, Scopus, Bandolier, PEDro and Web of Science</p> <p>References of eligible articles were screened</p>	<ul style="list-style-type: none"> <li>Eligible studies had to evaluate a physical exercise intervention with at least a quality of life or balance evaluation in cancer patients undergoing chemotherapy</li> <li>Preferably: Structured exercise protocols tailored for cancer patients undergoing treatment with diagnosed CIPN</li> <li>pre- and post-intervention comparisons</li> </ul>	<ul style="list-style-type: none"> <li>Physical function</li> <li>Balance control</li> <li>QoL</li> <li>Reduction of CIPN symptoms</li> </ul>	<p><b>5 Studies included in qualitative analysis:</b> 3 studies on CIPN supervised-training interventions, 2 studies on CIPN home-based interventions</p> <p><b>Sample sizes:</b> 14-56 subjects</p> <p><b>Sex:</b> Mostly female (57%)</p> <p><b>Average age :</b> 54.7 years</p> <p><b>Physical performance</b> (1/5 studies): Significant improvement from baseline to 12 and 24 weeks of exercise and follow-up for upper and lower body strengths; non-significant improvement for lower body functional capacity at 12 weeks of exercise training (1 study)</p> <p><b>CIPN symptoms</b> (4/5 studies): Findings from three studies : Significant decline in peripheral neuropathy symptoms (assessed with varying scores including the Modified Total Neuropathy Score (mTNS)) ;</p>	<p>Qualitative/ narrative evidence synthesis</p> <p>Quality of included studies assessed with modified Cochrane Back Review Group checklist (9 items; high quality if at least 5 items rated positive)</p> <p>Result of quality assessment: 2 studies of high quality; three studies of low quality:</p> <ul style="list-style-type: none"> <li>Randomization: 2 studies</li> <li>Reporting of in- an exclusion criteria: All studies</li> <li>Reporting of timing of outcome assessment: All studies</li> </ul>	<p>Fernandes. <i>International Journal of Rehabilitation Research</i> 2016</p> <p>Mizrahi. <i>International Journal of Gynecological Cancer</i> 2015</p> <p>Schwenk. <i>Gerontology</i> 2015</p> <p>Streckmann. <i>Annals of Oncology</i> 2014</p> <p>Wonders. <i>Health Psychology Research</i> 2013</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
		<p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• Cross sectional studies, case reports, published abstracts, dissertation materials, conference proceedings</li> </ul>		<p>Finding from one study : No significant differences in the Functional Assessment Cancer Therapy-Neurotoxicity (FACT-Neurotoxicity) scale</p> <p><b>Static balance control</b> (4/ 5 studies): Positive findings on measured sway paths during static monopodal stance (1 study); No meaningful differences in bipedal tasks with eyes closed (2 studies), meaningful differences in bipedal tasks with open eyes, on feet closed and semi tandem positions (1 study); Reduction in Medio-Lateral Center of Mass sway, hip sway, and ankle sway with feet closed and in Medio-Lateral Center of Mass sway, Antero-Posterior Center of Mass sway during evaluations in semitandem positions (1 study); Significant increase in field test performance after 12 and 24 weeks assessed by a single-leg balance test (1 study); Significant improvement in Berg Balance Scale after 15 session of seven kinematic chain exercises (1 study)</p> <p><b>Dynamic balance control</b> (2/5 studies): Significant reduction in sway path on mono- and bipedal with open eyes stance on foam pad adjusted on force platform and significant reduction in failed</p>	<ul style="list-style-type: none"> <li>• Reporting of drop-out ratio: 3 studies</li> <li>• Reporting of compliance ratio: 1 study</li> <li>• ITT applied: 1 study</li> <li>• Follow-up evaluations performed: 1 study</li> <li>• Single-blinding procedure: 1 study</li> </ul>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<p>attempts in monopodal stance (1 study); significant reduction in sway paths for bipedal tasks in antero-posterior and media-lateral oscillations and monopodal tasl on oscillating2D platforms (1 study), Accomplishment of all perturbation task in exercise group versus 60% in control group (1 study) Significant reduction in time to regain balance in exercise group (1 study); No significant chances in gait performance (1 study)</p> <p><b>QoL</b> (4/5 studies): QoL assessed with: EORTC-QLQ-C-30, SF-36, FACT-O): Significant differences in QoL after 12 weeks of exercise between groups (1 study) and within groups (1 study); Significant improvements in the global QoL after 12 weeks of exercise and 24 weeks of follow-up within group (1 study) Significant improvement in QoL after 36 weeks within group (1 study); Fear of alling assessed with: FES-I: No significant reduction in fear of falling after 3 weeks of exercise training (1 study); level of troublesome symptoms assessed with: McGill QoL Questionnaire: reduction of troublesome CIPN symptoms after 10 weeks of home-based exercise</p>		



Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
(Hunter, Gibson et al. 2017, Hunter, Gibson et al. 2017)  Systematic Review	<ul style="list-style-type: none"> <li>N=138 studies included in qualitative synthesis</li> <li>Included studies: <ul style="list-style-type: none"> <li>SRs, MAs, RCTs, cohort studies, case controlled studies, one group nonrandomized studies (pre- and posttest)</li> <li>Peer-reviewed full text publications, published between 1995</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>1) physical activity interventions, including exercise (25 articles) and complementary and alternative medicine (CAM; 26 articles)</li> <li>2) symptom management interventions, including pain, fatigue, and breathlessness (19 articles); lymphedema (12 articles); and physical agent</li> </ul>	effectiveness of cancer rehabilitation interventions within the scope of occupational therapy practice to address the activity and participation needs of adult cancer survivors in activities of daily living, instrumental activities of daily living, work, leisure, social participation, and rest and sleep	<b>Physical activity interventions:</b> <ul style="list-style-type: none"> <li>11 SRs and 14 RCTs related to exercise, 21 SRs and 5 RCTs related to complementary and alternative medicine</li> <li>Strong evidence : <ul style="list-style-type: none"> <li>exercise is safe and beneficial for the majority of cancer types, at all stages including end of life, and regardless of age</li> <li>Exercise increased muscle tone and strength and lung capacity</li> <li>Exercise was found not to cause lymphedema or to make existing lymphedema worse</li> </ul> </li> <li>Moderate evidence : <ul style="list-style-type: none"> <li>exercise improves HRQOL for some survivors.</li> <li>Rehabilitation using physical training (strength, interval, and home-based activities) was significantly better than usual care in terms of HRQOL</li> </ul> </li> </ul>	Study selection by a team of 3 reviewers  AOTA standard evidence model: <ul style="list-style-type: none"> <li><b>Level I:</b> SRs, MAs, RCTs</li> <li><b>Level II:</b> Two-group, nonrandomized studies (e.g., cohort, case control)</li> <li><b>Level III:</b> One-group, nonrandomized studies (e.g., pretest and posttest)</li> <li><b>Level IV:</b> Descriptive studies that include analysis of outcomes (e.g., single-subject design, case series)</li> <li><b>Level V:</b> Case reports and expert opinion that include narrative literature reviews and consensus statements.</li> </ul> Methodological quality: <ul style="list-style-type: none"> <li>Risk of Bias of individual studies was assessed using Cochrane Risk of Bias guidelines</li> </ul>	N =138 studies <ul style="list-style-type: none"> <li>N=25 : exercise</li> <li>N=26 : complementary medicine</li> <li>N= 18 rehabilitation</li> <li>N= 12 : lymphedema</li> <li>N=19 : physical symptoms</li> <li>N=4 : PAM</li> <li>N=3 : Work</li> <li>N=2 : sexuality</li> <li>M=29 : psychosocial</li> </ul> For detailed information please refer to the full publications.

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	<p>and 2014</p> <ul style="list-style-type: none"> <li>• Scope of practice of occupational therapy in cancer rehabilitation</li> <li>• Focus on cancer survivors</li> <li>• Excluded studies: <ul style="list-style-type: none"> <li>• Single-subject design, case series, case reports, expert opinions, including narrative reviews and consensus</li> </ul> </li> </ul>	<p>modalities (PAMs; 4 articles).</p>		<ul style="list-style-type: none"> <li>○ Supervised exercise was better than nonsupervised exercise</li> <li>○ counseling and telephone support were helpful in keeping people exercising</li> <li>○ Diet and exercise interventions reduced the rate of self-reported functional decline</li> <li>○ Exercise improved sleep quality for people undergoing cancer treatment</li> <li>○ yoga, regardless of type, benefits mental health, quality of life, sleep, and sense of well-being and decreases stress</li> <li>○ Qigong improved quality of life, mood, fatigue, and immune response and reduced inflammation</li> </ul> <p><b>Symptom Management Interventions</b></p> <ul style="list-style-type: none"> <li>• 5 SRs and 14 RCTs addressed pain, fatigue, breathlessness in cancer patients and survivors ; 6 SRs and 5 RCTs were related to lymphedema ; 1 SR and 3 RCTs</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of bias of SRs was based on the AMSTAR system</li> </ul> <p><b>Strong evidence</b> typically includes 2 or more well-designed RCTs.</p> <p><b>Moderate evidence</b> includes 1 RCT, 2 or more studies providing lower level evidence, or inconsistent findings from well-designed projects</p> <p>supported by the American Occupational Therapy Association as part of the Evidence-Based Practice Project</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	<p>state- ments</p> <ul style="list-style-type: none"> <li>• Studies focusing on caregivers, family members, friends</li> <li>• Interventions that required an academic degree other than occupational therapy (e.g. music therapy, neuropsychology)</li> </ul>			<p>were related to the use of PAMs to treat lymphedema</p> <ul style="list-style-type: none"> <li>• Strong evidence:                             <ul style="list-style-type: none"> <li>○ Exercise reduces CRF and increases quality of life</li> <li>○ Nonpharmacological interventions, such as problem solving, energy conservation, and education, reduced the symptom of breathlessness</li> <li>○ use of neuromuscular electrical stimulation in conjunction with traditional swallowing training facilitated greater recovery than swallowing training alone for adults after head and neck cancer treatment</li> <li>○ Regarding lymphedema management, compression bandages worn on a daily basis were found to be important for volume control</li> <li>○ Exercise was found not to make lymphedema</li> </ul> </li> </ul>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<p>worse and to improve mood, quality of life, range of motion, and weight loss</p> <ul style="list-style-type: none"> <li>• Moderate evidence :                             <ul style="list-style-type: none"> <li>○ Supporting sleep therapy modifications, education and problem solving for pain management, and cognitive-behavioral therapy in CRF management</li> <li>○ supports the use of PAMs, including low-frequency, low-intensity electrotherapy to reduce feelings of pain, heaviness, and tightness when treating lymphedema of the arm</li> </ul> </li> </ul> <p><b>Interventions in Multidisciplinary Rehabilitation Programs</b></p> <ul style="list-style-type: none"> <li>• 18 articles related to the use of multidisciplinary rehabilitation programs; 2 SRs. 12 RCTs, 2 Level II studies, 1 Level III study, and 1 article provided Level IV evidence.</li> <li>• Strong evidence :</li> </ul>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<ul style="list-style-type: none"> <li>○ Rehabilitation programs benefit survivors with many types of cancer</li> <li>○ Multidisciplinary rehabilitation programs resulted in improved function and participation regardless of type of cancer, stage of cancer, or age of survivor</li> <li>• Moderate evidence :                             <ul style="list-style-type: none"> <li>○ rehabilitation can be beneficial both before and after treatment</li> <li>○ Cognitive rehabilitation improved attention and overall quality of life</li> <li>○ Rehabilitation in advanced, progressive, recurrent cancer was found to be cost-effective and to increase quality of life</li> </ul> </li> <li><b>Psychosocial Interventions</b> <ul style="list-style-type: none"> <li>• 29 articles related to psychosocial interventions, 6 SRs, 21 RCTs, 1 Level II study, 1 Level III study</li> <li>• Strong evidence :</li> </ul> </li> </ul>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<ul style="list-style-type: none"> <li>○ Psychosocial strategies, including cognitive-behavioral and educational interventions (e.g., problem solving, knowledge of illness and side effects), reduce anxiety &gt;3 mo posttreatment and depression 1-3 mo posttreatment</li> <li>● Moderate evidence :                             <ul style="list-style-type: none"> <li>○ supports a variety of psychosocial interventions</li> <li>○ psychosocial interventions increased quality of life for people with advanced-stage cancer</li> <li>○ Short-term life review increased spiritual well-being for people with terminal cancer</li> <li>○ cognitive-behavioral therapy decreased symptom limitations for people undergoing chemotherapy and those with advanced-stage cancer</li> </ul> </li> </ul>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<ul style="list-style-type: none"> <li>○ Self-management training was beneficial in both group and individual interventions for improving quality of life</li> </ul> <p><b>Interventions for Sexuality</b></p> <ul style="list-style-type: none"> <li>• 1 SR and 1 RCT were related to sexuality and sexual function</li> <li>• Moderate evidence : supports exercise as beneficial for prostate cancer patients reporting an interest in sex. The systematic review pointed to three types of intervention used for return to sexual function: exercise, medical, and psychoeducational.</li> <li>• Limited evidence : supports the effectiveness of couple-based and psychoeducational interventions</li> </ul> <p><b>Interventions for Return to Work</b></p> <ul style="list-style-type: none"> <li>• 1 SR, 1 RCT and 1 Level III study were related to interventions for return to work</li> <li>• Moderate evidence:                             <ul style="list-style-type: none"> <li>○ high-intensity exercise (strength, interval, and home based) helped pa-</li> </ul> </li> </ul>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				<p>tients minimize the decrease in work ability after cancer and treatment</p> <ul style="list-style-type: none"> <li>○ multidisciplinary interventions that include physical and psychological aspects in addition to vocational support provided return-to-work benefits</li> <li>● Limited evidence : occupational therapy intervention helps cancer patients return to work</li> </ul>		

12.4.12.3.3. *Ergänzende Einzelstudien*

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
(Pergolotti, Deal et al. 2019)  RCT	<p>N = 51</p> <p>Recruiting period:</p> <p>Patient characteristics:</p> <ul style="list-style-type: none"> <li>- Aged 65y or older</li> <li>- Diagnosis or recurrence of cancer within the last 5 years</li> <li>- English speaking</li> <li>- At least one functional deficit</li> <li>- Able to safely participate in outpatient reha program</li> </ul>	<p>N=25</p> <p>CARE : Cancer REhabilitation Program : billable outpatient PT and OT services</p> <p>OTs focused on impro-</p>	<p>N= 26</p> <p>Standard Care: received a brochure outlining services and contact information for supportive care</p>	<ol style="list-style-type: none"> <li>1. NEADL</li> <li>2. PROMIS</li> <li>3. PACTS</li> </ol>	<ol style="list-style-type: none"> <li>1. <b>NEADL:</b> At FU assessment (3 months): clinically and statistically significant decline in functional status in both groups as measured by the NEADL (intervention: mean difference -4.4 (9.7), p = .02; control: mean difference: -4.0 (6.9), p = .03); between intervention and usual care, there was no significant difference (P = .88)</li> <li>2. PROMIS:</li> </ol>	<p>Follow up at 2-3 months</p> <p>Study period not described</p> <p>Accural stopped due to recruitment difficulties</p> <p>Per protocol analysis (flow chart available)</p> <p>COI: authors declared to have none</p>



Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
		ving the patient's functioning in performing IADLs/ADLs such as bathing, food preparation, managing medications, upper extremity function, and social participation. PTs focused on decreasing pain and improving movement for greater activity and participation.	programs available at the Lineberger Comprehensive Cancer Center.		<p>Mean difference (SD) scores per category for Intervention group: QoL GMH: -1.0 (5.9), QoL GPH: 0.0 (5.1), physical function: 1.5 (4.3), SR QoL: 0.1 (6.8)</p> <p>Mean difference (SD) scores per category for control group: QoL GMH: 2.6 (6.7), QoL GPH: 2.2 (5.5), physical function: 3.2 (7.0), SR QoL: 3.1 (6.9)</p> <p>No statistically significant difference between groups</p> <p>3. PActS: Mean difference (SD) for intervention group: -3.2 (12.1); for control group: 3.1 (6.9); p=0.04</p>	<p>Financial Disclosure: This work was supported by the National Cancer Institute (R25CA116339), the Lineberger Cancer Center University Cancer Research Fund (UL1RR025747), and the Clinical and Translational Science Award program of the National Center for Advancing Translational Sciences (1UL1TR001111). This research was also supported in part by the Lineberger Comprehensive Cancer Center (LCCC-0916); Grant R. Williams and Ashley L. Bryant were supported, in part, by the UNC Oncology Clinical Translational Research Training Program (NCI 5K12CA120780-07).</p>
(Pilegaard, la Cour et al. 2018)  RCT	N=242  Recruiting: 02.2015-10.2016	N=121 Cancer Home-Life Intervention (OT-based	N=121 Usual care: home-care, palliative care and/or	1. ADL performance (measured with AMPS)	1. <b>ADL motor ability:</b> decreased in both groups during T1-T3; The within-group change was small (intervention group: -0.14	T1: baseline T2: 6 weeks T3: 12 weeks

