Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-064-z Linvoseltamab

Stand: Mai 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Linvoseltamab
[zur Behandlung des multiplen Myeloms nach mindestens drei vorausgegangenen Therapien]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Panobinostat – Beschluss vom 17. März 2016 - Pomalidomid – Beschlüsse vom 17. März 2016 und 5. Dezember 2019 - Elotuzumab – Beschlüsse vom 1. Dezember 2016 und 16. Dezember 2021 - Carfilzomib – Beschlüsse vom 15. Februar 2018 und 15. Juli 2021 - Daratumumab – Beschlüsse vom 15. Februar 2018, 3. Februar 2022 und 15. September 2022 - Ixazomib – Beschluss vom 21. April 2022 - Isatuximab – Beschlüsse vom 4. November 2021 - Idecabtagen vicleucel – Beschluss vom 19. September 2024 - Melphalanflufenamid – Beschluss vom 16. März 2023 - Selinexor – Beschlüsse vom 16. März 2023 - Ciltacabtagen Autoleucel – Beschluss vom 17. August 2023 - Teclistamab – Beschluss vom 15. Februar 2024 - Talquetamab – Beschluss vom 7. März 2024 - Elranatamab – Beschluss vom 4. Juli 2024
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen	Siehe systematische Literaturrecherche

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Linvoseltamab
[zur Behandlung des multiplen Myeloms nach mindestens drei vorausgegangenen Therapien]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Therapie im Anwendungsgebiet gehören.	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Linvoseltamab Lynozyfic n.a.	<u>Positive Opinion vom 27.02.2025:</u> Lynozyfic ist indiziert als Monotherapie für die Behandlung erwachsener Patienten mit rezidiviertem oder refraktärem Multiplem Myelom, die mindestens drei vorangegangene Therapien erhalten haben, darunter einen Proteasom-Inhibitor, einen immunmodulatorischen Wirkstoff und einen monoklonalen Anti-CD38-Antikörper, und die während der letzten Therapie eine Krankheitsprogression hatten.
Chemotherapien	
Carmustin L01AD01 generisch	Carmustin-ratiopharm wird bei Erwachsenen angewendet. Carmustin-ratiopharm ist allein oder in Kombination mit anderen antineoplastischen Mitteln und/oder anderen therapeutischen Maßnahmen (Strahlentherapie, chirurgischer Eingriff) bei folgenden bösartigen Neubildungen wirksam: - […] - Multiples Myelom (in Kombination mit Glukokortikoiden wie z. B. Prednisolon) […]
Cyclophosphamid L01AA01 generisch	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - Remissionsinduktion bei Plasmozytom (auch in Kombination mit Prednison)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Doxorubicin L01DB01 generisch	Doxorubicinhydrochlorid Teva wird angewendet zur Behandlung von: […] - fortgeschrittenes multiples Myelom
Doxorubicin (pegyliert liposomal) L01DB01 Caelyx pegylated liposomal	Caelyx pegylated liposomal wird angewendet […] - in Kombination mit Bortezomib zur Behandlung des progressiven multiplen Myeloms bei Patienten, die zumindest eine vorangegangene Therapie erhalten haben, und die sich bereits einer Knochenmarkstransplantation unterzogen haben bzw. dafür ungeeignet sind.
Melphalan L01AA03 generisch	Melphalan-ratiopharm wird in der konventionellen intravenösen Dosierung zur Behandlung des multiplen Myeloms […] angewendet. Melphalan-ratiopharm wird in hoher intravenöser Dosierung mit oder ohne hämatopoetische Stammzelltransplantation zur Behandlung des multiplen Myeloms […] angewendet. […] Melphalan-ratiopharm kann in den oben genannten Anwendungsgebieten allein oder in Kombination mit anderen Zytostatika angewendet werden.
Melphalan flufenamid L01AA10 Pepaxti	Pepaxti ist in Kombination mit Dexamethason zur Behandlung von erwachsenen Patienten mit multiplem Myelom angezeigt, die zuvor mindestens drei Therapielinien erhalten haben, deren Erkrankung gegenüber mindestens einem Proteasom-Inhibitor, einem immunmodulatorischen Mittel und einem monoklonalen CD38-Antikörper refraktär ist und die ein Fortschreiten der Erkrankung während oder nach der letzten Therapie gezeigt haben. Bei Patienten mit vorangegangener autologer Stammzelltransplantation sollte die Zeit bis zur Progression nach der Transplantation mindestens 3 Jahre betragen.
Vincristin L01CA02 Vincristinsulfat-Teva	Vincristinsulfat-Teva 1mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: […] - multiplem Myelom […]
Weitere antineoplastische Arzneimittel	
Bortezomib L01XG01 generisch	Bortezomib medac als Monotherapie oder in Kombination mit pegyliertem, liposomalen Doxorubicin oder Dexamethason ist indiziert für die Behandlung erwachsener Patienten mit progressivem, multiplen Myelom, die mindestens 1 vorangehende Therapie durchlaufen haben und die sich bereits einer hämatopoetischen Stammzelltransplantation unterzogen haben oder für diese nicht geeignet sind.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Carfilzomib L01XG02 Kyprolis	Kyprolis ist in Kombination mit Daratumumab und Dexamethason, mit Lenalidomid und Dexamethason oder mit Dexamethason alleine zur Behandlung von erwachsenen Patienten mit multiplem Myelom indiziert, die mindestens eine vorangegangene Therapie erhalten haben.
Daratumumab L01FC01 Darzalex	Darzalex ist indiziert: - in Kombination mit Lenalidomid und Dexamethason oder Bortezomib und Dexamethason für die Behandlung erwachsener Patienten mit multiplem Myelom, die bereits mindestens eine Therapie erhalten haben. - in Kombination mit Pomalidomid und Dexamethason für die Behandlung erwachsener Patienten mit multiplem Myelom, die bereits eine vorherige Therapie mit einem Proteasom-Inhibitor und Lenalidomid erhalten haben und refraktär gegenüber Lenalidomid waren oder die bereits mindestens zwei vorherige Therapien erhalten haben, die Lenalidomid und einen Proteasom-Inhibitor enthielten, und die während oder nach der letzten Therapie eine Krankheitsprogression gezeigt haben - als Monotherapie für die Behandlung erwachsener Patienten mit rezidiviertem und refraktärem multiplen Myelom, die bereits mit einem Proteasom-Inhibitor und einem Immunmodulator behandelt wurden, und die während der letzten Therapie eine Krankheitsprogression zeigten
Elotuzumab L01FX08 Empliciti	Empliciti ist in Kombination mit Lenalidomid und Dexamethason zur Behandlung des Multiplen Myeloms bei Erwachsenen indiziert, welche mindestens eine vorangegangene Therapie erhalten haben. Empliciti ist in Kombination mit Pomalidomid und Dexamethason zur Behandlung des rezidivierten und refraktären Multiplen Myeloms bei Erwachsenen indiziert, die mindestens zwei vorausgegangene Therapien, darunter Lenalidomid und einen Proteasom-Inhibitor, erhalten haben und unter der letzten Therapie eine Progression gezeigt haben.
Elranatamab L01FX32 Elrexfio	Elrexfio wird angewendet als Monotherapie zur Behandlung erwachsener Patienten mit rezidiviertem und refraktärem multiplen Myelom, die zuvor bereits mindestens drei Therapien erhalten haben, darunter einen immunmodulatorischen Wirkstoff, einen Proteasom-Inhibitor und einen Anti-CD38-Antikörper, und die während der letzten Therapie eine Krankheitsprogression gezeigt haben.
Isatuximab L01FC02 Sarclisa	Sarclisa ist indiziert: - in Kombination mit Pomalidomid und Dexamethason zur Behandlung des rezidivierten und refraktären Multiplen Myeloms bei Erwachsenen, die mindestens zwei vorausgegangene Therapien, darunter Lenalidomid und einen Proteasom-Inhibitor, erhalten haben und unter der letzten Therapie eine Krankheitsprogression zeigten. - in Kombination mit Carfilzomib und Dexamethason zur Behandlung des Multiplen Myeloms bei Erwachsenen, die mindestens eine vorausgegangene Therapie erhalten haben.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ixazomib L01XG03 Ninlaro	Ninlaro ist in Kombination mit Lenalidomid und Dexamethason für die Behandlung des multiplen Myeloms bei erwachsenen Patienten indiziert, die mindestens eine vorausgegangene Therapie erhalten haben.
Lenalidomid L04AX04 generisch	Lenalidomid in Kombination mit Dexamethason ist indiziert für die Behandlung des multiplen Myeloms bei erwachsenen Patienten, die mindestens eine vorausgegangene Therapie erhalten haben.
Panobinostat L01XH03 Farydak	Farydak ist in Kombination mit Bortezomib und Dexamethason indiziert für die Behandlung erwachsener Patienten mit rezidiviertem und/oder refraktärem Multiplen Myelom, die mindestens zwei vorausgegangene Therapien, darunter Bortezomib und eine immunmodulatorische Substanz, erhalten haben.
Pomalidomid L04AX06 Imnovid	- Imnovid ist in Kombination mit Bortezomib und Dexamethason indiziert für die Behandlung des multiplen Myeloms bei erwachsenen Patienten, die mindestens eine vorausgegangene Therapie, darunter Lenalidomid, erhalten haben. - Imnovid ist in Kombination mit Dexamethason indiziert für die Behandlung des rezidivierten und refraktären multiplen Myeloms bei erwachsenen Patienten, die mindestens zwei vorausgegangene Therapien, darunter Lenalidomid und Bortezomib, erhalten haben und unter der letzten Therapie eine Progression gezeigt haben.
Selinexor L01XX66 Nexpovio	Nexpovio ist: - in Kombination mit Bortezomib und Dexamethason für die Behandlung des Multiplen Myeloms bei erwachsenen Patienten indiziert, die zuvor mindestens eine Therapie erhalten haben. - in Kombination mit Dexamethason für die Behandlung des Multiplen Myeloms bei erwachsenen Patienten indiziert, die zuvor mindestens vier Therapien erhalten haben und deren Erkrankung gegenüber mindestens zwei Proteasom-Inhibitoren, zwei immunmodulatorischen Arzneimitteln und einem monoklonalen Anti-CD38-Antikörper refraktär ist und bei denen unter der letzten Therapie eine Progression der Erkrankung aufgetreten ist.
Talquetamab L01FX29 Talvey	Talvey wird angewendet als Monotherapie zur Behandlung erwachsener Patienten mit rezidiviertem und refraktärem multiplem Myelom, die zuvor bereits mindestens 3 Therapien erhalten haben, darunter einen immunmodulatorischen Wirkstoff, einen Proteasom-Inhibitor und einen Anti-CD38-Antikörper, und die während der letzten Therapie eine Krankheitsprogression gezeigt haben.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Teclistamab L01FX24 Tecvayli	Tecvayli wird angewendet als Monotherapie zur Behandlung erwachsener Patienten mit rezidiviertem und refraktärem multiplen Myelom, die zuvor bereits mindestens drei Therapien erhalten haben, darunter einen Immunmodulator, einen Proteasom-Inhibitor und einen Anti-CD38-Antikörper, und die während der letzten Therapie eine Krankheitsprogression gezeigt haben
Glucocorticoide	
Dexamethason H02AB02 generisch	Palliativtherapie maligner Tumoren
Prednisolon H02AB06 generisch	Hämatologie / Onkologie: - akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, […] multiples Myelom […] - Palliativtherapie maligner Erkrankungen
Prednison H02AB07 generisch	Hämatologie / Onkologie: - akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, […] multiples Myelom - Palliativtherapie maligner Erkrankungen
CAR-T-Zelltherapien	
Ciltacabtagen Autoleucel L01XL05 Carvykti	Carvykti ist indiziert für die Behandlung erwachsener Patienten mit rezidiviertem und refraktärem multiplen Myelom, die zuvor bereits mindestens eine Therapie erhalten haben, darunter einen Immunmodulator und einen Proteasom-Inhibitor, und die während der letzten Therapie eine Krankheitsprogression zeigten und gegenüber Lenalidomid refraktär sind
Idecabtagen vicleucel L01XL07 Abecma	Abecma ist indiziert für die Behandlung des rezidivierten und refraktären multiplen Myeloms bei erwachsenen Patienten, die mindestens zwei vorausgegangene Therapien, einschließlich eines Immunmodulators, eines Proteasominhibitors und eines Anti-CD38-Antikörpers, erhalten und unter der letzten Therapie eine Krankheitsprogression gezeigt haben

