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: 2024-B-322-z Ciltacabtagen autoleucel

Stand: Januar 2025

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

Ciltacabtagen Autoleucel
[zur Behandlung des refraktären und rezidivierten Multiplen Myeloms]

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.	- Autologe Stammzelltransplantation - Allogene Stammzelltransplantation[1]
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	<u>Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V</u> - 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 – Beschluss vom 4. November 2021 - Idecabtagen vicleucel – Beschluss vom 16. Juni 2022 und 19. September 2024 - Melphalanflufenamid – Beschluss vom 16. März 2023 - Selinexor – Beschluss vom 16. März 2023 - Ciltacabtagen Autoleucel – Beschluss vom 17. August 2023 - Belantamab Mafodotin – Beschluss vom 5. Oktober 2023 - Teclistamab – Beschluss vom 15. Februar 2024 - Talquetamab – Beschluss vom 7. März 2024

[1] Bezüglich der Anwendung der allogenen Stammzelltransplantation gelten die Anforderungen der „Richtlinie des G-BA zur Erprobung der allogenen Stammzelltransplantation bei Multiplem Myelom jenseits der Erstlinientherapie“, des „Beschlusses des Gemeinsamen Bundesausschusses über Maßnahmen zur Qualitätssicherung der allogenen Stammzelltransplantation bei Multiplem Myelom (QS-B SZT MM) bzw. des § 137c SGB V.

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

Ciltacabtagen Autoleucel
[zur Behandlung des refraktären und rezidivierten Multiplen Myeloms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
	- Elranatamab – Beschluss vom 4. Juli 2024
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ciltacabtagen autoleucel L01XL05 Carvykti	Zugelassenes Anwendungsgebiet: Erwachsene Patienten mit rezidiviertem und refraktärem Multiplen Myelom, die zuvor bereits mindestens eine vorherige Therapie erhalten haben, darunter einen Immunmodulator und einen Proteasom-Inhibitor, und die während der letzten Therapie eine Krankheitsprogression zeigten und gegenüber Lenalidomid refraktär sind
Chemotherapien	
Carmustin L01AD01 Carmubris	Carmubris ist zur unterstützenden Behandlung chirurgischer Operationen und Bestrahlungen, oder als Kombinationsbehandlung mit anderen Substanzen bei folgenden Gewebsneubildungen angezeigt: - Multiples Myelom: in Kombination mit anderen Zytostatika und einem Nebennierenrindenhormon, besonders Prednison

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Cyclophosphamid L01AA01 Endoxan	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)
Doxorubicin L01DB01 Adrimedac	Fortgeschrittenes multiples Myelom
Doxorubicin (pegyliert liposomal) L01DB01 Caelyx	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 Alkeran	Multiples Myelom
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	Vincristin-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 Velcade	Bortezomib als Monotherapie oder in Kombination mit pegyliertem, liposomalen Doxorubicin oder Dexamethason ist indiziert für die Behandlung erwachsener Patienten mit progressivem, multiplem 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 Dexamethason alleine zur Behandlung von erwachsenen Patienten mit multiplem Myelom indiziert, die mindestens eine vorangegangene Therapie erhalten haben (siehe Abschnitt 5.1)
Daratumumab L01FC01 Darzalex	Daratumumab 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. - 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 - 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
Elotuzumab L01FX08 Empliciti	Emplicit 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 N.N. 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	- 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 Proteasominhibitor, 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 Revlimid	Revlimid 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
Teclistamab L01FX24 Tecvayli	Tecvayli ist indiziert als Monotherapie für die Behandlung erwachsener Patienten mit rezidiviertem und refraktärem multiplen Myelom, die mindestens drei vorherige Therapien erhalten haben, einschließlich eines Immunmodulators, Proteasom-Inhibitors und Anti-CD38 Antikörpers, und unter der letzte Therapie eine Krankheitsprogression gezeigt haben.
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	
Glucocorticoide	
Dexamethason H02AB02 Dexa-CT	Palliativtherapie maligner Tumoren
Prednisolon H02AB06 Decortin H	Hämatologie / Onkologie: - Akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, chronische lymphatische Leukämie, Morbus Waldenström, multiples Myelom - Palliativtherapie maligner Erkrankungen
Prednison H02AB07 Decortin	Hämatologie / Onkologie: - Akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, chronische lymphatische Leukämie, Morbus Waldenström, multiples Myelom Palliativtherapie maligner Erkrankungen
CAR-T-Zelltherapien	
Idecabtagen vicleucel L01XL07 Abecma[2]	Abecma ist indiziert für die Behandlung des rezidivierten und refraktären multiplen Myeloms bei erwachsenen Patienten, die mindestens drei 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

[2] Derzeit nicht auf dem deutschen Markt verfügbar.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-173 (Ciltacabtagene Autoleucel)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. August 2024

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 remission
CR	Complete response
DKG	Deutsche Krebsgesellschaft
DKH	Deutsche Krebshilfe
ECOG	Eastern Cooperative Oncology Group
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
IgG	Immunglobulin G
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

NMA	Netzwerk Metaanalyse
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 von erwachsenen Patienten mit rezidiviertem/refraktärem Multiplen Myelom.

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.

Die Erstrecherche wurde am 05.10.2023 durchgeführt, die folgende am 01.07.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 794 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. 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 9 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten CR identifiziert.

3.2 Systematische Reviews

Aquino de Moraes FC et al., 2024 [5].

Efficacy and Safety of Anti-CD38 Monoclonal Antibodies in Patients with Relapsed or Refractory Multiple Myeloma: A Meta-Analysis of Randomized Clinical Trials

Fragestellung

How effective is the addition of anti-CD38 monoclonal antibody to dexamethasone and immunomodulatory agent/proteasome inhibitor therapy for the treatment of patients with relapsed or refractory MM?

Methodik

Population:

- adult patients (≥18 years) with documented relapsed or refractory MM
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2

Intervention/Komparator:

- treatment regimens with dexamethasone and immunomodulatory agent/proteasome inhibitor for intervention and **control groups**
- and an anti-CD38 humanized IgG1-κ monoclonal antibody for the **intervention group** only

Endpunkte:

- The outcomes of interest were **PFS; OS;**
- patients with any grade and, in another analysis, grade ≥ 3 of (3) anemia; (4) febrile neutropenia; (5) lymphopenia; (6) neutropenia; (7) thrombocytopenia; (8) arthralgia; (9) asthenia; (10) back pain; (11) bronchitis; (12) constipation; (13) cough; (14) diarrhea; (15) dyspnea; (16) fatigue; (17) hypertension; (18) insomnia; (19) nausea; (20) peripheral edema; (21) pneumonia; (22) pyrexia; and (23) upper respiratory tract infection.

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library were searched on 29 January 2024.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool for randomized trials (RoB-2) Ergebnisse

Anzahl eingeschlossener Studien:

N=6 RCTs (n=2191 Patienten)

Charakteristika der Population/Studien:

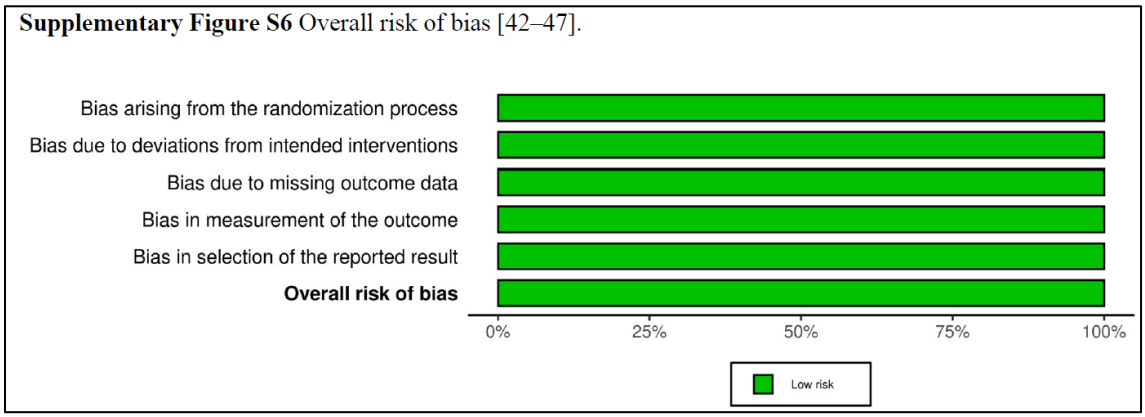
A total of 1162 patients with relapsed or refractory MM were randomized to receive anti-CD38 monoclonal antibodies and 1029 patients were assigned to the control group. The majority of patients had an ECOG performance status score of 0 (770 patients) and 811 patients had an ECOG ≥ 1.

Table 1. Design and characteristics of studies included in the meta-analysis.

Study	Designs	Sample Size	Intervention	Age †	Sex Male/Female	Race	ECOG Status, No (%)	Prior Lines of Therapy	International Staging System Disease Stage	Type of Measurable MM IgG/Non-IgG
APOLLO, 2021 [42]	RCT-phase III	IG:151 CG:153	IG: Daratumumab + polamalidomide + dexamethasone CG: Pomalidomide + dexamethasone	IG: 67 (42–86) CG: 68 (35–90)	IG: 79/72 CG: 82/71	IG: White-135 (89%); Non-white-16 (11%) CG: White-137 (90%); Non-white-16 (10%)	IG: 0–91 (60%); ≥1–60 (40%); CG: 0–77 (50%); ≥1–76 (50%)	IG: 1–16 (11%); 2/3–114 (75%); ≥4–21 (14%) CG: 1–18 (12%); 2/3–113 (74%); ≥4–22 (14%)	IG: I-68 (45%); II-50 (33%); III-33 (22%) CG: I-69 (45%); II-51 (33%); III-33 (22%)	IG: IgG-62 (41%); Non-IgG-89 (59%) CG: IgG-63 (41%); Non-IgG-90 (59%)
CASTOR, 2023 [47]	RCT-phase III	IG:251 CG:247	IG: Daratumumab + bortezomib + dexamethasone CG: Bortezomib + dexamethasone	Overall:64 (30–88)	IG:137/114 CG:148/99	IG: White-216 (86%); Non-white-35(14%) CG: White-219 (88%); Non-white-28 (12%)	IG: 0–106 (42%); ≥1–144 (58%); Not reported: 1 CG: 0–116 (47%); ≥1–131 (53%)	IG: 1–122 (48.6%); 2/3–107 (42.6%); ≥4–22 (9.2%) CG: 1–113 (45.7%); 2/3–106 (42.9%); ≥4–28 (11.4%)	IG: I-98 (39%); II-94 (37%); III-59 (24%) CG: I-96 (39%); II-100 (40%); III-42 (21%)	IG: IgG-125 (67%); Non-IgG-61 (33%); Unknown: 65 CG: IgG-138 (70%); Non-IgG-58 (30%); Unknown: 51
ICARIA-MM, 2022 [43]	RCT-phase III	IG:154 CG:153	IG: Isatuximab + pomalidomide + dexamethasone CG: Pomalidomide + dexamethasone	IG:68 CG:66	IG:89/65 CG:70/83	NA	NA	NA	IG: I-64 (42%); II-53 (34%); III-34 (22%); Unknown-3 (2%) CG: I-51 (33%); II-56 (37%); III-26 (14.5%); Unknown-1 (0.6%)	IG: IgG-102 (66%); Non-IgG-52 (34%) CG: IgG-100 (65%); Non-IgG-53 (35%)
IKEMA, 2023 [44]	RCT-phase III	IG:179 CG:123	IG: Isatuximab + carfilzomib + dexamethasone CG: Carfilzomib + dexamethasone	IG:65 (37–86) CG:63 (33–90)	NA	NA	NA	IG: 1–79 (44.1%); 2/3–97 (55.9%); ≥4–0 CG: 1–55 (44.7%); 2/3–66 (55.3%); ≥4–0	IG: I-89 (49.7%); II-63 (35.2%); III-34 (22%); Unknown-3 (2%) CG: I-71 (57.7%); II-31 (25.2%); III-20 (16.3%); Unknown-1 (0.8%)	NA
LEPUS, 2021 [45]	RCT-phase III	IG:141 CG:70	IG: Daratumumab + bortezomib + dexamethasone CG: Bortezomib + dexamethasone	IG:61.0 (28–79) CG:61.0 (43–82)	IG:85/56 CG:42/28	NA	IG: 0–64 (45.4%); ≥1–77 (54.6%); CG: 0–27 (38.6%); ≥1–43 (61.4%);	IG: 1–41 (29.1%); 2/3–70 (49.6%); ≥4–30 (21.3%) CG: 1–19 (27.1%); 2/3–33 (47.1%); ≥4–18 (25.7%)	IG: I-72 (51.1%); II-45 (31.9%); III-24 (17%) CG: I-34 (48.6%); II-22 (31.4%); III-14 (20%)	IG: IgG-52 (36.9%); Non-IgG-89 (63.1%) CG: IgG-28 (40%); Non-IgG-42 (60%)
POLLUX, 2023 [46]	RCT-phase III	IG:286 CG:283	IG: Daratumumab + lenalidomide + dexamethasone CG: lenalidomide + dexamethasone	IG:65.0 (34–89) CG:65.0 (42–87)	IG:173/113 CG:164/119	IG:: White-207 (72.4)%); Non-white-79 (27.6%) CG: White-186 (65.7%); Non-white-97 (34.3%)	IG: 0–139 (48.6%); ≥1–147 (51.4%); CG: 0–150 (53%); ≥1–133 (47%);	IG: 1–149 (52%); 2/3–123 (43%); ≥4–14 (5%) CG: 1–146 (51%); 2/3–118 (41.7%); ≥4–19 (7.3%)	IG: I-137 (48%); II-93 (32.5%); III-56 (19.5%) CG: I-140 (49.5%); II-86 (30.4%); III-57 (20.1%)	G: IgG-151 (73.6%); Non-IgG-54 (26.4%); Unknown: 81 CG: IgG-158 (74.9%); Non-IgG-53 (25.1%); Unknown: 72

† Median (range). CG, control group; ECOG, Eastern Cooperative Oncology Group; IG, interventional group; MM, multiple myeloma; RCT, randomized controlled trial.