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
	<p>Patient characteristics: home-living adults diagnosed with advanced cancer</p> <p>Living within a maximum radius of 60km from Aarhus University Hospital or on Funen</p> <p>Participants were living in a nursing home or hospice, were cognitively impaired or had insufficient Danish language skills</p>	programme) + usual care	rehabilitation that sometimes also involved occupational therapy (OT)	<p>2. Difficulties performing the participants' prioritized everyday activities (measured with IPPA)</p> <p>3. Autonomy and participation (measured with IPA-DK)</p> <p>4. HRQoL (measured with EORTC QLQ C-30)</p>	<p>logits (95% CI: -0.27 to 0.00)) (control group: -0.10 logits (95 CI: -0.24 to 0.05))</p> <p><b>ADL process ability (T1-T3):</b> Mean change in intervention group: -0.10 (-0.20 to -0.01) Mean change in control group: -0.04 (-0.14 to 0.06) Between group mean change: -0.06 (-0.20 to 0.07)</p> <p><b>2. IPPA score</b> mean change in intervention group: T1-T2: -1.27 (-2.01 to -0.53); T2-T3: -1.38 (-2.35 to -0.40) mean change in control group: T1-T2: -1.16 (-1.91 to -0.41); T2-T3: -1.03 (-2.00 to -0.05) Changes between groups were not statistically significant</p> <p><b>3. IPA-DK:</b> OR for no perceived participation restrictions (intervention vs control): Autonomy Indoor at T3: 1.03 (0.39 to 2.75) Family role at T3: 1.08 (0.59 to 1.99) Social relations at T3: 0.86 (0.28 to 2.69)</p> <p><b>4. HRQoL:</b> Mean change in Intervention group: T1-T2: -1.40 (-5.49 to 2.68); T2-T3: 1.50 (-2.97 to 5.97); Mean change in control group: T1-T2: -1.19 (-5.39 to 3.01); T2-T3: 3.11 (-1.52 to 7.74)</p>	<p>Analyses were performed masked for the group allocation</p> <p>COI: authors declared to have none</p> <p>The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The TrygFonden and the Danish Cancer Society (R53-A2783), the University of Southern Denmark, the Danish Association of Occupational Therapists (FF 2 14 - 3), and the Region of Southern Denmark (15/23775) funded the study</p>

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	methodische Bemerkungen/ Evidenzklasse
					Changes between groups were not statistically significant	

12.4.12.3.4. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/RCT	CIPN	-	-	-1	-	-	⊕⊕⊕⊖ moderate
	SR/RCT	Physical performance	-	-	-1	-	-	⊕⊕⊕⊖ moderate
	SR/RCT	QoL			-1			⊕⊕⊕⊖ moderate
	SR/RCT	Safety	-	-	-	-	-	Not reported

Indirekte Evidenz, da Krebspatienten untersucht, nicht speziell Patienten mit Myelom

### 12.4.13. Supportivtherapie

### 12.4.14. Antiresorptive Therapie

#### 12.4.14.1. Bei Patienten mit Multiplem Myelom und Osteolysen sollen Bisphosphonate oder RANK-L Inhibitoren zur Prophylaxe skelettaler Ereignisse angewandt werden.

##### 12.4.14.1.1. Evidenztabellen

##### 12.4.14.1.2. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
<ul style="list-style-type: none"> <li>•(Mhaskar, Kumar et al. 2017)</li> </ul> <p>Cochrane Systematic Review and network meta analysis (NMA)</p>	<ul style="list-style-type: none"> <li>•Any RCT comparing BPs versus placebo/no treatment/BPs</li> <li>•(Observational studies or case reports examining BP-related osteonecrosis of the jaw (ONJ))</li> <li>•Searches run in MEDLINE, Embase and CENTRAL until July 2017</li> </ul>	<ul style="list-style-type: none"> <li>•Clodronat</li> <li>•Etidronat</li> <li>•Pamidronat</li> <li>•Aledronat</li> <li>•Ibandronat</li> <li>•Zoledronat</li> <li>•Risedronat</li> <li>•Tiludronat</li> </ul>	<ul style="list-style-type: none"> <li>•OS</li> <li>•PFS</li> <li>•Pain</li> <li>•QoL</li> <li>•Hypercalcemia</li> <li>•gastrointestinal toxicities</li> <li>•ONJ</li> <li>•hypocalcemia</li> </ul>	<ul style="list-style-type: none"> <li>• 24 included studies including 7293 patients <ul style="list-style-type: none"> <li>• (20 BPs vs. Placebo/no treatment ; 4 RCTs involved another BP as a comparator)</li> </ul> </li> <li>• OS : HR 0.90 (95% CI 0.76 to 1.07) for BPs vs placebo/no treatment; 14 studies; 2706 patients ; moderate-quality evidence ; I<sup>2</sup>=65%</li> </ul>	<ul style="list-style-type: none"> <li>•GRADE approach applied ; see result section for certainty in evidence of every outcome</li> <li>•Hohes Bias-Risiko in den eingeschlossenen Studien</li> <li>•Hohe Heterogenität bei Pain</li> <li>•14/23 studies did not specify or report the primary number of lesions. 2/23 included any number of lesions and 7/23 at least one (-1 for indirectness)</li> </ul>	<ul style="list-style-type: none"> <li>•(Attal, Harousseau et al. 2006)</li> <li>•(Aviles, Nambo et al. 2007)</li> <li>•(Aviles, Neri et al. 2013)</li> <li>•(Belch, Bergsagel et al. 1991)</li> <li>•(Berenson, Lichtenstein et al. 1998b)</li> <li>•(Brincker and Abildgaard 1998)</li> <li>•(Daragon, Humez et al. 1993)</li> <li>•(Delmas, Charhon et al. 1982)</li> <li>•(Garcia-Sanz, Oriol et al. 2015)</li> <li>•(Gimsing, Carlson et al. 2010)</li> </ul>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<ul style="list-style-type: none"> <li>• <b>OS NMA:</b> Zoledronate vs etidronate HR 0.56 (95%CI 0.29 to 0.87) and zoleronate vs placebo HR 0.67 (95% CI 0.46 to 0.91); no difference between zoledronate and other BPs</li> <li>• <b>PFS:</b> HR 0.75 (95% CI 0.57 to 1.00) for BPs vs placebo/no treatment; 7 studies; 908 patients; low-quality evidence</li> <li>• <b>Non-vertebral fractures:</b> RR 1.03 (95% CI 0.68 to 1.56) for BPs vs placebo/no treatment; 6 studies; 1389 patients; moderate-quality evidence</li> <li>• <b>Prevention of pathological vertebral fractures:</b> RR 0.74 (95% CI 0.62 to 0.89) for BPs vs. Placebo/no treatment; 7 studies, 1116</li> </ul>		<ul style="list-style-type: none"> <li>•(Heim, Clemens et al. 1995)</li> <li>•(Kraj, Poglód et al. 2000)</li> <li>•(Lahtinen, Laakso et al. 1992)</li> <li>•(Leng, Chen et al. 2002)</li> <li>•(McCloskey, MacLennan et al. 1996)</li> <li>•(Menssen, Sakalová et al. 2002)</li> <li>•(Morgan, Davies et al. 2010)</li> <li>•(Musto, Falcone et al. 2003)</li> <li>•(Musto, Petrucci et al. 2008)</li> <li>•(Rosen, Gordon et al. 2003)</li> <li>•(Terpos, Palermos et al. 2000)</li> <li>•(Terpos, Viniou et al. 2003)</li> <li>•(Zhang, Chang et al. 2012)</li> </ul>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<p>patients, moderate-quality evidence</p> <ul style="list-style-type: none"> <li>• SREs: RR 0.74 (95% CI 0.63 to 0.88) for BPs vs. Placebo/no treatment; 10 studies, 2142 patients, moderate-quality evidence)</li> <li>• Less pain: RR 0.75 (95% CI 0.60 to 0.95) for BPs vs. Placebo/no treatment; 8 studies, 1281 patients; very low-quality evidence</li> <li>• ONJ: RR 4.61 (95% CI 0.99 to 21.35) for BPs vs. Placebo; 6 studies, 1284 patients; low-quality evidence</li> <li>• ONJ NMA: no evidence for a difference between BPs; 8 studies, 3746 patients</li> <li>• Increase of gastrointestinal symptoms: RR 1.23 (95%CI 0.95 to 1.59) for BPs vs. Placebo/no treatment; 7</li> </ul>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
				<p>studies, 1829 patients; low-quality evidence</p> <ul style="list-style-type: none"> <li>• Increase in frequency of hypocalcemia: RR 2.19 (95% CO 0.49 to 9.74) for BPS vs. Placebo/no treatment; 3 studies, 1090 patients, low-quality evidence</li> <li>• Increase in frequency of hypocalcemia, renal dysfunction, gastrointestinal toxicity NMA: no evidence for a difference between BPs</li> <li>• <b>QoL</b>: none of the included studies reported on QoL</li> </ul>		

**12.4.14.1.3. GRADE Bewertung**

Summary of findings for the main comparison (direct comparisons)

Bisphosphonates in multiple myeloma
<p>Patient or population: Patients with multiple myeloma</p> <p>Intervention: Bisphosphonates</p>

Bisphosphonates in multiple myeloma					
Control: No treatment/placebo					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Bisphosphonates			
Overall survival##	Medium-risk population#		HR 0.90 (0.76 to 1.07)	2706 (14 studies)	+++ moderate <sup>1,2,3</sup>
	410 per 1000	378 per 1000 (330 to 431)			
Progression-free survival###	Medium-risk population#		HR 0.75 (0.57 to 1.00)	908 (7 studies)	++ low <sup>1,4,11</sup>
	410 per 1000	379 per 1000 (304 to 470)			
Vertebral fractures	Medium-risk population#		RR 0.74 (0.62 to 0.89)	1116 (7 studies)	+++ moderate <sup>1,5</sup>
	360 per 1000	266 per 1000 (223 to 320)			
Non-vertebral fractures	Medium-risk population#		RR 1.03 (0.68 to 1.56)	1389 (6 studies)	+++ moderate <sup>1,6</sup>
	140 per 1000	144 per 1000 (95 to 218)			
	Medium-risk population#		RR 0.74	2141 (10 studies)	+++ moderate <sup>1,7</sup>



Bisphosphonates in multiple myeloma					
Skeletal-related events	400 per 1000	296 per 1000 (252 to 352)	(0.63 to 0.88)		
Pain	Medium-risk population#		RR 0.75 (0.60 to 0.95)	1281 (8 studies)	+ very low <sup>8,9</sup>
	540 per 1000	410 per 1000 (329 to 508)			
Osteonecrosis of jaw	Medium-risk population#		RR 4.61 (0.99 to 21.35)	1284 (6 studies)	++ low <sup>10,11</sup>
	NE	0 per 1000 (0 to 2)			
<p>* The basis for the assumed risks (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; HR: Hazard ratio; NE: not estimable due to rarity of events in the control arm; RR: Risk ratio.</p>					
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>					
<p>1: A total of 20 RCTs were included in the direct meta-analysis. Only 35% (7/20) of trials had adequate allocation concealment. Only 20% (4/20) of trials reported methods of randomization. Similarly, 15% (3/20) of trials reported blinding procedures and personnel who were blinded to the intervention assignment. However, sensitivity analyses based on the methodological quality domains did not change the estimates. Hence, the assessment of studies' limitations may represent the poor quality of reporting rather than true biased estimates.</p> <p>2: Downgraded the quality of evidence for the outcome overall survival (OS) by one for the observed inconsistency (<math>I^2 = 65\%</math>). However, we noticed that this heterogeneity in the pooled estimate is driven by studies by Aviles and colleagues (Aviles 2007; Aviles 2013); when we removed these RCTs heterogeneity disappeared.</p>					

### Bisphosphonates in multiple myeloma

3: Note that overall mortality data denotes the mortality rates, i.e. the number of events refers to the number of deaths.

4: Downgraded the quality of evidence by one level due to the potential for publication bias. The progression-free survival data were extractable from only 35% (7/20) of studies eligible for direct meta-analysis.

5: Downgraded the quality of evidence by one level due to the potential for publication bias. Data related to patients with vertebral fractures were extractable from only 35% (7/20) of studies eligible for direct meta-analysis.

6: Downgraded the quality of evidence by one level due to the potential for publication bias. Data related to patients with non-vertebral fractures were extractable from only 30% (6/20) of studies eligible for direct meta-analysis.

7: Downgraded the quality of evidence by one level due to the potential for publication bias. Skeletal-related events data were extractable from only 50% (10/20) of studies.

8: Downgraded the quality of evidence by one level due to variation in assessment instruments. There was significant variation in the assessment methods used to measure pain.

9: Downgraded the quality of evidence by one level due to variation in assessment of pain based on blinding of the assessors. Only 15% (3/20) of trials reported blinding procedures and personnel who were blinded to the intervention assignment. Moreover, we found that RCTs with double-blinding showed no significant benefit of bisphosphonates over placebo for amelioration of pain, while non-blinded RCTs favoured bisphosphonates over placebo for pain relief. We also downgraded the quality of evidence by one level due to imprecision.

10: Downgraded the quality of evidence by one level due to the potential for publication bias. Osteonecrosis of the jaw data were extractable from 30% (6/20) of studies eligible for direct meta-analysis.

11: Downgraded the quality of evidence by one level due to imprecision. All included RCTs and also the pooled estimate have wide confidence intervals.

# The moderate control risk was calculated via GRADEpro software based on average risk in the control arm of the included studies.

## We have calculated and presented overall mortality instead of OS. The expected events represent a median timeline of 5 years.

### PFS events represent death or progress or relapse. The expected events represent a median timeline of 5 years.

## 12.4.15. Immunglobuline

### 12.4.15.1. Eine Immunglobulinsubstitution sollte bei Patienten mit Multiplem Myelom mit Hyopgammaglobuinämie und rezidivierenden Infekten erfolgen.

#### 12.4.15.1.1. Evidenztabellen Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
<ul style="list-style-type: none"> <li>•(Raanani, Gafter-Gvili et al. 2009)</li> <li>•systematic review and metaanalysis</li> </ul>	<ul style="list-style-type: none"> <li>•Any RCT comparing the IVIG preparations with placebo/no treatment/ another immunoglobulin preparation/a different administration schedule/a different dose</li> <li>•Searches run in PUBMED (January 1966-December 2008), Central (up to 2008), LILACS, conference proceedings (2002 -2008): Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC),</li> </ul>	<ul style="list-style-type: none"> <li>•IVIG preparations vs. Placebo/no treatment/another immunoglobulin preparation/a different administration schedule/a different dose</li> </ul>	<ul style="list-style-type: none"> <li>all-cause mortality</li> <li>•major infections</li> <li>•any clinically documented infection</li> <li>•microbiologically documented bacterial infections</li> <li>•AEs</li> </ul>	<ul style="list-style-type: none"> <li>• 9 included studies including &gt; 408 patients</li> <li>• OS: n/r</li> <li>• all-cause mortality: RR 1.36 (95% CI 0.58–3.19) without statistical evidence of heterogeneity (P=0.60, I<sup>2</sup>=0%), 2 studies, both at 1 year</li> <li>• Major infections: statistically significant reduction in the occurrence of major infections, RR 0.45 (95% CI 0.27–0.75) without significant heterogeneity (P=0.23, I<sup>2</sup>=31.1%), absolute risk reduction</li> </ul>	<ul style="list-style-type: none"> <li>•Randomisation: yes</li> <li>•ITT : extraction preferentially by intention-to-treat</li> <li>•Blinding : assessed blinding</li> <li>•Publication bias:</li> </ul>	<ul style="list-style-type: none"> <li>•(Boughton, Jackson et al. 1995)</li> <li>•(Chapel, Lee et al. 1994)</li> <li>•(Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic, Gale et al. 1988)</li> <li>•(Gluck, Schnutenhaus et al. 1990)</li> <li>•(Hargreaves 1992)</li> <li>•(Molica, Musto et al. 1996)</li> <li>•(Musto, Brugiattelli et al. 1995)</li> <li>•(Sklenar, Schiffman et al. 1993)</li> <li>•</li> </ul>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen/ (ggf. Do- sierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemer- kungen	Literaturbelege/ eingeschlossene Publikationen
	<p>European Congress of Clinical Microbiology and Infectious Diseases, Annual Meeting of the American Society of Hematology and the annual Meeting of the European Hematology Association</p> <ul style="list-style-type: none"> <li>• Inclusion Criteria: randomized, controlled trials comparing IVIG preparations with placebo/ no treatment/another immunoglobulin preparation/a different administration schedule /dose for patients with LPD or PCD</li> </ul>			<p>= 19%, NNT to prevent a single major infection = 5 (95% CI 3-13) patients receiving IVIG for 1 year, 3 studies</p> <ul style="list-style-type: none"> <li>• OS NMA: n/r</li> <li>• PFS: n/r</li> <li>• Non-vertebral fractures: n/r</li> <li>• Prevention of pathological vertebral fractures: n/r</li> <li>• SREs: n/r</li> <li>• Less pain: n/r</li> <li>• ONJ: n/r</li> <li>• ONJ NMA: n/r</li> <li>• Increase in frequency of hypocalcemia: n/r</li> <li>• Increase in frequency of hypocalcemia, renal dysfunction, gastrointestinal toxicity NMA: n/r</li> <li>• QoL: n/r</li> </ul>		

12.4.15.1.2. GRADE Bewertung

Schlüsselfrage	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR	OS	-	-	-1	-1	-	⊕⊕⊕⊖ low
	SR	Reduktion Infektionen	-	-	-1	-1	-	⊕⊕⊕⊖ low
	SR	QoL						Not reported
	SR	Safety	-	-	-1	-	Großer Effekt, deutliche Zunahme an Nebenwirkungen	⊕⊕⊕⊕ high

Impräzision: breites Konfidenzintervall, schließt potentiellen Nutzen /Schaden von Immunglobulinen ein, Indirekte Evidenz: Studien mit diverse hämatonkologischen Patienten eingeschlossen, die meisten (30 von 40 Studien) bei Patienten, die eine Stammzelltransplantation erhielten

## **12.4 Evidenztabelle und Qualitätsbewertung der ASCO-LL**

Die nachfolgenden Evidenztabelle und Qualitätsbewertungen wurden aus dem "Data Supplement" der ASCO-LL übernommen (Tabelle 1-8, 21-23, 28-29; S. 2-28, 56-75, 81-87).