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-064z (Linvoseltamab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	8. April 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AHS	Alberta Health Service
ASCO	American Society of Clinical Oncology
ASCT	Autologe Stammzelltransplantation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CAR	Chimeric antigen receptor
CCO	Cancer Care Ontario
CR	Complete response
DKG	Deutsche Krebsgesellschaft
DKH	Deutsche Krebshilfe
ECRI	Emergency Care Research Institute
EMA	Europäische Arzneimittel-Agentur
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCT	Hematopoietic cell transplantation
HR	Hazard Ratio
i.v.	Intravenös
IMWG	International Myeloma Working Group
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LL	Leitlinie
LoE	Level of Evidence
MGUS	Monoklonale Gammopathie unklarer Signifikanz
MM	Multiples Myelom/Multiple myeloma
MR	Minor response
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NVL	Nationale Versorgungsleitlinien
OR	Odds Ratio
ORR	Objective response rate

OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Protease Inhibitors
PR	Partial response
RCT	Randomized controlled trial
RR	Relatives Risiko
RRMM	Relapsed/refractory multiple myeloma
s.c.	Subkutan
sCR/CR	Stringent complete response
SCT	Stem Cell Transplantation
SD	Stable disease
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematische Reviews/Systematic Reviews
TRAE	Treatment-related Adverse Events
TRIP	Turn Research into Practice Database
VGPR	Very Good Partial Response
WHO	World Health Organization

1 Indikation

Behandlung erwachsener mit rezidiviertem oder refraktärem Multiplem Myelom, die mindestens drei vorangegangene Therapien erhalten haben, darunter einen Proteasom-Inhibitor, einen immunmodulatorischen Wirkstoff und einen monoklonalen Anti-CD38-Antikörper, und die während der letzten Therapie eine Krankheitsprogression hatten.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Multiples Myelom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 14.03.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 780 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. *Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet.* Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf, wurden insgesamt 11 Referenzen eingeschlossen.

Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es liegen keine relevanten Cochrane Reviews vor.

3.2 Systematische Reviews

Costa BA et al., 2025 [2].

Addition of Elotuzumab to Backbone Treatment Regimens for Multiple Myeloma: An Updated Meta-Analysis of Randomized Clinical Trials.

Fragestellung

An up-to-date and comprehensive meta-analysis of RCTs evaluating the addition of this anti-SLAMF7 mAb to backbone antimyeloma regimens.

Methodik

Population:

- NDMM and **RRMM**

Intervention/Komparator:

- Standard backbone regimens for MM (doublets or triplets containing dexamethasone plus an IMiD and/or a PI) administered either alone (control arm) or in combination with an anti-SLAMF7 mAb (elotuzumab arm)

Endpunkte:

- PFS, Overall survival (OS), overall response rate (ORR), and very good partial response (VGPR) or better rate

Recherche/Suchzeitraum:

- MEDLINE (PubMed), Embase, and Cochrane Library from inception to April 1, 2024.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing the risk of bias in randomized trials" (RoB-2)

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs comprising 2705 patients (50% treated with elotuzumabcontaining regimens) met our predefined criteria. The selected studies included 3 RRMM trials (n = 915) and 5 NDMM trials (n = 1790).

Charakteristika der Population/Studien:

Table 1 Study Characteristics. Key Descriptive Information on Included Trials and Baseline Features From Study Populations. Abbreviations: *ASCT* = autologous stem cell transplantation; *DSMM* = deutsche studiengruppe multiples myelom; *ECOG* = eastern cooperative oncology group; *Elo* = elotuzumab; *GMMG* = German-speaking myeloma multicenter group; *IND* = induction; *ISS* = international staging system; *KRd* = carfilzomib/lenalidomide/dexamethasone; *LOTs* = lines of therapy; *Mdn* = median; *Min* = minimum; *MT* = maintenance therapy; *N/A* = not applicable; *NCT* = National Clinical Trial; *NDMM* = newly diagnosed multiple myeloma; *NR* = not reported; *Pd* = pomalidomide/dexamethasone; *RCT* = randomized controlled trial; *R-ISS* = revised-international staging system; *RRMM* = relapsed/refractory multiple myeloma; *Rd* = lenalidomide/dexamethasone; *SWOG* = southwest oncology group; *Vd* = bortezomib/dexamethasone; *VRd* = bortezomib/lenalidomide/dexamethasone; *WHO* = World Health Organization.

Study (NCT number)	Design (Country)	Population (Interventions Compared)	No. of Patients (Age, Years)		Performance Status		Disease Staging		High-Risk Cytogenetic Abnormalities		No. of Cycles Completed		Follow-Up Duration*
			Elo Arm	Control Arm	Elo Arm	Control Arm	Elo Arm	Control Arm	Elo Arm	Control Arm	Elo Arm	Control Arm	
DSMM XVII Trial, 2023 (NCT03948035)	Multicenter, open-label, phase III RCT (Austria and Germany)	NDMM, eligible for ASCT (Elo-KRd *vs.* KRd)	291 (Mdn, 59)	288 (Mdn, 58)	ECOG: 0, 55% 2, 7%	ECOG: 0, 54% 2, 10%	R-ISS: I, 40%; III, 10%	R-ISS: I, 36%; III, 11%	del(17p): 16/244 (7%); t(4;14): 21/240 (9%); t(14;16): 2/228 (1%)	del(17p): 16/248 (6%); t(4;14): 26/248 (10%); t(14;16): 2/236 (1%)	All 6 IND cycles: 92%	All 6 IND cycles: 92%	Min, 5.6 months†
ELOQUENT-1 Trial, 2022 (NCT01335399)	Multicenter, open-label, phase II RCT (Multinational)	NDMM, ineligible for ASCT (Elo-Rd *vs.* Rd)	374 (Mdn, 73)	374 (Mdn, 73)	ECOG: 0, 36% 2, 12%	ECOG: 0, 36% 2, 18%	ISS: I, 30%; III, 28%	ISS: I, 27%; III, 28%	del(17p), t(4;14), and/or t(14;16): 43/350 (12%)	del(17p), t(4;14), and/or t(14;16): 45/348 (13%)	Mdn, 26 (range, 9-53)	Mdn, 21 (range, 8-46)	Min, 65.3 months; Mdn, 70.6 months
ELOQUENT-2 Trial, 2015 (NCT01239797)	Multicenter, open-label, phase II RCT (Multinational)	RRMM, 1-3 prior LOTs (Elo-Rd *vs.* Rd)	321 (Mdn, 67)	325 (Mdn, 66)	ECOG: 0-1, 93% 2, 7%	ECOG: 0-1, 90% 2, 10%	ISS: I, 46%; III, 21%	ISS: I, 44%; III, 22%	del(17p): 102/315 (32%); t(4;14): 30/315 (10%); t(14;16): 11/313 (4%)	del(17p): 104/322 (32%); t(4;14): 31/321 (10%); t(14;16): 5/322 (2%)	Mdn, 19 (range, 1-91)	Mdn, 14 (range, 1-83)	Min, 70.6 months
ELOQUENT-3 Trial, 2018 (NCT02654132)	Multicenter, open-label, phase 2 RCT (Multinational)	RRMM, RRMM, ≥2 prior LOTs (Elo-Pd *vs.* Pd)	60 (Mdn, 69)	57 (Mdn, 66)	ECOG: 0-2, 100%	ECOG: 0-2, 100%	ISS: I/II, 88%; III, 12%	ISS: I/II, 88%; III, 12%	del(17p), t(4;14), and/or t(14;16): 16/49 (33%)	del(17p), t(4;14), and/or t(14;16): 18/46 (39%)	Mdn, 9 (range, 1-53)	Mdn, 5 (range, 1-50)	Min, 45 months
GMMG-HD6 Trial, 2024 (NCT02495922)	Multicenter, open-label, phase III RCT‡ (Germany)	NDMM, eligible for ASCT (Elo-VRd *vs.* VRd)	142 (Mdn, 59)	139 (Mdn, 59)	WHO: 0-1, 93% 2-3, 7%	WHO: 0-1, 94% 2-3, 6%	ISS: I, 39%; III, 25%	ISS: I, 40%; III, 20%	del(17p): 8/142 (6%) t(4;14): 11/142 (8%); t(14;16): 5/142 (4%);	del(17p): 21/139 (15%);	All 4 IND cycles: 92%; All 26 MT cycles: 54%§	All 4 IND cycles: 95%; All 26 MT cycles: 50%§	Min, 36 months; Mdn, 49.8 months