Qualität der Studien:



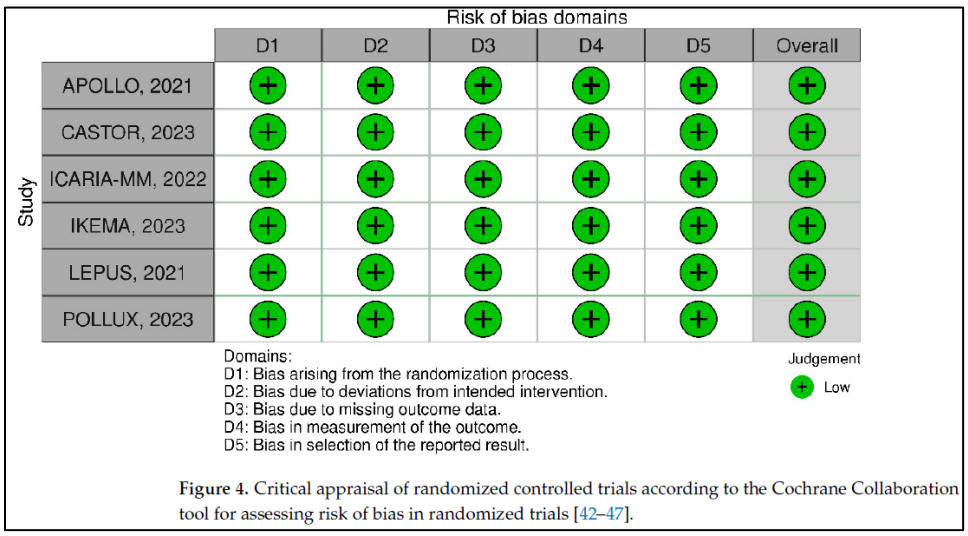


Figure 4. Critical appraisal of randomized controlled trials according to the Cochrane Collaboration tool for assessing risk of bias in randomized trials [42–47].

Studienergebnisse:

Progression-Free Survival

- PFS was evaluated in six RCTs, comprising a total of 2191 patients. Anti-CD38 monoclonal antibodies significantly improved PFS compared to the control group (HR 0.52, 95% CI 0.43–0.61; $p < 0.001$; $I2 = 57\%$).

Overall Survival

- OS was evaluated in four RCTs, comprising a total of 1562 patients. Anti-CD38 monoclonal antibodies significantly improved OS compared to the control group (HR 0.72, 95% CI 0.63–0.83; $p < 0.001$; $I2 = 31\%$;).

Adverse Events

Table 2. Adverse events of any grade.

Adverse Events	Events/Total Intervention	Events/Total Control	RR	95% CI	*p*-Value
Hematological adverse events					
Anemia	543/1144	434/1007	0.99	0.90–1.09	0.83
Febrile neutropenia	49/584	17/580	2.83	1.60–4.87	<0.01
Lymphopenia	155/815	73/736	1.62	0.96–2.74	0.07
Neutropenia	606/1144	376/1007	1.41	1.26–1.58	<0.01
Thrombocytopenia	607/1144	425/1007	1.14	1.02–1.27	0.02
Non-hematological adverse events					
Arthralgia	180/855	101/789	1.69	1.07–2.69	0.03
Asthenia	181/1004	168/939	1.00	0.81–1.24	0.97
Back pain	205/855	135/789	1.38	1.05–1.82	0.02
Bronchitis	187/855	97/789	1.89	1.30–2.75	<0.01
Constipation	199/818	164/735	1.01	0.71–1.43	0.96
Cough	246/843	98/708	2.19	1.77–2.70	<0.01
Diarrhea	458/1144	281/1007	1.41	1.23–1.63	<0.01
Dyspnea	198/855	102/789	1.72	1.38–2.13	<0.01
Fatigue	303/1004	218/939	1.36	0.97–1.91	0.08
Hypertension	124/560	54/427	2.38	0.81–6.99	0.11
Insomnia	198/843	139/708	1.20	0.99–1.45	0.07
Nausea	147/678	94/667	1.55	1.23–1.95	<0.01
Peripheral edema	151/678	88/667	1.70	1.27–2.28	<0.01
Pneumonia	263/1144	175/1007	1.34	1.13–1.59	<0.01
Pyrexia	222/967	122/885	1.63	1.33–1.99	<0.01
Upper respiratory tract infection	423/1144	224/1007	1.64	1.43–1.89	<0.01

Table 3. Adverse events of grade ≥ 3.

Adverse Events	Events/Total Intervention	Events/Total Control	RR	95% CI	*p*-Value
Hematological adverse events					
Anemia	205/1144	173/1007	1.00	0.81–1.24	0.99
Febrile neutropenia	49/584	17/580	2.83	1.65–4.87	<0.01
Lymphopenia	121/815	43/736	2.13	1.24–3.64	<0.01
Neutropenia	455/1144	276/1007	1.64	1.33–2.01	<0.01
Thrombocytopenia	330/1144	225/1007	1.25	1.08–1.44	<0.01
Non-hematological adverse events					
Arthralgia	15/855	7/789	1.62	0.65–4.04	0.30
Asthenia	29/1004	23/939	1.08	0.52–2.22	0.84
Back pain	23/855	11/789	1.98	0.97–4.04	0.06
Bronchitis	27/855	14/789	1.78	0.83–3.84	0.14
Constipation	4/818	4/735	0.88	0.10–7.90	0.91
Cough	1/843	2/708	0.52	0.02–14.73	0.70
Diarrhea	63/1144	25/1007	1.95	1.10–3.47	0.02
Dyspnea	42/855	7/789	5.32	2.39–11.84	<0.01
Fatigue	71/1004	46/939	1.86	1.19–2.91	<0.01
Hypertension	75/560	32/427	2.94	0.62–13.96	0.18
Insomnia	20/843	12/708	1.30	0.62–2.71	0.48
Nausea	8/678	2/667	3.31	0.81–13.56	0.10
Peripheral edema	6/678	4/667	1.25	0.36–4.27	0.73
Pneumonia	173/1144	117/1007	1.31	1.06–1.63	0.01
Pyrexia	19/967	12/885	1.47	0.73–2.98	0.28
Upper respiratory tract infection	44/1144	22/1007	1.97	1.02–3.79	0.04

Fazit der Autoren

In this systematic review and meta-analysis involving six RCTs and 2191 patients, we compared dexamethasone and immunomodulatory agent/proteasome inhibitor for both intervention and control groups and an anti-CD38 humanized IgG1-κ monoclonal antibody intervention for Relapsed or Refractory Multiple Myeloma. The main results of the pooled analyses were as follows: (1) PFS was better in patients in the anti-CD38 group; (2) OS showed a significant difference in favor of the anti-CD38 group; and (3) adverse events grade ≥ 3 such as neutropenia, thrombocytopenia, diarrhea, dyspnea, and pneumonia occurred in a significantly higher proportion of patients in the anti-CD38 group compared to the control.

This is the first meta-analysis of randomized clinical trials to evaluate the efficacy and safety of anti-CD38 therapy for the treatment of patients with relapsed or refractory multiple myeloma. Our results suggest that this therapy represents a potential treatment option, and its application in clinical practice should be encouraged.

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

- Ye L et al [9] basiert auf den gleichen Studien

Huang ZY et al., 2023 [1].

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
- Adults

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:

- N=5 RCTs(n=2003 patients)

Charakteristika der Population/Studien:

Table 1

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:

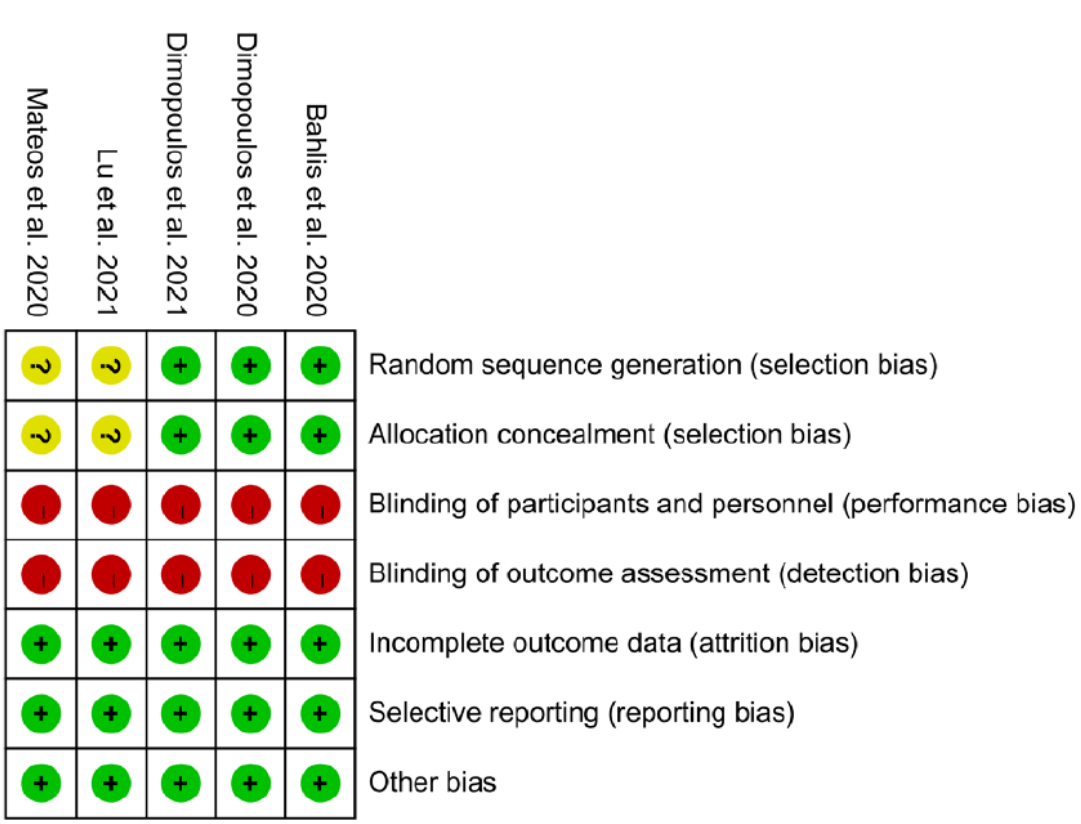


Figure 2. Summary of the risk of bias in the included studies.

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.

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

- Kiss, S. et al., 2021 [2].

Yang TL et al., 2023 [8].

Progression-Free Survival Efficacy in Refractory/Relapsed Multiple Myeloma among Elderly Patients: A Systematic Review

Fragestellung

While combination therapies show greater efficacy than traditional methods, limited research has targeted elderly patients who might be less resilient to treatments. Our study aimed to evaluate treatment efficacy for these elderly patients.

Thus, a network meta-analysis (NMA) of RCTs comparing the treatment efficacy for the elderly R/R MM population is necessary and of interest.

Methodik

Population:

- patients diagnosed with R/R MM
- For the purpose of our study, ‘elderly’ is broadly defined to include patients aged 65 and above. This range encompasses both the conventional definition of ‘elderly’ and extends to an older subgroup to account for variations in study designs that we came across.

Intervention/Komparator:

- The **experimental arm** of the studies involved patients receiving a nontraditional or new regimen,
- while the **control arm** included patients receiving a standard regimen for R/R MM.

Endpunkte:

- PFS
- OS

Recherche/Suchzeitraum:

- systematic literature search was from 1 January 2000 to 31 December 2022 (PubMed, Cochrane etc).

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

- An NMA was conducted to compare 14 different therapy options for PFS in R/R MM patients [19]. Dexamethasone was used as the reference treatment, and hazard risk (HR) with 95% confidence intervals (CIs) was calculated using the random-effect frequentist NMA following UK NICE guidance
- We assessed the assumption of network transitivity by visually examining tables containing patient characteristics. Incongruencies between direct and indirect effects within a single comparison in the network could result in potential inconsistencies. To identify such inconsistencies, we used a random-effects design-by-treatment interaction model and a node-splitting technique for each comparison

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 RCTs (3337 participants).

Charakteristika der Population/Studien:

Table 1. Basic characteristics of included randomized trials.

Trial Name/First Author	Number of Patients	Treatment Arm A	Treatment Arm B	Cut-Off Level of Age	Primary Objective
CASTOR (NCT02136134)	241	DaraBorDex	BorDex	65	PFS
ELOQUENT-2 (NCT01239797)	370	EloLenDex	LenDex	65	PFS
MM-003 (NCT01311687)	36	PomDex	Dex	75	PFS
PANORAMA1 (NCT01023308)	323	PanoBorDex	BorDex	65	PFS
POLLUX (NCT02076009)	296	DaraLenDex	LenDex	65	PFS
ENDEAVOR (NCT01568866)	496	CarDex	BorDex	65	PFS
VANTAGE 088 (NCT00773747)	256	VorinoBor	Bor	65	PFS
ASPIRE (NCT01080391)	393	CarLenDex	LenDex	65	PFS
Orlowski (NCT00103506)	250	Bor	PegDoxBor	65	TTP
Jakubowiak (NCT01478048)	85	EloBorDex	BorDex	65	PFS
MM-009 (NCT00056160) MM-010 (NCT00424047)	314	Dex	Dex	65	PFS
APEX (NCT00048230)	245	Bor	Dex	65	TTP
Tourmaline-MM1(NCT01564537)	32	IxaLenDex	LenDex	65	PFS

Qualität der Studien:

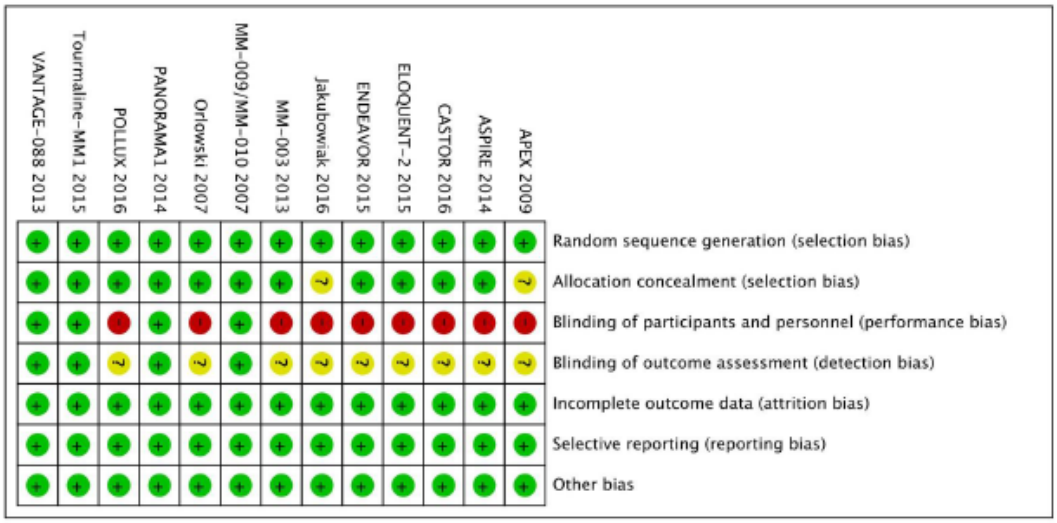


Figure S1. Risk of Bias Summary.