## Data Supplement 1: Evidence Table(s)

**TRANSPLANT ELIGIBLE POPULATION**

1. What criteria are used to assess eligibility for autologous stem cell transplant (SCT)?

**Table 1: Study Characteristics - RCTs**

Refid	Author/ year	Setting	Location	N of Study Sites	Pt Population	Interventions/comparisons	# of patients	Mean/ Median age	Males/Female	primary outcome
77	Straka- 2018	Multiple practice setting	Germany	40	newly diagnosed stage II or III MM according to Durie and Salmon and 60-70 years of age	Induction chemotherapy  vs.  no induction	207  213	65  65	119/88  117/96	PFS
<b>IFM 99- 06</b>  815	Facon 2007	Intergroupe Francophone du Myélome (IFM) centers	France, Belgium, and Switzerland.	73	previously untreated patients with MM aged between 65 and 75 years	melphalan and prednisone (MP)  melphalan and prednisone plus thalidomide (MPT)  reduced-intensity stem cell transplantation using melphalan 100 mg/m <sup>2</sup> (MEL100).	196  125  126	<u>Age (≥70 yrs):</u> 84  50  49	109/87  63/62  66/60	OS
925	Fernand 2005	Multiple practice setting	France	14	patients with symptomatic MM between the ages of 55 and 65 years.	conventional chemotherapy (CCT)  vs.  high-dose therapy (HDT) and autologous blood stem-cell transplantation	94  96	61  60	55  51	OS

**Table 2: Study outcomes - RCTS**

Refid	Author/ year	Interventions/comparisons	OS	PFS	Toxicity Grade 3/4	Duration of Tx	Other findings	length of F/U
77	Straka-2018	Induction chemotherapy  vs.  no induction	-	21.4 months  20.0 months [HR for progression or death 1.04, 95% CI; 0.84- 1.28; P=0.36]	infection - 17 mucositis – 4  infection - 4 mucositis – 0	7.7 months  4.6 months	-	5.2 years (range 0- 10.1 years)
<b>IFM 99-06</b>  815	Facon 2007	melphalan and prednisone (MP)  vs.  melphalan and prednisone plus thalidomide (MPT)  vs.  reduced-intensity stem cell transplantation using melphalan 100 mg/m2 (MEL100).	33.2 months (13.8-54.8)  51.6 months (26.6-not reached)  38.3 months (13.0-61.6)	-	-	-	The MPT regimen was associated with a significantly better overall survival than was the MP regimen (hazard ratio 0.59, 95% CI 0.46-0.81, p=0.0006) or MEL100 regimen (0.69, 0.49-0.96, p=0.027). No difference was seen for MEL100 versus MP	51.5 months (IQR 34.4- 63.2)



							(0.86, 0.65-1.15, p=0.32).	
925	Fernand 2005	conventional chemotherapy (CCT) vs. high-dose therapy (HDT) and autologous blood stem-cell transplantation	47.8 months  47.8 months	A trend to better EFS (P = .07) was observed in favor of HDT, whereas OS curves were not statistically different (P = .91).	-	-	median event-free survival (EFS) times were 25 and 19 months in the HDT and CCT groups, respectively  The period of time without symptoms, treatment, and treatment toxicity (TwiSTT) was significantly longer for the HDT patients than for the CCT patients (P = .03).	120 months

2. What are the options for initial therapy before transplant?
  - a. How many cycles of therapy are given prior to stem cell collection, are any drugs avoided?
  - b. Does depth of response to initial therapy matter? What response is required to proceed to SCT?
  - c. Should any patient receive tandem autologous SCT?
  - d. Can or should the initial SCT be delayed, for whom and why?
  - e. Should we collect for more than one SCT, if so what determines the number?
  - f. What is the ideal conditioning regimen for transplant?
  - g. When should allogeneic transplant be considered?

**Table 3: Systematic reviews/Meta-analysis**

Refid	author/year	SR objective	Pt Population	Interventions/comparisons	Lit Search range	# of studies included	# of pooled patients	length of F/u	Summary of result
125	Scott 2016	Assess effects of bortezomib on OS, PFS, RR, HRQoL, AEs, & TRD	newly diagnosed OR relapsed disease; included patients who were considered to be either transplant eligible or ineligible	Bortezomib versus no bortezomib with the same or different background therapy in each arm & Bortezomib dose comparisons and comparisons of different treatment administrations and schedules. subgroup analyses for induction, consolidation & maintenance	unspecified start date - 2016	16 RCTs (12 included in MA)	5626 (SR), 4910 (MA)	median 27 months	There is moderate-quality evidence that bortezomib prolongs OS (four studies, 1586 patients; Peto OR 0.77, 95% CI 0.65 to 0.92) and PFS (five studies, 1855 patients; Peto OR 0.65, 95% CI 0.57 to 0.74) from analysing trials of bortezomib versus no bortezomib with the same background therapy in each arm. There is high-quality evidence that bortezomib prolongs OS (five studies, 2532 patients; Peto OR 0.76, 95% CI 0.67 to 0.88) but low-quality evidence for PFS (four studies, 2489 patients; Peto OR 0.67, 95% CI 0.61 to 0.75) from analysing trials of bortezomib versus no bortezomib with different background therapy in each arm or compared to other agent(s). Four

									<p>trials (N = 716) examined different doses, methods of administrations and treatment schedules and were reviewed qualitatively only. We identified four trials in the meta-analysis that measured time to progression (TTP) and were able to extract and analyse PFS data for three of the studies, while in the case of one study, we included TTP data as PFS data were not available. We therefore did not analyse TTP separately in this review. Patients treated with bortezomib have increased risk of thrombocytopenia, neutropenia, gastro-intestinal toxicities, peripheral neuropathy, infection and fatigue with the quality of evidence highly variable. There is high-quality evidence for increased risk of cardiac disorders from analysing trials of bortezomib versus no bortezomib with different background therapy in each arm or versus other agents. The risk of TRD in either comparison group analysed is uncertain due to the low quality of the evidence. Only four trials analysed HRQoL and the data could not be meta-analysed. Subgroup analyses by disease setting revealed improvements in all outcomes, whereas for therapy setting, an improved benefit for bortezomib was observed in all outcomes and subgroups except for OS following consolidation therapy</p>
157	Wang 2016	comparing bortezomib, thalidomide, and lenalidomide in patients with multiple myeloma	patients included irrespective of transplant eligible	Induction chemotherapy. Maintenance chemotherapy	2005 - 2015	23 articles (17 RCTs)	6742	median 42months	These RCTs were separated according to the different agent-based regimens and to autologous stem-cell transplantation (ASCT). Complete response (CR), progression-free survival (PFS),

		(MM) for safety and efficacy							overall survival (OS), and adverse events (AE) were combined. The total weighted risk ratio (RR) of CR was 3.29 [95% confidence interval (95% CI): 2.22–4.88] (
221	Qiao 2015	evaluate efficacy and safety of lenalidomide for MM	Patients with newly diagnosed or previously treated MM	Induction chemotherapy. Maintenance chemotherapy	unspecified start date - 2013	7 RCTs	2357	NR	For patients with previously untreated MM, OR rate and CR rate was significantly higher in lenalidomide-containing group than the control group. For relapsed or refractory MM patients, lenalidomide-containing regimens significantly improved the OR rate, CR rate, 3-year PFS rate and 3-year OS rate. With regard to MM patients after autologous stem cell transplantation, lenalidomide maintenance therapy significantly improved 3-year PFS rate but did not result in improved 3-year OS rate. In terms of toxicities, lenalidomide therapy has a higher rate of Grade 3-4 grade cytopenias, infection, deep-vein thrombosis, and diarrhea. Furthermore, the incidence of second primary malignancies was significantly higher in the lenalidomide group. Previously untreated MM: OR & CR - P<0.00001; Relapsed/refractory MM: OR P < 0.00001; CR P=0.01, 3yr PFS P < 0.00001; Maintenance post ASCT: OS P = 0.75, 3 year PFS P<0.00001
285	Leiba 2014	differences in response rate and toxicity between VCD (bortezomib, cyclophosphamide and dexamethasone) nad VTD (Bortezomib, thalidomide and dexamethasone)	Prospective trials evaluating initial response in transplant eligible patients	VCD(157) v VTD(515)	unspecified start date - January 2013	8 (3 Phase III, 5 Phase 2)	672	median 28.3 months (4.7-42)	The main outcome measures were response rates and adverse events. Eight clinical trials were eligible for analysis. Overall 672 patients were treated with either VCD (n = 157) or VTD (n = 515) as induction therapy. Patients treated with VTD presented with a significantly higher complete/near complete response (34% vs. 6%, P = 0002) as well as a higher very good partial response

									rate or better, following induction therapy (62% vs. 27%, $P < 00001$ ). Although grade 3–4 neurotoxicity was more frequent during VTD therapy (11% vs. 6%, $P = 0057$ ), a higher incidence of overall grade 3–4 adverse events was found in the VCD-treated patients (74% vs. 51%, $P < 0001$ ). VTD induction therapy may be superior in achieving deeper response rate following induction therapy, and is better tolerated.
341	Nooka-2013	to test the hypothesis that the addition of bortezomib to induction therapy not only improves the depth of response but also improves post-transplant progression-free survival (PFS) and overall survival (OS) outcomes	newly diagnosed, transplant-eligible patients with myeloma	bortezomib-containing induction regimen (BCIR) or a nonbortezomib-containing induction regimen (NBCIR)	2003-2012	4 RCTs	2169	NA	The postinduction and post-transplant pooled odds ratio for achieving a complete response/near complete response or a very good partial response or better and the overall response rate were higher with BCIR. The pooled hazard ratios for 3-year PFS and OS were 0.71 (95% confidence interval, 0.60-0.83; $P < .00,001$ ) and 0.79 (95% confidence interval, 0.66-0.96; $P = .014$ ), respectively, favoring BCIR. The odds of developing selected grade $\geq 3$ toxicities (peripheral neuropathy and varicella-zoster virus reactivation) also were higher with BCIR.
390	Armeson 2013	to compare tandem autologous (TA) hematopoietic SCT (auto-HSCT) or single auto-HSCT followed by reduced intensity conditioning (RIC), allogeneic (AR) hematopoietic SCT in the upfront management of patients with multiple myeloma (MM)	newly diagnosed patients undergoing first autologous transplantation in both arms	tandem auto-HSCT v single auto-HSCT followed by RIC AR hematopoietic SCT	unspecified start date - 2011	6 clinical trials reported in 7 manuscripts and 1 meeting abstract	1822	NR	Six trials were identified yielding 1192 subjects in TA and 630 in AR. Patients in AR had higher likelihoods of TRM (relative risk (RR) = 3.3, 95% confidence interval (CI) = 2.2–4.8) and CR (RR = 1.4, 95% CI = 1.1–1.8). OS was not different in the first 36 months (hazard ratio (HR) = 1.15, 95% CI = 0.91–1.45) or after (HR = 0.74, 95% CI = 0.53–1.04) 36 months from assignment. Similar findings were seen for PFS. When compared with TA in the upfront management of MM, AR is associated with higher TRM and CR without improvement in PFS or OS.

418	Kharfan-Dabaja-2013	To compare auto-auto HCT with auto-allo HCT in patients with newly diagnosed MM	patients with newly diagnosed multiple myeloma	auto-allo HCT approach is compared to tandem autologous (auto-auto) HCT	NR	5 RCTs	1538	NR	Assessing response rates by achievement of at least a very good partial response did not differ among the treatment arms [risk ratio (RR) (95% CI) = 0.97 (0.87-1.09), p = 0.66]; but complete remission was higher in the auto-allo HCT arm [RR = 1.65 (1.25-2.19), p = 0.0005]. Event-free survival did not differ between auto-allo HCT group versus auto-auto HCT group using per-protocol analysis [hazard ratio (HR) = 0.78 (0.58-1.05)], p = 0.11) or using intention-to-treat analysis [HR = 0.83 (0.60-1.15), p = 0.26]. Overall survival (OS) did not differ among these treatment arms whether analyzed on per-protocol [HR = 0.88 (0.33-2.35), p = 0.79], or by intention-to-treat [HR = 0.80 (0.48-1.32), p = 0.39] analysis. Non-relapse mortality (NRM) was significantly worse with auto-allo HCT [RR (95%CI) = 3.55 (2.17-5.80), p < 0.00001].
444	Naumann-Winter 2012	Compare TASCT w/ SASCT as first-line treatment in patients with MM in regards to OS, EFS, QoL, TRM	patients with MM at first diagnosis. Prior treatment was accepted if patients had been treated conventionally (melphalan, prednisone) for a limited time span	first-line TASCT with SASCT	1995 to 2011	22 (8 RCTs) (5 RCTs included in MA)	5 RCTs - 1506	NR	Because we identified substantial clinical and methodological heterogeneity, we refrained from conducting a formal meta-analysis. While we included only previously untreated, symptomatic patients with MM the treatment regimens differed notably with respect to acute toxicity, between trials and also between study arms. Compared to state of the art treatment standards, the treatment regimens applied in all trials have to be considered as below standard from a contemporary perspective in at least one component. Three trials were likely to have the potential of being highly biased while two RCTs had a moderate potential for bias. The observed treatment effects in the set

									of included trials may have been influenced by a steep decrease in compliance with the second ASCT and the concomitant selection of patients. In addition, OS data were confounded by the treatment subsequent to first-line therapy. OS was statistically significantly improved in one trial only. While EFS was prolonged in four of the five trials, the median prolongation ranged between three to 12 months, with an uncertain direction of bias in the individual trials. QoL was not reported in any study. Results concerning treatment- or transplantation-related mortality could not be adequately assessed due to substantial differences in definitions between trials and low reporting quality.
493	Fausner 2012	Compare HDT with SDT to analyze OS and PFS	newly diagnosed patients with untreated multiple myeloma. did not specify eligible/ineligible	myeloablative HDT followed by single ASCT v SDT	2009 - 2010	9 RCTs	2600	NR	Patients undergoing HDT with stem cell transplantation had a significant PFS benefit (hazard ratio=0.73; 95% CI=0.56-0.95; p=0.02) but no OS benefit (HR 0.90; 95% CI 0.74-1.10; p=0.32) as compared to patients undergoing SDT. Conclusion: Although there is only a trend of OS benefit with HDT, it is currently still the first line treatment. Additional data from ongoing clinical trials and new studies using novel agents such as thalidomide, lenalidomide and bortezomib are warranted to finally evaluate the role of HDT in the treatment management of patients with newly diagnosed MM.