(continued on next page)

Jakubowiak et al., 2016 (NCT01478048)	Multicenter, open-label, phase II RCT (Multinational)	RRMM, 1-3 prior LOTs (Elo-Vd *vs.* Vd)	77 (Mean, 65)	75 (Mean, 65)	ECOG: 0, 51% 2, 3%	ECOG: 0, 61% 2, 8%	ISS: I, 43%; III, 18%	ISS: I, 35%; III, 29%	del(17p) and/or t(4;14): 0/36 (0%)¶	del(17p) and/or t(4;14): 5/33 (15%)¶	Mdn, 12	Mdn, 7	Min, 28.3 months; Mdn, 15.9 months (Elo-Vd)
Kubo et al., 2020 (NCT02272803)	Multicenter, open-label, phase 2 RCT (Japan)	NDMM, ineligible for ASCT (Elo-Rd *vs.* Rd)	40 (Mdn, 72)	42 (Mdn, 73)	ECOG: 0-2, 100%	ECOG: 0-2, 100%	ISS: I, 23%; III, 20%	ISS: I, 24%; III, 21%	del(17p) and/or t(4;14): 1/40 (3%)¶	del(17p) and/or t(4;14): 0/42 (0%)¶	Mdn, 13	Mdn, 12	6-72 months
SWOG-1211 Trial, 2021 (NCT01668719)	Multicenter, open-label, phase 2 RCT (United States)	High-risk# NDMM, ineligible for ASCT (Elo-VRd *vs.* VRd)	48 (Mdn, 62)	52 (Mdn, 66)	SWOG: >1, 15%	SWOG: >1, 18%	R-ISS: I, 13%; III, 15%	R-ISS: I, 4%; III, 21%	del(17p): 15/48 (31%); t(14;16): 7/48 (15%)	del(17p): 22/52(42%); t(14;16): 4/52 (8%)	Mdn, 14	Mdn, 8	Mdn, 72 months

Qualität der Studien:

- According to RoB-2, all included RCTs were deemed to have a low risk of bias. Although outcome assessors in all studies were not blinded to the treatment each participant received, measurements were unlikely to be influenced by the knowledge of the assigned interventions.

Studienergebnisse:

- (…) In RRMM settings, elotuzumab use significantly improved PFS (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.60-0.82; P < .001; I^2 = 0%).
- This benefit was consistent among patients with high-risk cytogenetics (HR, 0.62; 95% CI, 0.43-0.90; P = .01; I^2 = 0%) and was particularly evident in those previously treated with proteasome inhibitors (PIs) or immunomodulatory drugs (IMiDs).
- The RRMM cohort also demonstrated better OS, ORR, and ≥VGPR rate.
- he pooled safety population consisted of 2670 patients (50% with NDMM and 50% with RRMM)
  - Grade ≥3 infections were more common in the elotuzumab arm (HR, 1.58; 95% CI, 1.311.91; P < .001; I2 = 0%), but there were lower rates of grade ≥3 neutropenia compared to the control arm (HR, 0.62; 95% CI, 0.51-0.76; P < .001; I2 = 0%). No

significant differences were observed for grade ≥3 event rates of anemia, thrombocytopenia, or cardiac disorders. Absolute rates of SPMs were 8.6% (3.6% nonmelanoma skin cancers, 4.5% other neoplasms, 0.5% unknown category) in the elotuzumab arm and 7% (2.5% nonmelanoma skin cancers, 3.9% other neoplasms, 0.6% unknown category) in the control arm. Upon comparison, there was a similar cumulative risk of SPMs between the 2 groups (HR, 0.86; 95% CI, 0.58-1.26; P = .30; I^2 = 0%).

Fazit der Autoren

This systematic review and updated meta-analysis of RCTs found significant improvements in survival outcomes and response rates with the addition of elotuzumab to backbone regimens for RRMM, with demonstration of a consistent PFS benefit regardless of cytogenetic risk profile and particularly among patients with previous PI/IMiD exposure. Nevertheless, our results suggest against the application of this anti-SLAMF7 mAb in frontline settings. Apart from more grade ≥3 infections with elotuzumab, overall safety profiles were similar between treatment arms. Despite the heterogeneity of drug combinations and patient populations, these findings have the potential to inform clinical decision-making and guide the design of future research.

Ye L et al., 2023 [11].

Efficacy and safety of anti-CD38 monoclonal antibodies in patients with relapsed/refractory multiple myeloma: a systematic review and meta-analysis with trial sequential analysis of randomized controlled trials.

Fragestellung

to evaluate the safety and efficacy of antiCD38 monoclonal antibodies (mAbs) among patients with relapsed/refractory multiple myeloma (RRMM) through meta-analysis.

Methodik

Population:

- RRMM

Intervention:

- anti-CD38 mAbs in combination with IMiDs or PIs plus dexamethasone

Komparator:

- IMiDs or PIs plus dexamethasone

Endpunkte:

- PFS and OS, other efficacy results and TEAEs

Recherche/Suchzeitraum:

- June 2023, PubMed, Web of Science, Embase and the Cochrane Library

Qualitätsbewertung der Studien:

- modified Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 studies

Charakteristika der Population/Studien:

First author (year)	Region	Participants (E/C)	Age (E/C, years)	Intervention (E/C)	Previous lines of treatment	Follow-up time (months)	Trial
Richardson (2022)	102 hospitals in 24 countries across Europe, North America, and the Asia-Pacific regions	154/153	Median (IQR): 68 (60–74)/66 (59-71)	Isatuximab + pomalidomide + dexamethasone/ Pomalidomide + dexamethasone	≥ 2	35.3 (median)	ICARIA-MM
Usmani (2023)	102 medical centers in 19 countries across North America, Europe, Australia, and Asia	312/154	Median (IQR): 64.0 (57-70)/64.5 (59-71)	Daratumumab + carfilzomib + dexamethasone/ Carfilzomib + dexamethasone	1-3	50 (median)	CANDOR
Sonneveld (2023)	16 countries across Europe, North America, South America, Australia, and Asia	251/247	Median (range): 64 (30-88)/64 (33-85)	Daratumumab + bortezomib + dexamethasone/ Bortezomib + dexamethasone	≥ 1	72.6 (median)	CASTOR
Lu (2021)	Mainland China (25 sites) and Taiwan (2 sites)	141/70	Median (range): 61 (28-79)/61 (43-82)	Daratumumab + bortezomib + dexamethasone/ Bortezomib + dexamethasone	≥ 1	8.2 (median)	LEPUS
Martin (2023)	69 study centers in 16 countries across North America, South America, Europe, and the Asia-Pacific region.	179/123	Median (range): 65 (37-86)/63 (33-90)	Isatuximab + carfilzomib + dexamethasone/ Carfilzomib + dexamethasone	1-3	44 (median)	IKEMA
Dimopoulos (2021)	48 academic centers and hospitals in 12 European countries	151/153	Median (range): 67 (42-86)/68 (35-90)	Daratumumab + pomalidomide + dexamethasone/ Pomalidomide + dexamethasone	≥ 1	16.9 (median)	APOLLO
Bahlis (2020)	135 sites in 18countries across North America, Europe, and the Asia Pacific region	286/283	Median (range): 65 (34-89)/65 (42-87)	Daratumumab + lenalidomide + dexamethasone/ Lenalidomide + dexamethasone	≥ 1	44.3 (median)	POLLUX
Fu (2023)	Mainland China (25 sites) and Taiwan (2 sites)	141/70	Median (range): 61 (28-79)/61 (43-82)	Daratumumab + bortezomib + dexamethasone/ Bortezomib + dexamethasone	≥ 1	25.1 (median)	LEPUS
Usmani (2022)	102 medical centers in 19 countries across North America, Europe, Australia, and Asia	312/154	Median (IQR): 64.0 (57-70)/64.5 (59-71)	Daratumumab + carfilzomib + dexamethasone/ Carfilzomib + dexamethasone	1-3	27	CANDOR
Dimopoulos (2023)	135 sites in 18countries across North America, Europe, and the Asia Pacific region	286/283	Median (range): 65 (34-89)/65 (42-87)	Daratumumab + lenalidomide + dexamethasone/ Lenalidomide + dexamethasone	≥ 1	79.7 (median)	POLLUX
Mateos (2020)	16 countries across Europe, North America, South America, Australia, and Asia	251/247	Median (range): 64 (30-88)/64 (33-85)	Daratumumab + bortezomib + dexamethasone/ Bortezomib + dexamethasone	≥ 1	40 (median)	CASTOR

E, experimental arm; C, control arm; IQR, interquartile range.

Qualität der Studien:

- 9 included RCTs were assessed as high quality, because the study design had been detailly described. The remaining two studies were evaluated as low quality, as randomization, randomization concealment, and withdrawals and dropouts were not described in detail.