Studienergebnisse:

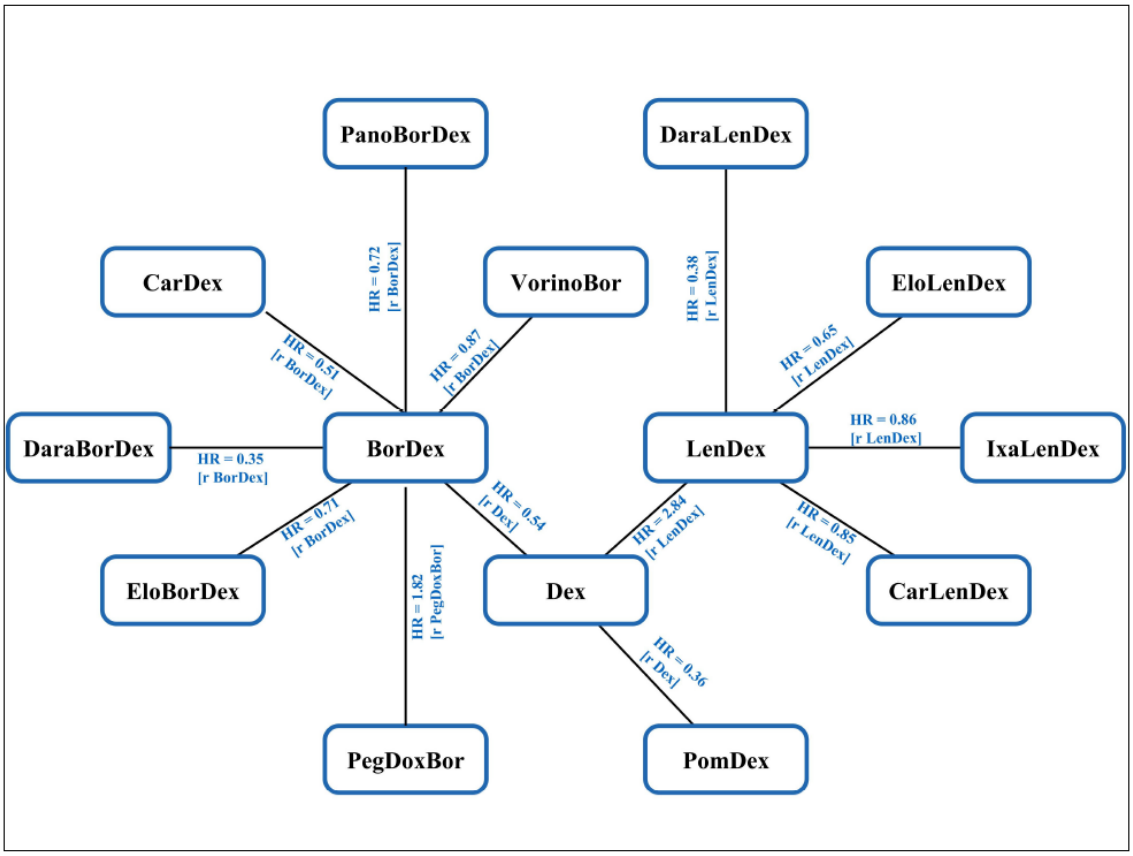


Figure 2. Visual representation illustrating the evidence network utilized in NMA. Directly comparable treatments are linked with a line. Parentheses indicate the reference treatment. Square brackets present the number of directly comparable trials. The HR of PFS is highlighted in blue and the r indicates reference. BorDex, bortezomib + dexamethasone; Dex, dexamethasone; LenDex, lenalidomide + dexamethasone; CarLenDex, carfilzomib + lenalidomide + dexamethasone; IxaLenDex, ixazomib + lenalidomide + dexamethasone; EloLenDex, elotuzumab + lenalidomide + dexamethasone; DaraLen- Dex, daratumumab + lenalidomide + dexamethasone; PomDex, pomalidomide + dexamethasone; VorinoBor, vorinostat + bortezomib; PanoBorDex, panobinostat + bortezomib + dexamethasone; CarDex, carfilzomib + dexamethasone; DaraBorDex, daratumumab + bortezomib + dexamethasone; EloBorDex, elotuzumab + bortezomib + dexamethasone; PegDoxBor, pegylated liposomal doxorubicin + bortezomib

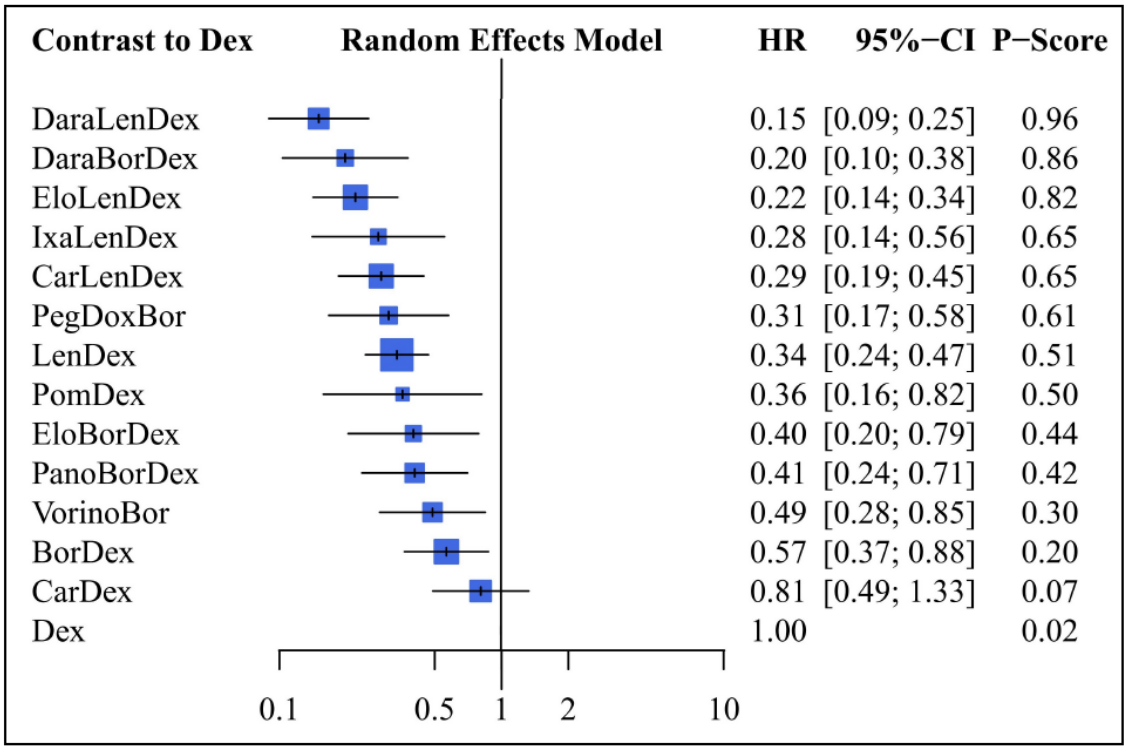


Figure 3. NMA results of treatment efficacy in PFS in R/R MM patients. HR, hazard ratio; P-score indicates the SUCRA (surface under the cumulative ranking curve); CI, confidence interval; BorDex, bortezomib + dexamethasone; Dex, dexamethasone; LenDex, lenalidomide + dexamethasone; Car- LenDex, carfilzomib + lenalidomide + dexamethasone; IxaLenDex, ixazomib + lenalidomide + dexamethasone; EloLenDex, elotuzumab + lenalidomide + dexamethasone; DaraLenDex, daratumumab + lenalidomide + dexamethasone; PomDex, pomalidomide + dexamethasone; VorinoBor, vorinostat + bortezomib; PanoBorDex, panobinostat + bortezomib + dexamethasone; CarDex, carfilzomib + dexamethasone; DaraBorDex, daratumumab + bortezomib + dexamethasone; EloBorDex, elotuzumab + bortezomib + dexamethasone; PegDoxBor, pegylated

Anmerkung/Fazit der Autoren

In conclusion, our network meta-analysis provides valuable information on the efficacy of various treatment options for refractory/relapsed multiple myeloma in elderly patients. Our findings suggest that the three-drug regimen of daratumumab, lenalidomide, and dexamethasone is the treatment with the highest efficacy for prolonging progression-free survival in this patient population.

Kommentare zum Review

Eingeschlossen wegen spezifischen Informationen zu älteren Patienten

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Noori M et al., 2023 [7].

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:

- relapsed/refractory multiple myeloma

Intervention/Komparator:

- Elotuzumab along with the concomitant treatments
- concomitant treatments alone

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:

- PubMed, 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:

- Five RCTs

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 (p interaction: 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%) (p interaction: 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.

Version 1.0 – Februar 2022

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 (Die Gültigkeitsdauer beträgt maximal 5 Jahre)

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

14.4	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Die Therapie im Rezidiv ***sollte,*** in Abhängigkeit des initialen Ansprechens, der Verträglichkeit, der Toxizität und des Patientenwunschs, bis zum Progress fortgeführt werden.
GRADE ⊕⊕⊖⊖ ⊕⊕⊖⊖	[450]; [146]; [451] Gesamtüberleben Progressionsfreies Überleben Unerwünschte Ereignisse und Lebensqualität: Not reported
	Starker Konsens

Wahl der Rezidivtherapie (1.-3. Rezidiv)

14.6	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	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.
GRADE ⊕⊕⊕⊕ ⊕⊕⊕⊕ ⊕⊕⊕⊕	[408]; [393]; [445]; [446]; [447]; [455]; [448]; [456]; [457]; [458]; [459]; [460]; [461]; [462]; [463]; [464]; [465]; [466]; [449] Gesamtüberleben Progressionsfreies Überleben Unerwünschte Ereignisse Lebensqualität: Not reported
	Starker Konsens
14.7	**Evidenzbasierte Empfehlung**
Empfehlungsgrad **B**	Eine autologe Stammzelltransplantation ***sollte*** allen transplantationsfähigen Patienten angeboten werden, bei denen keine Transplantation im Rahmen der Erstlinientherapie durchgeführt wurde.
GRADE ⊕⊕⊖⊖ ⊕⊕⊕⊖ ⊕⊕⊕⊖	[475] Gesamtüberleben Progressionsfreies Überleben Unerwünschte Ereignisse Lebensqualität: Not reported
	Starker Konsens

14.8	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Eine autologe Re-Transplantation ***kann*** erfolgen, wenn das progressionsfreie Überleben nach erster Transplantation in der Regel mindestens 18 Monate andauerte.
GRADE ⊕⊕⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖	[476]; [279]; [477]; [478]; [137]; [479]; [480] Gesamtüberleben Progressionsfreies Überleben Unerwünschte Ereignisse Lebensqualität: Not reported
	Starker Konsens

14.9	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Fitte Patienten mit frühem Rezidiv nach autologer Stammzelltransplantation, ***kann*** eine allogene Stammzelltransplantation angeboten werden.
GRADE ⊕⊕⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖	[375]; [373]; [478] Gesamtüberleben Progressionsfreies Überleben Unerwünschte Ereignisse Lebensqualität: Not reported
	Starker Konsens

14.11	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Patienten, bei denen eine allogene Stammzelltransplantation durchgeführt werden soll und bei denen kein verwandter Spender verfügbar ist, ***können*** auch von nicht verwandten HLA-kompatiblen Fremdspendern transplantiert werden.
GRADE ⊕⊖⊖⊖ ⊕⊖⊖⊖ ⊕⊖⊖⊖	[492]; [493] Gesamtüberleben Progressionsfreies Überleben Unerwünschte Ereignisse Lebensqualität: Not reported
	Starker Konsens

Wahl der Rezidivtherapie bei >3. Rezidiv (Ausschnitte)

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

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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 Lenalidomid refraktärem MM, wird die LL ergänzend dargestellt.

[*] *NCCN - Development and Update of Guidelines: https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines*

- Grundlage der Leitlinie
- Repräsentatives Gremium - **unklar**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt - **unklar**
- Systematische Suche, Auswahl und Bewertung der Evidenz – **trifft teilweise** zu *(Siehe Recherche/Suchzeitraum)*
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – **trifft teilweise zu** *(formaler Konsensusprozess dargelegt, nur internes Begutachtungsverfahren)* [*]
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – **trifft zu**

Regelmäßige Überprüfung der Aktualität gesichert – **trifft zu** *(All active NCCN Guidelines are reviewed and updated at least annually; Hintergrundtext wird zurzeit überarbeitet (Discussion update in progress)* [*]

Recherche/Suchzeitraum:

- Prior to the annual update of the NCCN Guidelines for Multiple Myeloma, an electronic search of the PubMed database was performed to obtain key literature published since the previous update, using the following search terms: Smoldering Multiple Myeloma, Solitary Plasmacytoma, Multiple Myeloma, Monoclonal Gammopathy of Undetermined

Significance, and POEMS syndrome. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

- The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; MetaAnalysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lowerlevel evidence and expert opinion.

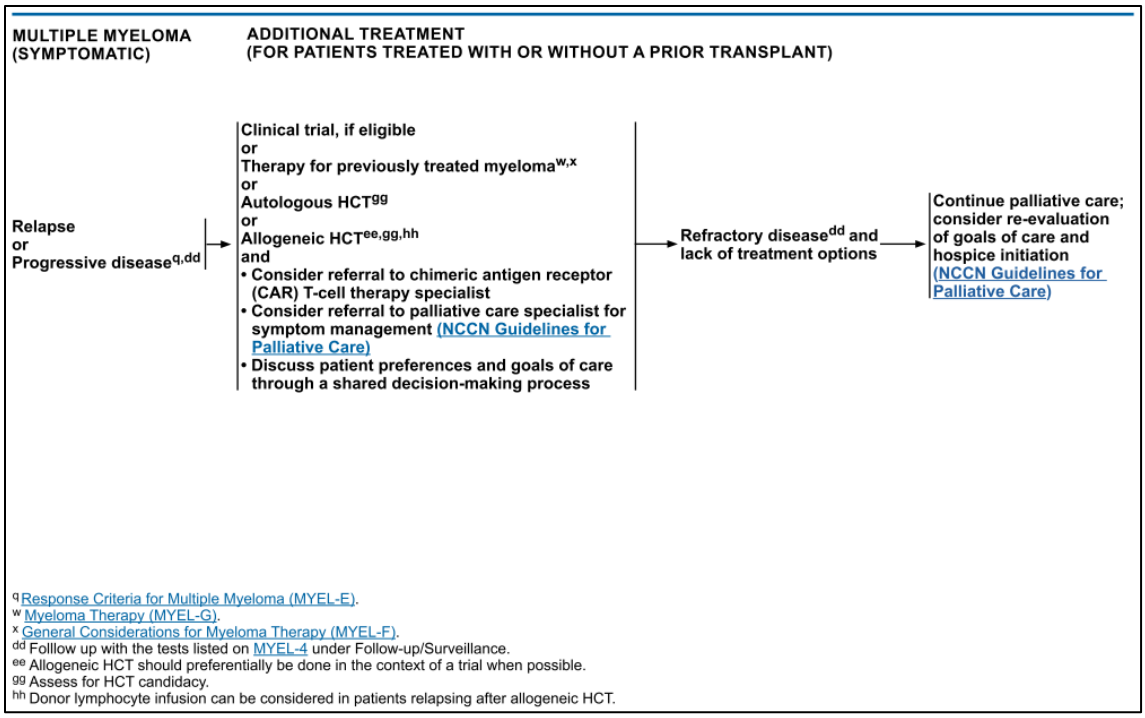
LoE/GoR:

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



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

Preferred Regimens*
Order of regimens does not indicate comparative efficacy

Bortezomib-Refractory[p]	Lenalidomide-Refractory[p]
• 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)	• Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Pomalidomide/bortezomib/dexamethasone (category 1) • Selinexor/bortezomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone • Elotuzumab/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) *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 therapy including IMiD and a PI, and refractory to lenalidomide
‣ Ciltacabtagene autoleucel (category 1)

After two prior 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).
[n] 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.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[p] Regimens without anti-CD38 should be considered for those refractory to anti-CD38 antibody as long as they have not received or are refractory to other agents in the regimen.
[q] If relapse occurs >6 months after stopping treatment, the primary regimen could be considered.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

MYEL-G

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-r]
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) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Daratumumab/cyclophosphamide/bortezomib/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

Useful in Certain Circumstances

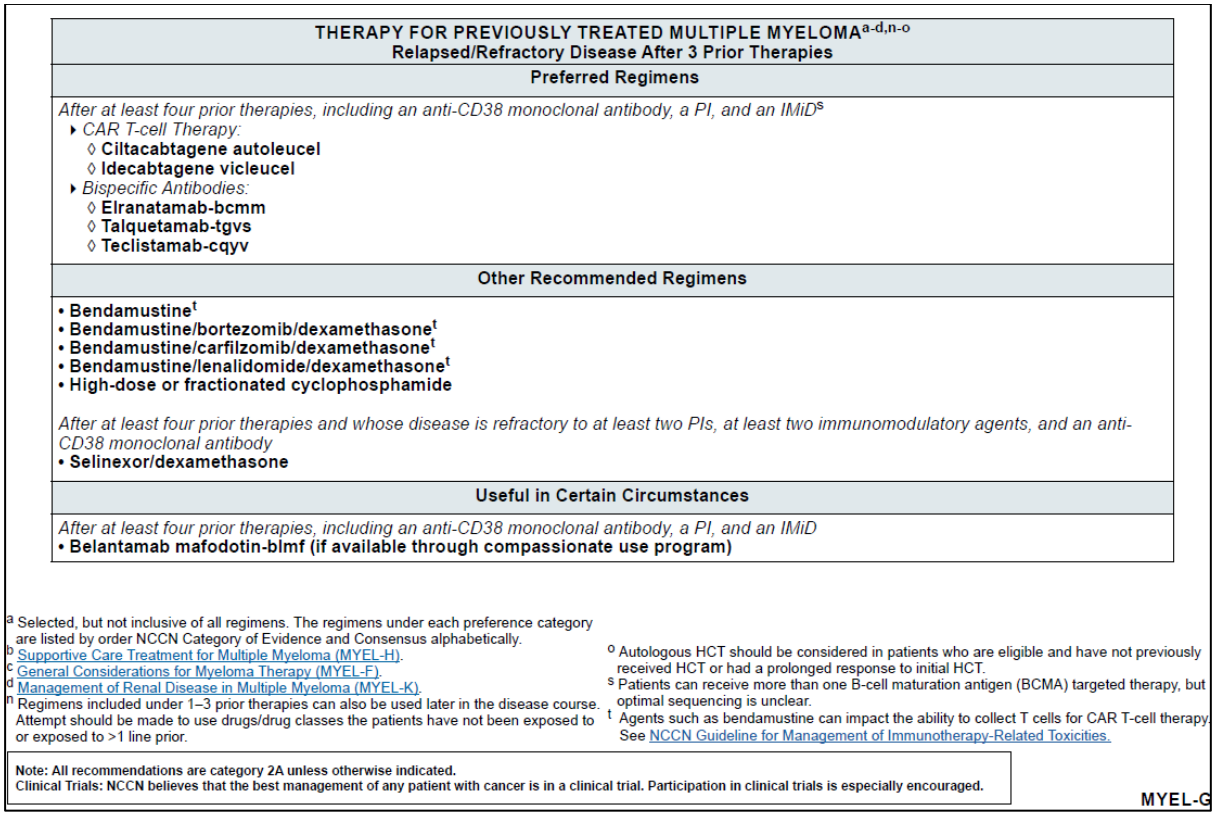
• Bortezomib/dexamethasone (category 1) • Bortezomib/liposomal doxorubicin/dexamethasone (category 1) • Lenalidomide/dexamethasone (category 1) • Carfilzomib/cyclophosphamide/thalidomide/dexamethasone • Carfilzomib (weekly)/dexamethasone • Selinexor/carfilzomib/dexamethasone • Selinexor/daratumumab/dexamethasone • 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) ‣ Ixazomib/pomalidomide/dexamethasone ‣ 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).
[n] 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.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[q] If relapse occurs >6 months after stopping treatment, the primary regimen could be considered.
[r] Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

MYEL-G



THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o] Relapsed/Refractory Disease After 3 Prior Therapies
Preferred Regimens
After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD[s] ▸ *CAR T-cell Therapy:* ◊ **Ciltacabtagene autoleucel** ◊ **Idecabtagene vicleucel** ▸ *Bispecific Antibodies:* ◊ **Elranatamab-bcmm** ◊ **Talquetamab-tgvs** ◊ **Teclistamab-cqyv**
Other Recommended Regimens
• **Bendamustine[t]** • **Bendamustine/bortezomib/dexamethasone[t]** • **Bendamustine/carfilzomib/dexamethasone[t]** • **Bendamustine/lenalidomide/dexamethasone[t]** • **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
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).
[n] 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.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[s] Patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy, but optimal sequencing is unclear.
[t] Agents such as bendamustine 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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MYEL-G

Hintergrund

Therapy for Previously Treated Multiple Myeloma

A variety of therapies are available for previously treated or relapsed/refractory MM. The choice of appropriate therapy for a specific patient depends on the context of clinical relapse such as prior treatment and duration of response.

The therapeutic options for previously treated MM include systemic therapy; autologous hematopoietic cell transplant (HCT) for eligible patients who did not receive HCT as part of their initial treatment; or clinical trial. For those who had autologous HCT as part of initial treatment and had a durable response or had stable disease, consideration may be given to a second transplantation at the time of relapse/disease progression. As a general principle, if the relapse occurs at greater than 6 months after completion of the initial primary therapy, patients may be retreated with the same primary regimen. This however does not apply to HCT where a longer remission would be needed to justify another transplant.

Preferred Regimens for Previously Treated Multiple Myeloma – After One to Three Prior Therapies

For patients that are still sensitive to bortezomib and/or lenalidomide, any of the regimens listed below may be appropriate. Since, however, bortezomib-containing or lenalidomide-containing regimens are often given as induction therapy, and it is likely that at relapse the disease is refractory to these agents, especially if relapse is well within 6 months of primary treatment completion other combinations are preferred.

The NCCN Panel has provided a list of regimens for bortezomib-refractory and lenalidomide-refractory disease after one to three prior therapies.

Preferred Regimens for Bortezomib or Lenalidomide-Refractory Disease

Daratumumab/Carfilzomib/Dexamethasone

A phase 1b, open-label, non-randomized, multicenter trial first studied this regimen in patients (n= 82) with relapsed or refractory MM. At a median follow-up of 16 months, the overall response rate (ORR) was 84%. In the overall treatment population, while the median progression free survival (PFS) was not reached, the 12-month and 18-month PFS rates were 74% and 66%, respectively.[197] In a multicenter, open-label phase 3 trial (CANDOR), the addition of daratumumab to carfilzomib plus dexamethasone showed deeper responses and improved PFS.[198] This response has been shown to be maintained with longer follow up analyses of about 27 months. PFS was 28.6 months in the daratumumab group versus 15.2 months in the carfilzomib alone group (Hazard ratio (HR) HR, 0.59; 95 CI, 0.45–0.78; P < .0001).[199] Based on the above data and the FDA approval, the NCCN Panel has included this regimen as a category 1, preferred option for relapsed/refractory MM, for patients with relapsed or refractory MM.

Isatuximab-irfc/Carfilzomib/Dexamethasone

A prospective, randomized, open label, phase 3 study (IKEMA) examined the utility of isatuximab/carfilzomib/dexamethasone vs carfilzomib/dexamethasone in 302 patients with relapsed/refractory MM who had received one to three prior lines of therapy (median two prior lines of therapy). Treatment was continued until disease progression or unacceptable toxicity, with the primary endpoint being PFS. Median PFS was 35.7 months in the isatuximab/carfilzomib/dexamethasone group vs a median PFS of 19.15 months in the carfilzomib/dexamethasone group (HR 0.53; 99% CI, 0.32-0.89, P = .0007). Grade 3 or higher treatment related adverse events occurred in 77% of patients in the isatuximab group vs 67% of patients in the control group. [200] Based on this data, the NCCN Panel has included isatuximab-irfc/carfilzomib/dexamethasone as a category 1, preferred regimen option for relapsed or refractory MM.

Carfilzomib/Pomalidomide/Dexamethasone

A phase II trial investigated carfilzomib/pomalidomide/dexamethasone followed by continuous pomalidomide/dexamethasone as second line therapy for relapsed/refractory MM in patients who had progression during lenalidomide maintenance therapy. Patients who were eligible for transplant and had not received it previously received HCT. On this regimen, 75% of patients had a VGPR, and 37% displayed CR. At 40- months of follow up, the median PFS was 26 months for patients who received therapy with HCT, and 17 months for patients who received carfilzomib/pomalidomide/dexamethasone therapy without HCT. The median OS was 67 months, with the most common grade 3 and 4 adverse events related to treatment including hematologic toxicity (41%), cardiovascular (6%) and respiratory (3%) events, and infections (17%).[201] Based on these data, the NCCN Panel has included carfilzomib/pomalidomide/dexamethasone as a preferred regimen option for relapsed or refractory MM.

Daratumumab/Pomalidomide/Dexamethasone

The combination of daratumumab/pomalidomide/dexamethasone was evaluated in an open-label, multicenter, phase 1b study (MMY1001). This study included patients (n = 103 patients) who had received at least two prior lines of therapy (excluding daratumumab or pomalidomide).[202] At a median follow-up of 13.1 months, the ORR was 60%. The median PFS and OS were 8.8 and 17.5 months, respectively, and estimated survival at 1 year was 66%.[202] Toxicities reported were similar to those seen in other trials of pomalidomide and daratumumab, except for increase in neutropenia.[202]

The open label phase III APOLLO trial randomly assigned patients with relapsed/refractory disease and at least one previous line of therapy (n=304) to receive pomalidomide/dexamethasone or daratumumab/pomalidomide/dexamethasone. With a median follow up time of 16.9 months, there was a statistically significant improvement in the primary endpoint of PFS for the added daratumumab group (12.4 months vs 6.9 months, P = .0018). Serious adverse events occurred in 50% of patients in the daratumumab group compared to 39% of patients in the pomalidomide/dexamethasone group, the most common being pneumonia and lower respiratory tract infections.[203]

The MM-014 study evaluated 112 patients with relapsed/refractory MM who had previously been treated with lenalidomide and assigned them to a regimen containing daratumumab/pomalidomide/dexamethasone. The primary endpoint was ORR which was achieved in 77.7% of patients in a median follow up of 17.2 months (median PFS was not reached at time of follow up). The most common adverse event of grade 3 or higher was infection, which developed in 31.3% of patients (13.4% with grade 3 or higher pneumonia).[204]

Based on the above data, the NCCN Panel has included daratumumab/pomalidomide/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received one prior therapy including an IMiD and a PI.

Isatuximab-irfc/pomalidomide/dexamethasone

In an open-label, multicenter, phase III trial (ICARIA-MM), patients (n= 307) with MM who had received at least two lines of prior therapy, including lenalidomide and a PI were randomized to receive pomalidomide/dexamethasone with or without isatuximab-irfc.[205] After a median follow-up of 12 months, a higher ORR (60% vs. 35%) and improved PFS (median 11.5 months vs. 6.5 months; HR, 0.6; 95% CI, 0.44–0.81) were reported in the isatuximabirfc/ pomalidomide/dexamethasone arm. In a prespecified subgroup analysis of this study, the addition of isatuximab-irfc showed improved ORR and PFS in patients with renal impairment.[206]

The NCCN Panel has included isatuximabirfc/ pomalidomide/dexamethasone as a category 1, preferred option for the treatment of patients with relapsed/refractory MM after two prior therapies including lenalidomide and a PI.

Ixazomib/Pomalidomide/Dexamethasone

In the phase I/II Alliance A061202 study (n=29), patients with lenalidomide/PI refractory MM were treated with ixazomib/pomalidomide/dexamethasone- with 51.7% of patients having a PR or better, a median PFS of 4.4 months, a median response duration of 16.8 months, and a median OS of 34.3 months. Common adverse events included hematologic toxicity, and gastrointestinal events.[207]

Another phase I/II study studied the safety and efficacy of ixazomib/pomalidomide/dexamethasone in patients who had multiple prior therapies, were refractory to lenalidomide alone, or were refractory to lenalidomide and bortezomib, or lenalidomide, bortezomib, and carfilzomib.[208] The ORR was 33% and 40% with two different doses of ixazomib.[208]

Considering promising preliminary response rates, especially in patients refractory to both lenalidomide and a PI, the NCCN Panel has included ixazomib/pomalidomide/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least two prior therapies including an IMiD and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Additional Preferred Regimens for Bortezomib-Refractory Disease:

In addition to the regimens listed in the section above, the following two lenalidomide-containing regimens may be used for lenalidomide-sensitive or naïve and bortezomib-refractory disease.

Daratumumab/Lenalidomide/Dexamethasone

In a multicenter, open-label phase 3 trial (POLLUX), patients (n= 569) with relapsed/refractory MM were randomized to receive lenalidomide/dexamethasone with or without daratumumab until disease progression or unacceptable toxicity.[209]

After a median follow-up of 13.5 months, daratumumab in combination with lenalidomide and dexamethasone was associated with better PFS and ORR compared with lenalidomide/dexamethasone alone. After a median follow-up of 25.4 months, a subsequent analysis reported that the higher ORR (92.9% vs. 76.4%, P < .001), and PFS (83% vs. 60% at 12 months; 68% vs. 41% at 24 months; HR 0.41, 95% CI 0.31-0.53) was maintained in those who had received daratumumab.[209]

The most common adverse events of grade 3 or 4 in patients treated with the daratumumab regimen versus lenalidomide/dexamethasone were neutropenia (51.9 vs. 37.0%), thrombocytopenia (12.7% vs. 13.5%), and anemia (12.4% vs. 19.6%). Daratumumab-associated infusion-related reactions (mostly grade 1 or 2) were reported in 47.7% of patients.