**Table 4: Study Characteristics - RCTs**

Refid	author/year	Setting	Location	N of Study Sites	Pt Population	Interventions/comparisons	# of patients	Mean/Median age of pts	Male/Female	Tumor type	Tumor stage	primary outcome
15	Cho 2017	Academic institution	United States	1	patients consecutively admitted for HSCT	2 of cryotherapy vs. 6 h of cryotherapy	73  73	58  58	46/27  44/29	-  -	-  -	noninferiority in severe mucositis and related secondary endpoints
38	Attal 2017	Multiple practice setting	Europe	69	patients were 65 years of age or younger and presented with symptomatic, measurable, newly diagnosed multiple myeloma	RVD-Alone Group Vs. Transplantation Group.  three cycles of RVD and then consolidation therapy with either five additional cycles of RVD (350 patients) or high-dose melphalan plus stem-cell transplantation followed by two additional cycles of RVD (350 patients).	350  350	59  60	208/142  214/136	IgG:209 IgA: 71 Light chain: 57 Other:13  IgG: 223 IgA: 73 Light chain: 46 Other:8	I:115 II:170 III:65  I:118 II:171 III:61	PFS
77	Straka-2016	Multiple practice setting	Europe	40	newly diagnosed stage II or III MM according to Durie and Salmon and were 60-70 years of age	Induction chemotherapy vs. no induction	207  213	65  65	119/88  117/96	-  -	-  -	PFS



GMM G- HD2	Mai- 2016	Multiple practice setting	Europe	48	Newly-diagnosed multiple myeloma stage 2 or 3 according to Durie and Salmon	single HDM/ASCT (melphalan 200 mg/m <sup>2</sup> on day -2 followed by reinfusion of autologous stem cells on day 0) in Arm A	177	55	106/70	-	-	the non- inferiority of single (Arm A) versus tandem (Arm B) HDM/ASCT with regard to EFS 2 years after randomiza tion
						vs. tandem HDM in Arm B (melphalan 200 mg/m <sup>2</sup> on day -2 followed by reinfusion of autologous stem cells on day 0, repeated after 3–6 months).  maintenance therapy with interferon (IFN, 39/week, 45 or 50 million international units s.c.) was applied in both study arms.	181	56	106/75			
IFM20 13-04	Morea u-2016	Multiple practice setting	Europe	56	patients were 65 years of age or younger and had untreated symptomatic MM	VTD	169	59	103/66	-	-	postinducti on very good partial response (VGPR) rate
						Vs. VCD	169	60	108/61			
158	Bensin ger- 2015	Multiple practice setting	United States	4	symptomatic MM pts	200 mg/m <sup>2</sup> (mel200)	65	55	42/23	-	-	rate of near complete response
						vs 280 mg/m <sup>2</sup> (mel280)	66	58	43/23			
173	Gay- 2015	Multiple practice setting	Australi a, Czech Republ ic and Italy	59	Patients aged ≤65 years with symptomatic, measurable, NDMM	Chemotherapy plus lenalidomide(CRD)	129	56	59/70	-	I:58 II:48 III:23	PFS
						vs. autologous transplantation (MEL200-ASCT)	127	57	61/66		I:64 II:45 III:18	

						vs lenalidomide + prednisone	117	57	58/59		I:60 II:43 III:14	
						vs lenalidomide maintenance	106	56	50/56		I:51 II:39 III:17	
<b>MM5</b> 207	Mai Leuk 2015	Multiple practice setting	Europe	106	newly diagnosed, transplant- eligible multiple myeloma patients	bortezomib/cyclophosphamide/dexamethasone (VCD)  vs  bortezomib/doxorubicin/dexamethasone (PAD)	251	59	153/98	-	-	non-inferiority of VCD compared to PAD
519	Krishnan- 2011	transplant centers of the Blood and Marrow Transplant Clinical Trials Network	United States	37	Patients (<70 years old) with adequate organ function who had completed at least three cycles of systemic antimyeloma therapy within the past 10 months	autologous HSCT followed by an allogeneic HSCT (auto-allo group) or tandem autologous HSCTs (auto-auto group) on the basis of the availability of an HLA- matched sibling donor.  Patients in the auto-auto group subsequently underwent a random allocation (1:1) to maintenance therapy (thalidomide plus dexamethasone) or observation.	<u>Standard Risk:</u> Auto-Auto (n=436)	55	260/176	-	<u>Durie- Salmon</u> Stage I- II:142 Stage III: 294	3 yr PFS
							Auto-Allo (n=189)	53	111/78		Stage I- II:59 Stage III: 130	
							<u>High risk:</u> Auto-Auto (n=48)	57	27/21		Stage I- II:10 Stage III: 38	
							Auto-Allo (n=37)	51	21/16		Stage I- II:9 Stage III: 28	
662	Palumbo- 2009	Italian Bone Marrow	Italy	31	newly diagnosed myeloma patients younger than 65 years	2 courses of MEL200  vs	149	58	78/71	IgG:88 IgA:33 Bence Jones protein:27	I:60 II:49 III:18 Missing:22	OS

		Transplantation Units				2 courses of MEL100	149	57	78/71	Other: 0 IgG:83 IgA:42 Bence Jones protein:21 Other:3	I:71 II:38 III:23 Missing:17	
PATH EMA 928	Blade-2005	Academic institution	Spain	29	Patients with newly diagnosed and untreated symptomatic stage II or III MM who were younger than 65 years	VBMCP/BAD chemotherapy (arm A)	83	56	43/40	-	-	OS
						Vs HDT/SCT intensification (arm B, 24 received melphalan-140 [MEL-140]/TBI and 57 received MEL-200).	81	57	52/29			
1554	Durie 2016	SWOG and NCTN institutions	United States	139	patients with newly diagnosed multiple myeloma aged 18 years and older	bortezomib with lenalidomide and dexamethasone (VRd group)	242	<u>Age ≥85</u> 93	153/89	-	-	PFS
						vs lenalidomide and dexamethasone (Rd group)	229	109	122/107			

Table 5: Study outcomes - RCTs

Refid	author/year	Interventions/comparisons	Response	Tx discontinuation rate from toxicity	OS	PFS	Second malignancy	Toxicity Grade 3/4	Duration of Tx	length of F/u	Other relevant data
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15	Cho 2017	2 h of cryotherapy vs. 6 h of cryotherapy	-	-	-	-	-	62.3% (n 5 91) of patients had grade 1–3 oral mucositis, and no patient experienced a grade 4 event. In total, 45.2% (66/146) of patients had at worst grade 1 mucositis, 13.7% (20/ 146) had at worst grade 2, and 3.4% (5/146) had at worst grade 3 events.  The rate of severe mucositis, of at least grade 3, was not different (noninferior) between the randomized groups.	-	-	patients who received 2 h of cryotherapy did not have a higher rate of mucositis (of any grade) (58.9% in the 2-h cohort vs. 65.8% in the 6-h cohort, risk difference: – 6.8%, 90% CI: – 20.0, 6.3%) or of grade 2 or above (2-h: 16.4% (n 5 12), 6-h: 17.8% (n 5 13), risk difference: – 1.4%, 90% CI: – 11.6%, 8.9%)  Severe mucositis was observed in 2.7% (n 5 2) and 4.1% (n 5 3) of patients receiving 2 or 6 h of cryotherapy, respectively (difference in risk: –1.4%, 90% confidence interval (CI): – 6.3%, 3.6%).
38	Attal 2017	RVD-Alone Group vs. Transplantation Group	48	32	81%	36 months	1.1 cases per 100 patient-years	blood and lymphatic-system disorders (95% vs. 64%, P<0.001).	-	44 months	-
			59	39	82%	50 Months (adjusted)				43 months	

			(P=0.03)			hazard ratio for disease progression or death, 0.65; 95% CI, 0.53 to 0.80; P<0.001)	1.5 cases per 100 patient years (P=0.37)	gastrointestinal disorders (28% vs. 7%, P<0.001)			
77	Straka-2016	Induction chemotherapy vs. no induction	-	-	-	21.4 months	-	infection - 17 mucositis - 4	7.7 months	5.2 years (range 0- 10.1 years)	-
						20.0 months [HR for progression or death 1.04, 95% CI, 0.84- 1.28; P=0.36]		infection - 4 mucositis - 0	4.6 months		
112	Mai-2016	single HDM/ASCT in Arm A vs. tandem HDM in Arm B	In the ITT and PP set of the tandem arm, the rates of complete responses increased from first to second HDM/ASCT (both P = 0.04)	-	Ten-year OS for the entire ITT was 34% (95% confidence interval: 29-40%). OS after first relapse was significantly shortened in the tandem arm (P = 0.04)	-	-	-	-	11 years	Neither EFS (P = 0.53) nor overall survival (OS) (P = 0.33) differences were observed in the ITT population. In the tandem arm, 26% (n = 47/181) of patients refused a second HDM/ASCT due to non-medical reasons. A per-protocol (PP) analysis, including patients who received the intervention (single/tandem

											HDM/ ASCT: n = 156/93) and patients who did not receive a second HDM/ASCT due to medical reasons (12%, n = 22/181), did not yield differences in EFS (P = 0.61) or OS (P = 0.16).
117	Morea u-2016	VTD Vs. VCD	92.3%  83.4%  P = .01	-	-	-	-	63.9  v 68.2  p=0.40	-	NR	After 4 cycles, on an intent-to-treat basis, 66.3% of the patients in the VTD arm achieved at least a very good partial response (primary end point) vs 56.2% in the VCD arm (P = .05).
158	Bensinger-2015	200 mg/m <sup>2</sup> (mel200)  vs  280 mg/m <sup>2</sup> (mel280)	nCR 22%  39%, (P=0.03)  <u>PR</u> 57%  74%, (P=0.04)	-	PFS at 1 and 3 years were 83 and 46%, respectively, for mel200 and 78 and 54%, respectively, for mel280.	-	-	Amifostine and mel280 were well tolerated, with no grade 4 regimen-related toxicities and only one grade 3 mucositis (none with mel200) and three grade 3 gastrointestinal (GI) toxicities (two in mel200). Hospitalization rates were more frequent in the mel280 group	-	-	The hazard of mortality was not statistically significantly different between groups (mel200 vs mel280; hazard ratio (HR)=1.15 (95% confidence interval (CI), 0.62-2.13, P=0.66)) nor was the rate of progression/mortality (HR=0.81

								(59 vs 43%, P=0.08).			(0.52-1.27, P=0.36)).
173	Gay-2015	Chemotherapy plus lenalidomide(CRD)  vs.  autologous transplantation (MEL200-ASCT)  vs  lenalidomide + prednisone  vs  lenalidomide maintenance			PFS did not differ between maintenance treatments (median 37.5 months [95% CI 27.8-not evaluable] with lenalidomide plus prednisone vs 28.5 months [22.5-46.5] with lenalidomide alone; HR 0.84, 95% CI 0.59-1.20; p=0.34).	PFS during consolidation was significantly shorter with chemotherapy plus lenalidomide compared with high-dose melphalan and ASCT (median 28.6 months [95% CI 20.6-36.7] vs 43.3 months [33.2-52.2]; hazard ratio [HR] for the first 24 months 2.51, 95% CI 1.60-3.94; p<0.0001).		neutropenia (nine [8%] of 117 patients assigned lenalidomide plus prednisone vs 14 [13%] of 106 allocated lenalidomide alone), infection (eight [8%] vs five [5%]), and systemic toxicities (seven [6%] vs two [2%]). Non-haematological serious adverse events were reported in 13 (11%) patients assigned lenalidomide plus prednisone versus ten (9%) allocated lenalidomide alone.	52.0 months (IQR 30.4-57.6)	The trial is ongoing and some patients are still receiving maintenance  Four patients died because of adverse events, three from infections (two during induction and one during consolidation) and one because of cardiac toxic effects.	
207	Mai Leuk 2015	bortezomib/cyclophosphamide/dexamethasone (VCD)  vs  bortezomib/doxorubicin/dexamethasone (PAd)	VGPR rates 37.0  34.3%.  P=0.001.	-	-	-	-	-	-	-	The rates of progressive disease were 0.4% (VCD) versus 4.8% (PAd; P=0.003).
519	Krishnan-2011	autologous HSCT followed by an allogeneic HSCT (auto-allo group) or	-	-	overall survival also did not differ at 3 years (77% [95%	3-year PFS were 43% (95% CI 36-51) in the auto-allo	-	87 (46%) of 189 patients in the auto-allo group had grade 3-5 adverse events	-	40 months (IQR 38-43	-

		tandem autologous HSCTs (auto-auto group) on the basis of the availability of an HLA-matched sibling donor. Patients in the auto-auto group subsequently underwent a random allocation (1:1) to maintenance therapy (thalidomide plus dexamethasone) or observation.			CI 72-84] vs 80% [77-84]; p=0.191.	group and 46% (42-51) in the auto-auto group (p=0.671)		as did 185 (42%) of 436 patients in the auto-auto group.		months )	
662	Palumbo-2009	2 courses of MEL200  vs  2 courses of MEL100	complete remission 22 of 149 (15%); partial remission 95 of 149 (64%), for an overall response rate of 79%.  complete remission 12 of 149 (8%); partial remission 95 of 149 (64%), for an overall response	-	Overall survival did not differ (P = .13)	31.4months  26.2 months  P = .01	-	Treatment-related mortality was 3.1% in the MEL200 and 2.9% in the MEL100 group.	-	44.6 (range, 0.5-79.9) months	median time to progression (34.4 vs 27.0 months, P = .014) were longer in the MEL200



			rate of 72%.								
928	Blade-2005	VBMCP/VBAD chemotherapy (arm A)  Vs  HDT/SCT intensification (arm B)	complete remission (CR) rate was significantly higher with HDT (30% vs 11%; P = .002).	-	61 months  66 months	42 months  33 months  P = not significant				56 months	survival after relapse was identical in the 2 arms (15.9 vs 16.4 months).
1554	Durie 2016	bortezomib with lenalidomide and dexamethasone (VRd group)  vs  lenalidomide and dexamethasone (Rd group)	82%  72%	-	75 months  64 months  HR 0.709, 95% CI 0.524-0.959; two-sided p value 0.025	43 months  30 months  stratified hazard ratio [HR] 0.712, 96% CI 0.56-0.906; one-sided p value 0.0018	-	There were no treatment-related deaths in the Rd group, and two in the VRd group.	-	55 months (IQR 48-68)	198 (82%) of 241 patients in the VRd group and 169 (75%) of 226 patients in the Rd group; 55 (23%) and 22 (10%) patients discontinued induction treatment because of adverse events, respectively.

3. What post-transplant therapy should be recommended?
  - a. Is there a role for consolidation therapy? If so, how many cycles?
  - b. What maintenance therapy should patients receive and for how long?
  - c. Should maintenance therapy be modified based on risk or response post SCT?

**Table 6: Systematic reviews/Meta-analysis**

Refid	author/year	SR objective	Pt Population	Interventions/comparisons	Lit Search range	# of studies included	# of pooled patients	length of F/u	Summary of result
9	McCarthy 2017	to evaluate the effect of postASCT lenalidomide maintenance on outcomes, including OS, in patients with NDMM.	patients with NDMM	lenalidomide maintenance vs placebo or observation	NR	3 RCTs	1,208(total) 605 603	79.5 months (range, 0.0 to 114.3 months)	The median PFS was 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group (hazard ratio, 0.48; 95% CI, 0.41 to 0.55). At a median follow-up time of 79.5 months for all surviving patients, the median OS had not been reached for the lenalidomide maintenance group, whereas it was 86.0 months for the placebo or observation group (hazard ratio, 0.75; 95% CI, 0.63 to 0.90; P = .001). The cumulative incidence rate of a second primary malignancy before disease progression was higher with lenalidomide maintenance versus placebo or observation, whereas the cumulative incidence rates of progression, death, or death as a result of myeloma were all higher with placebo or observation versus lenalidomide maintenance.
176	Wang 2015	To evaluate the impact of IMiD-based	included both studies in the transplantation	IMiD maintenance therapy	unspecified start date - 2015	18 RCTs	7730	NR	IMiD-based maintenance therapy statistically significantly prolonged progression-free

		maintenance therapy on survival outcomes and serious adverse events associated with the therapy	setting and those in the nontransplantation setting						survival (PFS; hazard ratio (HR) = 0.62, 95% confidence interval (CI) = 0.57 to 0.67, $P < .001$ ) but failed to improve overall survival (OS; HR = 0.93, 95% CI = 0.85 to 1.01, $P = .082$ ). Stratified analyses demonstrated that both thalidomide and lenalidomide provided PFS but not OS benefit in transplantation as well as nontransplantation settings. IMiD-based maintenance therapy in MM led to a higher risk of grade 3–4 thromboembolism (risk ratio = 2.52, 95% CI = 1.41 to 4.52, $P = .002$ ). Thalidomide maintenance therapy increased the risk of peripheral neuropathy; lenalidomide maintenance therapy increased the risks of myelosuppression and second primary hematological malignancies.
303	Gao 2014	To analyze OS, PFS, and AEs of lenalidomide maintenance therapy after ASCT vs placebo therapy in patients with MM	patients with MM	lenalidomide maintenance therapy after ASCT vs placebo therapy after ASCT	unspecified start date - 2014	2 phase 3 RCTs	1074	NR	There was a marked benefit in PFS with lenalidomide (Odds Ratio [OR] = 2.5, 95% confidence interval [CI] = 1.93 to 3.24). There was statistically non-significant tendency toward benefit in OS with lenalidomide (OR = 1.21, 95% CI = 0.65 to 2.24). For adverse events, more patients in lenalidomide treatment arm experienced neutropenia (OR = 4.88, 95% CI = 3.67 to 6.50), infection (OR = 2.82, 95% CI = 1.67 to 4.73), hematologic cancers (OR = 3.31, 95% CI = 1.30 to 8.41), and solid tumors (OR = 2.24, 95% CI = 1.01 to 4.98). No significant differences were seen with deep vein thrombosis

									(OR = 2.15, 95% CI = 0.92 to 5.06), peripheral neuropathy (OR = 1.50, 95% CI = 0.53 to 4.25), thrombocytopenia (OR = 1.05, 95% CI = 0.12 to 9.54), and anemia (OR = 1.36, 95% CI = 0.02 to 83.86).
320	Palumbo 2014	To pool and analyse available data to compare the incidence of second primary malignancies in patients with and without lenalidomide exposure	patients with MM	lenalidomide v no lenalidomide	2000-2012	7 (phase 3 RCTs)	3218	Median: lenalidomide-25 (11-39); no lenalidomide 28 (20-37)	Cumulative incidences of all second primary malignancies at 5 years were 6.9% (95% CI 5.3-8.5) in patients who received lenalidomide and 4.8% (2.0-7.6) in those who did not (hazard ratio [HR] 1.55 [95% CI 1.03-2.34]; p=0.037). Cumulative 5-year incidences of solid second primary malignancies were 3.8% (95% CI 2.7-4.9) in patients who received lenalidomide and 3.4% (1.6-5.2) in those that did not [HR 1.1 [95% CI 0.62-2.00]; p=0.72], and of haematological second primary malignancies were 3.1% (95% CI 1.9-4.3) and 1.4% (0.0-3.6), respectively (HR 3.8 [95% CI 1.15-12.62]; p=0.029). Exposure to lenalidomide plus oral melphalan significantly increased haematological second primary malignancy risk versus melphalan alone (HR 4.86 [95% CI 2.79-8.46]; p<0.0001). Exposure to lenalidomide plus cyclophosphamide (HR 1.26 [95% CI 0.30-5.38]; p=0.75) or lenalidomide plus dexamethasone (HR 0.86 [95% CI 0.33-2.24]; p=0.76) did not increase haematological second primary malignancy risk versus melphalan alone.