Studienergebnisse:

- Compared with IMiDs (or PIs) and dexamethasone alone, anti-CD38 mAbs in combination with IMiDs (or PIs) and dexamethasone significantly prolonged PFS (HR: 0.552, 95% CI = 0.461 to 0.659, 95% PI = 0.318 to 0.957) and OS (HR: 0.737, 95% CI = 0.657 to 0.827, 95% PI = 0.626 to 0.868) in patients with RRMM
- RRMM patients receiving anti-CD38 mAbs in combination with IMiDs (or PIs) and dexamethasone achieved higher rates of overall response (RR: 1.281, 95% CI = 1.144 to 1.434, 95% PI = 0.883 to 1.859), complete response or better (RR: 2.602, 95% CI = 1.977 to 3.424, 95% PI = 1.203 to 5.628), very good partial response (VGPR) or better (RR: 1.886, 95% CI = 1.532 to 2.322, 95% PI = 0.953 to 3.731), and minimum residual disease (MRD)-negative (RR: 4.147, 95% CI = 2.588 to 6.644, 95% PI = 1.056 to 16.283) than those receiving IMiDs (or PIs) and dexamethasone alone.
- For TEAEs, the rates of hematologic and nonhematologic TEAEs, including thrombocytopenia, neutropenia, upper respiratory tract infection (URTI), pneumonia, bronchitis, dyspnea, diarrhea, pyrexia, back pain, arthralgia, fatigue, insomnia, and hypertension, were higher in the anti-CD38 mAbs in combination with IMiDs (or PIs) and dexamethasone group than in the IMiDs (or PIs) and dexamethasone group

Fazit der Autoren

Taken together, our meta-analysis demonstrated that anti-CD38 mAbs in combination with IMiDs (or PIs) and dexamethasone improved PFS and OS in patients with RRMM, and achieved higher rates of overall response, complete response or better, VGPR or better, andMRD-negative compared with IMiDs (or PIs) and dexamethasone alone. The rates ofhematologic and nonhematologic TEAEs, including thrombocytopenia, neutropenia, URTI, pneumonia, bronchitis, dyspnea, diarrhea, pyrexia, back pain, arthralgia, fatigue, insomnia, and hypertension, were also higher in the anti-CD38 mAbs in combination with IMiDs (or PIs) and dexamethasone group than in the IMiDs (or PIs) and dexamethasone group.

Qureshi Z et al., 2024 [10].

Efficacy and safety of teclistamab in relapsed or refractory multiple myeloma: a systematic review and meta-analysis.

Fragestellung

To synthesize the evidence on the efficacy and safety of teclistamab in treating relapsed/refractory multiple myeloma (RRMM).

Methodik

Population:

- dult (> 18 years) patients diagnosed with RRMM

Intervention:

- Teclistamab

Komparator:

- Siehe Ergebnisse

Endpunkte:

- overall response rate, adverse events, complete response or better and very good partial response or better

Recherche/Suchzeitraum:

- PubMed, Web of Science, EMBASE, and Google Scholar databases until June 2024

Qualitätsbewertung der Studien:

- Newcastle Ottawa Scale (NOS)
  - Furthermore, the overall methodological quality was rated as poor (NOS score 0–3), fair (NOS score 4–6) or good (NOS score 7–9)

Ergebnisse

Anzahl eingeschlossener Studien:

- Five studies with 661 patients diagnosed with RRMM

Charakteristika der Population/Studien:

Table 1 Study characteristics

Study ID	Study design	Study location	Patient characteristics					
			Sample, *n*	Age (years)	M/F	Prior BCMA therapy (%)	Lines of prior therapy	Refractory status
Moreau et al.2022 [1]	Phase I/II open-label multicenter non-randomized study	United States, China, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, and the United Kingdom	165	64 (33–84)	96/69	Not allowed	5 (2–14)	Triple-class (165) Penta-drug (116)
Riedhammer et al.2024 [19]	Multicenter retrospective study	Germany	123	67 (35–87)	70/53	37.4	6 (3–14)	Triple-class (113) Penta-drug (74)
Mohan et al.2024 [20]	Multicenter retrospective study	United States	110	68 (37–89)	56/54	35	6 (3–13)	Triple-class (95) Penta-drug (84)
Usmani et al.2021 [21]	Multicenter open-label phase I study	United States, China, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, and the United Kingdom	157	63 (57–69)	85/72	Not allowed	6 (4–7)	Triple-class (128) Penta-drug (61)
Dima et al.2024 [22]	Multicenter retrospective study	United States	106	66.5 (35–87)	49/57	53	6 (4–17)	Triple-class (97) Penta-drug (68)
Study ID	Study design	Follow-up (months)	Outcomes					
			ORR (%)	≥VGPR (%)	≥CR (%)	CRS (grade > 3)	Neurotoxicity (grade > 3)	Any adverse event (grade > 3)
Moreau et al.2022 [1]	Phase I/II open-label multicenter non-randomized study	14.1	63	58.8	39.4	1 (0.6%)	1 (0.6%)	156 (94.5%)
Riedhammer et al.2024 [19]	Multicenter retrospective study	5.5	59.3	48	22	2 (1.6%)	1 (0.8%)	NR
Mohan et al.2024 [20]	Multicenter retrospective study	3.5	62	51	20	5 (4.5%)	5 (4.5%)	NR
Usmani et al.2021 [21]	Multicenter open-label phase I study	7.1	65	58	40	0 (0%)	NR	134 (85%)
Dima et al.2024 [22]	Multicenter retrospective study	3.8	66	46.2	29	1 (0.9)	3 (2.8)	NR

Qualität der Studien:

Table 3 Methodological quality using the Newcastle Ottawa Scale

Study ID	Exposed cohort representativeness	Non-exposed cohort selection	Exposure verification	Initial outcome absence	Cohort comparability	Outcome evaluation	Sufficient follow-up	Cohort follow-up	Total score	Overall quality
Moreau et al.2022 [13]	0	0	1	1	2	0	1	1	6	Fair
Riedhammer et al.2024 [19]	1	0	1	1	1	0	0	1	5	Fair
Mohan et al.2024 [20]	1	0	1	1	2	0	0	1	6	Fair
Usmani et al.2021 [21]	0	0	1	1	0	0	1	1	4	Fair
Dima et al.2024 [22]	1	0	1	1	2	0	0	1	6	Fair

Studienergebnisse:

- The pooled results showed that teclistamab led to an overall response rate (ORR) of 62.8% (95% Confidence Interval (CI): 58.6–66.8), a ≥ very good partial response or better (VGPR) of 52.1% (95% CI: 46.8–57.3), and a ≥ complete response or better (CR) of 29.5% (95% CI: 21.9–38.4).
- When the ORR was assessed in different subgroups, we found that patients with extramedullary disease (EMD) had considerably lower ORR than those without EMD (45% vs. 71%, p < 0.0001).
- The ORR was significantly lower in patients with prior (B-cell maturation antigen) BCMA-directed therapy (OR: 2.24, p = 0.002) and those with stage III disease (OR: 3.69, p = 0.0001).
- subgroup analyses showed no considerable difference in the ORR between patients with high or standard-risk cytogenetics (OR: 1.05 p = 0.82) and those with penta-drug or tripleclass-refractory disease (OR: 0.97 p = 0.89).
- Regarding the safety of teclistamab, the pooled results showed that the incidence of grade ≥ 3 adverse events was high (90.7%). However, grade ≥ 3 cytokine release syndrome (CRS) and neurotoxic events were low (1.5% and 2.2%, respectively).

Fazit der Autoren

In summary, RRMM patients treated with teclistamab display good response rates. Furthermore, research suggests that these responses are durable and deepen over time. However, more research in long-term follow-up studies is required to establish the durability of these responses. Additionally, evidence suggests that prior BCMA-directed therapy, the presence of EMD and stage III disease are associated with poor response rates. However, the response rates for patients with prior BCMA-related therapy are relatively high. Therefore, teclistamab can be a valuable therapeutic option for these patients. Adverse events are also common with the teclistamab treatment. However, severe toxic events such as CRS and neurotoxicity are generally low. Therefore, with appropriate measures, resources, and infrastructure, teclistamab can be safely administered to patients with RRMM.

Chen H et al., 2023 [1].

Comparative efficacy of novel-drugs combined therapeutic regimens on relapsed/refractory multiple myeloma: a network meta-analysis.

Fragestellung

the aim to identify treatments that could be more effective than others in RRMM.

Methodik

Population:

- patients with RRMM

Intervention/Komparator:

- enalidomide, pomalidomide, carfilzomib, ixazomib, vorinostat, panobinostat, elotuzumab, daratumumab, isatuximab, selinexor and venetoclax

Endpunkte:

- teatment response rate, which was defined as overall ORR. The ORR comprised partial, very good partial, complete, and stringent complete responses in accordance with the International Myeloma Working Group (IMWG) criteria

Recherche/Suchzeitraum:

- Cochrane Library, PubMed, Embase, and Web of Science for identifying eligible clinical trials from inception date to 15 June 2022.

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 22 RCTs: Among 22 RCTs, there were 13 kinds of therapeutic regimens according to the use of novel drugs: (1) dexamethasone (Dex), (2) bortezomib (Bor): bortezomib ± dexamethasone, (3) lenalidomide (Len): lenalidomide + dexamethasone, (4) pomalidomide (Pom): pomalidomide + dexamethasone, pomalidomide + bortezomib + dexamethasone, (5) carfilzomib (Car): carfilzomib + dexamethasone, carfilzomib + lenalidomide + dexamethasone, (6) ixazomib (Ixa): ixazomib + lenalidomide + dexamethasone, (7) vorinostat (Vorino): vorinostat + bortezomib, (8) panobinostat (Pano): panobinostat + bortezomib + dexamethasone, (9) elotuzumab (Elo): elotuzumab + lenalidomide + dexamethasone, elotuzumab + pomalidomide + dexamethasone, elotuzumab + bortezomib + dexamethasone, (10) daratumumab (Dara): daratumumab+ bortezomib+dexamethasone, daratumumab + carfilzomib + dexamethasone, daratumumab + lenalidomide + dexamethasone, daratumumab + pomalidomide + dexamethasone, (11) isatuximab (Isa): isatuximab+ carfilzomib + dexamethasone, isatuximab + pomalidomide + dexamethasone, (12) selinexor (Sel): selinexor + bortezomib + dexamethasone, (13) venetoclax (Ven): venetoclax + bortezomib + dexamethasone

Charakteristika der Population/Studien:

- The median age ranged from 61 to 69 years, and patients received one to eleven prior lines of treatments.