With an extended follow-up of 3.5 years, the improvements in PFS and ORR continued to be maintained in patients treated with the daratumumab regimen (PFS 16.7 vs. 7.1 months; HR, 0.31; 95%; CI, 0.25- 0.40; P < .0001). In a subgroup of patients with one prior line of therapy, the median PFS was 27.0 months with daratumumab versus 7.9 months with daratumumab and lenalidomide (HR, 0.22; 95% CI, 0.15-0.32; P < .0001). The ORR rates for patients with one prior line of therapy for those receiving the daratumumab-regimen was 92% compared with 74% in those receiving daratumumab/dexamethasone.[210]

Based on the above data, the NCCN Panel has added daratumumab/lenalidomide/dexamethasone as a category 1, preferred option for the treatment of patients with relapsed/refractory MM.

Carfilzomib/Lenalidomide/Dexamethasone

The randomized, multicenter, phase III ASPIRE trial, studied the combination of lenalidomide and dexamethasone with or without carfilzomib in patients (n=792) with relapsed/refractory MM who had received one to three prior lines of therapy. The primary endpoint of the study was PFS. The results showed that addition of carfilzomib to lenalidomide and dexamethasone significantly improved PFS by 8.7 months (26.3 months for the carfilzomib arm vs. 17.6 months for lenalidomide and low-dose dexamethasone; HR for progression or death, 0.69; 95% CI, 0.57–0.83; P = .0001). The median duration of treatment was longer in the carfilzomib group (88.0 weeks vs. 57 weeks). The incidence of peripheral neuropathy was nearly identical in both arms (17%). Non-hematologic adverse effects (≥ grade 3) that were higher in the carfilzomib group compared with lenalidomide and dexamethasone included dyspnea (2.8% vs. 1.8%), cardiac failure (3.8% vs. 1.8%), and hypertension (4.3% and 1.8%). There were fewer discontinuations due to side effects in the carfilzomib arm (15.3% vs. 17.7%). Patients in the carfilzomib arm reported superior health-related quality of life than those who received lenalidomide and dexamethasone alone.[211]

Based on the above data, the NCCN Multiple Myeloma Panel has included the combination of carfilzomib with lenalidomide and dexamethasone as a category 1, preferred option for patients with relapsed/refractory MM.

Additional Preferred Regimens for Lenalidomide refractory Disease

In addition to the regimens listed in the section for bortezomib- and lenalidomide refractory disease, the following bortezomib-containing regimens may be used for bortezomib-sensitive or naïve and lenalidomide-refractory disease.

Daratumumab/Bortezomib/Dexamethasone

A phase III trial showed that adding daratumumab to bortezomib and dexamethasone markedly improved outcomes for patients with recurrent/refractory MM.[212] Patients (n = 498) were randomized to receive daratumumab/bortezomib/dexamethasone or bortezomib/dexamethasone. The ORR in the daratumumab arm was 82.9% compared to 63.2% in the control arm (P < .001).[212] The rates of VGPR and CR were double in the daratumumab arm compared to the control arm (59.2% vs. 29.1%, P < .001 and 19.2% vs. 9.0%, P = .001, respectively). The 12-month estimated rate of PFS was significantly higher in the daratumumab arm compared to the control arm (60.7% vs. 26.9%).[212] The most common grade 3 or 4 adverse events reported in the daratumumab and control groups were thrombocytopenia (45.3% and 32.9%, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%,

respectively).[212] Grade 1 or 2 infusion-related reactions associated with daratumumab were reported in 45.3% of the patients in the daratumumab group and grade 3 in 8.6% of the patients. These infusion-related reaction rates are consistent with findings from previous trials of daratumumab.[213,214]
After a median follow-up of 40 months, patients receiving the daratumumab containing regimen demonstrated a 69% reduction in the risk of disease progression or death (median PFS, 16.7 months vs 7.1 months; HR, 0.31; 95% CI, 0.25–0.40; P < .0001); showed significantly better ORR (85% vs 63%; P < .0001).[215] Patients who received one prior line of therapy demonstrated the greatest benefit with daratumumab (median PFS, 27.0 months vs 7.9 months; HR, 0.22; 95% CI, 0.15–0.32; P <.0001).
Based on the above phase III data, the NCCN Panel has added daratumumab/bortezomib/dexamethasone as a category 1, preferred option for the treatment of patients with relapsed/refractory MM.
Pomalidomide/Bortezomib/Dexamethasone
A phase 3 open-label, multicenter, randomized, trial (OPTIMISMM) evaluated pomalidomide/bortezomib/dexamethasone (n=281) versus bortezomib/dexamethasone in patients (n= 278) with relapsed or refractory MM who previously received lenalidomide.[216] After a median follow-up of 15.9 months, a significantly improved PFS was seen in the pomalidomide arm (median 11.20 months vs. 7.10 months; HR, 0.61; 95% CI, 0.49–0.77; P < .0001). The most common grade 3/4 treatment-related adverse events in the pomalidomide arm reported in this trial were neutropenia, infections, and thrombocytopenia.[216] A post-hoc subgroup analysis of the OPTIMISSM trial evaluated outcomes in 226 patients at first relapse that had only received one prior line of therapy. Analyses were conducted by lenalidomide-refractory status, prior bortezomib exposure, and prior HCT. There were statistically significant improvements in PFS in both lenalidomide refractory (17.8 vs 9.5 months, P = .0276) and lenalidomide non-refractory (22.0 vs 12.0 months, P = .0491) patients. There were also statistically significant improvements in PFS in patients who had received prior bortezomib (17.8 vs. 12 months), and patients with (22 vs. 13.8 months) and without (16.5 vs 9.5 months) prior HCT. [217]
Based on the above data, the NCCN Panel has included pomalidomide/bortezomib/dexamethasone as a category 1, preferred option preferred option for the treatment of patients with relapsed/refractory MM.
Selinexor/Bortezomib/Dexamethasone
An ongoing phase 3, randomized open label trial (BOSTON) compared selinexor/bortezomib/dexamethasone with bortezomib/dexamethasone in patients with previously treated MM (one to three prior lines of therapy, including PIs). Four hundred two patients were randomized to the selinexor/bortezomib/dexamethasone and 206 to the bortezomib/dexamethasone group. After a median follow up duration of 13.2 months in the selinexor/bortezomib/dexamethasone group, the median PFS was 13.93 months compared to a median follow up duration of 16.5 months and median PFS of 9.46 months in the bortezomib/dexamethasone group (HR 0.70; 95% CI, 0.53 – 0.93; P=.0075). The most frequent adverse events of grade 3-4 that were more common in the selinexor/bortezomib/dexamethasone group were thrombocytopenia (39% vs. 17%), fatigue (13% vs 1%), and anemia (16% vs 10%).[218]
Based on the above data the NCCN Panel has included once weekly selinexor in combination with bortezomib and dexamethasone as a category 1, other recommended regimen option for previously treated MM
Elotuzumab/Pomalidomide/Dexamethasone
In a phase II study, patients (n=117) with refractory/relapsed MM and refractory to lenalidomide and a PI were randomized to receive pomalidomide/dexamethasone or elotuzumab/pomalidomide/dexamethasone.[219] After a follow-up of 9.1 months, the median PFS and ORR were both more than double with elotuzumab (PFS, 10.3 months vs. 4.7; ORR, 53% vs. 26%).[219] Median OS was also significantly improved with elotuzumab/pomalidomide/dexamethasone compared with pomalidomide/dexamethasone (29.8 months vs. 17.4 months; HR 0.59 (95% CI, 0.37 to 0.93; P = .0217).[220]
The NCCN Panel has included the combination of pomalidomide/dexamethasone/elotuzumab as an option for patients who have received at least two prior therapies including an IMiD and a PI.
Other Recommended Regimens for Relapse After One to Three Prior Therapies
Carfilzomib (twice weekly)/Dexamethasone
The results of the phase III ENDEAVOR trial in patients with relapsed/refractory MM treated with multiple prior lines of therapy showed a two-fold improvement in median PFS with carfilzomib/dexamethasone compared to bortezomib/dexamethasone (18.7 months vs. 9.4 months; HR, 0.53; P < .0001).[221] ORR was 77% in the carfilzomib group versus 63% in the bortezomib group; rates of CR or better were 13% and 6% and rates of VGPR were 42% and 22%, respectively. The median duration of response was 21.3 months in the carfilzomib group and 10.4 months in the bortezomib group. Adverse events (grade 3 or higher) in the carfilzomib arm compared to the bortezomib arm included hypertension (6% vs. 3%), anemia (12% vs. 9%), thrombocytopenia (10% vs. 14%), and dyspnea (5% vs. 2%). Rate of grade ≥2 peripheral neuropathy was 6% in the carfilzomib group and 32% in the bortezomib group.[221]
The OS analysis showed that those treated with carfilzomib/ dexamethasone lived 7.6 months longer (median OS was 47.6 months in the carfilzomib group vs. 40 months in the bortezomib group; HR, 0.791

[95% CI, 0.648–0.964]; P = .010).[222] The most frequent grade 3 or worse adverse events in the carfilzomib arm compared to the bortezomib arm included hypertension (15% vs. 3%), anemia (16 % vs. 10%), dyspnea (6% vs. 2%), decreased lymphocyte count (6% vs. 2%), diarrhea (4% vs. 9%), and peripheral neuropathy (1% vs. 6%).[222] Rates of thrombocytopenia, pneumonia, and fatigue were similar in both groups.[222]
Based on the above phase III data, the NCCN Multiple Myeloma Panel has included the combination of carfilzomib (twice weekly) and dexamethasone as a category 1, preferred option for patients with relapsed/refractory MM.

Elotuzumab/Lenalidomide/Dexamethasone

The FDA has approved elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received one to three prior therapies. This is based on the results of the phase III trial, ELOQUENT-2. The trial randomized 646 patients (1:1) to receive either elotuzumab in combination with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone.[223]
The rates of PFS at the end of 1 and 2 years were higher for those receiving the elotuzumab-containing regimen (68% at 1 year and 41% at 2 years) compared with those receiving lenalidomide and dexamethasone alone (57% at 1 year and 27% at 2 years).[223] Median PFS in the group receiving the elotuzumab-containing regimen was 19.4 months versus 14.9 months in those receiving lenalidomide and dexamethasone alone (HR for progression or death in the elotuzumab group, 0.70; 95% CI, 0.57–0.85; P < .001) indicating a relative reduction of 30% in the risk of disease progression or death.[223] Common grade 3 or 4 adverse events in both arms of the trial were lymphocytopenia, neutropenia, fatigue, and pneumonia. Infusion reactions occurred in 33 patients (10%) in the elotuzumab group and were grade 1 or 2 in 29 patients.[223]
Consistent with the above findings, a subset analysis of 3-year follow-up reported a reduced risk of progression by 27% with the elotuzumab/lenalidomide/dexamethasone combination compared with lenalidomide/dexamethasone.[224]
The final results of the ELOQUENT-2 study have demonstrated that the addition of elotuzumab to lenalidomide/dexamethasone improved OS in patients with MM who received one to three prior lines of therapy (48.3 months vs. 39.6 months).[225] Based on the above data and FDA approval the NCCN Panel has included elotuzumab in combination with lenalidomide and dexamethasone as a category 1 option for previously treated MM.

Ixazomib/Lenalidomide/Dexamethasone

A double-blind, randomized, placebo-controlled, phase III TOURMALINE MM1 trial randomized 722 patients with relapsed and/or refractory MM to a combination of ixazomib plus lenalidomide and dexamethasone or lenalidomide and dexamethasone alone (control group). This trial was designed based on the promising results of a phase I/II study (discussed under Other Recommended Primary Therapy Regimens for Transplant Candidates. See nccn.org).[106] The results of the TOURMALINE MM1 trial show a significant improvement in PFS with the ixazomib-containing regimen. After a median follow-up of almost 15 months, a 35% improvement in PFS was seen in the group treated with the ixazomib regimen compared with the control group (HR, 0.74; P = .01).[226] Median PFS was 20.6 months in the ixazomib-treated group versus 14.7 months in the group receiving lenalidomide and dexamethasone alone. In the ixazomib-treated group versus the control group, the ORR (78% vs. 72%, P = .035) and CR (11.7% vs. 6.6%, P = .019) were also improved. Of note, patients with high-risk cytogenetics enrolled in the trial receiving ixazomib had a similar HR for PFS as the entire study population (HR, 0.596 and 0.543, respectively).[226] Grade ≥3 adverse events were reported in 74% and 69% of patients in the ixazomib-treated and control groups, respectively. These included anemia (9% with ixazomib/lenalidomide/dexamethasone vs. 13% with lenalidomide/dexamethasone), thrombocytopenia (19% vs. 9%), and neutropenia (23% vs. 24%).[226] The addition of the ixazomib/lenalidomide/dexamethasone group had a slightly higher rate of peripheral neuropathy compared to lenalidomide/dexamethasone (27% vs. 22%). Based on the results of the phase III TOURMALINE MM1 trial [226] the NCCN Panel has included ixazomib/lenalidomide/dexamethasone as a category 1, preferred regimen option for previously treated MM after one to three prior therapies.

Bortezomib/Cyclophosphamide/Dexamethasone

The effects of adding an alkylating agent (such as cyclophosphamide) and a novel agent (such as lenalidomide or bortezomib) to dexamethasone have been investigated for patients with relapsed/refractory MM. The combination of bortezomib, dexamethasone, and cyclophosphamide was found to be effective in patients with relapsed/refractory MM with an acceptable toxicity profile.[227,228] The NCCN Multiple Myeloma Panel members have included bortezomib/cyclophosphamide/dexamethasone as an other recommended regimen for relapsed/refractory MM after one to three prior therapies.

Bortezomib/Lenalidomide/Dexamethasone

Data from preclinical studies showed lenalidomide sensitizes myeloma cells to bortezomib and dexamethasone. The results of phase I and phase II studies show that bortezomib/lenalidomide/dexamethasone is well tolerated and active, with durable responses in heavily pretreated patients with relapsed and/or refractory MM, including patients who have had prior lenalidomide, bortezomib, thalidomide, and HCT.[229,230] After a median follow-up of 44 months, the median

PFS was 9.5 months and median OS was 30 months (95% CI, 24–37).[230] The NCCN Multiple Myeloma Panel members have included bortezomib/lenalidomide/dexamethasone as other recommended regimen for relapsed/refractory MM after one to three prior therapies.