**Table 7: Study Characteristics**

Refid	author/year	Setting	Location	N of Study Sites	Pt Population	Interventions/comparisons	# of patients	Mean/Median age of pts	Male/Female	Tumor type	Tumor stage	primary outcome
19	Rosinol 2017	Academic institution	Europe	1	patients 65 years old or younger with newly diagnosed symptomatic multiple myeloma	TV (thalidomide 100 mg daily plus one cycle of intravenous bortezomib at 1.3 mg/m <sup>2</sup> ) on days 1, 4, 8 and 11 every 3 months) vs T (100 mg daily) Vs alfa2-IFN (3 MU three times per week) for up to 3 years.	91  88  92	56  59  55	54/37  51/37  66/26	-	-	Response
282	Palumbo-2014	Multiple practice setting	Italy and Israel	62	Patients with symptomatic, measurable, newly diagnosed multiple myeloma who were 65 years of age or younger	Lenalidomide Maintenance (N=116) No Maintenance (N=115)  Consolidation: High-Dose Melphalan (N=141) MPR (N=132)	402	58	219/183	-	-	PFS
Myeloma .10 407	Stewart-2013	Multiple practice setting	Canada, United States	22	patients who had undergone autologous stem cell transplantation with melphalan 200 mg/m <sup>2</sup> .	thalidomide-prednisone vs. observation	166  166	58  58	108/58  110/56	-	-	-
446	Maicolino-2012	Multiple practice setting	Brazil	4	symptomatic MM in accordance with the International	Dexamethasone (Arm A)	52	55	29/23	IgG: 29 IgA: 13 Light chain:10	-	PFS

					Myeloma Working Group criteria, [6] age 18–70 years	vs. Dexamethasone + Thalidomide (Arm B)	56	52	30/26	Nonsecretory: 0 IgG: 28 IgA: 15 Light chain: 10 Nonsecretory: 3		
465	Usmani-2012	Multiple practice setting	United States	-	pts with newly diagnosed MM	control group (no thalidomide) or to the experimental group (thalidomide during induction, between transplantations, and during consolidation and maintenance).	1148	-	697/451	-	-	second primary malignancies (SPMs)
490	Attal 2012	Multiple practice setting	France, Belgium and Switzerland.	77	patients younger than 65 years of age who had nonprogressive disease after first-line transplantation	lenalidomide (10 mg per day for the first 3 months, increased to 15 mg if tolerated) vs placebo until relapse.	307 307	55 55	169/138 181/126	IgG: 192 IgA: 62 Light-chain: 47 Other: 6 IgG: 169 IgA: 78 Light-chain: 55 Other: 5	-	PFS
722	Spencer 2009	Multiple practice setting	Australia and New Zealand	29	patients with newly diagnosed MM	indefinite prednisolone maintenance therapy (control group) vs same + 12 months of thalidomide consolidation (thalidomide group)	114 129	57 57	68/46 79/50	-	-	PFS & OS

Table 8: Study outcomes

Refid	author/year	Interventions/comparisons	Response	Tx discontinuation rate from toxicity	OS	PFS	Second malignancy	Toxicity Grade 3/4	Duration of Tx	length of F/u	Other relevant data
19	Rosino   2017	TV (thalidomide 100 mg daily plus one cycle of intravenous bortezomib at 1.3 mg/m <sup>2</sup> ) on days 1, 4, 8 and 11 every 3 months)  vs T (100 mg daily)  Vs alfa2-IFN (3 MU three times per week) for up to 3 years.	(CR) 21%  11%  17% (P, not significant)	-	NS	50.6 months  40.3 months  32.5 months, P=0.03	-	Grade 2-3 peripheral neuropathy was observed in 48.8%, 34.4% and 1% of patients treated with TV, T and alfa2-IFN	-	58.6 months	-
282	Palumbo-2014	High-Dose Melphalan + Lenalidomide Maintenance  vs No Maintenance  MPR Lenalidomide Maintenance  vs No Maintenance	-	-	78.4%  66.6%  70.2%  58.7%	54.7 months  37.4 months  34.2 months  21.8 months	-	Grade 3 or 4 neutropenia was significantly more frequent with high-dose melphalan than with MPR (94.3% vs. 51.5%), as were gastrointestinal adverse events (18.4% vs. 0%) and infections (16.3% vs. 0.8%); neutropenia and dermatologic toxic effects were	-	51.2 months (range, 1 to 66)	-

								more frequent with lenalidomide maintenance than with no maintenance (23.3% vs. 0% and 4.3% vs. 0%, respectively).			
407	Stewart-2013	thalidomide-prednisone vs. observation	-	-	68%  60% (HR 0.77; P .18)	-	9  6	111 deaths, including 50 in those allocated to thalidomide-prednisone and 61 in those allocated to observation	-	4.1 years	thalidomide-prednisone was associated with superior myeloma-specific progression-free survival and progression-free survival (for both outcomes, the 4-year estimates were 32% vs 14%; hazard ratio = 0.58; P < .0001)
446	Maiolino-2012	Dexamethasone (Arm A) vs. Dexamethasone + Thalidomide (Arm B)	-	-	70%  85% P = 0.27	19 months  36 months,	-  -	4  19 (P = 0.001)	-	27 months	a 2-year progression-free survival (PFS) of 30% in arm A (95% CI 22-38) and 64% in arm B (95% CI 57-71; P = 0.002),
465	Usmani-2012	control group (no thalidomide) or to the experimental group (thalidomide during induction, between transplantations and during	-	-	-	-	The cumulative incidence of SPMs did not differ significantly among the TT trial components when measured from enrollment (P	-	-	TT2: 112 months ; TT3A: 75 Months ; TT3B: 46 months	a pairwise comparison of the TT2 arms suggested a lower incidence of hematologic SPMs in the thalidomide maintenance arm (hazard



		consolidation and maintenance).					= .78) or from initiation of maintenance (P = .82).				ratio = 0.38; P = .09).
490	Attal 2012	lenalidomide (10 mg per day for the first 3 months, increased to 15 mg if tolerated) vs placebo until relapse.	-	-	-	41 months, 23 months	3.1 per 100 patient-years 1.2 per 100 patient-years (P<0.002).	The rates of grade 3 or 4 peripheral neuropathy were similar in the two groups	-	45 months	Median event-free survival (with events that included second primary cancers) was significantly improved with lenalidomide (40 months, vs. 23 months with placebo; P<0.001).
722	Spencer 2009	indefinite prednisolone maintenance therapy (control group) vs same + 12 months of thalidomide consolidation (thalidomide group)	-	-	86% 75% (P = .004; HR, 0.41; 95% CI, 0.22 to 0.76)	42% 23% (P < .001; hazard ratio [HR], 0.5; 95% CI, 0.35 to 0.71)	-	Neurological toxicities were more common in the thalidomide arm but there were no differences between arms for thromboembolic events	-	3 years	-

**RELAPSED DISEASE**

7. What factors influence choice of first relapse therapy?
  - a. What is the definition of relapse (clinical CRAB criteria vs rise in M protein)?
    - i. When should we start therapy? Biochemical or clinical?
  - b. Is there an ideal therapy at first relapse? Doublet or Triplet, PI or IMiD or mAB?
  - c. What is the ideal length of therapy at relapse?
    - i. Should this be response based and or risk based?
  - d. Is there an ideal sequence of therapy in relapsed myeloma?
  - e. What is the role of SCT in relapsed MM?

**Table 21: Systematic reviews/Meta-analysis**

Refid	author/ year	SR objective	Interventions/ comparisons	Lit Search range	# of studies included	# of pooled patients	length of F/u	Summary of result
1554	Dimopoulos 2018	to use an NMA to compare IMiD-based combination regimens for patients with RRMM	IMiD-containing regimens	1995 -, 2016.	8 RCTS (4 used in NMA)	-	-	The results indicated that triplet combinations are more effective than doublet combinations. Of the triplet combinations, daratumumab, lenalidomide, dexamethasone (DRd) was significantly better in improving progression-free survival in patients with RRMM than were other IMiD-containing regimens (lenalidomide, dexamethasone [Rd]: hazard ratio [HR], 0.37; carfilzomib, Rd: HR, 0.54; elotuzumab, Rd: HR, 0.54; ixazomib, Rd: HR, 0.50). Similar trends were observed for overall survival and overall response. DRd showed the greatest probability of being the best treatment for all clinical efficacy outcomes. The subgroup analyses results were consistent with the base-case results.

34	Sun 2017	assess the efficacy and toxicities of triplet versus doublet combination regimens for the treatment of relapsed or refractory multiple myeloma (RRMM)	triplets versus doublet combination therapy	Up to May 2016	5 phase III studies	3179	the follow-up periods differ between the trials, and survival data is not mature at the time of data cutoff.	The pooled results demonstrated that triplet combination therapies significantly improve OS (HR 0.83, 95%CI: 0.71–0.94, $p = 0.004$ ) and PFS (HR 0.68, 95%CI: 0.62–0.74, $p < 0.001$ ). The pooled RRs of ORR, very good partial response (VGPR) and complete response (CR) with triplets vs. doublets were 1.19 (95%CI: 1.10–1.27), 1.44 (95%CI: 1.18–1.77), and 1.76 (95%CI: 1.04–2.97), respectively, indicating that the RRs of achieving deeper responses were higher with triplets, though the RRs of overall $\geq$ grade 3 adverse events (RR 1.11, $p = 0.001$ ) and $\geq$ grade 3 thrombocytopenia (RR 1.64, $p = 0.009$ ) was higher with triplets.
37	van Beurden-Tan, 2017	to synthesize all efficacy evidence, enabling a comparison of all current treatments for R/R MM.	18 treatment options	1999 - 2016	17 phase III RCTs	8605	-	The combination of daratumumab, lenalidomide, and dexamethasone was identified as the best treatment. It was most favorable in terms of (1) hazard ratio for progression-free survival (0.13; 95% credible interval, 0.09 to 0.19), and (2) probability of being best (99% of the simulations). This treatment combination reduced the risk of progression or death by 87% versus dexamethasone, 81% versus bortezomib plus dexamethasone, and 83% versus lenalidomide plus dexamethasone.
253	Lopuch, 2014	to evaluate the efficacy and safety of targeted agents used as monotherapy or combined therapy in patients with relapsed/refractory multiple myeloma (MM)	Maintenance chemotherapy	Up to May 2013.	4 RCTs	997	70 weeks; 7.2 months; 13.3 months	The meta-analysis showed that combined therapy significantly improved progression-free survival compared with monotherapy ( $P < 0.05$ ). However, there was not a significant difference between monotherapy and combined therapy in overall survival ( $P > 0.05$ ). The combined therapy also significantly increased the risk of serious adverse events and grade 3/4 AEs compared to monotherapy ( $P < 0.05$ ). Overall, the results of comparisons between monotherapy and combined therapy in individual trials were differentiated, and some combinations

								were not more effective than monotherapy (bortezomib plus bevacizumab vs. bortezomib and thalidomide plus INFo vs. thalidomide) which emphasizes the role of individualized therapy in relapsed/refractory MM especially in the elderly or patients with significant comorbidities
1033*	Botta 2016	to evaluate the efficacy of regimens that have been directly compared with bortezomib or immunomodulatory imide drugs (IMiDs) in head-to-head clinical trials and a network meta-analysis (NMA) to determine the relevance of each regimen on the basis of all the available direct and indirect evidence.	there were 10 trials (4371 patients)10,11,33-37,39-41 in which an experimental treatment was compared with a bortezomib-based conventional treatment and 6 trials (3129 patients)11,24-27,42 in which an experimental treatment was compared with an IMiD-based conventional treatment.	Up to June 2016.	19 RCTs with or without blinding	8997	-	Sixteen trials were included in the pairwise meta-analyses, and 18 trials were included in the NMA. Pairwise meta-analyses showed that a 3-drug regimen (bortezomib- or IMiD-based) was superior to a 2-drug regimen in progression-free-survival (PFS) and overall response rate (ORR). NMA showed that an IMiD backbone associated with anti-MM monoclonal antibodies (mAbs) (preferably) or proteasome inhibitors had the highest probability of being the most effective regimen with the lowest toxicity. The combination of daratumumab, lenalidomide, and dexamethasone ranked as the first regimen in terms of activity, efficacy, and tolerability according to the average value between surface under the cumulative ranking curve of PFS, overall survival, ORR, complete response rate, and safety.
1234	Liu 2017	To analyze the treatment of newly diagnosed and relapsed/refractory multiple myeloma (NDMM/RRMM) patients with del(17p).	One study reported the outcomes of NDMM patients with del(17p) treated with VAD (vincristine, adriamycin, and dexamethasone), three reported the outcomes of bortezomib combination regimens in NDMM patients with del(17p), three reported the outcomes of lenalidomide	-	13	3,187	-	Thirteen prospective studies that evaluated 3,187 MM patients, including 685 with del(17p), were included in our metaanalysis. The incidence of del(17p) in NDMM and RRMM patients was similar (13% vs. 14%, respectively, P = 0.64, I2 = 94%). The overall response rate (ORR) to new agents was 40.5% and 67.1%, respectively, in RRMM patients with or without del(17p) (P = 0.1, I2 = 63.9%). NDMM patients with del(17p) treated with PAD (bortezomib, adriamycin, and dexamethasone) induction therapy followed by bortezomib maintenance

			combination regimens in RRMM patients with del(17p), three reported the outcomes of pomalidomide combination regimens in RRMM patients with del(17p), and three reported the outcomes of carfilzomib combination regimens in RRMM patients with del(17p)					therapy had higher progression-free survival (PFS) (25.7 vs. 12-14.6 months) and overall survival (OS) (62% vs. 8% at 36 months) than those treated with PD (bortezomib and dexamethasone) or VAD (vincristine, adriamycin, and dexamethasone). PFS among RRMM patients with del(17p) treated with D (single-agent dexamethasone), Rd/VRd (lenalidomide and dexamethasone/bortezomib and Rd), KRd (carfilzomib and Rd), IRd (ixazomib and Rd), ERd (elotuzumab and Rd), or P+D (pomalidomide and dexamethasone) was 1.1, 2-14.9, 24.5, 15.7, 21.2, and 4.6-7.3 months, respectively. The OS of patients treated with D or K (single-agent carfilzomib), Rd/VRd, ERd, or P+D was 7.7, 7, 4.7-36.4, > 42.3, and 12-12.6 months, respectively. PFS among RRMM patients without del(17p) treated with D, Rd/VRd, ERd, or P+D was 2.3, 8.2-14.8, 18.5, and 4.2 months, while OS was 9, 23-40.8, 42.3, and 14 months, respectively.
1235	Liu 2016	to observe the efficacy of panobinostat combined with other drugs by calculating the overall response rate, clinical benefit rate, rate of stable disease and rate of progressive disease.	8 studies were trials about ponobinostat combined with proteasome inhibitor (bortezomib or carfilzomib), and 5 of them were combined with both bortezomib and dexamethasone.	2000 - 2015	11 clinical trials were identified including a phase III study, 4 phase II studies, 2 phase III studies and 4 phase I studies.	700	-	The ORR varied between 0.08 and 0.67. Pooled analyses showed the results that the ORR was 0.45 (95% CI: 0.31-0.59, I <sup>2</sup> =90.5%, P=0.000) for panobinostat combined with any other kind of drugs. The most common Grade 3/4 adverse effects were thrombocytopenia, neutropenia, lymphopenia, anemia, diarrhea, fatigue, nausea and so on.
1328	Nooka 2016	to test the hypothesis that triplets are tolerable, improve ≥ CR, ≥ VGPR, ORR rates and would translate to an improved PFS.	impact of triplets versus doublets	2000 - 2016	5 phase 3 RCTs	3197	-	The pooled odds ratios of ORR, ≥ VGPR and ≥ CR with triplets vs. doublets were 1.811 (P< 0.000), 1.962 (P< 0.001), 2.325 (P< 0.000) respectively, indicating that the odds of achieving deeper responses are higher with triplets. The pooled hazard ratios (HR) for PFS was HR 0.674 (95% CI 0.613-0.741; P= 0.000) in favor of

								<p>triplets. Q-statistic for PFS (P= 0.719; df= 4; I2 = 0.00) suggests homogeneity across studies. Though the relative risk (RR) of selected ≥ grade 3 serious adverse events (G3 SAE) was higher with triplets (diarrhea, fatigue, thrombocytopenia 2.232, 1.654 and 2.161 respectively (P= 0.000), the overall G3 SAE were almost comparable with a RR 1.438 (P= 0.000), though favoring doublets.</p>
1423	Ruggeri 2015	to compare all treatments in mMM via a mixed treatment comparison (MTC), taking into account prior lines of therapy.	20 different treatment regimens	Up to December 2014.	24 RCTs	-	5.59 to 36 months.	<p>total of 24 RCTs reporting relevant outcomes for 20 different treatment regimens were identified for data extraction. It was not possible to link all 20 regimens within a single evidence network, but the majority (16) were incorporated within two networks (see figure 1). As a result, the analysis estimated all pairwise comparisons within each of the networks; it is not possible to draw conclusions for comparisons across networks. Results are presented in figure 2 for the yellow (larger) and blue networks (smaller). Three studies were excluded from the presented analysis as median PFS had not yet been reached at follow up. Median follow up across all identified studies ranged from 5.59 to 36 months. Within the yellow network, carfilzomib in combination with lenalidomide and dexamethasone was the most effective treatment, followed by lenalidomide and dexamethasone and then bortezomib. In the smaller blue evidence network, bortezomib in combination with dexamethasone and panobinostat was the most effective treatment.</p>
1550	Zhang 2017	evaluated elotuzumab and/or daratumumab for the treatment of patients with RRMM	elotuzumab or daratumumab	-	13 studies	1,472	-	<p>The overall response rate (ORR) was 57% (95% confidence interval [CI]: 38-76%), and the at least very good partial response rate (VGPR) was 32% (95% CI: 19-46%). mAb-based regimens</p>



								prolonged progression-free survival (PFS, hazard ratio: 0.52, 95% CI: 0.36-0.75) compared to non-mAb-based regimens. Additionally, the efficacy of triplet regimens was superior to that of single or doublet regimens. The same trend was observed in a subgroup analysis of daratumumab and elotuzumab. The most common grade 3/4 adverse events included neutropenia, lymphopenia, thrombocytopenia, anemia, leukopenia, pneumonia, and fatigue. Elotuzumab and daratumumab improved the ORR, at least VGPR, and PFS compared to non-mAb-based regimens. In a pooled analysis, both mAbs had promising efficacy and safety profiles, particularly in triplet regimens. The same trend was observed in daratumumab and elotuzumab-based regimens.
1553	Zou 2017	To understand the efficacy and safety of carfilzomib (CFZ) and pomalidomide (POM)	carfilzomib and pomalidomide	Up to May 2018	37 prospective studies	3432	the follow-up periods differ between the trials, and survival data is not mature at the time of data cutoff.	Analysis of subgroup differences between carfilzomib single-agent and CFZ/DEX dual combination showed significantly ( $P < 0.001$ , $I^2 = 98.3\%$ ), suggesting the overall response rate (ORR) of 66% attained from CFZ/DEX dual combination seemed to be higher than that of 28% from carfilzomib single-agent. And, the same trend favoring CFZ/DEX dual combination was found in $\geq$ VGPR and CBR analysis. The ORR of 31% attained from POM/DEX dual combination was superior to that of 19% from pomalidomide single-agent ( $P < 0.001$ , $I^2 = 94.4\%$ ). And, the same trend favoring POM/DEX dual combination was found in $\geq$ VGPR and CBR analysis. However, the ORR of 83% attained from POM/BOR/DEX triplet combination was superior to that of 31% from POM/DEX dual combination ( $P < 0.001$ , $I^2 = 99.1\%$ ). And, the same trend favoring POM/BOR/DEX triplet combination was found in $\geq$ VGPR analysis.

Table 22: Study Characteristics - RCTs

Refid	author/ year	Setting	Location	N of Study Sites	Pt Population	Interventions/ comparisons	# of patients	Mean/Me dian age of pts	Male/ Female	Tumor type	Tumor stage	primary outcome
4	Kropff 2017	Multiple practice setting	Germany	42	relapsed or refractory MM (1- 3 previous lines of therapy)	bortezomib- dexamethasone (VD)  v  bortezomib- dexamethasone plus oral cyclophosphamide (VCD)	46  47	68  71	25/21  26/21	-	I: 6, II: 9, III: 30  I: 8, II: 13, III: 26	time to disease progressi on (TTP)
11	Dimopo ulos 2015	Multiple practice setting	North america, Europe, South America, Asia- Pacific	198	relapsed or refractory multiple myeloma	carfilzomib- dexamethasone  v  bortezomib- dexamethasone	464  465	65  65	240/224  229/236	-	I: 205, II-III: 259  I: 204, II-III: 261	PFS
14	Dimopo ulos 2017	-	-	-	relapsed/ refractory MM with 1-3 previous therapies	elotuzumab + lenalidomide/dexametha sone (ELd)  v  lenalidomide/dexametha sone (Ld)	319  316	character istics describ ed in other article (Lonial 2015)	-	-	-	PFS and ORR
29	Chng 2016	Multiple practice setting	North America, Europe,	-	relapsed or refractory	carfilzomib- dexamethasone (Kd)	High-risk (Kd: 97, Vd: 113)	High-risk (Kd: 65 , Vd: 65)	High-risk (Kd: 52/45, Vd: 48/65)	-	High-risk (Kd (I: 35, II-III: 62) .	PFS

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	ASPIRE		Asia-Pacific		multiple myeloma (MM)	v bortezomib-dexamethasone (Vd)  subgroup analysis by cytogenetic risk	Standard-risk (Kd: 284, Vd: 291),  Unknown/Missing (Kd: 83, Vd: 61)	Standard-risk (Kd: 65, Vd: 65),  Unknown/Missing (Kd: 66, Vd: 66)	Standard-risk (Kd: 145/139, Vd: 152/139),  Unknown/Missing (Kd: 43/40, Vd: 29/32)		Vd (I: 36, II-III: 77)  Standard-risk (Kd (I: 123, II-III: 161), Vd(I: 137, II-III: 154),  Unknown/Missing (Kd(I: 47, II-III: 36), Vd(I: 31, II-III: 30)	
32	Dimopoulos 2017	Multiple practice setting	North America, Europe, Middle East	-	Adult patients with relapsed MM who had received 1–3 prior treatments	carfilzomib-lenalidomide-dexamethasone  v lenalidomide-dexamethasone  Secondary analysis by age	<70 years: Carfilzomib group: 293, Control group: 281  ≥70 years: Carfilzomib group: 103, Control group: 115	<70: Carfilzomib: 60.0, Control: 62.0  ≥70: Carfilzomib: 74.0, Control: 74.0	-	-	-	not included in this secondary analysis
60	Moreau 2016	Multiple practice setting	-	-	detectable MM that was relapsing or progressing at study entry	carfilzomib - dexamethasone (Kd)  v bortezomib-dexamethasone (Vd)  subanalysis based on prev treatment (1 prior v ≥ 2 prior lines of treatment)	1 prior line, Kd: 232, Vd: 232  ≥ 2 prior lines, Kd: 232, Vd: 233	1 prior, Kd: 66.0, Vd: 63.5  ≥ 2, Kd: 64.0, Vd: 66.0	-	-	1 prior, Kd: Stage 1: 109, 2: 68, 3: 55, Vd: 1: 115, 2: 62, 3: 55  ≥ 2, Kd: 1: 103, 2: 70, 3: 59, Vd: 1: 90, 2: 89, 3: 54	-

63	Jones-2016	Multiple practice setting	UK	-	newly diagnosed myeloma patients aged 18 years or over	thalidomide, lenalidomide and bortezomib induction combinations and lenalidomide ± vorinostat as maintenance  (grouped into transplant eligible (TE) and transplant noneligible (TNE))	TE: 1509  TNE:1223	61  74	-	-	-	OS & PFS, SPM
97	Dimopoulos 2016	Multiple practice setting	Europe	91	patients with refractory or relapsed and refractory multiple myeloma, refractory to their last treatment	Single arm: pomalidomide 4 mg on days 1-21 of a 28-day cycle + dexamethasone	682	66	381/301		I-II: 414, III: 236, Missing: 32	Incidence of AEs including SPMs
104	Weisel 2016	Multiple practice setting	United States, Australia, Europe, Asia, Canada	93	refractory or relapsed and refractory MM	POM + LoDEX  v  HiDex  this is a subanalysis of the study based on renal impairment	LoDEX: baseline <60: 93; baseline >60: 205  HiDEX: baseline <60: 56; baseline >60: 93	<60: 69, > 60: 61 <60: 69, >60: 61	<60: 46%/54%, >60: 67%/33%	-	<60: I: 11%, II: 38%, III:51%; >60: I: 36%, II:42%, III:22%  <60: I: 11%, II: 28%, III:61%; >60: I: 33%, II:45%, III:22%	PFS
105	Cook 2016	Multiple practice setting	UK	51	symptomatic, measurable multiple myeloma w/ need for treatment for first	melfalan+salvage ASCT  v	89	61  61	65/24	IgG: 60, IgA: 13, Light chain: 7, IgM/IgD:	I: 24, II: 24, III: 16, Missing: 25	TTP (previously reported)

					progressive or relapsed disease	cyclophosphamide	85		61/24	1, Non-secretory: 3 IgG: 57, IgA: 18, Light chain: 7, IgM/IgD: 1, Non-secretory: 2	I: 31, II: 27, III: 8, Missing: 19	
119	Ozaki 2016	Hospital	-	16	Patients aged 60–85 years with relapsed and/ or refractory disease after at least one prior treatment regimen	bortezomib (1.3 mg/m <sup>2</sup> ), intravenously) and dexamethasone (20 mg) on days 1, 8, and 15 of every 4-week cycle.	47	75	21/26	IgG: 34 IgA: 7 IgD: 1 BJP: 5	I: 12 II: 19 III: 16	response rate
145	Richardson 2016	Multiple practice setting	-	-	relapsed or relapsed and refractory MM	PAN-BTZ-Dex v Pbo-BTZ-Dex subgroup analysis based on prior IMiD or BTZ treatment.	Prior IMiD (PAN-BTZ-Dex: 245, Pbo-BTZ-Dex: 240);  Prior BTZ + IMiD: (PAN-BTZ-Dex: 94, Pbo-BTZ-Dex: 99)  ≥ 2 prior regimens including BTZ and IMiD (PAN-BTZ-Dex: 73, Pbo-	Prior IMiD (PAN-BTZ-Dex: 62, Pbo-BTZ-Dex: 62);  Prior BTZ + IMiD: (PAN-BTZ-Dex: 60, Pbo-BTZ-Dex: 61)  ≥ 2 prior regimens including BTZ and IMiD (PAN-BTZ-Dex: 61, Pbo-	Prior IMiD (PAN-BTZ-Dex: 125/120, Pbo-BTZ-Dex: 130/110);  Prior BTZ + IMiD: (PAN-BTZ-Dex: 52/42, Pbo-BTZ-Dex: 49/50)  ≥ 2 prior regimens including BTZ and IMiD (PAN-BTZ-Dex: 41/32, Pbo-BTZ-Dex: 33/41)	-	-	PFS

190	Dimopoulos 2015	Multiple practice setting	EU, Russia, Switzerland, Australia, Canada, US	93	refractory or refractory and relapsed MM	ponalidomide + LoDEX v HiDEX	BTZ-Dex: 74) LoDEX: 302  HiDEX: 153	BTZ-Dex: 61) 64  65	-	-	I-II: 196, III: 92, Missing: 14  I-II: 92, III: 28, Missing: 3	PFS
191	San Miguel 2015	Multiple practice setting	-	93	RRMM treated with ≥ 2 prior antimyeloma regimens, been refractory to their last prior treatment	POM + LoDEX v HiDEX subanalysis of previously reported study	302  153	reported in another study	-	-	-	PFS
297	Cook 2014	Multiple practice setting	UK	51	MM - 1st progressive or relapsed disease	high dose melphalan+salvage ASCT v cyclophosphamide	89  85	61  61	65/24  61/24	IgG: 60, IgA: 13, Light-chain: 7, IgM/IgD: 1  IgG: 57, IgA: 18, Light-chain: 7, IgM/IgD: 1	I: 24, II: 24, III: 16, Missing: 25  I: 31, II: 27, III: 8, Missing: 19	time to progression of disease
567	Moreau, 2011	Multiple practice setting	Europe, Asia, and South America	53	patients were aged 18 years and older; had measurable, secretory multiple myeloma; had received one to three previous lines of therapy; and had evidence of disease	subcutaneous bortezomib v intravenous bortezomib	148  74	64.5  64.5	74/74  47/27	IgG: 96; IgA: 38; IgD: 1; IgM: 1; Light Chain: 12  IgG: 53; IgA: 14; IgD: 0; IgM: 1; Light Chain: 6	I: 40; II: 60; III: 48  I: 20; II: 30; III: 24	Noninferiority, RR

					progression since last therapy							
714	Stadtmaier, 2009	-	-	-	patients with MM who had received at least one prior treatment,	lenalidomide + dexamethasone v dexamethasone + placebo.	133 220	62.1 63.1	82/51 128/92	-	-	PFS
788	San-Miguel 2008	Multiple practice setting	United States, Canada, Europe, and Israel	93	relapsed MM who had received 1-3 prior therapies and who had varying degrees of renal impairment	Bortezomib v High dose dexamethasone	330 323	62 61	57%/43% 45%/55%	-	I: 42%; II: 31%; III: 25%  I: 42%; II: 26%; III: 30%	TTP
1526	Weisel 2013	-	-	-	Pts had to be refractory to last prior Tx (PD during Tx or within 60 days) and exhausted BORT and LEN after ≥ 2 consecutive cycles of each (alone or in combination)	POM + DEX v DEX	302 153	-	-	-	I: 6, II: 9, III: 30  I: 8, II: 13, III: 26	time to disease progression (TTP)

Table 23: Study outcomes - RCTs

Refid	author /year	Interventions/ comparisons	Response	Tx discontinuation rate from toxicity	OS (Median/%)	PFS (Median/%)	Second malignancy	Toxicity Grade 3/4	Duration of Tx	length of F/u	Other relevant data
4	Kropff 2017	bortezomib-dexamethasone (VD) v bortezomib-dexamethasone plus oral cyclophosphamide (VCD)	74%  70%	35% (16 patients)  32% (15 patients)	Not determined  41 months	same as TTP	-	63% (29 patients)  77% (36 patients)	-	24 months	TTP: 12.6 months TTP: 9.9 months  TTP: P =0.192
11	Dimopoulos 2015	carfilzomib-dexamethasone v bortezomib-dexamethasone	objective response 77%  63%	65  73	not reached	18.7 months  9.4 months	-	No summary of 3/4 AEs. Anaemia: 67 (14%), Hypertension 41 (9%), Thrombocytopenia 39 (8%), Pneumonia: 32 (7%)  Anaemia: 45 (10%), Hypertension 12 (3%), Thrombocytopenia 43 (9%), Pneumonia: 36 (8%)	39.9 weeks  26.6 weeks	11.9 months  11.1 months	PFS: p<0.0001, Objective response: p<0.0001,  duration of response: 21.3 months  duration of response: 10.4
14	Dimopoulos 2017	elotuzumab + lenalidomide/dexamethasone (ELD)	79%	30 (9%)	43.9 months, 1yr: 91%, 2yr: 73%, 3yr: 60%	3yr: 26%	36	248 (78.0%)	-	PFS and ORR min. 33 months: Patients who did	ORR: P=0.0002, OS: P=0.0257, PFS: 0.0014

		v lenalidomide/dexamethasone (Ld)	66%	44 (14%)	39.6 months, 1yr: 83%, 2yr: 69%, 3yr: 53%	3yr: 18%	20	212 (66.9%)		not progress, median: 32.4 months	
29	Chng 2016	carfilzomib-dexamethasone (Kd) v bortezomib-dexamethasone (Vd)  subgroup analysis by cytogenetic risk	High-risk (Kd: 70 (72.2%), Vd: 66 (58.4%))  Standard-risk (Kd: 225 (79.2%), Vd: 192 (66.0%))  Unknown/Missing (Kd: 62 (74.7%), Vd: 33 (54.1%))	High-risk (Kd: 18 (18.6%), Vd: 22 (19.8%))  Standard-risk (Kd: 56 (19.8%), Vd: 62 (21.6%))  Unknown/Missing (Kd: 18 (21.7%), Vd: 11 (19.0%))	-	High-risk (Kd: 8.8 months, Vd: 6.0 months)  Standard-risk (Kd: not estimable, Vd: 10.2 months)  Unknown/Missing (Kd: 15.4, Vd: 12.2)	-	High-risk (Kd: 68 (70.1%), Vd: 70 (63.1%))  Standard-risk (Kd: 209 (73.9%), Vd: 196 (68.3%))  Unknown/Missing (Kd: 62 (74.7%), Vd: 39 (67.2%))	High-risk (Kd: 30.3 weeks, Vd: 22.0) - medians  Standard-risk (Kd: 40.9, Vd: 28.0),  Unknown/Missing (Kd: 36.9, Vd: 21.3)	NR	PFS: high-risk: P = 0.0075, standard-risk: P<0.0001, Unknown/missing: P= 0.058
32	Dimopoulos 2017	carfilzomib-lenalidomide-dexamethasone v lenalidomide-dexamethasone Secondary analysis by age	<70: Carfilzomib: 86.0%, Control: 66.9%  ≥70: Carfilzomib: 90.3%, Control: 66.1%	<70: Carfilzomib: 23.2%, Control: 20.9%  ≥70: Carfilzomib: 34.0%, Control: 34.8%	-	<70: Carfilzomib: 28.6 months, Control: 17.6 months  ≥70: Carfilzomib: 23.8, Control: 16.0	-	<70: Carfilzomib: 236 (81.7%), Control: 215 (77.6%)  ≥70: Carfilzomib: 92 (89.3%), Control: 99 (88.4%)	<70: Carfilzomib: 97.0 weeks, Control: 57.0  ≥70: Carfilzomib: 74.0, Control: 57.6	NR	-
60	Moreau 2016	carfilzomib-dexamethasone (Kd) v	1, Kd: 81.9%, Vd: 65.5%  ≥ 2, Kd: 72.0%, Vd: 59.7%	1, Kd: 40 (17.2%), Vd: 42 (18.5%)  ≥ 2, Kd: 52 (22.5%),	-	1, Kd: 22.2 months, Vd: 10.1  ≥ 2, Kd: 14.9, Vd: 8.4	-	1, Kd: 162 (69.8%), Vd: 145 (63.9%)  ≥ 2, Kd: 177 (76.6%), Vd: 180 (69.9%)	1, Kd: 41.6 weeks, Vd: 31.0  ≥ 2, Kd: 38.0, Vd: 29.0	-	PFS (1 & ≥2): p<0.0001

		bortezomib-dexamethasone (Vd)  subanalysis based on prev treatment (1 prior v ≥ 2 prior lines of treatment)		Vd: 53 (23.1%)							
63	Jones-2016	thalidomide, lenalidomide and bortezomib induction combinations and lenalidomide ± vorinostat as maintenance  (grouped into transplant eligible (TE) and transplant noneligible (TNE))	-	-	-	-	104 SPMs were confirmed in 96 of 2732	-	-	34.3 (TE) and 24.2 months (TNE)	The cumulative incidence of SPM was 0.7% (95% confidence interval (CI) 0.4-1.0%), 2.3% (95% CI 1.6-2.7%) and 3.8% (95% CI 2.9-4.6%) at 1, 2 and 3 years, respectively. Patients receiving maintenance lenalidomide had a significantly higher SPM incidence overall (P=0.011). Age is a risk factor with the highest SPM incidence observed in transplant non-eligible patients aged >74 years receiving lenalidomide maintenance. The 3-year cumulative incidence in this group was 17.3% (95% CI 8.2-26.4%), compared with 6.5% (95% CI 0.2-12.9%) in



											observation only patients (P=0.049). There was a low overall incidence of haematological SPM (0.5%).
97	Dimopoulos 2016	Single arm: pomalidomide 4 mg on days 1-21 of a 28-day cycle + dexamethasone	32.6% ; median time to response 1.9mo (0.5-17.5)	40 (5.9%)	11.9 months	4.6 months	15	AEs: Neutropenia: 49.7%, Anemia: 33.0%, Thrombocytopenia: 24.1%, Febrile Neutropenia: 5.3%, Infections: 28.1% (10.9% pneumonia), Fatigue: 5.9%, Pyrexia: 2.9%	4.9 months	16.8 months	VGPR: 7.8%, CR:0.6%
104	Weisel 2016	POM + LoDEX v HiDEX  this is a subanalysis of the study based on renal impairment	LoDEX - <60: 28%, >60:34%  HiDEX - <60: 11%, >60:12%	<60: 13%, >60: 8%  <60: 11%, >60: 10%	-	median(months): <60: 4.0, > 60:4.0  <60: 1.9; >60:2.0	-	-	-	15.4 months	-
105	Cook 2016	melphalan+salvage ASCT v cyclophosphamide	-	-	67 months  52 months	19 months, PFS2: 67 months  11 months, PFS2: 35 months	7  5	previously reported	-	52 months	TTP: 19 months TTP: 11 months  TTP: p<0.0001; PFS & PFS2: p<0.0001, OS: p=0.022
119	Ozaki 2016	bortezomib (1.3 mg/m <sup>2</sup> ), intravenously)	Best responses were	-	35.1 months	9.6 months	-	-	-	21.6 months (range)	After progression, 11 patients were retreated with

		and dexamethasone (20 mg) on days 1, 8, and 15 of every 4-week cycle.	stringent complete response (sCR) in 5 patients, very good partial response (VGPR) in 3, PR in 15, stable disease (SD) in 18, and disease progression (PD) in 6							2.8– 48.2 months)	bortezomib-based regimens and another 24 patients with immunomodulatory drugs. Multivariate analysis revealed that ISS 3, t(4;14), and <4 therapy cycles were significantly poor prognostic factors and that subsequent therapy with bortezomib-based regimens was a favorable factor for extended OS.
145	Richardson 2016	PAN-BTZ-Dex v Pbo-BTZ-Dex subgroup analysis based on prior IMiD or BTZ treatment	<p>Prior IMiD (PAN-BTZ-Dex: 62%, Pbo-BTZ-Dex: 50%);</p> <p>Prior BTZ + IMiD: (PAN-BTZ-Dex: 58.5%, Pbo-BTZ-Dex: 41.4%)</p> <p>≥ 2 prior regimens including BTZ and IMiD (PAN-BTZ-Dex: 58.9%,</p>	<p>Prior IMiD (PAN-BTZ-Dex: 83, Pbo-BTZ-Dex: 43);</p> <p>Prior BTZ + IMiD: (PAN-BTZ-Dex: 29, Pbo-BTZ-Dex: 18)</p> <p>≥ 2 prior regimens including BTZ and IMiD (PAN-BTZ-Dex: 23, Pbo-</p>	-	<p>Prior IMiD (PAN-BTZ-Dex: 12.3, Pbo-BTZ-Dex: 7.4);</p> <p>Prior BTZ + IMiD: (PAN-BTZ-Dex: 10.6, Pbo-BTZ-Dex: 5.8)</p> <p>≥ 2 prior regimens including BTZ and IMiD (PAN-BTZ-Dex: 12.5, Pbo-BTZ-Dex: 4.7)</p>	-	<p>Prior IMiD (PAN-BTZ-Dex: 230, Pbo-BTZ-Dex: 197);</p> <p>Prior BTZ + IMiD: (PAN-BTZ-Dex: 91, Pbo-BTZ-Dex: 85)</p> <p>≥ 2 prior regimens including BTZ and IMiD (PAN-BTZ-Dex: 71, Pbo-BTZ-Dex: 62)</p>	<p>Prior IMiD (PAN-BTZ-Dex: 6.67 months, Pbo-BTZ-Dex: 6.03);</p> <p>Prior BTZ + IMiD: (PAN-BTZ-Dex: 6.41, Pbo-BTZ-Dex: 5.13)</p> <p>≥ 2 prior regimens including BTZ and IMiD (PAN-BTZ-Dex: 6.42, Pbo-BTZ-Dex: 4.85)</p>	NR	-

			Pbo-BTZ-Dex: 39,2%)	BTZ-Dex: 13)							
190	Dimopoulos 2015	pomalidomide + LoDEX v HIDEX	LoDEX	9%	13.1 months	4.0 months	-	-	-	15.4 months	PFS: P<0.001, OS: P=0.009
			HIDEX	10%	8.1 months	1.9 months					
191	San Miguel 2015	POM + LoDEX v HIDEX subanalysis of previously reported study	32%	28	13.1 months	4.0 months	-	-	-	15.4 months	PFS and ORR: P < 0.001; OS: P = 0.009
			11%	16	8.1 months	1.9 months					
297	Cook 2014	high dose melphalan+salv age ASCT v cyclophosphami de	74 (83%)	-	3yr: 80.3%	19 months	1	no summary data; individual AEs: Neutropenia: 75%, Thrombocytopo nia: 72%, Anaemia: 22%, Infection: 4%, Diarrhoea: 12%, Nausea: 8%, Vomiting: 3%, Sensory neuropathy: 3%	-	31 months (ASCT: 34 mos., cyclopho sphamide: 23 mos.)	TTP: 19 months TTP: 11 months  TTP: p<0.0001, PF: p<0.0001
			64 (75%)		3yr: 62.9%	11 months	2	Neutropenia: 13%, Thrombocytopo nia: 4%, Anaemia: 1%, Infection: 0%, Diarrhoea: 1%, Nausea: 1%, Vomiting: 1%, Sensory neuropathy: 0%			

567	Morea u, 2011	subcutaneous bortezomib v intravenous bortezomib	31 (42%);  38 (52%)  after 4 cycles: 61 (42%); after 8 cycles: 76 (52%)	33 (22%)  20 (27%)	1 year 72.8%  76.7%	-	-	84 (57%)  52 (70%)		11.8 months	-
714	Stadtm auer, 2009	lenalidomide + dexamethasone v dexamethasone + placebo.	89 (66.9%)  125 (56.8%)	14.3%  14.5%	30.8 months;  35.8 months  median not reached; follow-up based on data as of December 2008: median OS of 42.0 months	14.1 months  9.5 months	-	-	12.5 months (0.3–24.1)  9.2 months (0.03–24.8)	17.8 months (range: 11.0– 25.6);  median follow-up duration for surviving patients was 51 months (range: 0.8– 66.5).	-
788	San- Miguel 2008	Bortezomib v High dose dexamethasone	120 (38%)  53 (17%)	-	29.8 months (23.2-NE)  23.7 months (19.1-31.4)	TTP 6.2 months (4.9- 6.9)  TTP 3.5 months (2.9- 4.2)	-	-	-	22 months	-

1526	Weisel 2013	POM + DEX V DEX	31% 10%	9% 10%	4.9 mos; 10.0 mos modified high risk: 9.9 months; standard risk: 14.1 months	-	-	-	4.2 mos 3.9 mos	10 months	TTP: P =0.192
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Data Supplement 2: Study Quality Assessment

Table 28: Quality of included studies [RCTs]

Refid/Trial name	Adequate randomization	Allocation concealment	Blinding	Blinding					Infrequent loss to follow-up	Selective outcome reporting	Other sources of bias	Assessment of Bias
				Patients	Healthcare providers	Data collectors	Outcome assessors	Data analysts				
4 - Kropff 2017	Definitely yes (low risk of bias)	Probably no	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Probably yes	Probably no	Definitely no (high risk of bias)	High risk of bias for one or more key domains.
<b>FIRST</b> 7 - Bahis 2017 79 - Hulin 2016 142 - Dimopoulos 2015 281 - Benboubker 2014 216 - Delforge-2015	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Low risk of bias for all key domains.
<b>ENDEAVOR</b> 11 - Dimopoulos 2015 29 - Chng 2016 60 - Marzau 2016 162 - Dimopoulos 2016	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Mostly no	Mostly no	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.
15 - Cho 2017	Probably no	Probably no	Probably no	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Probably yes	Probably yes	Probably no	High risk of bias for one or more key domains.
19 - Rosinol 2017	Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Probably yes	Probably yes	Probably yes	High risk of bias for one or more key domains.
38 - Attal 2017	Probably yes	Probably yes	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Probably yes	Probably yes	Probably yes	Unclear risk of bias for one or more key domains.
63 - Jones-2016	Probably yes	Probably no	Probably no	Mostly no	Mostly no	Mostly no	Mostly yes	Mostly yes	Probably yes	Probably yes	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.

77 - Straka-2016	Probably yes	Probably no	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Probably no	Definitely no (high risk of bias)	High risk of bias for one or more key domains.
<b>CASTOR</b> 89 - Palumbo 2016	Probably yes	Probably no	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably no	Unclear risk of bias for one or more key domains.
102 - Orlowski 2016	Probably yes	Probably no	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Probably yes	Probably yes	Definitely no (high risk of bias)	High risk of bias for one or more key domains.
<b>BSBMT/UKMF Myeloma X Relapse [Intensive]</b> 105 - Cook 2016 297 - Cook 2014	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Low risk of bias for all key domains.
<b>PETHEMA/ GEM2010MAS65</b> 107 - Palva 2016 (Phase 2 RCT)	Probably yes	Probably yes	Probably yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Probably yes	Definitely yes (low risk of bias)	Probably yes	Unclear risk of bias for one or more key domains.
<b>GMMG-HD2</b> 112 - Mai 2016	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably no	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	High risk of bias for one or more key domains.
<b>IFM2013-04</b> 117 - Moreau 2016	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	High risk of bias for one or more key domains.
<b>TOURMALINE</b> 123 - Moreau 2016	Definitely yes (low risk of bias)	Probably yes	Definitely yes (low risk of bias)	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.
136 - Zweegman 2016	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	High risk of bias for one or more key domains.



137 - Magarotto 2016	Probably yes	Probably yes	Definitely no (high risk of bias)	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Probably yes	Probably yes	High risk of bias for one or more key domains.
158 - Bensinger-2015	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Probably yes	Definitely yes (low risk of bias)	Probably yes	Unclear risk of bias for one or more key domains.
173 - Gay-2015	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.
175 - Niesvizky 2015	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.
<b>ECOG E1A06</b> 196 - Stewart 2015	Definitely yes (low risk of bias)	Probably yes	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	High risk of bias for one or more key domains.
<b>ELOQUENT-2</b> 14 - Dimopoulos 2017 203 - Lonial 2015	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	High risk of bias for one or more key domains.
<b>MMS</b> 207 - Mai Leuk 2015	Definitely yes (low risk of bias)	Probably yes	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Mostly yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	High risk of bias for one or more key domains.
<b>PANORAMA 1</b> 145 - Richardson 2016 279 - San-Miguel 2014	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Low risk of bias for all key domains.
282 - Palumbo-2014	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	High risk of bias for one or more key domains.
<b>MM-003</b> 104 - Waisel 2016 190 - Dimopoulos 2015	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	High risk of bias for one or more key domains.



191 - San Miguel 2015 1526 - Weisel 2013 15540 - San Miguel 2013													
<b>ASPIRE</b> 32 - Dimopoulos 2017 88 - Avet-Loiseau 2016 248 - Stewart 2015	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Mostly No	Mostly No	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.
<b>POLLUX</b> 81 - Dimopoulos 2016	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Mostly yes	Mostly Yes	Mostly Yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	High risk of bias for one or more key domains.
<b>MRC Myeloma IX</b> 235 - Rawstron 2015 345 - Morgan 2013	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	High risk of bias for one or more key domains.
<b>GEM2005</b> 280 - Mateos 2014 626 - Mateos 2010	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	High risk of bias for one or more key domains.
<b>Myeloma.10</b> 407 - Stewart 2013	Probably yes	Probably yes	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Probably yes	Unclear risk of bias for one or more key domains.
446 - Maiolino 2012	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely no (high risk of bias)	Probably no	Definitely no (high risk of bias)	Definitely no (high risk of bias)	High risk of bias for one or more key domains.
490 - Attal 2012	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Low risk of bias for all key domains.
<b>MM-015</b> 298 - Dimopoulos 2014 387 - Dimopoulos 2013 492 - Palumbo 2012	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Low risk of bias for all key domains.

506 - Neben-2011	Probably yes	Probably yes	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Probably yes	Probably yes	Probably yes	Unclear risk of bias for one or more key domains.
519 - Krishnan-2011	Definitely yes (low risk of bias)	Probably yes	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Probably yes	Probably no	Unclear risk of bias for one or more key domains.
538 - Shah-2011	Definitely yes (low risk of bias)	Probably yes	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.
567 - Moreau, 2011	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Low risk of bias for all key domains.
613 - Palumbo 2010	Probably yes	Probably yes	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Probably yes	Probably yes	Unclear risk of bias for one or more key domains.
662 - Palumbo-2009	Definitely yes (low risk of bias)	Probably yes	Probably yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably no	Unclear risk of bias for one or more key domains.
722 - Spencer 2009	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.
<b>VISTA</b> 227 - Mateos, 2015 473 - Dellorge 2012 764 - San Miguel 2008 657 - Mateos, 2008	Definitely yes (low risk of bias)	Probably yes	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.
<b>APEX</b> 788 - San-Miguel 2008 947 - Richardson 2005	Definitely yes (low risk of bias)	Probably yes	Probably yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Unclear risk of bias for one or more key domains.
<b>IFM 99-06</b> 815 - Facon 2007 911 - Facon 2006	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Mostly yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Unclear risk of bias for one or more key domains.

900 - Kyle, 2006	Probably yes	Probably yes	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Probably yes	Probably yes	Definitely no (high risk of bias)	High risk of bias for one or more key domains.
925 - Fermand 2005	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably no	Mostly no	Mostly no	Mostly no	Mostly no	Mostly no	Probably yes	Probably yes	Probably yes	Unclear risk of bias for one or more key domains.
<b>PATHEMA</b> 928 - Blade-2005	Probably yes	Probably yes	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Definitely no (high risk of bias)	Probably yes	Probably yes	Probably yes	High risk of bias for one or more key domains.
1554 - Durie 2016	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Low risk of bias for all key domains.

Ref: Guyatt GH, Busse JW. Modification of Cochrane Tool to assess risk of bias in randomized trials.  
<https://www.evidencepartners.com/resources/methodological-resources/>

**Table 29: Quality of included studies [Meta-analysis]**

Refid	Author/year	Well-described and reproducible methods	Rated quality of the Evidence	Based on systematic review	Planned pooling stated a priori	Limitations of the study	Funding source reported	Overall risk of bias assessment
9	McCarthy 2017	Yes	No	Yes	Yes	Yes	Yes	Intermediate
34	Sun-2017	Yes	Yes	Yes	Yes	Yes	Yes	Low
37	van beurden 2017	Yes	No	Yes	Yes	Yes	Yes	Intermediate
48	van de velde 2017	Yes	No	Yes	Yes	Yes	Yes	Intermediate
59	Munshi-2017	Yes	No	Yes	Yes	Yes	Yes	Intermediate
66	Landgren-2016	Yes	No	Yes	Yes	No	Yes	Intermediate
125	Scott-2016	Yes	Yes	Yes	Yes	Yes	Yes	Low
157	Wang-2016	Yes	Yes	Yes	Yes	Yes	Yes	Low
176	Wang-2016	Yes	No	Yes	Yes	Yes	Yes	Intermediate
221	Qiao 2015	Yes	Yes	Yes	Yes	Yes	No	Low
253	Lopuch 2015	Yes	Yes	Yes	Yes	Yes	Yes	Low
285	Leiba-2014	Yes	Yes	Yes	Yes	Yes	No	Low
303	Gao-2014	Yes	Yes	Yes	Yes	Yes	Yes	Low
320	Palumbo 2014	Yes	No	Yes	Yes	Yes	Yes	Intermediate
341	Nooka-2013	Yes	No	Yes	Yes	Yes	Yes	Intermediate
390	Armeson-2012	Yes	No	Yes	Yes	Yes	Yes	Intermediate
418	Kharfan-Dabaja-2013	Yes	Yes	Yes	Yes	Yes	No	Low
493	Faussner-2012	Yes	Yes	Yes	Yes	No	Yes	Low
1033	Botta 2017	Yes	Yes	Yes	Yes	Yes	Yes	Low
1234	Liu 2107	Yes	Yes	Yes	Yes	Yes	No	Low
1235	Liu 2016	Yes	No	Yes	Yes	Yes	Yes	Intermediate
1550	Zhang 2017	Yes	No	Yes	Yes	Yes	Yes	Intermediate
1553	Zou 2017	Yes	No	Yes	Yes	Yes	Yes	Intermediate

## 12.5. GRADE-Bewertung adaptierter Empfehlungen

### 12.5.1. GRADE-Bewertung zu Empfehlung: Alle Patienten, die potenziell für eine autologe Transplantation in Frage kommen, sollten in einem Transplantationszentrum zur Prüfung der Transplantationsfähigkeit vorgestellt werden.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Retrospektive	Gesamtüberleben	-	-	-1	-	-	⊕⊕⊕⊕ Very Low
	Retrospektive	Lebensqualität	-	-	-	-	-	Not reported
	Retrospektive	Erhalt einer systemischen Therapie	-	-	-1	-	-	⊕⊕⊕⊕ Very Low

Retrospektives Studiendesign, daher Start bei geringem Vertrauen.

Indirekt, da amerikanisches Patientenregister zugrunde gelegt.

a: ASCO-LL Adaptation (dort aufgeführt: (Fakhri, Fiala et al. 2018))

### 12.5.2. GRADE-Bewertung zu Empfehlung: Chronologisches Alter und Nierenfunktion sollten nicht allein die Transplantationsfähigkeit entscheiden.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCTs/retrospective studies	Gesamtüberleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	RCTs/retrospective studies	Progressionsfreies Überleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	RCTs/retrospective studies	Harms	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	RCTs/retrospective studies	Lebensqualität	-	-	-	-	-	Not reported

Hohes Verzerrungsrisiko, da verschiedene Studientypen, mit unterschiedlicher Studienqualität eingeschlossen.

Indirekt, da supportive Therapie seitdem verbessert.

a: ASCO-LL Adaptation (dort aufgeführt: (Alvares, Davies et al. 2006, Facon, Mary et al. 2007, Stewart, Trudel et al. 2013, Auner, Szydlo et al. 2015, Garderet, Beohou et al. 2016, Mahindra, Hari et al. 2017)

### 12.5.3. GRADE-Bewertung zu Empfehlung: Die Stammzellsammlung sollte nach 4 bis 6 Zyklen Induktionstherapie erfolgen.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCTs	Gesamtüberleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	RCTs	Very good partial response	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	RCTs	Harms	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	RCTs	Lebensqualität	-	-	-	-	-	Not reported

Hohes Verzerrungsrisiko, da hohes oder unklares Biasrisiko in mindestens einer Domäne in beiden eingeschlossenen RCTs.

Indirekt, da optimale Dauer der Induktionstherapie nicht in Studien untersucht

a: ASCO-LL Adaptation (dort aufgeführt: (Breitkreutz, Lokhorst et al. 2007, Kumar, Dispenzieri et al. 2007, Chakraborty, Muchtar et al. 2018)

#### 12.5.4. GRADE-Bewertung zu Empfehlung: Die Hochdosistherapie sollte unabhängig vom Ansprechen in der Induktionstherapie erfolgen.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Retrospektive	Gesamtüberleben	-	-	-	-	-	⊕⊕⊕⊖ Low
	Retrospektive	Progressionsfreies Überleben	-	-	-	-	-	⊕⊕⊕⊖ Low
	Retrospektive	Harms	-	-	-	-	-	Not reported
	Retrospektive	Lebensqualität	-	-	-	-	-	Not reported

Retrospektives Studiendesign, daher Start bei geringem Vertrauen.

a: ASCO-LL Adaptation (dort aufgeführt: (Kapoor, Kumar et al. 2013, Vij, Kumar et al. 2015, Chakraborty, Muchtar et al. 2018, Lehnert, Becker et al. 2018, Blocka, Hielscher et al. 2020)



### 12.5.5. GRADE-Bewertung zu Empfehlung: Eine allogene Stammzelltransplantation in der Erstlinientherapie soll beim Multiplen Myelom nicht routinemäßig erfolgen.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCTs	Gesamtüberleben	-1	-	-	-	-	⊕⊕⊕⊖ Moderate
	RCTs	Progressionsfreies Überleben	-1	-	-	-	-	⊕⊕⊕⊖ Moderate
	RCTs	Harms	-1	-	-	-	-	⊕⊕⊕⊖ Moderate
	RCTs	Lebensqualität	-	-	-	-	-	Not reported

Unklares Verzerrungsrisiko, da unklares Biasrisiko in mindestens einer Domäne.

a: ASCO-LL Adaptation (dort aufgeführt: (Garban, Attal et al. 2006, Bruno, Rotta et al. 2007, Rosiñol, Pérez-Simón et al. 2008, Björkstrand, Iacobelli et al. 2011, Krishnan, Pasquini et al. 2011, Lokhorst, van der Holt et al. 2012)

### 12.5.6. GRADE-Bewertung zu Empfehlung: Als Erhaltungstherapie soll bei Standardrisikopatienten Lenalidomid gegeben werden.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA, RCT	Gesamtüberleben	-1	-	-	-	-	⊕⊕⊕⊖ Moderate
	SR/MA, RCT	Progressionsfreies Überleben	-1	-	-	-	-	⊕⊕⊕⊖ Moderate
	SR/MA, RCT	Harms	-1	-	-	-1	-	⊕⊕⊕⊖ Low
	SR/MA, RCT	Lebensqualität	-	-	-	-	-	Not reported

Unklares Verzerrungsrisiko, da unklares Biasrisiko in mindestens einer Domäne.

Impräzise, da kleine Stichprobengröße und wenig Ereignisse

a: ASCO-LL Adaptation (dort aufgeführt: (Attal, Lauwers-Cances et al. 2012, McCarthy, Owzar et al. 2012, Kumar 2013, Palumbo, Cavallo et al. 2014, Bahlis, Corso et al. 2017, McCarthy, Holstein et al. 2017, Gay, Jackson et al. 2018, Jackson, Davies et al. 2019)

### 12.5.7. GRADE-Bewertung zu Empfehlung: Die Lenalidomid-Erhaltungstherapie soll mindestens 2 Jahre und sollte bis zum Progress fortgeführt werden.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA	Gesamtüberleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	SR/MA	Progressionsfreies Überleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	SR/MA	Harms	-1	-	-1	-1	-	⊕⊕⊕⊖ Very Low
	SR/MA	Lebensqualität	-	-	-	-	-	Not reported

Unklares Verzerrungsrisiko, da unklares Biasrisiko in mindestens einer Domäne.

Indirekt, da optimale Dauer nicht untersucht.

Impräzise, da kleine Stichprobengröße und wenig Ereignisse

a: ASCO-LL Adaptation (dort aufgeführt: (Attal, Lauwers-Cances et al. 2012, McCarthy, Owzar et al. 2012, Kumar 2013, Palumbo, Cavallo et al. 2014, Bahlis, Corso et al. 2017, McCarthy, Holstein et al. 2017, Gay, Jackson et al. 2018, Jackson, Davies et al. 2019)

### 12.5.8. GRADE-Bewertung zu Empfehlung: Patienten mit initialem Kreatinin > 2mg/dl und/oder del 17p13 kann als Alternative zu Lenalidomid eine Erhaltungstherapie mit Bortezomib angeboten werden.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCTs	Gesamtüberleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungs- risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCTs	Progressionsfr eies Überleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	RCTS	Harms	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	RCTs	Lebensqualität	-	-	-	-	-	Not reported

Hohes Verzerrungsrisiko, da Studien mit hohesm Biasrisiko in mindestens einer Domäne eingeschlossen.

Indirekt, da Studien nicht darauf angelegt, den Nutzen von Bortezomib als Erhaltungstherapie zu untersuchen.

a: ASCO-LL Adaptation (dort aufgeführt: (Neben, Lokhorst et al. 2012, Sonneveld, Schmidt-Wolf et al. 2012, Scheid, Sonneveld et al. 2014, Gay, Jackson et al. 2018, Goldschmidt, Lokhorst et al. 2018)

### 12.5.9. GRADE-Bewertung zu Empfehlung: Alle Patienten mit symptomatischem Myelom-Rezidiv sollen zeitnah therapiert werden.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA	Gesamtüberleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	SR/MA	Progressionsfreies Überleben	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	SR/MA	Harms	-1	-	-1	-	-	⊕⊕⊕⊖ Low
	SR/MA	Lebensqualität	-1	-	-1	-	-	⊕⊕⊕⊖ Low

Hohes Verzerrungsrisiko, da moderates bis hohes Biasrisiko in eingeschlossenen Studien.

Indirekt, da Studien nicht darauf angelegt, den optimalen Zeitpunkt der Rezidivtherapie zu untersuchen.

a: ASCO-LL Adaptation (dort aufgeführt: (Dimopoulos, Oriol et al. 2016, Moreau, Masszi et al. 2016, Palumbo, Chanan-Khan et al. 2016, Richardson, Hungria et al. 2016, Dimopoulos, Lonial et al. 2017, Dimopoulos, Stewart et al. 2017))

### 12.5.10. GRADE-Bewertung zu Empfehlun: Die Therapie im Rezidiv sollte, in Abhängigkeit des initialen Ansprechens, der Verträglichkeit, der Toxizität und des Patientenwunschs, bis zum Progress fortgeführt werden.

Schlüssel- frage	Design <sup>a</sup>	Endpunkt	Verzerrungs- risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Retrospective	Gesamtüberleben	-	-	-	-	-	⊕⊕⊕⊖ Low
	Retrospective	Progressionsfreies Überleben	-	-	-	-	-	⊕⊕⊕⊖ Low
	Retrospective	Harms	-	-	-	-	-	Not reported
	Retrospective	Lebensqualität	-	-	-	-	-	Not reported

Retrospektives Studiendesign, daher Start bei geringem Vertrauen.

a: ASCO-LL Adaptation (dort aufgeführt: (Fouquet, Tardy et al. 2013, Zago, Oehrlein et al. 2014) (Hari, Romanus et al. 2018))

### 12.5.11. GRADE-Bewertung zu Empfehlung: Eine Triple-Kombinationstherapie mit zwei neuen Substanzen und einem Steroid soll bei Multiplen Myelom Patienten im ersten Rezidiv, unter Berücksichtigung der erhöhten Toxizität, angewendet werden.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	SR/MA	Gesamtüberleben	-	-	-	-	-	⊕⊕⊕⊕ High
	SR/MA	Progressionsfreies Überleben	-	-	-	-	-	⊕⊕⊕⊕ High
	SR/MA	Harms	-	-	-	-	-	⊕⊕⊕⊕ High
	SR/MA	Lebensqualität	-	-	-	-	-	Not reported

a: ASCO-LL Adaptation (dort aufgeführt: (Łopuch, Kawalec et al. 2015, Ruggeri, Maguire et al. 2015, Dimopoulos, Moreau et al. 2016, Dimopoulos, Oriol et al. 2016, Moreau, Masszi et al. 2016, Nooka, Kaufman et al. 2016, Palumbo, Chanan-Khan et al. 2016, Richardson, Hungria et al. 2016, Botta, Ciliberto et al. 2017, Chng, Goldschmidt et al. 2017, Dimopoulos, Goldschmidt et al. 2017, Dimopoulos, Lonial et al. 2017, Dimopoulos, Stewart et al. 2017, Durie, Hoering et al. 2017, Kropff, Vogel et al. 2017, Moreau, Joshua et al. 2017, Sun, Zheng et al. 2017, van Beurden-Tan, Franken et al. 2017, Zhang, Wang et al. 2017))

### 12.5.12. GRADE-Bewertung zu Empfehlung: Eine autologe Stammzelltransplantation sollte allen transplantationsfähigen Patienten angeboten werden, bei denen keine Transplantation im Rahmen der Erstlinientherapie durchgeführt wurde.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	Gesamtüberleben	-1	-	-	-1	-	⊕⊕⊕⊖ Low
	RCT	Progressionsfreies Überleben	-1	-	-	-	-	⊕⊕⊕⊖ Moderate
	RCT	Harms	-1	-	-	-	-	⊕⊕⊕⊖ Moderate
	RCT	Lebensqualität	-	-	-	-	-	Not reported

Unklares Verzerrungsrisiko, da moderates Biasrisiko in mindestens einer Domäne in eingeschlossener Studie.

Impräzise, da Konfidenzintervall Vor- und Nachteil der Intervention einschließt.

a: ASCO-LL Adaptation (dort aufgeführt: (Attal, Lauwers-Cances et al. 2017))



### 12.5.13. GRADE-Bewertung zu Empfehlung: Eine autologe Re-Transplantation kann erfolgen, wenn das progressionsfreie Überleben nach erster Transplantation in der Regel mindestens 18 Monate andauerte.

Schlüsselfrage	Design <sup>a</sup>	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	Gesamtüberleben	-	-	-2	-	-	⊕⊕⊕⊖ Low
	RCT	Progressionsfreies Überleben	-	-	-2	-	-	⊕⊕⊕⊖ Low
	RCT	Harms	-	-	-2	-	-	⊕⊕⊕⊖ Low
	RCT	Lebensqualität	-	-	-	-	-	Not reported

Starke Indirektheit, da Übertragbarkeit der Ergebnisse auf Therapie mit weiteren neuen Substanzen unklar und Studie nicht darauf angelegt, den optimalen Zeitpunkt der Re-Transplantation zu untersuchen.

a: ASCO-LL Adaptation (dort aufgeführt: (Crawley, Lalancette et al. 2005, Alvares, Davies et al. 2006, Kumar, Mahmood et al. 2008, Sellner, Heiss et al. 2013, Cook, Williams et al. 2014, Giral, Garderet et al. 2015, Gay, Engelhardt et al. 2018))

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