Qualität der Studien:

- The quality of all studies was high

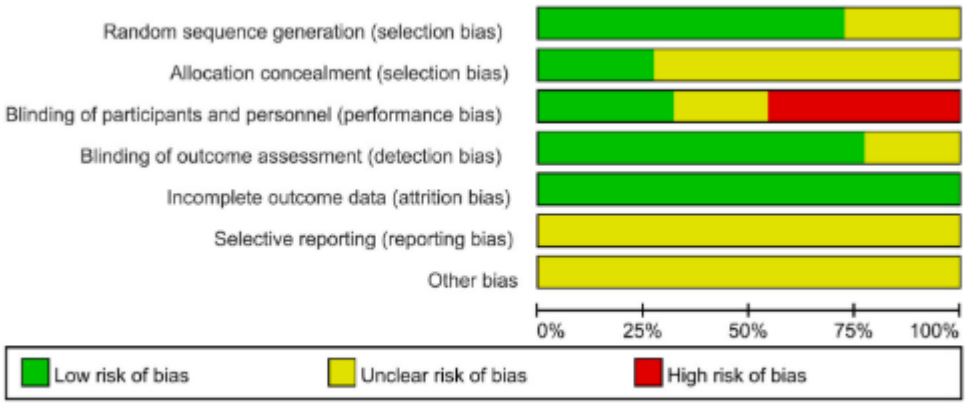


Figure 2. Risk of bias summary.

Studienergebnisse:

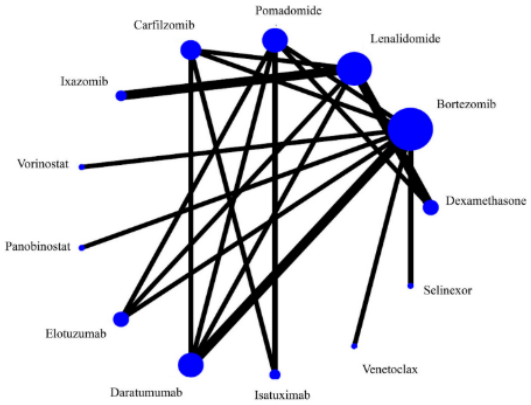


Figure 3. Network plot for overall response rate between different regimens.

- 22 studies, yielding 79 pairwise comparisons, 20 of which were statistically significant: Compared with Dex, Bor (OR: 0.22, 95%CI: 0.09– 0.56), len (OR: 0.22, 95%CI: 0.11–0.44), Pom (OR: 0.15, 95%CI: 0.07–0.23), Car (OR: 0.09, 95%CI: 0.04–0.23), Ixa (OR: 0.12, 95%CI: 0.04–0.34), Vorino (OR: 0.12, 95% CI: 0.03–0.47), Pano (OR: 0.17, 95%CI: 0.04–0.69), Elo (OR: 0.11, 95%CI: 0.04–0.27), Dara (OR: 0.06, 95%CI: 0.03–0.16), Isa (OR: 0.06, 95%CI: 0.02–0.19), Sel (OR: 0.11, 95%CI: 0.03–0.47), and Ven (OR: 0.11, 95%CI: 0.02–0.45) all had higher ORRs. Car (OR: 0.41, 95%CI: 0.21–0.82), Dara (OR: 0.29, 95%CI: 0.16–0.53), and Isa (OR: 0.27, 95%CI: 0.10–0.72) had better ORRs than Bor. Dara (OR: 0.29, 95%CI: 0.14–0.59), Isa (OR: 0.27, 95%CI: 0.10–0.76), and Car (OR: 0.41, 95%CI: 0.20– 0.86) had better ORRs than Len. Dara (OR: 0.43, 95% CI: 0.22–0.85), and isa (OR: 0.40, 95%CI: 0.17–0.96) had better ORRs than Pom.

- The ORRs of the 13 kinds of treatments were ranked from best to worst as follows: Dara (86.6%), Isa (85.9%), Car (68.7%), Elo (61.7%), Ven (61.3%), Sel (56.3%), Ixa (55.6%), Vorino (54.5%), Pom (40.8%), Pano (37.1%), Len (21.4%), Bor (20.1%), and Dex (0.1%).

Fazit der Autoren

Our network meta-analysis performed a complete review of the ORRs of all current available novel-drugs based regimens for RRMM. By using the clinical data all from randomized controlled studies, daratumumab- and isatuximab-based treatments were identified to be the best treatments receiving better response quality.

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Minakata D et al., 2023 [7].

Huang ZY et al., 2023 [5].

Efficacy and safety of daratumumab in the treatment of relapsed/refractory multiple myeloma: A meta-analysis of randomized controlled trials.

Fragestellung

to evaluate the clinical outcomes of daratumumab in patients with RRMM and provide a theoretical foundation for the treatment of these patients.

Methodik

Population:

- RRMM

Intervention:

- daratumumab-containing regimens

Komparator:

- non-daratumumab-containing regimens

Endpunkte:

- overall response rate (ORR), complete response (CR) rate, progression-free survival (PFS), or minimal residual disease (MRD) negativity rate

Recherche/Suchzeitraum:

- PubMed, Web of Science, Embase, and Cochrane Central Register of Controlled Trials databases up to December 2022.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- of 5 randomized controlled trials comprising 2003 patients

Charakteristika der Population/Studien:

Main characteristics of the five selected studies in this meta-analysis.

Study, year	Study design	Registration number	Number of patients	Prior lines of therapy	Regimens	Median age, years	Dose of daratumumab, mg
Bahlis et al 2020	RCT	NCT02076009	286:283	≥1	DRd vs Rd	65	16
Dimopoulos et al 2020	RCT	NCT03158688	312:154	≥1	KdD vs Kd	64/64.5	8/16
Dimopoulos et al 2021	RCT	NCT03180736	151:153	≥1	DPd vs Pd	67/68	16
Lu et al 2021	RCT	NCT03234972	141:70	≥1	DVd vs Vd	61	16
Mateos et al 2020	RCT	NCT02136134	251:247	≥1	DVd vs Vd	64	16

DRd = daratumumab + lenalidomide + dexamethasone, DPd = daratumumab + pomalidomide + dexamethasone, DVd = daratumumab + bortezomib + dexamethasone, Kd = carfilzomib + dexamethasone, KdD = carfilzomib + dexamethasone + daratumumab, Pd = pomalidomide + dexamethasone, RCT = randomized clinical trial, Rd = lenalidomide + dexamethasone, Vd = bortezomib + dexamethasone.

Qualität der Studien:

- All 5 studies used random grouping, although 2 did not provide details about the random grouping method and 2 did not describe the allocation hiding method, which may have introduced selective bias. None of the 5 randomized controlled trials used blinding, which could have introduced implementation and measurement bias. Despite these limitations, the research results were considered accurate, reliable, and complete, and no other potential sources of bias were identified upon careful review of the literature.

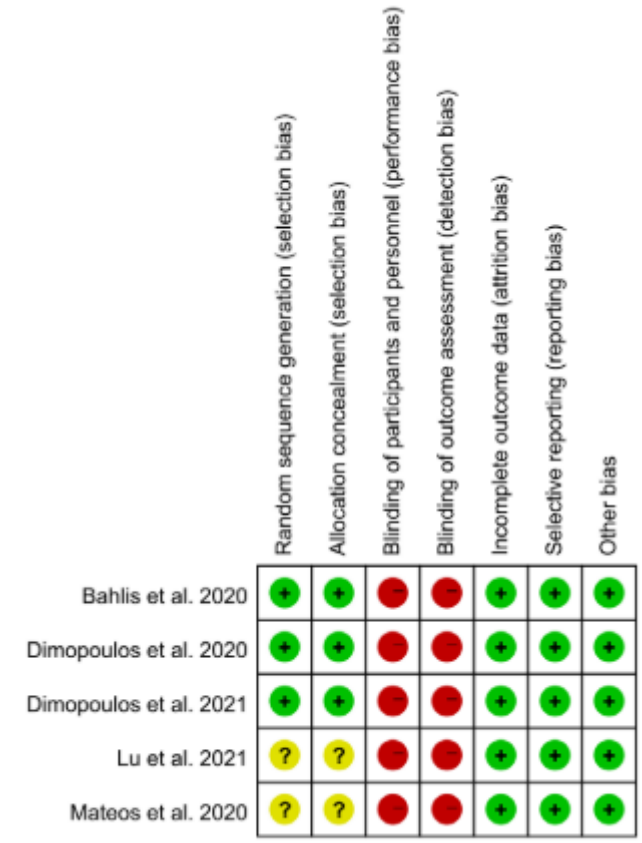


Figure 2. Summary of the risk of bias in the included studies.

Studienergebnisse:

- The results showed that daratumumab-based regimens significantly improved progression-free survival compared to control regimens (hazard ratio = 0.44, 95% CI 0.32–0.60, P < .00001).
- Additionally, daratumumab-based regimens significantly improved overall response rate compared to control regimens (RR = 1.25, 95% CI 1.16–1.36, P < .00001).
- The rate of minimal residual disease was also significantly higher in the daratumumab-based regimens (RR = 6.10, 95% CI 4.09–9.11, P < .00001).
- There was an increased risk of pneumonia, upper respiratory tract infections, and diarrhea in the daratumumab-based regimens.

Fazit der Autoren

In conclusion, our meta-analysis provides evidence that daratumumab-containing regimens are effective in improving the ORR, CR, and PFS in patients with RRMM. However, the increased risk of adverse events associated with daratumumab therapy should not be overlooked and requires careful consideration and management. Moreover, when choosing treatment regimens for RRMM, the head-to-head results of daratumumab compared to other drugs should be taken into account. Further studies are still needed to determine the optimal use of daratumumab in RRMM treatment and to assess its long-term safety and efficacy.

Noori M et al., 2023 [9].

Safety and efficacy of Elotuzumab combination therapy for patients with multiple myeloma: A systematic review and meta-analysis.