Carfilzomib/Cyclophosphamide/Dexamethasone

Carfilzomib/cyclophosphamide/dexamethasone has been shown to be well tolerated with the toxicity profile of carfilzomib being similar to that seen in other trials.[231] A phase II trial (MUKfive) compared the safety and toxicity of carfilzomib/cyclophosphamide/dexamethasone with bortezomib/cyclophosphamide/dexamethasone in patients with relapsed/refractory MM, who had received one prior regimen.[231] A higher proportion of patients receiving carfilzomib achieved VGPR or better and was non-inferior to bortezomib. Carfilzomib/cyclophosphamide/dexamethasone was well tolerated with the toxicity profile of carfilzomib being similar to that seen in other trials.[231] This study also included a maintenance phase and demonstrated a median PFS of 11.9 versus 5.6 months in favor of carfilzomib maintenance versus observation. Another phase II trial compared treatment with cyclophosphamide plus carfilzomib and dexamethasone to treatment with carfilzomib and dexamethasone in patients (n=197) with relapsed/refractory MM after one to three prior lines.[232] After a median follow-up of 37 months, median PFS was 19.1 with the 3-drug regimen compared to 16.6 months with the 2-drug regimen (P= .577).[232] The combination of cyclophosphamide with carfilzomib and dexamethasone did not improve outcomes significantly compared with carfilzomib and dexamethasone alone in the overall population. However, in a sub-group analysis of the lenalidomide refractory population, the addition of cyclophosphamide to carfilzomib and dexamethasone resulted in a PFS benefit of 18.4 versus 11.3 months (HR, 1.7; 95% CI, 1.1–2.7; P = .043).[232] The NCCN Panel has included carfilzomib/cyclophosphamide/dexamethasone as treatment as an other recommended regimen for relapsed/refractory MM after one to three prior therapies.

Daratumumab/Cyclophosphamide/Bortezomib/Dexamethasone

In the LYRA study,[99] among the small cohort of patients with relapsed MM (n = 14), after 4 cycles of induction therapy ORR was 12.3% and VGPR or better was seen in 57.1% of patients.[99] The ORR after 4 induction cycles was 71.4%. The median PFS was 13.3 months (95% CI, 6.8–13.3). At 12-months, the OS rate was 54.5% (95% CI, 8.6%– 86.1%).[99] Based on this, the NCCN Panel has included daratumumab/bortezomib/cyclophosphamide/dexamethasone as treatment option for relapsed/refractory MM.

Elotuzumab/Bortezomib/Dexamethasone

Numerous randomized trials have shown that three-drug combinations are consistently more effective than 2-drug combinations for the treatment of MM. A phase II trial studied the effect of addition of elotuzumab to bortezomib/dexamethasone in patients with relapsed/refractory MM.[233] Interim analysis results demonstrated a 28% reduction in risk of disease progression or death for patients in the elotuzumab-containing triple-drug arm compared to patients treated with bortezomib/dexamethasone (HR, 0.72; 70% CI, 0.59–0.88). Median PFS was significantly higher in the elotuzumab-containing arm (9.7 months vs. 6.9 months). After 2 years the addition of elotuzumab continued to show an efficacy benefit compared to bortezomib/dexamethasone alone with a 24% relative risk reduction in PFS (HR, 0.76; 70% CI, 0.63–0.91).[233] Based on the above phase II trial data, the NCCN Panel has included elotuzumab/bortezomib/dexamethasone as an other recommended regimen for relapsed/refractory MM after one to three prior therapies.

Ixazomib/cyclophosphamide/dexamethasone

This regimen has been shown to be tolerable and efficacious in newly diagnosed patients.[95,234] A phase II study evaluated this regimen in the relapsed/refractory setting in patients with a median age of 63.5 years and found that it is well tolerated. At a median follow-up of 15.2 months in the phase II study, median PFS was 14.2 months. The PFS trend with this regimen was better in patients aged 65 and older compared with those less than 65 years (median 18.7 months vs. 12.0 months; HR 0.62, P = .14).[235] The NCCN Panel has included this all oral regimen under the list of “other recommended regimens” for relapsed/refractory MM.

Lenalidomide/Cyclophosphamide/Dexamethasone

A retrospective analysis to assess the efficacy of lenalidomide in combination with cyclophosphamide and dexamethasone showed that this regimen is effective in heavily pre-treated patients with manageable adverse effects.[236] The NCCN Panel has included cyclophosphamide/lenalidomide/dexamethasone treatment as an other recommended regimen for relapsed/refractory MM after one to three prior therapies.

Pomalidomide/Cyclophosphamide/Dexamethasone

A phase II study compared the combination of pomalidomide/cyclophosphamide/dexamethasone to pomalidomide/dexamethasone in patients (n = 70) with relapsed/refractory MM who had received more than two prior therapies.[237] The triple-drug combination significantly improved the ORR (≥PR, 64.7% vs. 38.9%; P = .0355). The median PFS reported was 9.5 months versus 4.4 months. There were no significant differences in adverse event reports between the treatment arms; grade 3 and 4 anemia, neutropenia,

and thrombocytopenia, respectively, were reported in 11%, 31%, and 6% of patients treated with pomalidomide/dexamethasone and 24%, 52%, and 15% of patients treated with the triplet regimen.[237] Similar results were reported by a single-center retrospective study of patients (n = 20) with relapsed/refractory MM who received pomalidomide/cyclophosphamide/dexamethasone until transplant or disease.[238] Response to the triple-drug regimen was 63%, with nearly half of patients (42%) after 1 cycle with a median time to response of 3 cycles. One-year median PFS was 80.7% and 65% of patients were relapsefree.[238] Based on the above phase II trial data, the NCCN Panel has included pomalidomide/cyclophosphamide/dexamethasone as other recommended treatment option for patients with relapsed/refractory MM who have received two prior therapies, including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy.

Regimens Useful In Certain Circumstances for Previously Treated MM – Early Relapse (one to three prior therapies)

Bortezomib/Liposomal Doxorubicin/Dexamethasone

Bortezomib with liposomal doxorubicin (PLD) was approved by the FDA as a treatment option for patients with MM who have not previously received bortezomib and have received at least one prior therapy. The approval was based on a priority review of data from an international phase III trial (n = 646) showing that use of the combination significantly extended the median time to disease progression compared with bortezomib alone (9.3 vs. 6.5 months).[239] Median duration of response was increased from 7.0 months to 10.2 months with the combination therapy. Based on these results, the NCCN Multiple Myeloma Panel considers bortezomib with the PLD regimen as a category 1 option that is useful in certain circumstances for patients with relapsed/refractory MM.

Bortezomib/Dexamethasone

The addition of dexamethasone to bortezomib in patients with relapsed/ refractory MM who had PD during bortezomib monotherapy resulted in improvement of response in 18% to 34% of patients.[240-242] The NCCN Multiple Myeloma Panel members have included the bortezomib and dexamethasone regimen as an option that is useful in certain circumstances for patients with relapsed/refractory MM (category 1).

Lenalidomide/Dexamethasone

Lenalidomide combined with dexamethasone received approval from the FDA as a treatment option for patients with MM who had received at least one prior treatment. This was based on the results of two studies of a total of 692 patients randomized to receive dexamethasone either with or without lenalidomide. The primary efficacy endpoint in both studies was TTP. A pre-planned interim analysis of both studies reported that the median TTP was significantly longer in the lenalidomide arm compared to the control group.[243,244] The updated clinical data from the pivotal North American phase III trial (MM-009) in 353 previously treated patients with MM reported increased OS and median time to disease progression in patients receiving lenalidomide plus dexamethasone compared to patients receiving dexamethasone plus placebo.[244] Similar results were seen in the international trial MM-010.[243] Patients in both of these trials had been heavily treated before enrollment. Many had three or more prior lines of therapies with other agents and more than 50% of patients had undergone HCT.[243,244] Most adverse events and grade 3/4 adverse events were more frequent in patients with MM who received the combination of lenalidomide/dexamethasone compared to placebo and dexamethasone. Thrombocytopenia (61.5%) and neutropenia (58.8%) were the most frequently reported adverse events observed. The NCCN Multiple Myeloma Panel now considers this regimen as a category 1 option that is useful in certain circumstances for patients with relapsed/refractory MM.

Carfilzomib/Cyclophosphamide/Thalidomide/Dexamethasone:

The results of the phase I/II trial showed that this 4-drug regimen is efficacious with an ORR of 91%, with 59% achieving VGPR or greater after 4 cycles in patients with MM.[245] The PFS and OS at 24 months (median 17.5 months) was 76% and 96%, respectively.[245] This regimen has now been included under the list of regimens “useful in certain circumstances” for relapsed/refractory MM.

Carfilzomib (weekly)/dexamethasone

In the phase III A.R.R.O.W. trial, patients (n = 578) with relapsed and refractory MM previously treated with two or three treatments, including PI and IMiD were randomly assigned (1:1) to receive carfilzomib once a week (70 mg/m^2) or twice a week (27 mg/ m^2). All patients received dexamethasone. The media PFS was higher in the once weekly (11.2 months) compared with those who received twice weekly carfilzomib (7. 6 months; HR 0.69, 95% CI 0.54-0.83; P=.0029). The overall safety was comparable between the two groups.[246] The NCCN panel has included this combination on the list of regimens “useful in certain circumstances” for relapsed/refractory MM.

Selinexor/daratumumab/dexamethasone

A phase Ib/II trial assessed the safety and efficacy of adding daratumumab to selinexor dexamethasone. Patients (n=34) enrolled in the trial had received three or more prior lines of therapy, including a PI and an IMiD. In daratumumab naïve patients, the ORR was 73%, with 11 VGPR, and 11 PR. The median PFS was 12.5 months. This regimen has been included under the list of regimens useful in certain circumstances for relapsed/refractory MM.

Selinexor/Carfilzomib/Dexamethasone
In a study of 32 patients who had received a median of four prior therapies were assigned to receive once weekly selinexor, carfilzomib, and dexamethasone. The ORR was 78% with a median PFS of 15 months. The most common grade 3 or higher treatment-related adverse events were thrombocytopenia (47%), nausea (6%), anemia (19%), and fatigue (9%).[247] Another analysis of a subset of this patient population that had triple class refractory MM also showed an ORR of 66.7% with a median PFS of 13.8 months, and median OS of 33 months.[248] This regimen has now been included under the list of regimens "useful in certain circumstances" for relapsed/refractory MM.
Venetoclax/Dexamethasone with or without Daratumumab or PI for t(11;14) Patients
A phase I study of patients (n=66) with relapsed/refractory MM who received a median of 5 prior lines of therapy studied venetoclax monotherapy and reported an ORR in 21% of patients with the response rate being higher in patients (n=30) with t(11;14) compared with those without t(11:14) (40% vs. 6%).[249] Similar higher response rates have been found in patients with t(11:14) in real-world experience as well.[250] An open label phase I/II study examined venetoclax/dexamethasone in heavily pretreated t(11;14) patients. In this phase II part of the study, patients had received a median of 5 prior lines of therapy. At a median follow-up of 9.2 months, the ORR was 48%, with a median TTP of 10.8 months.[251] Several prospective trials have reported on the efficacy and tolerability of venetoclax/dexamethasone containing combination regimens in relapsed t(11;14) MM. A phase I study found that venetoclax/dexamethasone in combination with daratumumab with or without bortezomib produced high rates of durable responses in patients with relapsed or refractory MM with t(11;14) translocation.[252] In patients with no prior treatment with carfilzomib, venetoclax/dexamethasone plus carfilzomib was found to be safe and efficacious especially in those with t(11;14) translocations.[253] This finding has been supported by case studies.[254] The NCCN Panel had included venetoclax/dexamethasone with or without daratumumab or a PI as options for patients with t(11:14) translocation.
Pomalidomide/Dexamethasone
Pomalidomide, like lenalidomide, is an analogue of thalidomide. It possesses potent immunomodulatory and significant anti-myeloma properties.[255] A phase III, multicenter, randomized, open-label study (MM-003) conducted in Europe compared the efficacy and safety of pomalidomide and low-dose dexamethasone (n = 302) versus high-dose dexamethasone (n = 153) in patients with relapsed MM who were refractory to both lenalidomide and bortezomib.[256] After a median follow-up of 10 months, PFS, the primary endpoint of the study, was significantly longer in patients who received pomalidomide and low-dose dexamethasone compared with those who received high-dose dexamethasone (4 months vs. 1.9 months; HR, 0.45; P < .0001).[256] The median OS was significantly longer in the patients who received pomalidomide and low-dose dexamethasone as well (12.7 months vs. 8.1 months; HR, 0.74; P = .0285).[256] The most common hematologic grade 3 and 4 adverse effects found to be higher with the low-dose dexamethasone compared with the high-dose dexamethasone were neutropenia and pneumonia.[256] Other phase III studies of pomalidomide plus low-dose dexamethasone in combination with other agents (eg, bortezomib) are currently ongoing (Clinical Trial ID: NCT01734928). A European multicenter, single-arm, open-label, phase IIIb trial evaluated the safety and efficacy of pomalidomide and low-dose dexamethasone in a large patient population (N = 604).[257] The median PFS reported was 4.2 months and OS was 11.9 months. Whether the patients received prior lenalidomide or bortezomib, the PFS, OS, and ORR reported were similar.[257] The results of this trial are consistent with those observed in the pivotal MM-003 trial.[256] In addition, several complementary phase II studies have been published evaluating the use of pomalidomide and dexamethasone in patients with MM relapsed/refractory to lenalidomide and/or bortezomib. A phase II study investigated two different dose regimens of pomalidomide and dexamethasone in 84 patients with advanced MM. Pomalidomide (4 mg) was given orally on days 1 to 21 or continuously over a 28-day cycle, and dexamethasone (40 mg) was given orally once weekly.[258] ORR was 35% and 34% for patients in the 21-day and 28-day groups, respectively. With a median follow-up of 23 months, median duration of response, PFS, and OS were 7.3, 4.6, and 14.9 months across both groups, respectively. All patients experienced similar adverse events in both groups. The adverse events were primarily due to myelosuppression.[258] Another phase II trial evaluated two doses of pomalidomide 2 or 4 mg/day with dexamethasone 40 mg weekly in heavily pre-treated patients (n = 35).[259] The ORR in the 2-mg cohort was 49% versus 43% in the 4-mg cohort. OS at 6 months was 78% and 67% in the 2- and 4-mg cohort, respectively. Myelosuppression was the most common toxicity.[259] The FDA has approved pomalidomide for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. The FDA-recommended dose and schedule of pomalidomide is 4 mg orally on days 1 to 21 of repeated 28- day cycles with cycles repeated until disease progression along with the recommendation to monitor patients for hematologic toxicities, especially neutropenia. Based on the above data, the NCCN Panel has included pomalidomide plus dexamethasone as a therapeutic option in patients who have received at least two prior therapies, including an IMiD and a PI, and have demonstrated disease progression on or within 60 days of completion of the last therapy (category 1).

Selinexor/Pomalidomide/Dexamethasone

An abstract presented at the 2021 ASCO Annual Meeting presented data from an ongoing phase I/II clinical trial that contains one arm evaluating the regimen of selinexor/pomalidomide/dexamethasone (NCT02343042). Sixty-five patients were enrolled initially in phase I with a median of three prior lines of therapy. After determining a recommended phase II dose, it was administered to 20 patients. Among these patients, the ORR was 65% and the median PFS was not reached in a median follow up of 3.9 months.[260] Based on the above data, the NCCN Panel has included selinexor/pomalidomide/dexamethasone as a therapeutic option in patients who have received at least two prior therapies, including an IMiD and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy (category 1).

Daratumumab

Daratumumab is a human IgG kappa monoclonal antibody that targets the CD38 surface protein on myeloma cells.[213] In a phase I/II study, patients who had received more than three lines of therapy including an IMiD and a PI or were double refractory to PI and IMiD were randomized to two different doses of daratumumab (8 mg/kg vs. 16 mg/kg). Findings from 106 patients who received 16 mg/kg noted an ORR of 29.2% in 31 patients (3 sCR, 10 VGPR, and 18 PR). The median duration of response was 7.4 months and median TTP was 3.7 months. The estimated 1-year OS rate was 65%.[214] Adverse events reported were fatigue (39.6%), anemia (33.0%), nausea (29.2%), and thrombocytopenia (25.5%). Grade 1 and 2 infusion-related reactions were seen in 42.5% of patients, mainly during first infusion. No patients discontinued the study due to infusionrelated reactions.[214] Based on the above phase II results and FDA approval, the panel has added daratumumab as an option for the treatment of patients with MM who have received at least three prior lines of therapy including a PI and an IMiD or who are double refractory to a PI and IMiD.

DCEP and VTD-PACE for Aggressive MM

Patients with an aggressive relapse may need multi-drug combinations such as DCEP,[261-263] TD-PACE (thalidomide, dexamethasone, cisplatin, doxorubicin, high-dose cyclophosphamide, and etoposide),[264,265] and VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide)[266-268] for effective disease control.

Preferred Regimens for Relapse After Four Prior Therapies

Currently there are three bispecific antibodies (elranatamab-bcmm, talquetamab-tgvs, and teclistamab-cqyv) and two chimeric antigen receptor (CAR) T-cell therapies (idecabtagene vicleucel and ciltacabtagene autoleucel) approved by the FDA and included as preferred options by the NCCN Panel for relapsed/refractory MM after at least four prior therapies including an anti-CD38 monoclonal antibody, a PI, and an IMiD.

Bispecific Antibodies:

Elranatamab-bcmm:

Elranatamab-bcmm is a bispecific T-cell engager (BiTE) that binds CD3 on T cells and to B-cell maturation antigen (BCMA) on myeloma cells. In the phase II, MagnetisMM-3 trial, patients with relapsed/refractory MM received subcutaneous elranatamab once weekly.[269] The primary population in whom the efficacy was seen were patients (n= 123) without prior BCMA-directed therapy. The findings indicated an ORR of 61.0% (75/123) and 35.0% greater than or equal to CR. Fifty responders switched to biweekly dosing, and 40 of those (80.0%) improved or maintained their response for ≥ 6 months. Common adverse events reported were infections, cytokine release syndrome, anemia, and neutropenia. With biweekly dosing, grade 3–4 adverse events decreased from 58.6% to 46.6%.[269]

Talquetamab-tgvs:

Talquetamab is a T cell redirecting bispecific antibody targeting both GPRC5D and CD3 on T cells. In the single-arm, open-label, multicenter trial, MMY1001 (MonumenTAL-1) patients (n=187) who had previously received at least four prior systemic therapies received talquetamab-tgvs subcutaneously weekly or talquetamab-tgvs biweekly until disease progression or unacceptable toxicity.[270] The most common adverse reactions reported with weekly and biweekly dosing were cytokine release syndrome (in 77% and 80% of the patients, respectively), skin-related events (in 67% and 70%), and dysgeusia (in 63% and 57%).[270]

Teclistamab-cqyv:

Teclistamab-cqyv, similar to elranatamab-bcmm, is a BiTE that binds to CD3 on T cells and BCMA on myeloma cells. A phase I/II study examined the T-cell-redirecting bispecific antibody teclistamabcqyv in 165 patients who had triple class refractory disease, with a median of five prior lines of therapy. [271] After a median follow up of 14.1 months, the ORR was 63% and 39.4% of patients demonstrated a CR or better. The median PFS was 11.3 months, with a median response duration of 18.4 months. Common adverse events included cytokine release syndrome in 72.1% of patients (0.6% grade 3) and grade 3 or 4 hematologic toxicity including neutropenia (64.2%), anemia (37%), and thrombocytopenia (21.2%). Infections were also common, with grade 3 or 4 infection occurring in 44.8% of patients.

CAR T-Cell Therapies:

Idecabtagene vicleucel:
Idecabtagene vicleucel is a BCMA-directed CART cell therapy. In a phase II study (n=128) patients with relapsed and refractory MM who had received at least three prior regimens (including a PI, an IMiD, and an anti-CD38 antibody) received idecabtagene vicleucel. Patients had received a median of 6 previous regimens for MM and 94% had received HCT. In this population of heavily pretreated patients, after a median 13 months follow up, 73% of patients demonstrated response, with 33% having a CR or better. The median time to response was 1 month and median time to a CR or better was 2.8 months. High response rates (> 50%) were found in several examined subgroups including older patients, patients with high-risk cytogenetic abnormalities, penta-refractory disease, and high tumor burden. Adverse events at grade 3 or 4 were common and included neutropenia (91%), anemia (70%), and thrombocytopenia (63%). Twenty eight patients were retreated with idecabtagene vicleucel following disease progression and 21% demonstrated a second response. Grade 3 or 4 adverse events were common and were reported in 99% of patients. The most common adverse events were related to hematologic toxicity such as neutropenia (89%), anemia (60%), and thrombocytopenia (52%). Infections (69%) and cytokine release syndrome (84%) were also common treatment related adverse events, although the incidence of grade 3 or higher cytokine release syndrome was lower (5%).[272] The NCCN Panel has included idecabtagene vicleucel as an option for patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.
Ciltacabtagene autoleucel:
Ciltacabtagene autoleucel is another BCMA directed CAR T-cell therapy. The CARTITUDE-1 trial (n=97) was an open label phase Ib/II study that looked to assess the safety and efficacy of ciltacabtagene autoleucel in patients with relapsed or refractory MM who had received three or more previous lines of therapy (including an IMiD, PI, and andti-CD38 antibody).[273] The median amount of prior therapies was six. After a median 12.4 months of follow up, the ORR was 97%, with 67% of patients achieving sCR. The PFS rate was 77% with an 89% OS rate. Adverse events included neutropenia in 95% of patients and anemia in 68%. Other common adverse events included thrombocytopenia (60%), leukopenia (61%), and lymphopenia (50%). Cytokine release syndrome also occurred in 95% of patients. There were six deaths due to treatment related adverse events.[273] A follow up analysis at 18 months showed that responses were durable; 18-month PFS and OS rates were 66.0% and 80.9% respectively, with no new observed safety signals.[274]
Other Recommended Regimens for Relapse After Three Prior Therapies
Bendamustine
In a trial by Knop and colleagues, 31 patients who had experienced relapse after autologous transplantation were enrolled to receive increasing doses of bendamustine.[275] The ORR was 55%, with a median PFS of 26 weeks for all patients and 36 weeks for patients who received higher doses of bendamustine (90–100 mg/m^2). The toxicity was mild and mainly hematologic. A retrospective analysis of 39 patients has reported that bendamustine is effective and tolerable in patients with advanced progressive MM, with an ORR of 36%.[276] The ECOG studied treatment with high-dose cyclophosphamide in patients with poor-risk features who had disease that was refractory to prior chemotherapy.[277] The ORR reported was 43% (29% response rate in patients refractory to prior therapy with cyclophosphamide).[277] Bendamustine is currently a treatment option for relapsed/refractory MM.
Bendamustine/Bortezomib/Dexamethasone
A phase II study evaluated bendamustine/bortezomib/dexamethasone administered over six 28-day cycles and then every 56 days for 6 more cycles in patients (n = 75; median age 68 years) with relapsed/refractory MM treated with multiple prior therapies and not refractory to bortezomib. The PR rate was 71.5% (16% CR, 18.5% VGPR, 37% partial remission). At 12-month follow-up, median TTP was 16.5 months, and 1-year OS was 78%.[278]
Bendamustine/carfilzomib/dexamethasone
A multicenter trial evaluated combination therapy with bendamustine/carfilzomib/and dexamethasone in 63 patients with relapsed/refractory MM (with at least two lines of prior therapy). Fifty two percent of patients achieved a PR or better and 32% achieved a VGPR or better. After a median follow up of 22 months, the median PFS was 11.6 months with a median OS of 30.4 months. The most common adverse events of grade 3 or higher included lymphopenia (29%), neutropenia (25%), and thrombocytopenia (22%).[279] The NCCN Panel has included carfilzomib in combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory MM.
Bendamustine/Lenalidomide/Dexamethasone
A multicenter phase I/II trial investigated the combination of bendamustine, lenalidomide, and dexamethasone as treatment for patients (n = 29) with relapsed/refractory MM.[280] PR was seen in 52% (n = 13) of patients, with VGPR in 24% (n = 6) of patients. The median PFS in the trial was 6.1 months (95% CI, 3.7–9.4 months), and the one-year PFS rate was 20% (95% CI, 6%–41%).[280] The NCCN Panel has included lenalidomide in combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory MM.
High Dose or Fractionated Cyclophosphamide

Studies have reported that high-dose cyclophosphamide or hyperfractionated cyclophosphamide is efficacious particularly in patients needing immediate disease control who have received multiple prior treatments.[281,282] Therefore the NCCN Panel has included high dose or fractionated cyclophosphamide as an option for relapsed/refractory MM.

Selinexor/Dexamethasone:

Selinexor in combination with dexamethasone was studied in a phase IIb trial (STORM) in patients with relapsed/refractory MM.[283] The patients in the trial had multiple prior therapies and were refractory to IMIDs (lenalidomide and pomalidomide), PIs (bortezomib and carfilzomib), and the CD38 antibody daratumumab. A total of 122 patients were included in the intent-to-treat population. PR or better was observed in 26% of patients (95% CI, 19- 35 with sCR in 2%, VGPR in 5%, and PR in 20% of the patients. The most common adverse events reported during treatment were thrombocytopenia in 73% of the patients, fatigue in 73%, nausea in 72%, and anemia in 67%. Based on the above results, the NCCN Panel has included selinexor/dexamethasone under other recommended options for patients with relapsed/refractory MM who have received at least four prior therapies and whose disease is refractory to at least two PI, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.[247]

Regimens Useful in Certain Circumstances for Relapse After Four Prior Therapies

Belantamab Mafodotin-blmf

Belantamab mafodotin-blmf is a BCMA antibody, conjugated to a microtubule disrupting agent—monomethyl auristatin—via a stable, protease resistant linker. It is the first in its class. In the open-label phase II trial (DREAMM-2), belantamab mafodotin was evaluated in patients whose MM was refractory to multiple agents. Responses were seen in approximately one-third of patients.[284] The most common grade 3/4 adverse events in the safety population were keratopathy, thrombocytopenia, and anemia.[284] In November 2022, it was announced that belantamab mafodotin-blmf is being withdrawn as it did not meet the primary end point of having a superior PFS compared to pomalidomide/dexamethasone in the DREAMM-3 trial (HR 1.03; 95% CI, 0.72–1.47). The PFS with belantamab mafodotin-blmf was 11.2 months compared with 7 months for pomalidomide plus dexamethasone, however this was not statistically significant. Since, patients already receiving belantamab mafodotin-blmf and those enrolled on the FDA Risk Evaluation and Mitigation Strategy (REMS) program have been able to continue to receive the drug through a compassionate use program. There are other ongoing trials with belantamab mafodotin-blmf, the NCCN Panel has included this as an option useful in certain circumstance for those after 4 prior therapies (including a PI, an IMiD, and an anti-CD38 monoclonal antibody).

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 07 of 12, July 2024) am 01.07.2024

#	Suchfrage
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}
5	#4 with Cochrane Library publication date from July 2019 to present

Systematic Reviews in PubMed am 01.07.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	Multiple Myeloma[mj]
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 (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] 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 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

#	Suchfrage
	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[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	((#5) AND ("2019/07/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 01.07.2024

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

#	Suchfrage
1	Multiple Myeloma[mj]
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*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
6	(((#5) AND ("2019/07/01"[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]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 01.07.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- 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)

- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-173

Verfasser	
Institution	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
Datum	3. September 2024

Indikation
Erwachsene mit rezidiviertem und refraktärem Multiplen Myelom, die zuvor bereits mindestens eine vorherige Therapie erhalten haben, darunter einen Immunmodulator und einen Proteasom-Inhibitor, und die während der letzten Therapie eine Krankheitsprogression zeigten und gegenüber Lenalidomid refraktär sind
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Das Kollektiv der Patientinnen und Patienten (Pat.) mit Multiplem Myelom, die zuvor bereits mindestens eine vorherige Therapie erhalten haben, darunter einen Immunmodulator und einen Proteasom-Inhibitor, und die während der letzten Therapie eine Krankheitsprogression zeigten und gegenüber Lenalidomid refraktär sind, ist heterogen. Das ist zum einen durch die biologische und klinische Vielfalt der Grundkrankheit, zum anderen durch die Erfahrungen aus den vorherigen Therapien bedingt.

Empfohlen wird:

- Ciltacabtagen Autoleucel oder
- Pomalidomid / Bortezomib / Dexamethason (PVd) oder
- Bortezomib oder Carfilzomib / Cyclophosphamid / Dexamethason (VCd / KCd) oder
- Selinexor / Bortezomib / Dexamethason (SVd) oder
- Daratumumab oder Isatuximab / Pomalidomid / Dexamethason (DaraPd, Isa Pd) oder
- Daratumumab oder Isatuximab / Carfilzomid / Dexamethason (DaraKd, IsaKd) oder
- Daratumumab / Bortezomib / Dexamethason (DaraVd) oder
- Elranatamab oder Teclistamab oder Talquetamab.

Aufgrund des Fehlens direkter Vergleiche zwischen den empfohlenen Therapieoptionen erfolgt die individuelle Entscheidung nach ärztlicher Maßgabe, insbesondere unter Berücksichtigung von Komorbidität, Vortherapien und Patientenpräferenz.

Fragestellung

Die Fragestellung ist sehr weit gefasst und umfasst formal auch Pat. nach multiplen Vortherapien. Wir haben uns auf das Kollektiv der Pat. mit Lenalidomid-Refraktärität beschränkt.

Stand des Wissens

Beim rezidivierten / refraktären Multiplen Myelom r/r MM bestehen derzeit sehr viele Therapieoptionen [1, 2]. Die meisten der empfohlenen Kombinationen wurden in den Zulassungsstudien gegenüber älteren Therapiestandards, aber nicht gegeneinander verglichen. Die den Empfehlungen zugrunde liegende Evidenz kann folgendermaßen zusammengefasst werden:

Ciltacabtagen Autoleucel (Cilta-Cel)

Ciltacabtagen Autoleucel (Cilta-Cel) ist ein Anti-BCMA-CAR-T-Zellprodukt. Es ist ab dem ersten Rezidiv zugelassen für Pat., die zuvor mit einem Immunmodulator und einen Proteasom-Inhibitor behandelt wurden, die während der letzten Therapie eine Krankheitsprogression zeigten und die gegenüber Lenalidomid refraktär sind.

Die Empfehlung zum Einsatz von Cilta-Cel in dieser Indikation beruht auf der Studie CARTITUDE-4 bei Pat. mit r/r MM nach 1-3 Vortherapien. In CARTITUDE-4 führte Cilta-Cel gegenüber einer Therapie mit PVd (Pomalidomid / Bortezomib / Dexamethason) oder DPd (Daratumumab / Pomalidomid / Dexamethason) zur Steigerung der Remissionsrate ≥CR 21,8 auf 73,1% (p<0,001), zur Steigerung der Rate MRD-negativer Pat. von 15,6 auf 60,6% (p<0,001) und zur Verlängerung des progressionsfreien Überlebens (HR 0,26; p<0,001). Die Daten zur Gesamtüberlebenszeit sind noch unreif. Ein Zytokinfreisetzungssyndrom (CRS) trat bei 76,1% der Pat. auf. 17% der Pat. hatten neurologische Nebenwirkungen (ICANS), die meisten im CTCAE Grad 1 oder 2. Nach Cilta-Cel wird keine Erhaltungstherapie durchgeführt [3].

Pomalidomid / Bortezomib / Dexamethason (PVd)

Die Kombination Pomalidomid / Bortezomib / Dexamethason (PVd) Daratumumab ist zugelassen nach mindestens einer Vorbehandlung, darunter Lenalidomid. In der OPTIMISMM-Studie führte PVd gegenüber Bortezomib / Dexamethason zur signifikanten Steigerung der Remissionsrate ≥VGPR von 45,7 auf 81,5%, zur Verlängerung der progressionsfreien Überlebenszeit (HR 0,58; p<0,001) und zur Verlängerung der Zeit bis zur nächsten Therapie, nicht zur Verlängerung der Gesamtüberlebenszeit [4, 5]. Schwere unerwünschte Ereignisse traten mit 57 vs 42% häufiger im Pomalidomid-Arm auf. Nebenwirkungen im CTCAE Grad 3/4, die häufiger im Pomalidomid-Arm auftraten, waren Neutropenie (42%) und Infektionen (31%). Venöse thrombembolische Ereignisse traten bei 11,2% der Pat. im Pomalidomid-Arm gegenüber 2,6% im Kontrollarm auf.

Bortezomib oder Carfilzomib / Cyclophosphamid / Dexamethason (VCd / KCd)

Bortezomib ist in Kombination mit Dexamethason bei Pat. zugelassen, die mindestens eine vorangehende Therapie erhalten haben und sich bereits einer hämatopoetischen Stammzelltransplantation unterzogen haben oder für diese nicht geeignet sind. Carfilzomib ist in

Kombination mit Dexamethason allein zur Behandlung von Pat. indiziert, die mindestens eine vorangegangene Therapie erhalten haben.

In einer in Deutschland bei nicht vorbehandelten Pat. durchgeführten Phase-III-Studie zum Vergleich von Bortezomib / Cyclophosphamid / Dexamethason (VCd) gegenüber Bortezomib / Doxorubicin / Dexamethason führte VCd zu einer Remissionsrate ≥VGPR von 37,0%. VCd war dem Anthrazyklin-haltigen Schema nicht unterlegen. Häufigste Nebenwirkung im Grad 3/4 war Leukozytopenie / Neutropenie bei 35,2% der Pat. [6]. In einer Phase-II-Studie mit 414 Pat. fand sich kein Unterschied in den Remissionsraten zwischen Pat. mit günstiger oder ungünstiger Zytogenetik [7].

In der ENDEAVOR-Studie zeigte sich die Kombination Carfilzomib / Dexamethason gegenüber der Kombination Bortezomib /Dexamethason hinsichtlich Ansprechrate mit 77% vs 63%, Erreichen einer VGPR mit 54% vs 29%, einer Verlängerung des progressionsfreien Überlebens mit 18,7 vs 9,4 Monate sowie des Gesamtüberlebens mit 47,6 vs 40 Monaten überlegen [8]. In einer spanischen Phase-II-Studie verlängerte die Hinzunahme von Cyclophosphamid das progressionsfreie Überleben, insbesondere bei lenalidomidrefraktären Pat. mit 18,4 vs 11,3 Monaten (p=0,043) [9].

Carfilzomib / Cyclophosphamid / Dexamethason (KCd) führte bei vorbehandelten Pat. in der MUK*five* – Studie gegenüber Bortezomib / Cyclophosphamid / Dexamethason (VCd) zu einer höheren Remissionsrate ≥VGPR von 40,2 vs 31,9% (nicht unterlegen). Das Neuropathie-Risiko war höher im Bortezomib-Arm, kardiale Komplikationen traten nur im Carfilzomib-Arm auf [10].

Selinexor / Bortezomib / Dexamethason (SVd)

Die Kombination Selinexor / Bortezomib / Dexamethason (SVd) ist zugelassen für Pat. mit r/r MM, die zuvor mindestens eine Therapie erhalten haben. Selinexor blockiert Exportin 1 (XPO1). In der Zulassungsstudie BOSTON führte SVd gegenüber Bortezomib / Dexamethason zur Erhöhung der Remissionsrate ≥VGPR von 32,4 auf 44,6% und zur Verlängerung des progressionsfreien Überlebens (HR 0,71; p=0,0075). Die Gesamtüberlebenszeit wurde nicht verlängert. Häufigste Nebenwirkungen im Selinexor-Arm waren Übelkeit, Thrombozytopenie und Fatigue [11].

Daratumumab – Isatuximab / Pomalidomid / Dexamethason (DaraPd / IsaPd)

Daratumumab ist zugelassen in Kombination mit Pomalidomid und Dexamethason bei Pat. mit r/r MM, 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. Isatuximab ist zugelassen in Kombination mit Pomalidomid und Dexamethason bei Pat. mit r/r MM, die mindestens zwei vorangegangene Therapie einschl. einem Proteasom-Inhibitor und Lenalidomid erhalten haben.

In der APOLLO-Studie führte Daratumumab / Pomalidomid / Dexamethason gegenüber Pomalidomid / Dexamethason zur Steigerung der Remissionsrate ≥VGPR von 20,0 auf 49,6% und zur Verlängerung der progressionsfreien Überlebenszeit in der Gesamtstudie (HR 0,63; p=0,0018), das mediane Gesamtüberleben konnte von 23.7 auf 34.4 Monate verlängert werden. Unerwünschte Ereignisse im CTCAE Grad 3/4 traten bei 88,0% der Patient*innen im DaraPd-Arm vs 85,6% der Pat.

im Kontrollarm auf. Häufigste unerwünschte Ereignisse waren Neutropenie, Anämie und Thrombozytopenie. Im Daratumumab-Arm traten häufiger Pneumonien auf [12, 13].

In der ICARIA-MM-Studie führte Isatuximab / Pomalidomid / Dexamethason gegenüber Pomalidomid / Dexamethason zur Steigerung der Remissionsrate ≥VGPR von 8,3 auf 31,8% und zur Verlängerung der progressionsfreien Überlebenszeit (HR 0,60; p=0,0010). Die Gesamtüberlebenszeit wurde ebenfalls verlängert, aber nicht statistisch signifikant (HR 0,69; p=0,0613). Schwere unerwünschte Ereignisse im CTCAE Grad 3/4 traten bei 91% der Pat. im IsaPD vs 76% der Pat. im Pomalidomid/Dexamethason-Arm auf. Dabei traten im Isatuximab-Arm u. a. häufiger Neutropenie und febrile Neutropenie auf [14, 15].

Daratumumab – Isatuximab / Carfilzomib / Dexamethason (DaraKd, IsaKd)

Daratumumab und Isatuximab sind jeweils zugelassen in Kombination mit Carfilzomib / Dexamethason bei Pat. mit r/r MM, die bereits mindestens eine vorherige Therapie erhalten haben.

In der CANDOR-Studie führte Daratumumab / Carfilzomib / Dexamethason gegenüber Carfilzomib / Dexamethason zur Steigerung der Remissionsrate ≥VGPR von 49 auf 69% und zur Verlängerung der progressionsfreien Überlebenszeit (HR 0,63; p=0,0027), nicht der Gesamtüberlebenszeit (HR 0,76; p=0,118). Schwere unerwünschte Ereignisse im CTCAE Grad 3/4 traten bei 82% der Patient*innen im Carfilzomib/Daratumumab/Dexamethason vs 74% der Patient*innen im Carfilzomib/Dexamethason-Arm auf. Dabei traten im Daratumumab-Arm häufiger Thrombozytopenie, Diarrhoe, Infekte der oberen Luftwege und Fatigue auf. Die Herzinsuffizienzrate aller Schweregrade lag unter Daratumumab / Carfilzomib / Dexamethason bei 9,4%, unter Carfilzomib / Dexamethason bei 11,2% [16, 17].

In der IKEMA-Studie führte Isatuximab / Carfilzomib / Dexamethason gegenüber Carfilzomib / Dexamethason zur Steigerung der Rate von Pat. ohne minimale Resterkrankung von 13,0 auf 29,6% sowie zur Verlängerung des progressionsfreien Überlebens (HR 0,53; p=0,0013), nicht der Gesamtüberlebenszeit [18]. Dabei traten im Isatuximab-Arm u. a. häufiger Infektionen, Pneumonie, Stoffwechselstörungen und psychiatrische Erkrankungen auf. Die Herzinsuffizienzrate lag in den beiden Studienarmen bei 8,5 bzw. 7,4%.

Daratumumab / Bortezomib / Dexamethason (DaraVd)

Daratumumab ist zugelassen in Kombination mit Bortezomib / Dexamethason (DaraVd) Pat. mit r/r MM, die bereits mindestens eine vorherige Therapie erhalten haben.

In der CASTOR-Studie führte Daratumumab / Bortezomib / Dexamethason gegenüber Bortezomib / Dexamethason zur Steigerung der Remissionsrate ≥VGPR von 27,5 auf 60,2%, zur Verlängerung der progressionsfreien Überlebenszeit (HR 0,31; p<0,0001) und der Gesamtüberlebenszeit (HR 0,74; p=0,0075) [20, 21]. Besonders relevant bei Bortezomib ist das Neuropathie-Risiko, es kann durch subkutane statt intravenöser Gabe gesenkt werden.

Elranatamab

Eltranatamab ist ein bispezifischer, Anti-BCMA-gerichteter Antikörper. Er ist zugelassen als Monotherapie für Pat., **di**e mindestens 3 vorangegangene Therapien erhalten haben, darunter einen Proteasom-Inhibitor, einen immunmodulatorischen Wirkstoff und einen anti-CD38-Antikörper. Elranatamab wird in fixer Dosierung gegeben.

Basis ist die Phase-II-Studie MagnetisMM-3. In der Zulassungsstudie führte Elranatamab zu führte zu einer Ansprechrate ≥CR von 51,9% in der Gesamtpopulation und von 61,0% in der Kohorte ohne BCMA-gerichtete Vortherapie. Das mediane progressionsfreie Überleben in der Gesamtpopulation lag bei 10,0 Monaten, der Median der Gesamtüberlebenszeit bei 17,3 Monaten. Schwere Nebenwirkungen im CTCAE Grad 3/4 traten bei 90,9% der Pat. auf. Am häufigsten waren Neutropenie, Anämie und Infektionen. Ein CRS aller Schweregrade trat bei 58,8% der Pat. auf, bei einem Pat. im Schweregrad 3. Ein ICANS wurde bei 4,3% der Pat. dokumentiert [22].

Teclistamab

Teclistamab ist ein bispezifischer, Anti-BCMA-gerichteter Antikörper. Er ist zugelassen als Monotherapie für Pat., **di**e mindestens 3 vorangegangene Therapien erhalten haben, darunter einen Proteasom-Inhibitor, einen immunmodulatorischen Wirkstoff und einen anti-CD38-Antikörper. Elranatamab wird in gewichtsadaptierter Dosierung gegeben.

Basis ist die Phase I/II-Studie MajesTEC-1. Teclistamab führte zu einer Ansprechrate ≥CR von 63%, zu einem medianen progressionsfreien von 11,3 Monaten und einem Median der Gesamtüberlebenszeit von 18,3 Monaten. Schwere Nebenwirkungen im CTCAE Grad 3/4 traten bei 94,5% der Pat. auf. Im Vordergrund stand die hämatologische Toxizität. Ein CRS aller Schweregrade trat 72,1% der Pat. auf, ein ICANS bei 14,5% [23].

Talquetamab

Talquetamab ist ein bispezifischer, Anti- GPRC5D-gerichteter Antikörper. Er ist zugelassen als Monotherapie für Pat., di**e** mindestens 3 Vortherapien erhalten haben, einschl. eines Immunmodulators, eines Proteasom-Inhibitors und eines Anti-CD38-Antikörpers. Talquetamab wird in gewichtsadaptierter Dosierung gegeben.

Basis der Zulassung war die Phase I/II-Studie MonumenTAL-1 mit unterschiedlichen Kohorten in Bezug auf Applikation (subkutan wöchentlich vs zweiwöchentlich) und Dosierungen (405 µg/kg vs 800 µg/kg). Die Remissionsraten beider getesteten Dosierungsstufen lagen bei 74 vs 70%, davon erreichten 33 bzw 40% mindestens eine Komplettremission. Das mediane PFÜ lag bei 7,5 vs 11,2 Monaten. Ein Zytokinfreisetzungssyndrom (CRS) aller Schweregrade trat bei 79% bzw 75% der Pat. auf, schwere Grad 3/4 CRS oder Immuneffektorzell-assoziiertes Neurotoxizitätssyndrome (ICANS) wurden nicht beobachtet. Weitere nicht hämatologische Nebenwirkungen waren Geschmacksveränderungen in 72% bzw 71%, der Patienten, Nagelveränderungen in 57% bzw 73% und Hautveränderungen in 40% bzw 30%, diese waren zumeist in Grad 1/2 und nach Absetzen reversibel. Schwere Nebenwirkungen im CTCAE Grad 3/4 traten bei 87% und 86% der Pat. auf. Am häufigsten waren dies Neutropenie (31% bzw 21%), Anämie (32% bzw 25%), sowie Infektionen bei 22% bzw 20% [24].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
Ja, diese sind oben dargestellt.

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