Fragestellung

evaluate the efficacy and safety of Elotuzumab, an immunostimulatory monoclonal antibody, in combination with concomitant treatment regimens for multiple myeloma (MM) patients.

Methodik

Population:

- participants were diagnosed with relapsed/refractory multiple myeloma

Intervention/Komparator:

- Elotuzumab along with the concomitant treatments were given to the experimental group, and concomitant treatments alone had been assigned to the control group

Endpunkte:

- overall survival (OS), progression-free survival (PFS), objective response rate (ORR), stringent complete response (sCR)/CR, very good partial response (VGPR), partial response (PR), minor response (MR), stable disease (SD), and progressive disease (PD), as well as safety outcomes

Recherche/Suchzeitraum:

- ubMed, Scopus, Web of Science, and EMBASE databases were searched systematically up to 2 August 2022.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias (RoB 2) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- eight articles comprising five unique trials and three updated follow-up results were included in the final analysis

Charakteristika der Population/Studien:

Table 1. Characteristics of included trials.

First author	Year of publication	Trial name	NCT identifier	Phase	Status of enrolled patients	NO. of patients*	Median age (years)*	Sex (males)*	ECOG performance status*	ISS*	Median treatment cycles*	Intervention treatments	Control treatments
Dimopoulos et al. [25]	2022	ELOQUENT-1	NCT01335399	3	Newly diagnosed/ Untreated MM	374 vs. 374	73 (68–78) vs. 73 (69–78)†	211 vs. 201	0: 134 vs. 0: 135 1: 196 vs. 1: 172 2: 44 vs. 2: 67	I: 114 vs. I: 101 II: 155 vs. II: 170 III: 105 vs. III: 103	26 VS. 21	Elotuzumab/ lenalidomide/ dexamethasone	lenalidomide/ dexamethasone
Usmani et al. [24]	2021	SWOG-1211	NCT01668719	2	Newly diagnosed/ Untreated MM	48 vs. 52	62 (58–69) vs. 66 (56–71)†	29 vs. 31	NA	I: 13 vs. I: 13 II: 20 vs. II: 24 III: 15 vs. III: 15	14 VS. 8	Elotuzumab/ lenalidomide/ bortezomib/ dexamethasone	lenalidomide/ bortezomib/ dexamethasone
Dimopoulos et al. [26,28]	2018 (year of update: 2021)	ELOQUENT-3	NCT02654132	3	Relapsed/ Refractory MM	60 vs. 57	69 (43–81) vs. 66 (36–81)‡	32 vs. 35	NA	I&II: 53 vs. I&II: 50 III: 7 vs. III: 7	9 VS. 5	Elotuzumab/ pomalidomide/ dexamethasone	pomalidomide/ dexamethasone
Jakubowiak et al. [21]	2016	NA	NCT01478048	2	Relapsed/ Refractory MM	77 vs. 75	65 (25–82) vs. 65 (30–85)‡	42 vs. 37	0: 38 vs. 0: 46 1: 35 vs. 1: 23 2: 2 vs. 2: 6	I: 26 vs. I: 19 II: 23 vs. II: 20 III: 11 vs. III: 16	12 VS. 7	Elotuzumab/ bortezomib/ dexamethasone	bortezomib/ dexamethasone
Lonial et al. [22,23,27]	2015 (year of updates: 2018 and 2020)	ELOQUENT-2	NCT01239797	3	Relapsed/ Refractory MM	321 vs. 325	67 (37–88) vs. 66 (38–91)‡	192 vs. 193	0: 159 vs. 0: 145 1: 138 vs. 1: 146 2: 24 vs. 2: 34	I: 141 vs. I: 138 II: 102 vs. II: 105 III: 66 vs. III: 68	19 VS. 14	Elotuzumab/ lenalidomide/ dexamethasone	lenalidomide/ dexamethasone

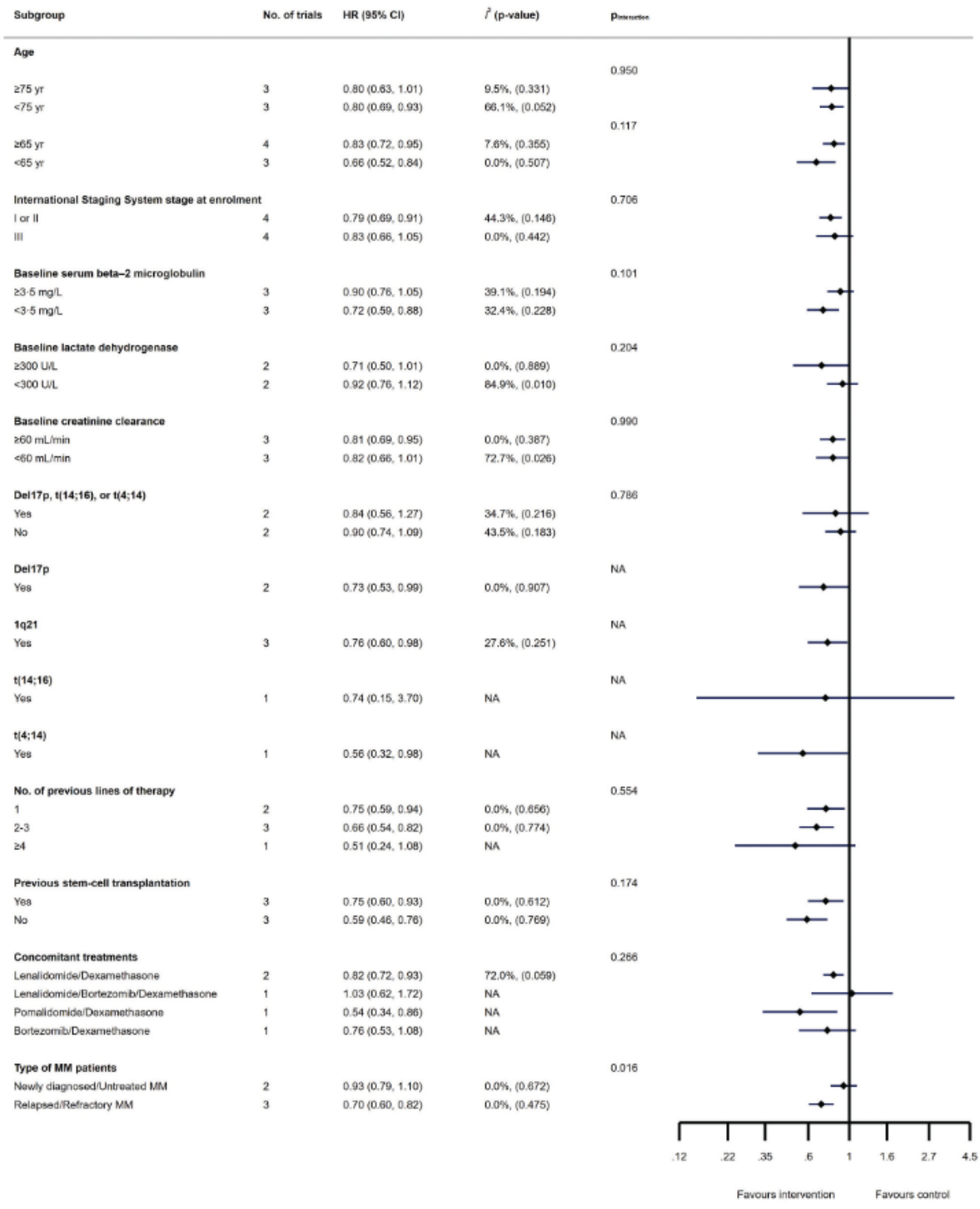
†Median (inter-quartile range [IQR]), ‡Median (range), * Data presented as 'Elotuzumab combination group vs non-Elotuzumab treatment regimen group,' Abbreviations: MM: multiple myeloma, ECOG: eastern cooperative oncology group, ISS: international staging system, NA: not available.

Qualität der Studien:

- Following the assessment of the quality of included trials, all studies were rated as having a high methodological risk of bias. The main domain that downgraded the quality of included trials was the randomization process because all trials were designed as open-label, and participants and investigators were not blinded to the treatments. The other high-risk domain was missing outcome data which was considered an intrinsic feature of time-to-event analyses where censored participants may have affected the final outcomes.

Studienergebnisse:

- PFS:
  - In three trials that examined the effectiveness of Elotuzumab-based treatment according to the prior lines of therapy, patients who had received one line (HR 0.75, 95%CI 0.59–0.94; I2 = 0.0%) or two-three lines (HR 0.66, 95%CI 0.54– 0.82; I2 = 0.0%) of treatments before trial initiation experienced longer PFS in the experimental group compared to the control group. However, patients on four or more prior lines of therapy could not derive benefit from Elotuzomab (HR 0.51, 95%CI 0.24–1.08; I2 = NA). In addition, the PFS benefit did not differ between subgroups (pinteraction: 0.554).
  - Besides, in both groups of patients who had (HR 0.75, 95%CI 0.60–0.93; I2 = 0.0%) or did not have (HR 0.59, 95%CI 0.46–0.76; I2 = 0.0%) previous stem cell transplantation, the PFS substantially improved by receiving Elotuzumab with greater but not significant benefit for those patients that had no history of transplantation (pinteraction: 0.174).
  - Finally, Elotuzumab-based therapy was found to be more effective than non-Elotuzumab-based treatment in improving PFS for relapsed/refractory MM patients (HR 0.70, 95%CI 0.60– 0.82; I2 = 0.0%), while it was not beneficial for newly diagnosed/untreated MM patients (HR 0.93, 95%CI 0.79–1.10; I2 = 0.0%). Notably, a substantial greater PFS benefit was evident in relapsed/refractory MM patients relative to newly diagnosed/untreated MM patients (p interaction: 0.016).



- OS:
  - The pooled results indicated that while one prior line of therapy had no impact on OS (HR 1.00, 95%CI 0.76–1.31; I2 = NA), patients who experienced two-three (HR 0.72, 95% CI 0.57–0.92; I2 = 0.0%) and four or more than four (HR 0.42, 95%CI 0.20–0.89; I2 = NA) lines of prior therapy had significantly longer OS when received Elotuzumab compared to the control group.
  - Interestingly, the level of OS benefit significantly differed between the subgroups of patients, with the greatest benefit being the patients who received ≥4 prior lines of therapy (pinteraction: 0.046). Moreover, in both groups of patients who had undergone stem-cell transplantation (HR 0.83, 95%CI 0.65–1.05; I2 = 0.0%) or had not

had transplantation experience (HR 0.78, 95%CI 0.60–1.00; I2 = 84.1%), the OS was comparable between experimental and control group (pinteraction: 0.724).

- The only concomitant regimen that improved OS in the Elotuzumab group relative to the control group was Pomalidomide plus Dexamethasone (HR 0.59, 95%CI 0.37–0.94; I2 = NA).
- However, concurrent administration of either Lenalidomide plus Dexamethasone (HR 0.90, 95%CI 0.79–1.03; I2= 47.2%), or Lenalidomide plus Bortezomib plus Dexamethasone (HR 0.78, 95%CI 0.40–1.54; I2= NA), or Bortezomib plus Dexamethasone (HR 0.61, 95%CI 0.32–1.16; I2 = NA) regimens along with Elotuzumab had no impact on OS of MM patients. The difference in OS benefit was not significant between the subgroups of concomitant treatments (pinteraction: 0.232).
- Furthermore, relapsed/refractory MM patients showed remarkable longer OS in Elotuzumab group (HR 0.77, 95%CI 0.65–0.91; I2 = 9.0%), while newly diagnosed/ untreated MM patients showed no improvement in OS after Elotuzumab therapy (HR 0.97, 95%CI 0.81–1.17; I2 = 0.0%) (pinteraction: 0.06)

- Safety:
  - Regarding TRAEs, the results of the pooled analysis showed that the rate of serious AEs was substantially higher in the group of Elotuzumab combination therapy relative to the group of non-Elotuzumab treatment regimen (RR 1.12, 95% CI 1.05–1.20; I2 = 47.0%). However, the rate of any AEs (RR 1.01, 95%CI 1.00–1.02; I2 = 37.6%), grade 3–4 AEs (RR 1.03, 95%CI 0.90–1.18; I2 = 73.5%), grade 5 AEs (RR 1.00, 95%CI 0.95–1.07; I2 = 73.5%), AEs led to treatment discontinuation (RR 1.09, 95%CI 0.97–1.22; I2 = 1.9%), and hematologic AEs (RR 0.98, 95%CI 0.91–1.06; I2 = 42.9%) did not differ between experimental and control groups. In the case of AEs of special interest, a higher rate of infection (RR 1.09, 95%CI 1.04–1.16; I2 = 0.0%) and cardiac disorders (RR 1.32, 95%CI 1.12–1.57; I2 = 0.0%) were observed in Elotuzumab group, while the rate of second primary malignancies (RR 0.98, 95%CI 0.48–2.04; I2= 76.2%) was comparable between the two groups

Fazit der Autoren

In conclusion, the constant development of novel treatment approaches in patients with MM in recent years promises a more prolonged survival and lower mortality in these patients. The completion of multiple RCTs on the Elotuzumab combination therapy and the publication of their updated results with long median follow-ups prompted a pooled analysis. Our findings showed that Elotuzumab combination therapy significantly prolongs OS and PFS compared to non-Elotuzumab treatments in patients with MM, particularly those with relapsed/refractory disease. However, further investigations are required to establish the most effective combination of the Elotuzumab regimen, taking patients' drug resistance and comorbidities into account. Moreover, identifying response markers that determine patients more likely to benefit from Elotuzumab therapies could optimize treatment regimen selection for each individual.

3.3 Leitlinien

Leitlinienprogramm Onkologie (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH)), 2022 [3].

Siehe auch: Leitlinienprogramm Onkologie (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH)), 2022 [4]

Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplen Myelom; S3-Leitlinie; Langversion.

Zielsetzung/Fragestellung

Therapie des MM.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Letzte Recherche: 05.04.2019

LoE/GoR

Tabelle 3: Evidenzgraduierung nach GRADE (http://www.gradeworkinggroup.org)

Sicherheit in die Evidenz	Beschreibung	Symbol
Hohe Sicherheit	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.	⊕⊕⊕⊕
Moderate Sicherheit	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.	⊕⊕⊕⊖
Geringe Sicherheit	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.	⊕⊕⊖⊖
Sehr geringe Sicherheit	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.	⊕⊖⊖⊖

Tabelle 4: Schema der Empfehlungsgraduierung

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

Tabelle 5: Konsensstärke

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

Empfehlungen

Wahl der Rezidivtherapie bei >3. Rezidiv

14.12	Konsensbasierte Empfehlung
EK	Bei Patienten mit 4 oder mehr Vortherapien ***sollte*** geprüft werden, ob eine moderne Triplet-Therapie (siehe Kapitel 14.3) nach Stand der Vortherapien sinnvoll und möglich ist.
	Starker Konsens

14.13	Konsensbasierte Empfehlung
EK	Bei Patienten mit 4 oder mehr Vortherapien ***sollte*** geprüft werden, ob „klassische" Chemotherapeutika (Bendamustin, Doxorubicin, Cyclophosphamid) ggf. in Kombination mit neuen Substanzen eingesetzt werden können.
	Starker Konsens

14.14	Konsensbasierte Empfehlung
EK	Bei Patienten mit 4 oder mehr Vortherapien und aggressivem Verlauf ***sollte*** geprüft werden, ob Polychemotherapien (VTD-PACE, DCEP, CVAD, TCID) sinnvoll eingesetzt werden können.
	Starker Konsens

14.15	Konsensbasierte Empfehlung
EK	Unter der Betrachtung der Therapiemöglichkeiten und des individuellen Verlaufs ***kann*** gemeinsam mit dem Patienten auch eine Therapiezieländerung mit Abkehr von einer Myelomspezifischen Therapie und Einsatz von Best Supportive Care beschlossen werden
	Starker Konsens

Mikhael J et al., 2019 [6].

American Society of Clinical Oncology (ASCO)
Treatment of multiple myeloma: ASCO and CCO Joint clinical practice guideline, l Last *Updated: February 6, 2025*

Zielsetzung/Fragestellung

To provide evidence-based recommendations on the treatment of multiple myeloma to practicing physicians and others.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- from 2005 through 2018

LoE/GoR

- GRADE methodology

Recommendations

Relapsed Disease

- 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).
- 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).

- 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).
- 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).
- Recommendation 7.5. Prior therapies should be taken into consideration when selecting the treatment at first relapse. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. Triplet regimens are preferred based on tolerability and comorbidities (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).
- 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 (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).
- Recommendation 8.1. The risk status of the patients should be assessed using the Revised International Staging System for all patients at the time of diagnosis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.2. Repeat risk assessment at the time of relapse should be performed and should include bone marrow with fluorescence in situ hybridization for myeloma abnormalities seen with progression, including 17p and 1q abnormalities. Fluorescence in situ hybridization for primary abnormalities (translocations and trisomies), if seen in the initial diagnostic marrow, does not need to be repeated (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.3. Assessment of other risk factors such as renal insufficiency, age, presence of plasma cell leukemia/circulating plasma cells, extramedullary disease, and frailty, should also be considered/ performed (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.4. In patients with genetic high-risk disease, a triplet combination of PI, immunomodulatory drug, and a steroid should be the initial treatment, followed by one or two ASCTs, followed by a PIbased maintenance until progression (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.5. In patients with renal insufficiency, drugs should be modified based on renal clearance (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.6. In patients with plasma cell leukemia or extramedullary disease, cytotoxic chemotherapy may have a role (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 9.1. The IMWG revised response criteria should be used for response assessment (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

- Recommendation 9.2. All measurable parameters need to be followed, including light and heavy chain analysis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 9.3. All responses excluding marrow and imaging should be confirmed as per IMWG criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 9.4. Response assessment should be performed after one cycle of therapy, and once a response trend is observed, it may be done every other cycle and less frequently once patient is in a plateau (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

National Comprehensive Cancer Network (NCCN), 2024 [8].

Multiple myeloma: NCCN clinical practice guidelines in oncology; Version 01.2025.

Zielsetzung/Fragestellung

Management of MM.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, hinsichtlich der Fragestellung zur aktuellen Therapie für Patienten mit 4 oder mehr Vortherapien, wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium unklar;
- Interessenkonflikte und finanzielle Unabhängigkeit unklar;
- Systematische Suche, Auswahl und Bewertung der Evidenz unklar;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt unklar;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- PubMed database. Suchzeitraum nicht angegeben.

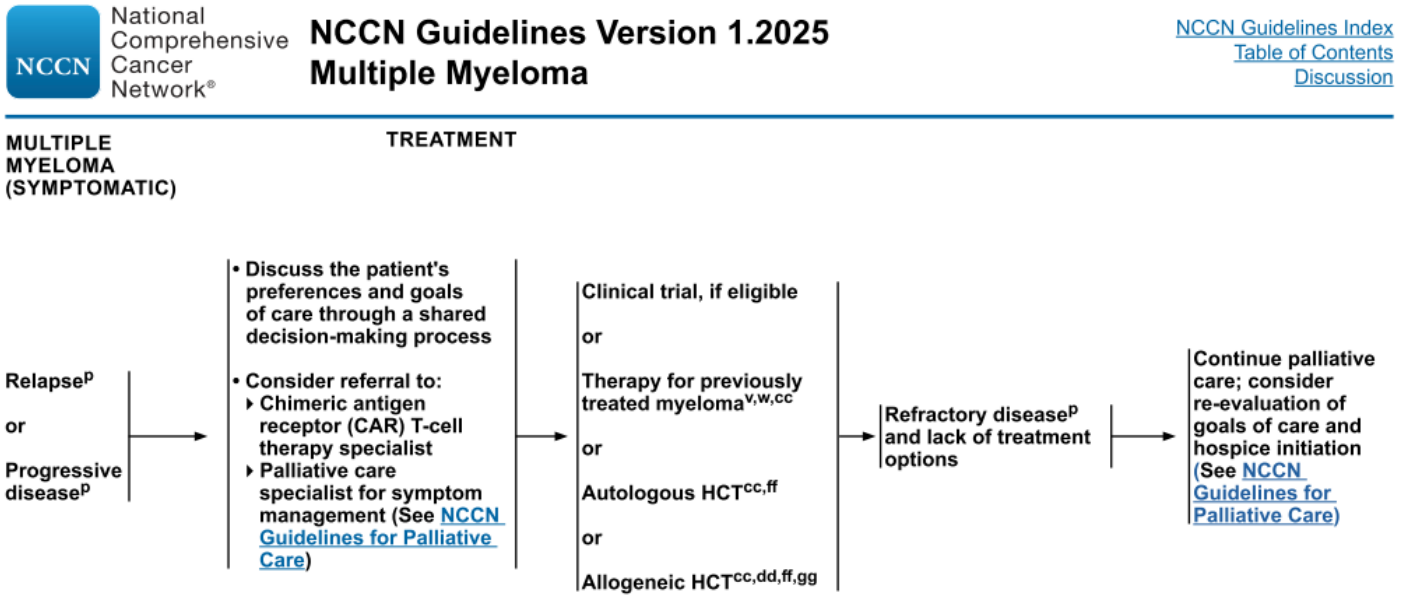
LoE/GoR:

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

Recommendations



[p] Response Criteria for Multiple Myeloma (MYEL-E).
[v] Myeloma Therapy (MYEL-G).
[w] General Considerations for Myeloma Therapy (MYEL-F).
[cc] Folllow up with the tests listed on MYEL-4 under Follow-up/Surveillance.
[dd] Allogeneic HCT should preferentially be done in the context of a trial when possible.
[ff] Assess for HCT candidacy.
[gg] Donor lymphocyte infusion can be considered in patients with disease relapse after allogeneic HCT.

Note: All recommendations are category 2A unless otherwise indicated.

MYEL-6

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THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-o]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Preferred Regimens*
Order of regimens does not indicate comparative efficacy

Anti-CD-38 Refractory	Bortezomib-Refractory	Lenalidomide-Refractory
• Carfilzomib/lenalidomide/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone • Pomalidomide/bortezomib/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Elotuzumab/pomalidomide/dexamethasone ***After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Ixazomib/pomalidomide/dexamethasone	• Carfilzomib/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone ***After one prior therapy including lenalidomide and a PI*** ▸ Daratumumab/pomalidomide/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▸ Elotuzumab/pomalidomide/dexamethasone	• Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Pomalidomide/bortezomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone ***After one prior therapy including lenalidomide and a PI*** ▸ Daratumumab/pomalidomide/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▸ Elotuzumab/pomalidomide/dexamethasone ***After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Ixazomib/pomalidomide/dexamethasone
CAR T-Cell Therapy ***After one prior line of therapy including IMiD and a PI, and refractory to lenalidomide*** ▸ Ciltacabtagene autoleucel (category 1) ***After two prior lines of therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI*** ▸ Idecabtagene vicleucel (category 1)		

* For Other Recommended Regimens and for regimens Useful in Certain Circumstances for Relapsed/Refractory Disease After 1–3 Prior Therapies, see MYEL-G 4 of 5

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[l] Regimens included under 1–3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
[m] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[n] In order to maximize benefit of systemic therapy, agents/regimens may be reconsidered or repeated if relapse is after at least 6 months of stopping therapy.
[o] Alkylating agents can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.

Note: All recommendations are category 2A unless otherwise indicated.

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THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-p] Relapsed/Refractory Disease After 1–3 Prior Therapies	
Other Recommended Regimens	
• Carfilzomib (twice weekly)/dexamethasone (category 1) • Elotuzumab/lenalidomide/dexamethasone (category 1) • Ixazomib/lenalidomide/dexamethasone (category 1) • Selinexor/bortezomib/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Daratumumab/cyclophosphamide/bortezomib/dexamethasone • Daratumumab/carfilzomib/pomalidomide/dexamethasone • Elotuzumab/bortezomib/dexamethasone • Ixazomib/cyclophosphamide/dexamethasone • Lenalidomide/cyclophosphamide/dexamethasone	***After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy*** ▸ Pomalidomide/cyclophosphamide/dexamethasone (category 1)
Useful in Certain Circumstances	
• Bortezomib/dexamethasone (category 1) • Bortezomib/liposomal doxorubicin/dexamethasone (category 1) • Lenalidomide/dexamethasone (category 1) • Carfilzomib/cyclophosphamide/thalidomide/dexamethasone • Carfilzomib (weekly)/dexamethasone • Selinexor/carfilzomib/dexamethasone • Selinexor/daratumumab/dexamethasone • Venetoclax/dexamethasone ± daratumumab or PI only for t(11;14) patients	***After two prior therapies including IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Pomalidomide/dexamethasone (category 1) ▸ Selinexor/pomalidomide/dexamethasone ***For treatment of aggressive MM*** ▸ Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) ▸ Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) ***After at least three prior therapies including a PI and an IMiD or are double-refractory to a PI and an IMiD*** ▸ Daratumumab

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[l] Regimens included under 1–3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
[m] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[n] In order to maximize benefit of systemic therapy, agents/regimens may be reconsidered or repeated if relapse is after at least 6 months of stopping therapy.
[o] Alkylating agents can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.
[p] Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.

Note: All recommendations are category 2A unless otherwise indicated.

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Discussion

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-o] Relapsed/Refractory Disease After 3 Prior Lines of Therapy
Preferred Regimens[q]
▸ ***CAR T-cell Therapy:*** ◊ Ciltacabtagene autoleucel ◊ Idecabtagene vicleucel ***After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD*** ▸ *Bispecific Antibodies:* ◊ Elranatamab-bcmm ◊ Talquetamab-tgvs ◊ Teclistamab-cqyv
Other Recommended Regimens
• Bendamustine • Bendamustine/bortezomib/dexamethasone • Bendamustine/carfilzomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • High-dose or fractionated cyclophosphamide ***After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody*** • Selinexor/dexamethasone
Useful in Certain Circumstances[q]
After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD • Belantamab mafodotin-blmf (if available through compassionate use program)

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[l] Regimens included under 1–3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
[m] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[n] In order to maximize benefit of systemic therapy, agents/regimens may be reconsidered or repeated if relapse is after at least 6 months of stopping therapy.
[o] Alkylating agents can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.
[q] Patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy. Optimal sequencing of sequential BCMA targeted therapies is not known; however accumulated data suggests immediate follow on with second BCMA directed therapy after relapse may be associated with lower response rates

Note: All recommendations are category 2A unless otherwise indicated.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2025) am 14.03.2025

#	Suchschritt
1	[mh "Multiple Myeloma"]
2	((multiple OR (plasma NEXT cell*)) AND (myeloma OR myelomas)):ti,ab,kw
3	((Kahler NEXT disease*) OR myelomatos*s):ti,ab,kw
4	{OR #1-#3} with Cochrane Library publication date from Mar 2020 to Feb 2023
5	{OR #1-#3} with Cochrane Library publication date from Mar 2023 to present

Leitlinien und systematische Reviews in PubMed am 14.03.2025

verwendeter Suchfilter für Leitlinien ohne Änderung:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	Multiple Myeloma[mh]
2	(multiple[tiab] OR plasma-cell[tiab] OR "plasma cells"[tiab]) AND (myeloma[tiab] OR myelomas[tiab])
3	"Kahler Disease*"[tiab] OR myelomatosis[tiab] OR myelomatoses[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	((((#5) AND ("2020/03/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
7	(#4) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR

#	Suchschritt
	overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
8	(((#7) AND ("2020/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
9	(#8) NOT (#6)
10	(#9) AND ("2023/03/01"[PDAT] : "3000"[PDAT])
11	#9 NOT #10

Iterative Handsuche nach grauer Literatur, abgeschlossen am 14.03.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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2. **Costa BA, Costa TA, Chagas GCL, Mouhieddine TH, Richter J, Usmani SZ, et al.** Addition of Elotuzumab to backbone treatment regimens for multiple myeloma: an updated meta-analysis of randomized clinical Trials. Clin Lymphoma Myeloma Leuk 2025;25(1):32-44.
3. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplen Myelom; S3-Leitlinie; Langversion [online]. AWMF-Registernummer 018-035OL. Berlin (GER): Deutsche Krebsgesellschaft (DKG); 2022. [Zugriff: 17.03.2025]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Multiples_Myelom/LL_Multiples_Myelom_Langversion_1.0.pdf.
4. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplen Myelom; S3-Leitlinie; Leitlinienreport [online]. AWMF-Registernummer 018-035OL. Berlin (GER): Deutsche Krebsgesellschaft (DKG); 2022. [Zugriff: 15.03.2025]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Multiples_Myelom/LL_Multiples_Myelom_Leitlinienreport_1.0.pdf.
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6. **Mikhael J, Ismaila N, Cheung MC, Costello C, Dhodapkar MV, Kumar S, et al.** Treatment of multiple myeloma: ASCO and CCO joint clinical practice guideline [online]. 02.2025. Alexandria (USA): 2019. [Zugriff: 20.03.2025]. (American Society of Clinical Oncology (ASCO)). URL: https://www.asco.org/guidelines/GUIDELINEASCO35681.
7. **Minakata D, Fujiwara SI, Yokoyama D, Noguchi A, Aoe S, Oyama T, et al.** Relapsed and refractory multiple myeloma: a systematic review and network meta-analysis of the efficacy of novel therapies. Br J Haematol 2023;200(6):694-703.
8. **National Comprehensive Cancer Network (NCCN).** Multiple myeloma, vers. 1.2025 [online]. 09.2024. Plymouth Meeting (USA): NCCN; 2024. [Zugriff: 17.03.2025]. URL: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.
9. **Noori M, Fayyaz F, Rezaei N.** Safety and efficacy of Elotuzumab combination therapy for patients with multiple myeloma: a systematic review and meta-analysis. Expert Rev Anticancer Ther 2023;23(3):327-338.
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[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO