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: 2021-B-254-z Isatuximab

Stand: Juli 2021

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

Isatuximab
[in Kombination mit Pomalidomid und Dexamethason zur Behandlung des Multiplen Myeloms nach mindestens zwei vorherigen Therapien]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Panobinostat – Beschluss vom 17. März 2016 • Pomalidomid – Beschluss vom 17. März 2016 • Pomalidomid – Beschluss vom 5. Dezember 2019 • Elotuzumab – Beschluss vom 1. Dezember 2016 • Elotuzumab – Beschluss vom 2. April 2020 • Ixazomib – Beschluss vom 6. Juli 2017 • Carfilzomib – Beschluss vom 15. Februar 2018 • Carfilzomib – Beschluss vom 15. Juli 2021 • Daratumumab – Beschluss vom 15. Februar 2018 • Belantamab Mafodotin – Beschluss vom 4. März 2021
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:	
Isatuximab L01XC38 SARCLISA	<u>Anwendungsgebiet laut Zulassung</u> SARCLISA ist in Kombination mit Pomalidomid und Dexamethason zur Behandlung des rezidivierten und refraktären Multiplen Myeloms (MM) bei Erwachsenen indiziert, die mindestens zwei vorausgegangene Therapien, darunter Lenalidomid und einen Proteasom-Inhibitor (PI), erhalten haben und unter der letzten Therapie eine Krankheitsprogression zeigten.
Chemotherapien	
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)
Melphalan L01AA03 Alkeran®	Multiples Myelom
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.
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
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

II. Zugelassene Arzneimittel im Anwendungsgebiet

Weitere antineoplastische Arzneimittel	
Belantamab Mafodotin L01XC39 Blenrep®	Blenrep ist indiziert als Monotherapie zur Behandlung des multiplen Myeloms bei erwachsenen Patienten, die bereits mindestens vier Therapien erhalten haben und deren Erkrankung refraktär gegenüber mindestens einem Proteasom-Inhibitor, einem Immunmodulator und einem Anti-CD38-Antikörper ist, und die während der letzten Therapie eine Krankheitsprogression zeigten.
Bortezomib L01XX32 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.
Carfilzomib L01XX45 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 L01XC24 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 L01XC23 Empliciti®	Emplicit ist in Kombination mit Lenalidomid und Dexamethason zur Behandlung des Multiplen Myeloms bei Erwachsenen indiziert, welche mindestens eine vorangegangene Therapie erhalten haben (siehe Abschnitte 4.2 und 5.1) 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 (siehe Abschnitte 4.2 und 5.2).
Isatuximab L01XC38 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 L01XX50 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 L01XX42 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®	<u>Inoffizielle deutsche Übersetzung</u> - Selinexor ist indiziert in Kombination mit Dexamethason für die Behandlung von erwachsenen Patienten mit multiplem Myelom, die mindestens vier vorhergehende Therapien erhalten haben und dessen Erkrankung refraktär gegenüber mindestens zwei Proteasominhibitoren, gegenüber mindestens zwei Immunmodulatoren und gegenüber einem antiCD38-Antikörper ist, und die unter der letzten Therapie eine Progression gezeigt haben.
Glucocorticoide	
Dexamethason H02AB02 Dexa-CT®	Palliativtherapie maligner Tumoren
Prednisolon H02AB06 Decortin® H	<u>Hämatologie / Onkologie</u>: - Akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, chronische lymphatische Leukämie, Morbus Waldenström, multiples Myelom - Palliativtherapie maligner Erkrankungen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Prednison H02AB07 Decortin®	Hämatologie / Onkologie: - Akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, chronische lymphatische Leukämie, Morbus Waldenström, multiples Myelom Palliativtherapie maligner Erkrankungen
Immunstimulanzien	
Interferon alfa-2b L03AB05 IntronA®	Als Erhaltungstherapie bei Patienten, die nach einer initialen Induktions-Chemotherapie eine objektive Remission erreichten (mehr als 50%ige Reduktion des Myelomproteins). Gegenwärtige klinische Erfahrungen zeigen, dass eine Erhaltungstherapie mit Interferon alfa-2b die Plateauphase verlängert; jedoch wurden Effekte auf die Gesamtüberlebenszeit nicht endgültig bewiesen.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-254-z

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. Juli 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IMiDs	immunomodulatory drugs
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LOT	Line of therapy
NICE	National Institute for Health and Care Excellence
NMA	Network metaanalysis
OR	Odds Ratio
OS	Gesamtüberleben
RR	Relatives Risiko
PI	proteasome inhibitor
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse events
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	TRIP Database
WHO	World Health Organization

1 Indikation

Behandlung des Multipen Myeloms nach mind. 1 Vortherapie

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Multiples Myelom* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 09.06.2020 durchgeführt, die Folgerecherchen am 05.01.2021 und 11.03.2021. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherchen übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 750 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 19 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

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3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2021 [4].
Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Belantamab-Mafodotin (Multiples Myelom, mind. 4 Vortherapien, Monotherapie) vom 04. März 2021

Anwendungsgebiet (lt. Zulassung vom 25.August 2020)

Blenrep ist indiziert als Monotherapie zur Behandlung des multiplen Myeloms bei erwachsenen Patienten, die bereits mindestens vier Therapien erhalten haben und deren Erkrankung refraktär gegenüber mindestens einem Proteasom-Inhibitor, einem Immunmodulator und einem monoklonalen Anti-CD38-Antikörper ist, und die während der letzten Therapie eine Krankheitsprogression zeigten.

Fazit / Ausmaß des Zusatznutzens

Belantamab-Mafodotin ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 11 1. Halbsatz SGB V gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen, weil die wissenschaftliche Datengrundlage eine Quantifizierung nicht zulässt.

G-BA, 2020 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. April 2020 – Elotuzumab (neues Anwendungsgebiet: Multiples Myelom, Kombination mit Pomalidomid und Dexamethason)

Neues Anwendungsgebiet (laut Zulassung vom 23. August 2019)

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.

Zweckmäßige Vergleichstherapie

- Bortezomib in Kombination mit Dexamethason oder
- Lenalidomid in Kombination mit Dexamethason oder
- Pomalidomid in Kombination mit Dexamethason
- Elotuzumab in Kombination mit Lenalidomid und Dexamethason oder
- Carfilzomib in Kombination mit Lenalidomid und Dexamethason oder
- Carfilzomib in Kombination mit Dexamethason oder

- Daratumumab in Kombination mit Lenalidomid und Dexamethason oder
- Daratumumab in Kombination mit Bortezomib und Dexamethason

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Elotuzumab gegenüber Pomalidomid in Kombination mit Dexamethason:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA, 2020 [8].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Juli 2017 / 5. September 2019 / 05. November 2020 – Ixazomib

Anwendungsgebiet

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.

Fazit / Ausmaß des Zusatznutzens:

Ixazomib ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 1. Halbs. SGB V gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Ausmaß des Zusatznutzens: nicht quantifizierbar

G-BA, 2019 [7].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 05. Dezember 2019 – Pomalidomid (neues Anwendungsgebiet: Kombinationstherapie Multiples Myelom)

Anwendungsgebiet

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.

Zweckmäßige Vergleichstherapie

- Bortezomib in Kombination mit pegyliertem liposomalen Doxorubicin oder
- Bortezomib in Kombination mit Dexamethason oder
- Lenalidomid in Kombination mit Dexamethason oder
- Elotuzumab in Kombination mit Lenalidomid und Dexamethason oder
- Carfilzomib in Kombination mit Lenalidomid und Dexamethason oder
- Carfilzomib in Kombination mit Dexamethason oder
- Daratumumab in Kombination mit Lenalidomid und Dexamethason oder
- Daratumumab in Kombination mit Bortezomib und Dexamethason

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Pomalidomid in Kombination mit Bortezomib und Dexamethason gegenüber Bortezomib in Kombination mit Dexamethason:

- Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [10].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Februar 2018 – Daratumumab

(erneute Nutzenbewertung, Überschreitung 50 Mio € Grenze, Erstbewertung neues Anwendungsgebiet: Multiples Myelom nach mind. 1 Vortherapie)

gültig bis: Die zu der Patientengruppe a) „Daratumumab 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“ getroffenen Feststellungen in den Nummern 1, 2, 3 und 4 sind bis zum 1. Oktober 2021 befristet

Indikation

Neues Anwendungsgebiet (laut Zulassung vom 28. April 2017):

Darzalex ist indiziert in Kombination mit Lenalidomid und Dexamethason oder Bortezomib und Dexamethason für die Behandlung erwachsener Patienten mit multiplem Myelom, die bereits mindestens eine Therapie erhalten haben.

Anwendungsgebiet (laut Zulassung vom 20. Mai 2016):

Darzalex ist indiziert 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.

Vergleichstherapie

a) Daratumumab 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.

Zweckmäßige Vergleichstherapie:

- Bortezomib in Kombination mit pegyliertem, liposomalen Doxorubicin
  oder
- Bortezomib in Kombination mit Dexamethason
  oder
- Lenalidomid in Kombination mit Dexamethason
  oder
- Elotuzumab in Kombination mit Lenalidomid und Dexamethason

b) Daratumumab 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.

Zweckmäßige Vergleichstherapie:

Eine patientenindividuelle Therapie nach Maßgabe des Arztes, insbesondere in Abhängigkeit von den Vortherapien sowie der Ausprägung und Dauer des Ansprechens sowie unter Beachtung der Zulassung der jeweiligen Arzneimittel.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Zu a)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Lenalidomid in Kombination mit Dexamethason oder Bortezomib in Kombination mit Dexamethason: Hinweis auf einen beträchtlichen Zusatznutzen.

Zu b)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie: Ein Zusatznutzen ist nicht belegt.

.G-BA, 2018 [9].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Februar 2018 – Carfilzomib

Indikation

Kyprolis ist in Kombination mit entweder Lenalidomid und Dexamethason oder Dexamethason allein zur Behandlung von erwachsenen Patienten mit multiplem Myelom indiziert, die mindestens eine vorangegangene Therapie erhalten haben

Vergleichstherapie

a) Carfilzomib in Kombination mit Lenalidomid und Dexamethason für die Behandlung erwachsener Patienten mit multiplem Myelom, die bereits mindestens eine Therapie erhalten haben.

Zweckmäßige Vergleichstherapie:

- Bortezomib in Kombination mit pegyliertem, liposomalen Doxorubicin
  oder
- Bortezomib in Kombination mit Dexamethason
  oder
- Lenalidomid in Kombination mit Dexamethason
  oder
- Elotuzumab in Kombination mit Lenalidomid und Dexamethason

b) Carfilzomib in Kombination mit Dexamethason für die Behandlung erwachsener Patienten mit multiplem Myelom, die bereits mindestens eine Therapie erhalten haben.

Zweckmäßige Vergleichstherapie:

- Bortezomib in Kombination mit pegyliertem, liposomalen Doxorubicin
  oder
- Bortezomib in Kombination mit Dexamethason
  oder
- Lenalidomid in Kombination mit Dexamethason

oder

- Elotuzumab in Kombination mit Lenalidomid und Dexamethason

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Zu a)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Lenalidomid in Kombination mit Dexamethason:

Anhaltspunkt für einen beträchtlichen Zusatznutzen

Zu b)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Bortezomib in Kombination mit Dexamethason:

Anhaltspunkt für einen beträchtlichen Zusatznutzen

G-BA, 2016 [5].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Dezember 2016 – Elotuzumab

Anwendungsgebiet

Empliciti ist in Kombination mit Lenalidomid und Dexamethason zur Behandlung des Multiplen Myeloms bei Erwachsenen indiziert, welche mindestens eine vorangegangene Therapie erhalten haben (siehe Abschnitt 4.2 und 5.1 der Fachinformation)

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Empliciti in Kombination mit Lenalidomid und Dexamethason zur Behandlung des Multiplen Myeloms bei Erwachsenen, welche mindestens eine vorangegangene Therapie erhalten haben, ist:

- Bortezomib als Monotherapie oder
- Bortezomib in Kombination mit pegyliertem, liposomalen Doxorubicin oder
- Bortezomib in Kombination mit Dexamethason oder
- Lenalidomid in Kombination mit Dexamethason

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Lenalidomid in Kombination mit Dexamethason: Anhaltspunkt für einen geringen Zusatznutzen

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G-BA, 2016 [11].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 17. März 2016 – Panobinostat.

Indikation

Zugelassenes Anwendungsgebiet (laut Zulassung vom 28.08.2015):

Panobinostat (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.

Fazit / Ausmaß des Zusatznutzens

Panobinostat ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß 5. Kapitel § 12 Absatz 1 Nummer 1 Satz 2 der Verfahrensordnung des G-BA (VerfO) das Ausmaß des Zusatznutzens für die Anzahl der Patienten und Patientengruppen, für die ein therapeutisch bedeutsamer Zusatznutzen besteht. Diese Quantifizierung des Zusatznutzens erfolgt am Maßstab der im 5. Kapitel § 5 Absatz 7 Nummer 1 bis 4 VerfO festgelegten Kriterien.

Ausmaß des Zusatznutzens: nicht quantifizierbar

G-BA, 2016 [12].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 17. März 2016 – Pomalidomid.

Indikation

Pomalidomid (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.

Vergleichstherapie

Pomalidomid ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden.

Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß 5. Kapitel § 12 Absatz 1 Nummer 2 der Verfahrensordnung des G-BA (VerfO) die Wahrscheinlichkeit und das Ausmaß des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie für die Anzahl der Patienten und Patientengruppen, für die ein therapeutisch bedeutsamer Zusatznutzen besteht, wenn der Umsatz des Arzneimittels für seltene Leiden mit der gesetzlichen Krankenversicherung zu Apothekenverkaufspreisen einschließlich Umsatzsteuer in den letzten zwölf Kalendermonaten einen Betrag von 50 Millionen Euro übersteigt.

Zweckmäßige Vergleichstherapie:

In Abhängigkeit von den Vortherapien sowie der Ausprägung und Dauer des jeweiligen Ansprechens sowie unter Beachtung der Zulassung der jeweiligen Arzneimittel,

– eine patientenindividuelle Therapie nach Maßgabe des Arztes.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer patientenindividuellen Therapie nach Maßgabe des Arztes:

1) Patienten, für die Dexamethason (hochdosiert) die patientenindividuelle Therapie nach Maßgabe des Arztes darstellt: Anhaltspunkt für einen beträchtlichen Zusatznutzen.

2) Patienten, für die Dexamethason (hochdosiert) nicht die patientenindividuelle Therapie nach Maßgabe des Arztes darstellt: Ein Zusatznutzen ist nicht belegt

3.2 Cochrane Reviews

Scott K et al., 2016 [16].

Bortezomib for the treatment of multiple myeloma

Fragestellung

We assessed the effects of bortezomib treatment in comparison to other therapies, different doses, treatment administration and schedules of bortezomib, on overall survival (OS), progression free survival (PFS), response rate (RR), health-related quality of life (HRQoL), adverse events (AE) and treatment-related death (TRD).

Methodik

Population:

- Patients with any diagnosis of multiple myeloma who were either newly diagnosed (had received no prior therapy) or patients with relapsed disease. We also included patients who were considered to be either transplant eligible or ineligible. Patient eligibility for stem cell transplant is determined primarily by age, as well as performance status, frailty, and presence of comorbidities. We did not define transplant eligibility for this review and therefore selected studies that included all types of patients.

Intervention/Komparator:

We included RCTs that investigated the following comparisons.

- Bortezomib versus no bortezomib with the same background therapy in each arm
- Bortezomib versus no bortezomib with different background therapy in each arm or compared to other agent(s)
- Bortezomib dose comparisons and comparisons of different treatment administrations and schedules

Endpunkte:

- OS, PFS, ORR, PRR, TTP, CRR, AE, HRQoL

Recherche/Suchzeitraum:

- MEDLINE, the Cochrane Central Register of Controlled Trials and EMBASE (till 27 January 2016)

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

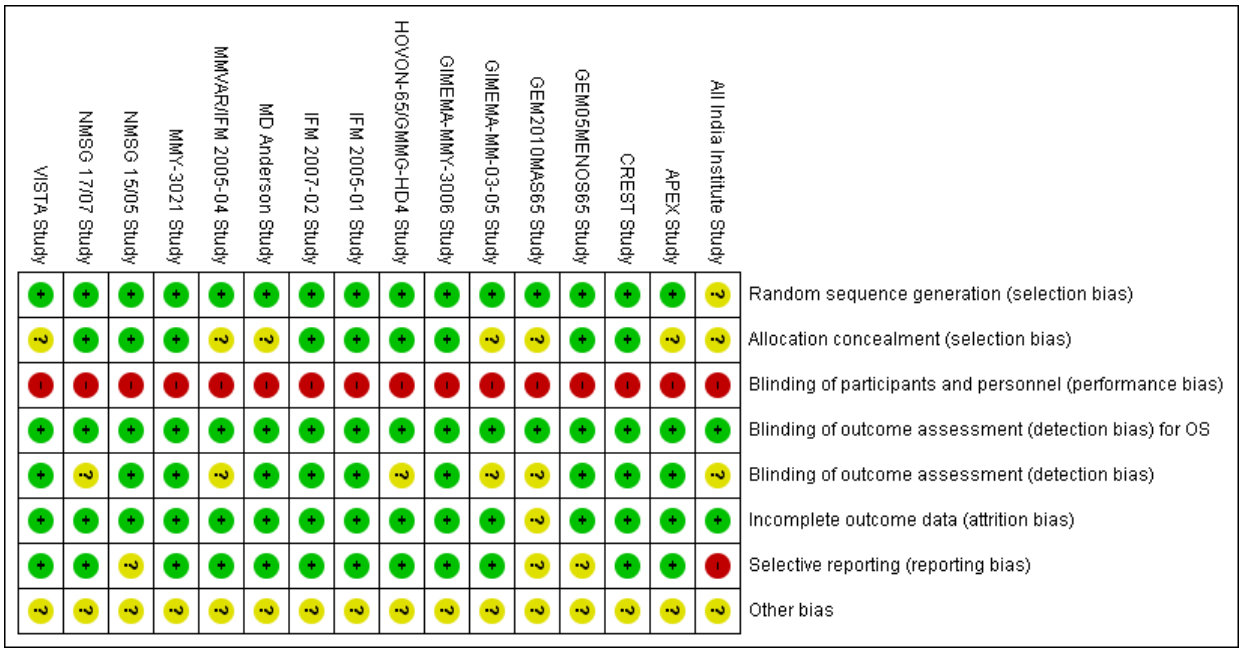
- 16 relevant RCTs involving 5626 patients; 12 trials included in the meta-analyses.
  - 5 trials in patients with relapsed/refractory myeloma (APEX Study; CREST Study; MMVAR/IFM 2005-04 Study; MMY-3021 Study; NMSG 17/07 Study).

Studiencharakteristika: Hier Studien zu relapsed/refractory myeloma

- APEX Study (IV bortezomib vs Oral dexamethasone)

- MMVAR/IFM 2005-04 Study (IV bortezomib vs Oral thalidomide and oral dexamethasone)
- NMSG 17/07 Study (IV Bortezomib + oral Dexamethasone vs oral Thalidomide + oral Dexamethasone)
- CREST Study (Bortezomib 1.0 mg/m^2 IV vs Bortezomib 1.3 mg/m^2 IV)
- MMY-3021 Study (Bortezomib 1.3 mg/m^2 by SC vs Bortezomib 1.3 mg/m^2 by IV)

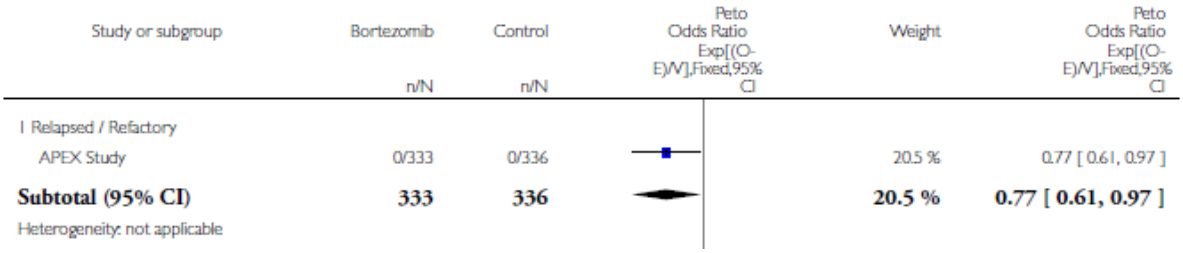
Qualität der Studien:



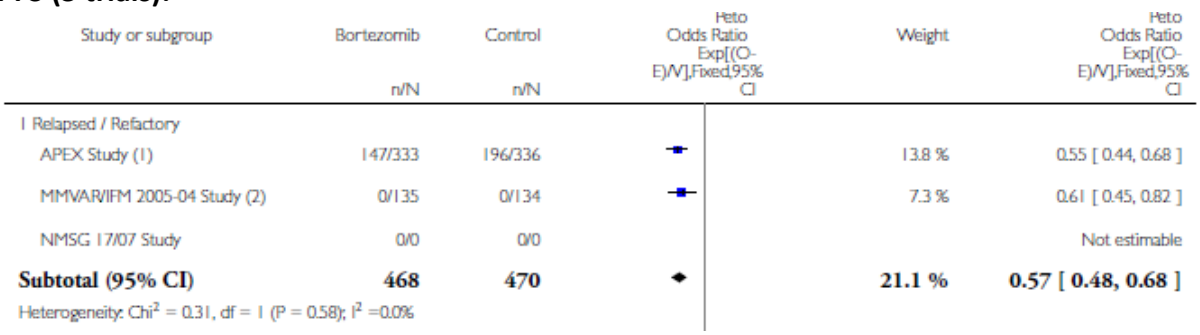
Studienergebnisse:

nur Darstellung der Ergebnisse für relapsed/refractory myeloma

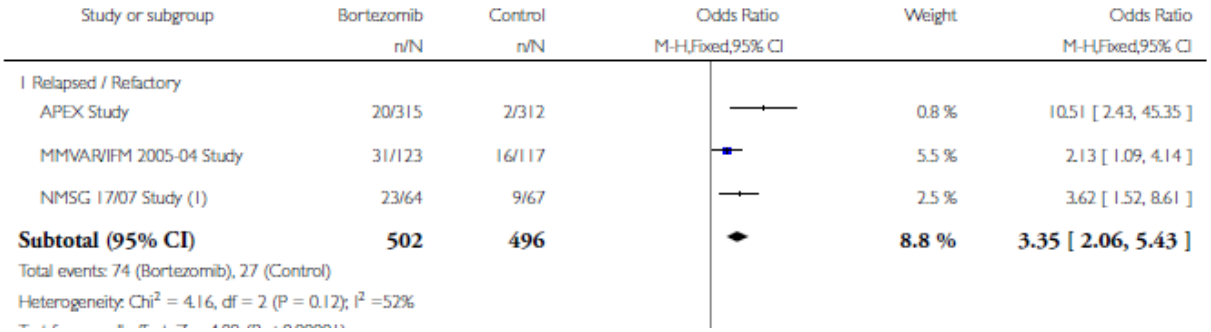
OS (1 trial):



PFS (3 trials):



Complete response rate (3 trials):



Health-related quality of life (2 trials on RRMM)

- data from the APEX Study (bortezomib versus no bortezomib with different background therapy or versus other agent(s)) indicated that patients treated with bortezomib had significantly better mean Global Health Status when compared to patients receiving dexamethasone. Patients treated with bortezomib also had significantly better physical health, role, cognitive, and emotional functioning scores, lower dyspnoea and sleep symptom scores. Better NTX questionnaire scores were observed on the bortezomib arm when compared to the dexamethasone arm, despite a significantly greater incidence of greater than or equal to grade three peripheral neuropathy in those who received bortezomib. This observation could be due to the range of measures assessed by the NTX scale that are not related to peripheral neuropathy.
- In the NMSG 17/07 Study of bortezomib and dexamethasone versus thalidomide and dexamethasone in melphalan-refractory patients (bortezomib versus no bortezomib with different background therapy or versus other agent(s)), no difference was seen for any of the quality of life domains measured, with the exception of fatigue which was observed to be worse in the bortezomib arm (P = 0.04). A significantly higher score for sleep disturbance was observed in the bortezomib arm at 12 weeks of treatment (P < 0.01).

AE (alle Patienten; keine Subgruppenanalysen für RRMM verfügbar)

- Patients treated with bortezomib have increased risk of thrombocytopenia, neutropenia, gastro-intestinal toxicities, peripheral neuropathy, infection and fatigue with the quality of evidence highly variable.
- There is high-quality evidence for increased risk of cardiac disorders from analysing trials of bortezomib versus no bortezomib with different background therapy in each arm or versus other agents.

- The risk of treatment-related death in either comparison group analysed is uncertain due to the low quality of the evidence.

Fazit der Autoren (bezogen auf alle untersuchten Patientenpopulationen)

Patients receiving bortezomib had better response rates, longer time without progression and appeared to live longer compared to those not receiving bortezomib, however patients receiving bortezomib experienced more side effects. Other proteasome inhibitor drugs have also been developed, therefore further research should focus on whether these newer drugs provide additional benefits and fewer side effects than bortezomib. More studies on health-related quality of life are also needed.

3.3 Systematische Reviews

Arcuri LJ et al. 2021 [1].

Treatment of relapsed/refractory multiple myeloma in the bortezomib and lenalidomide era: a systematic review and network-meta-analysis.

Fragestellung

Due to the abundance of new treatment options for MM and the fact that direct comparisons are unlikely (at least in the short term), we conducted a network meta-analysis to review the available evidence of novel treatments for relapsed/refractory MM, in the setting of new drugs, and to identify combinations that could fare better than others.

Methodik

Population:

- Patients with relapsed/refractory MM

Intervention:

- Vorinostat
- Panabinostat
- Pomalidomide
- Pegylated doxorubicin
- Cyclophosphamide
- Elotuzumab
- Pembrolizumab
- ASCT
- Venetoclax
- Carfilzomib
- Ixazomib
- Daratumumab
- Isatuximab
- Selinexor

Komparator:

- lenalidomide
- bortezomib

Endpunkte:

- PFS
- OS
- number of SAE (if not available: grades III/IV AE)

Recherche/Suchzeitraum:

- Januar 2007 bis Dezember 2020

Qualitätsbewertung der Studien:
Cochrane RoB

NMA-spezifische Angaben

- A network meta-analysis with fixed effect, or random effects if I2 was higher than 40%, was carried out and presented as table and forest plots.
- We performed a sensitivity analysis categorizing the control arms into two groups: immunomodulatory-based (lenalidomide and pomalidomide) or bortezomib-based, and we were able to show that both treatments are equivalent, supporting our decision to group these categories into a single one […] making the path for indirect comparisons shorter, which increases the power to detect differences.
- Nachträgliche Erweiterung der Kontrollintervention um pomalidomide und carfilzomib.

Ergebnisse

Anzahl eingeschlossener Studien:

- After discussion, two studies with pomalidomide and one with carfilzomib in the control arm were also included.
- In brief, all but three had lenalidomide (6) or bortezomib (8) in the control arm with or without dexamethasone; one had carfilzomib and two had pomalidomide in the control arm.
- Intervention arms included vorinostat (1), panobinostat (1), pomalidomide (1), pegylated doxorubicin (1), cyclophosphamide (1), elotuzumab (1), pembrolizumab (1), autologous stem cell transplantation (ASCT, 1), venetoclax (1), carfilzomib (2), ixazomib (2), daratumumab (3), isatuximab (1), and selinexor (1).
- Intervention arms were combinations of three drugs except for two, which were a combination of carfilzomib and dexamethasone, and bortezomib and vorinostat without dexamethasone.

Charakteristika der Population:

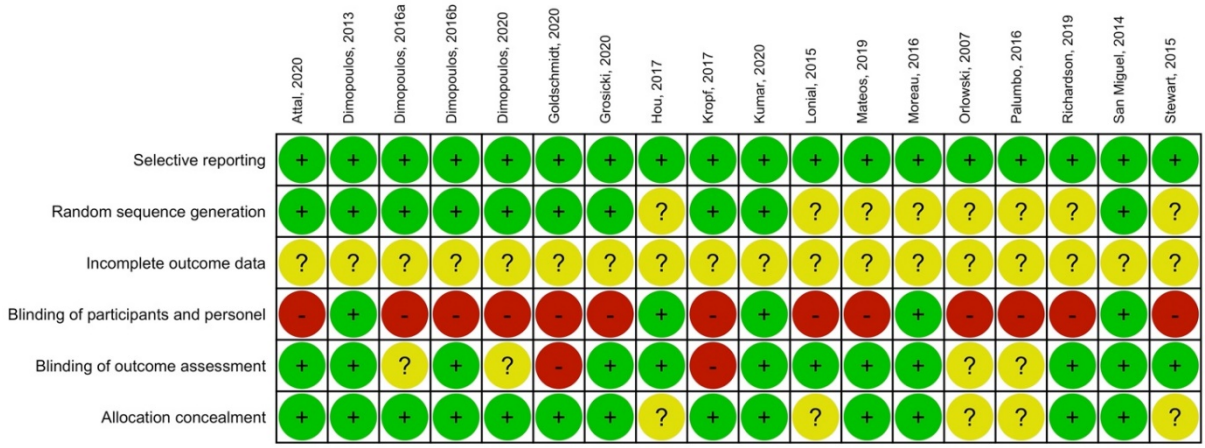
- In total, 4609 patients were included in the intervention arms, and 4357 in the control arms.

Table 1 Characteristics of the included studies

Nome	Author	Intervention	Control	Ni	Nc	Median follow-up (months)	PFSi (months)	PFSc (months)	Age range	Previous therapy
VANTAGE 088	Dimopoulos, 2013	Bortezomib and vorinostat	Bortezomib	317	320	14,2	7,63	6,83	29-86	1-3
POLLUX	Dimopoulos, 2016a	Daratumumab, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	286	283	13,5	NR	18,4	34-89	1+
ENDEAVOR	Dimopoulos, 2016b	Carfilzomib and dexamethasone	Bortezomib and dexamethasone	464	465	11,9	18,7	9,4	NA	1+
TOURMALINE-MM1-China	How, 2017	Ixazomib, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	57	58	20,5	6,7	4	NA	1-3
NCT00813150	Kropf, 2017	Cyclophosphamide, bortezomib, and dexamethasone	Bortezomib and dexamethasone	46	47	24	12,6	9,9	NA	1+
ELOQUENT-2	Lonial, 2015	Elotuzumab, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	321	325	24,5	19,4	14,9	37-91	1-3
KEYNOTE-183	Mateos, 2019	Pembrolizumab, pomalidomide, and dexamethasone	Pomalidomide and dexamethasone	125	124	8,1	5,6	8,4	NA	2+
TOURMALINE-MM1	Moreau, 2016	Ixazomib, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	360	362	14,7	20,6	14,7	30-91	1-3
DOXIL-MMY-3001	Orlowski, 2007	Pegylated liposomal doxorubicin and bortezomib	Bortezomib	324	322	7,2	9	6,5	NA	1+
CASTOR	Palumbo, 2016	Daratumumab, bortezomib, and dexamethasone	Bortezomib and dexamethasone	251	247	7,4	NR	7,2	30-88	1+
OPTIMISMM	Richardson, 2019	Pomalidomide, bortezomib, and dexamethasone	Bortezomib and dexamethasone	281	278	15,9	11,2	7,1	NA	1-3
PANORAMA1	San Miguel, 2014	Panobinostat, bortezomib, and dexamethasone	Bortezomib and dexamethasone	387	381	6	11,99	8,08	NA	1-3
ASPIRE	Stewart, 2015	Carfilzomib, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	396	396	31,9	26,3	17,6		1-3
BELLINI	Kumar, 2020	Venetoclax, bortezomib, and dexamethasone	Bortezomib and dexamethasone	194	97	18.7	22.4	11.5	NA	1-3
GMMG ReLApsE	Goldschmidt, 2020	ASCT, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	139	138	36.8	20.7	18.8	NA	1-3
BOSTON	Grosicki, 2020	Selinexor, bortezomib, and dexamethasone	Bortezomib and dexamethasone	195	207	14.9	13.93	9.46	NA	1-3
CANDOR	Dimopoulos, 2020	Daratumumab, carfilzomib, and dexamethasone	Carfilzomib and dexamethasone	312	154	17	NR	15.8	NA	1-3
ICARIA-MM	Attal, 2020	Isatuximab, pomalidomide, and dexamethasone	Pomalidomide and dexamethasone	154	153	11.6	11.5	6.5	NA	1-3

* At least 12 months after the first high-dose chemotherapy; Ni and Nc: number of patients in investigational and control arms; PFSi and PFSc: median progression-free survival in investigational and controls arms; NA: not available; NR: not reached

Qualität der Studien:



Studienergebnisse:

- PFS
  - Forest plots for PFS […] suggest that triplet regimens containing daratumumab achieve better progression-free survival.
  - Pembrolizumab was an outlier, and PFS was actually worse with pembrolizumab.
  - Heterogeneity (I^2) = 64%

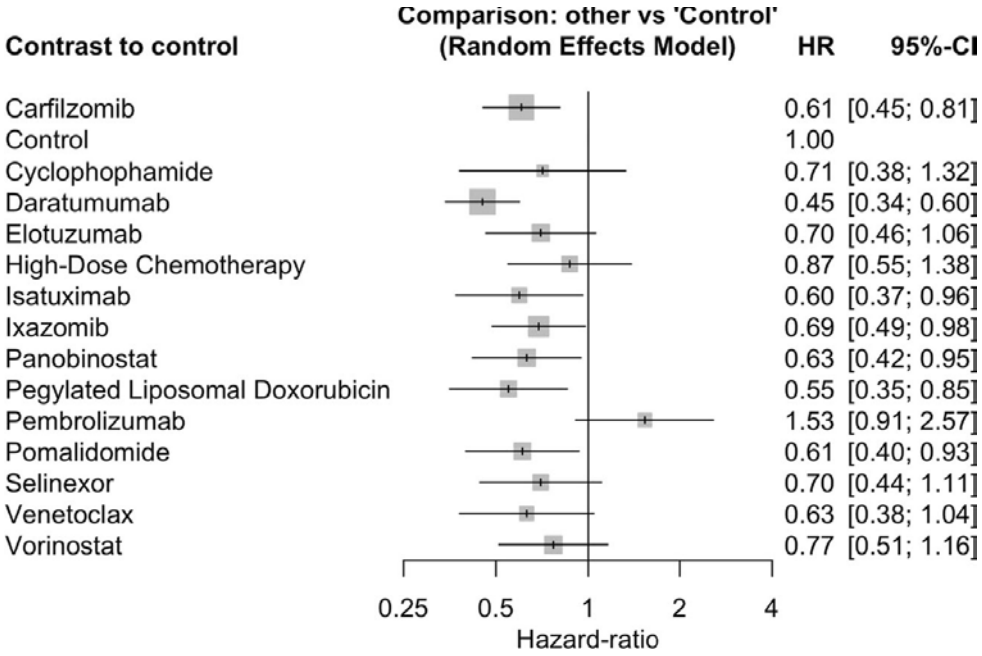


Table 2 Hazard ratios for PFS

Carfilzomib	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0.61 [0.45; 0.81]	Control	.	.	.	.	.	.	.	.	.	.	.	.	.
0.85 [0.43; 1.69]	1.41 [0.76; 2.63]	Cy	.	.	.	.	.	.	.	.	.	.	.	.
1.34 [0.90; 2.00]	**2.21 [1.68; 2.92]**	1.57 [0.79; 3.11]	Dara	.	.	.	.	.	.	.	.	.	.	.
0.86 [0.52; 1.43]	1.43 [0.95; 2.16]	1.01 [0.48; 2.14]	**0.65 [0.39; 1.06]**	Elotuzumab	.	.	.	.	.	.	.	.	.	.
0.70 [0.40; 1.20]	1.15 [0.72; 1.82]	0.82 [0.38; 1.77]	**0.52 [0.30; 0.89]**	0.80 [0.43; 1.49]	High-dose chemo	.	.	.	.	.	.	.	.	.
1.02 [0.58; 1.77]	**1.68 [1.04; 2.70]**	1.19 [0.54; 2.61]	0.76 [0.44; 1.32]	1.17 [0.63; 2.20]	1.46 [0.75; 2.83]	Isatuximab	.	.	.	.	.	.	.	.
0.88 [0.56; 1.38]	**1.45 [1.02; 2.06]**	1.03 [0.50; 2.11]	0.66 [0.42; 1.02]	1.02 [0.59; 1.74]	1.26 [0.71; 2.25]	0.86 [0.48; 1.56]	Ixazomib	.	.	.	.	.	.	.
0.96 [0.58; 1.58]	**1.59 [1.06; 2.38]**	1.13 [0.54; 2.37]	0.72 [0.44; 1.17]	1.11 [0.62; 1.98]	1.38 [0.75; 2.56]	0.95 [0.51; 1.77]	1.09 [0.64; 1.87]	Pano	.	.	.	.	.	.
1.10 [0.65; 1.87]	**1.82 [1.17; 2.83]**	1.29 [0.60; 2.77]	0.82 [0.49; 1.39]	1.27 [0.70; 2.33]	1.58 [0.84; 3.00]	1.08 [0.57; 2.08]	1.25 [0.71; 2.20]	1.15 [0.63; 2.09]	Pegylated liposomal doxorubicin	.	.	.	.	.
0.40 [0.22; 0.72]	0.65 [0.39; 1.10]	0.46 [0.21; 1.04]	**0.30 [0.16; 0.53]**	**0.46 [0.24; 0.89]**	0.57 [0.28; 1.14]	**0.39 [0.19; 0.79]**	**0.45 [0.24; 0.84]**	**0.41 [0.21; 0.80]**	**0.36 [0.18; 0.71]**	Pembro	.	.	.	.
0.99 [0.59; 1.66]	**1.64 [1.07; 2.51]**	1.16 [0.55; 2.48]	0.74 [0.45; 1.23]	1.15 [0.64; 2.07]	1.43 [0.76; 2.67]	0.98 [0.52; 1.85]	1.13 [0.65; 1.96]	1.03 [0.57; 1.86]	0.90 [0.49; 1.66]	**2.51 [1.28; 4.91]**	Poma	.	.	.
0.86 [0.50; 1.48]	1.43 [0.90; 2.26]	1.01 [0.47; 2.20]	0.65 [0.38; 1.10]	1.00 [0.54; 1.85]	1.24 [0.65; 2.38]	0.85 [0.44; 1.65]	0.98 [0.55; 1.75]	0.90 [0.49; 1.66]	0.78 [0.42;1.48]	**2.19 [1.09;4.3-6]**	0.87 [0.47;1.6-3]	Selinexor	.	.
0.96 [0.54; 1.72]	1.59 [0.96; 2.63]	1.13 [0.51; 2.51]	0.72 [0.40; 1.28]	1.11 [0.58; 2.13]	1.38 [0.70; 2.74]	0.95 [0.47; 1.89]	1.09 [0.59; 2.02]	1.00 [0.52; 1.91]	0.87 [0.45; 1.70]	**2.43 [1.18; 5.01]**	0.97 [0.50; 1.87]	1.11 [0.56; 2.19]	Venetoclax	.
0.79 [0.48; 1.30]	1.30 [0.86; 1.95]	0.92 [0.44; 1.94]	**0.59 [0.36; 0.96]**	0.91 [0.51; 1.62]	1.13 [0.61; 2.09]	0.77 [0.41; 1.45]	0.90 [0.52; 1.53]	0.82 [0.46; 1.46]	0.71 [0.39; 1.30]	**1.99 [1.03; 3.85]**	0.79 [0.44; 1.43]	0.91 [0.49; 1.68]	0.82 [0.43; 1.56]	Vorinostat

Comparisons are columns against rows. For example, HR of carfilomib, compared with control, is 0.61 (first column, second row). Cy: cyclophosphamide; Dara: daratumumab; Panobino: panobinostat Poma: pomalidomide; HDT: high-dose therapy (autologous stem-cell transplantation); Pembro: pembrolizumab; Poma: pomalidomide. In bold are statistically significant results

- OS
  - more potent therapies lead to better survival (HR = 0.83; 95CI 0.76–0.90)
  - Heterogeneity (I^2) = 0%

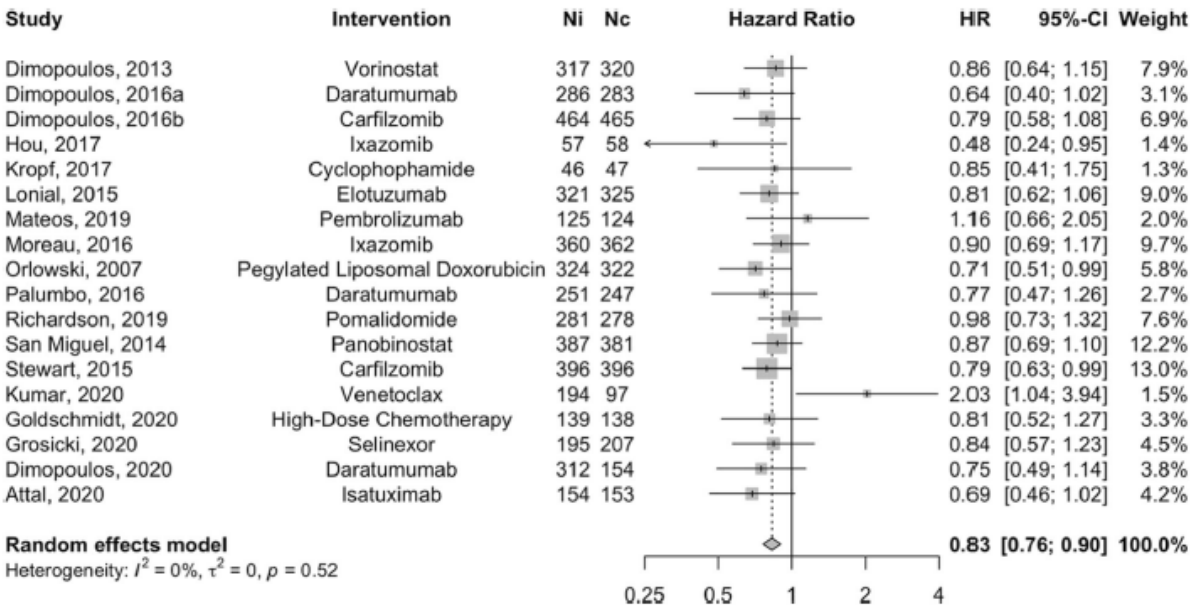


Fig. 4 Standard forest plot for OS

- SAE
  - Seventeen studies reported data on SAE and one only one, grade III-IV AE.
  - Heterogeneity (I^2) = 0%

Fig. 5 Network meta-analysis forest plot for SAE

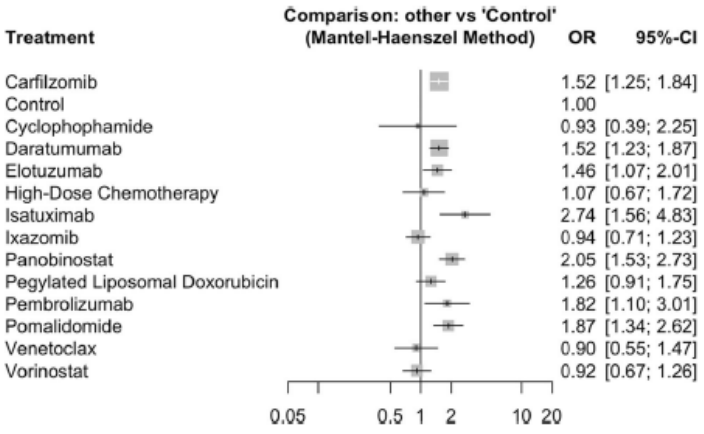


Table 3 Ranking of investigational agents

Treatment	*P* score for PFS		*P* score for OS		*P* score for SAE	
Daratumumab	0.924	#1	0.769	#2	0.377	#8
Pegylated liposomal doxorubicin	0.735	#2	0.766	#3	0.552	#7
Isatuximab	0.651	#3	0.787	#1	0.044	#14
Carfilzomib	0.648	#4	0.639	#4	0.377	#8
Pomalidomide	0.631	#5	0.310	#12	0.198	#12
Panobinostat	0.597	#6	0.476	#11	0.134	#13
Venetoclax	0.593	#7	0.019	#15	0.821	#2
Ixazomib	0.495	#8	0.549	#7	0.819	#3
Selinexor	0.483	#9	0.534	#8	NA	
Elotuzumab	0.481	#10	0.595	#5	0.412	#10
Cyclophosphamide	0.476	#11	0.522	#9	0.743	#5
Vorinostat	0.380	#12	0.501	#10	0.832	#1
High-dose chemotherapy	0.273	#13	0.580	#6	0.688	#6
Control	0.120	#14	0.235	#13	0.762	#4
Pembrolizumab	0.015	#15	0.218	#14	0.240	#11

The *P* score of treatment should be interpreted as the certainty that one treatment is better than another one. It ranges from 0 (worst) to 1 (best). PFS: progression-free survival; OS: overall survival; SAE: serious adverse event; NA: not available

- Sensitivitätsanalysen:
  - We performed a sensitivity analysis categorizing the control arms by immunomodulatory agent-based (IMiD/ lenalidomide or pomalidomide) or proteasome-inhibitorbased (bortezomib or carfilzomib). Daratumumab remained the best treatment regarding PFS, followed by pegylated liposomal doxorubicin, carfilzomib, and isatuximab. For the overall survival, the best treatments, in order, were pegylated doxorubicin, daratumumab, isatuximab, and carfilzomib.
  - HR for bortezomib in the control arms, compared with lenalidomide or pomalidomide in the control arms, was 1.02 (95CI 0.62–1.70) for PFS and 1.06 (95CI 0.76–1.47).

Treatment¤	PFS¤	OS¤	¤
daratumumab¤	0,974¤	0,784¤	¤
pld¤	0,781¤	0,794¤	¤
isatuximab¤	0,769¤	0,755¤	¤
carfilzomib¤	0,726¤	0,638¤	¤
pomalidomide¤	0,646¤	0,367¤	¤
panobinostat¤	0,599¤	0,539¤	¤
venetoclax¤	0,596¤	0,025¤	¤
elotuzumab¤	0,566¤	0,569¤	¤
ixazomib¤	0,544¤	0,524¤	¤
cy¤	0,459¤	0,554¤	¤
selinexor¤	0,454¤	0,581¤	¤
vorinostat¤	0,325¤	0,557¤	¤
ASCT¤	0,303¤	0,557¤	¤
IMID¤	0,156¤	0,24¤	¤
PI¤	0,094¤	0,304¤	¤
pembrolizumab¤	0,008¤	0,212¤	¤

Anmerkung/Fazit der Autoren

Our results show that triplet regimens containing daratumumab or pegylated liposomal doxorubicin could be preferred over other regimens in relapsed/refractory MM.

Kommentare zum Review

- weiterführende spezifische Details zum statistischen Vorgehen werden nicht berichtet

---

Giri S et al., 2020 [13].

Evaluation of Daratumumab for the Treatment of Multiple Myeloma in Patients with High-risk Cytogenetic Factors: A Systematic Review and Meta-analysis.

Fragestellung

To measure PFS associated with adding daratumumab to backbone MM regimens among patients with HRMM.

Methodik

Population:

- newly diagnosed or relapsed or refractory HRMM

Intervention/Komparator:

- backbone MM regimens vs. the same regimen plus daratumumab

Endpunkte:

- PFS, OS

Recherche/Suchzeitraum:

- MEDLINE, Embase, PubMed, Scopus, Web of Science Core Collection, Cochrane Library, clinical trials registries, and meeting libraries were searched from inception to January 2, 2020,

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 phase 3 trials were eligible, including 3 trials for newly diagnosed MM (2528 patients; 358 with HRMM) and 3 trials for relapsed or refractory MM (1533 patients; 222 with HRMM)

Qualität der Studien:

Five of 6 studies had a low risk for bias in random sequence generation (selection bias, 83%) and allocation concealment (selection bias, 83%). For the CANDOR study,[16] the risk of bias could not be evaluated owing to the availability of limited published data in abstract form only.[16] All included studies were open-label studies and none reported blinding of outcome assessment, potentially indicating the presence of detection bias, although 3 studies (MAIA,[10] CASTOR,[14] and POLLUX[15]) reported using a validated computer algorithm to evaluate treatment response and progression. All included studies had a low risk for bias of incomplete outcome data (attrition bias) or selective reporting (reporting bias) (eFigure in the Supplement). All studies reported survival analysis using intention-to-treat analysis and response rates and toxic effect results with per-protocol analysis.

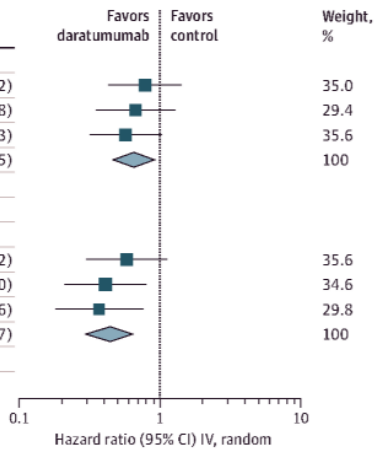
Studienergebnisse:

PFS:

- The addition of daratumumab to backbone regimens was associated with improved PFS among patients with relapsed or refractory standard or high risk MM.

Figure 2. Outcomes Associated With the Addition of Daratumumab to Backbone Multiple Myeloma Regimens for Patients With High-risk Multiple Myeloma

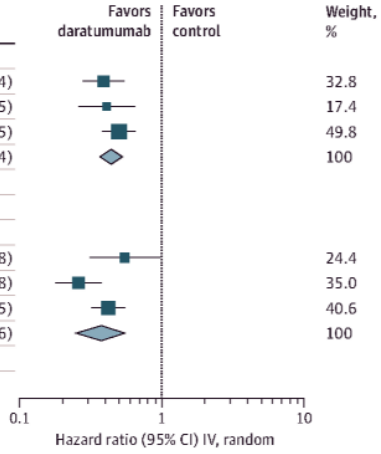
Source	Log (hazard ratio)	SE	Daratumumab total	Control total	Hazard ratio (95% CI) IV, random	Weight, %
Newly diagnosed high-risk multiple myeloma						
ALCYONE,[11] 2018	-0.2485	0.3038	53	45	0.78 (0.43-1.42)	35.0
CASSIOPEIA,[12] 2019	-0.4005	0.3313	82	86	0.67 (0.35-1.28)	29.4
MAIA,[13] 2019	-0.5621	0.301	48	44	0.57 (0.32-1.03)	35.6
Subtotal			183	175	0.67 (0.47-0.95)	100
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=0.54$; $P=.76$; $I^2=0\%$						
Overall effect: $z=2.25$; $P=.02$						
Relapsed or refractory high-risk multiple myeloma						
CANDOR,[16] 2019	-0.5447	0.3364	48	26	0.58 (0.30-1.12)	35.6
CASTOR,[19] 2019	-0.8916	0.3414	41	37	0.41 (0.21-0.80)	34.6
POLLUX,[18] 2019	-0.9943	0.3676	35	35	0.37 (0.18-0.76)	29.8
Subtotal			124	98	0.45 (0.30-0.67)	100
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=0.93$; $P=.63$; $I^2=0\%$						
Overall effect: $z=3.98$; $P<.001$						



Significant improvement in progression-free survival was seen among patients with first-line and relapsed or refractory disease. Squares represent mean values, with the size of the squares representing the weight, and horizonal lines represent 95% CIs. Diamonds are pooled means with the points representing 95% CIs. IV indicates inverse variance.

Figure 3. Outcomes Associated With the Addition of Daratumumab to Backbone Multiple Myeloma Regimens for Patients With Standard-Risk Multiple Myeloma

Source	Log (hazard ratio)	SE	Daratumumab total	Control total	Hazard ratio (95% CI) IV, random	Weight, %
Newly diagnosed standard-risk multiple myeloma						
ALCYONE,[11] 2018	-0.9416	0.1691	261	257	0.39 (0.28-0.54)	32.8
CASSIOPEIA,[12] 2019	-0.8916	0.2324	460	454	0.41 (0.26-0.65)	17.4
MAIA,[13] 2019	-0.6931	0.1373	271	279	0.50 (0.38-0.65)	49.8
Subtotal			992	990	0.45 (0.37-0.54)	100
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 1.45$; $P = .48$; $I^2 = 0\%$						
Overall effect: $z = 8.35$; $P < .001$						
Relapsed or refractory standard-risk multiple myeloma						
CANDOR,[16] 2019	-0.5978	0.2925	104	52	0.55 (0.31-0.98)	24.4
CASTOR,[19] 2019	-1.3471	0.1876	140	137	0.26 (0.18-0.38)	35.0
POLLUX,[18] 2019	-0.8675	0.1387	193	176	0.42 (0.32-0.55)	40.6
Subtotal			437	365	0.38 (0.26-0.56)	100
Heterogeneity: $\tau^2 = 0.08$; $\chi^2_2 = 6.19$; $P = .05$; $I^2 = 68\%$						
Overall effect: $z = 4.83$; $P < .001$						



Significant improvement in progression-free survival was seen among patients with first-line and relapsed or refractory disease. Squares represent mean values, with the size of the squares representing the weight, and horizonal lines represent 95% CIs. Diamonds are pooled means with the points representing 95% CIs. IV indicates inverse variance.

OS:

Among the included studies, mature overall survival data stratified by cytogenetic group were only available for the ALCYONE study,[9] with less-pronounced benefits associated with daratumumab among patients with HRMM (HR, 0.91; 95% CI, 0.50-1.65) than in patients with SRMM (HR, 0.49; 95% CI, 0.35-0.69). Therefore, we were unable to report pooled overall survival data.

Anmerkung/Fazit der Autoren

This study suggests that incorporating daratumumab to backbone regimens may be associated with improved PFS among patients with newly diagnosed HRMM or relapsed or refractory HRMM.

Ball S et al., 2020 [2].

Risk of kidney toxicity with carfilzomib in multiple myeloma: a meta-analysis of randomized controlled trials.

Fragestellung

to perform a systematic review and meta-analysis of randomized clinical trials (RCTs) comparing carfilzomib-based with non-carfilzomib- based treatment regimens in MM to definitively characterize the risk of kidney toxicity with carfilzomib.

Methodik

Population:

- patients with MM

Intervention:

- carfilzomib-based regimens

Komparator:

- non-carfilzomib-based regimens

Endpunkte:

- Adverse events

Recherche/Suchzeitraum:

- Ovid MEDLINE, Ovid EMBASE, Web of Science, Cochrane Central Register of Controlled Trials, and Clinical Trials.gov databases from inception through March 20, 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs with 2954 patients (1486 in carfilzomib arms and 1468 in control arms)
- All studies except CLARION were performed in patients with relapsed/refractory MM

Charakteristika der Population:

Table 1 Characteristics of studies included in the final analysis

Study name		ASPIRE		ENDEAVOR		FOCUS		CLARION	
Author, year		Stewart, 2015		Dimopoulos, 2015		Hajek, 2017		Facon, 2019	
Disease phase		RRMM		RRMM		RRMM		NDMM	
Prior lines of treatment		1–3 (median, 2)		1–3 (median, 2)		3–17 (median, 5)		0	
Carfilzomib	Dose	20/27 mg/m^2		20/56 mg/m^2		20/27 mg/m^2		20/36 mg/m^2	
	Schedule	Twice weekly		Twice weekly		Twice weekly		Twice weekly	
	Infusion length	10 min		30 min		10 min		30 min	
Study arm		Carfilzomib	Control	Carfilzomib	Control	Carfilzomib	Control	Carfilzomib	Control
Age at diagnosis (years), median (range)		64 (38–87)	65 (31–91)	65 (35–89)	65 (30–88)	63 (32–85)	66 (43–81)	72 (42–89)	72 (43–91)
Regimen used		KRd	Rd	Kd	Vd	K	Steroids ± Cy	KMP	VMP
Median duration of treatment		88 weeks	57 weeks	39.9 weeks	26.8 weeks	16.3 weeks	10.7 weeks	52.3 weeks	52.1 weeks
Total no. of patients		392	389	463	456	157	153	474	470

NDMM, newly diagnosed multiple myeloma; *RRMM*, relapsed/refractory multiple myeloma; *KRd*, carfilzomib-lenalidomide-dexamethasone; *Rd*, lenalidomide-dexamethasone; *Kd*, carfilzomib-dexamethasone; *Vd*, bortezomib-dexamethasone; *Cy*, cyclophosphamide; *KMP*, carfilzomib-melphalan-prednisone; *VMP*, bortezomib-melphalan-prednisone

Qualität der Studien:

- All trials were open label. Masking of outcome assessment was performed in two trials (ASPIRE and ENDEAVOR).

Supplementary Appendix C							
Trial, Author, Year	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Masking/ Blinding of Participant and Personnel (Performance Bias)	Masking/ Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Data)	Selective Reporting (Reporting Bias)	Other Bias
ASPIRE; Stewart, 2015	+	+	-	+	+	+	?
ENDEAVOR; Dimopoulos, 2015	+	+	-	+	+	+	+
FOCUS; Hajek, 2017	+	+	-	-	+	?	?
CLARION; Facon, 2019	+	+	-	?	+	?	?
+: Low risk of Bias -: High risk of bias ?: Risk of bias unclear							

Studienergebnisse:

- The cumulative rate of kidney toxicities in the carfilzomib arms was 21.3% for all grades and 8.3% for grades 3–5 toxicities, with acute kidney injury being the predominantly reported event.
- Patients receiving a carfilzomib-based regimen had a significantly higher risk of total kidney toxicity compared with those in the control arms, with pooled RR of 1.79 (95% CI, 1.43–2.23, $p < 0.001$) and 2.29 (95% CI, 1.59–3.30; $p < 0.001$), for all grades and grades 3–5 toxicities, respectively. Despite adjustment for the duration of exposure in treatment arms, pooled incidence rate ratios (IRR) for kidney toxicity was significantly increased in the carfilzomib arm compared with control (pooled IRR of1.28 for all grades and 1.66 for grades 3–5 toxicity)
- Subgroup analysis treatment setting (newly diagnosed vs. relapsed/ refractory MM): No statistically significant subgroup effect.

Anmerkung/Fazit der Autoren

In conclusion, our study will guide clinicians in counseling patients and estimating kidney toxicity risk with carfilzomib-based regimens. Since carfilzomib can lead to improvement in kidney function in patients with myeloma-related kidney impairment and the pharmacokinetics are not impacted by the degree of kidney dysfunction, risk-benefit profile should be assessed pragmatically. For example, if the underlying kidney dysfunction is mostly driven by the light chain burden, it would be reasonable to administer carfilzomib-based combination regimens in the appropriate clinical context and closely monitor kidney function. Future studies should prospectively characterize the trajectory and pathophysiology of kidney toxicities with carfilzomib and identity patient-related, disease-related, and treatment-related risk factors for severe kidney AEs.

Weisel K et al., 2019 [19].

A comparison of the efficacy of immunomodulatory-free regimens in relapsed or refractory multiple myeloma: a network meta-analysis

Fragestellung

Patients experiencing a first relapse after IMiD-based induction therapy should be switched to IMiD-free regimens. The current study used an NMA to examine specifically comparisons of IMiD-free combination regimens in patients with RRMM.

Methodik

Population:

- Adult patients with primary diagnosis of RRMM

Additional criteria added to the NMA

- Patients who were relapsed and/or refractory were randomized to treatment (exclusion of patients who had responded to initial treatment in a prerandomized phase, and then randomized to treatment)

Intervention/Komparator:

- Inclusion of studies that compared two or more licensed treatments that were considered relevant comparators in RRMM. This included treatments undergoing, or being prepared for, regulatory body prelicensing review, already licensed, or routinely used treatments
- Exclusion of studies examining the efficacy of interferon alpha, conditioning chemotherapy to prepare for stem cell transplantation, maintenance therapy, preferred sequence of treatments, and treatments aimed at managing complications of RRMM

Additional criteria added to the NMA:

- Studies that compared two or more active IMiD-free regimens
- Exclusion of studies that only compared the different regimens of the same active drug or compared dose escalations of the same drug

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- In Medline + Embase + Cochrane Library from January 1, 1995 to November 3, 2016

Qualitätsbewertung der Studien:

- Study quality was assessed using the Centre for Reviews and Dissemination guidance document checklist, with each trial being assigned an overall rating of quality, as appropriate

NMA-spezifische Angaben

- An assessment was made on the feasibility of conducting an NMA of efficacy outcomes in the identified RCTs. This was informed by eliciting views from key opinion-leaders and clinical experts on the comparability of the patient-selection criteria that had been used in the individual studies. RCTs were considered for the NMA only if they had two or more treatment arms of interest for the network of IMiD-free regimens.

- All analyses were conducted within a Bayesian framework
- As there was only one study per treatment comparison, only fixed effects models were fitted, and it was not possible to test for statistical heterogeneity or inconsistency in effects.
- To assess the robustness of results from the base-case analysis, subgroup analyses for PFS were conducted. These explored whether or how clinically meaningful treatment-effect modifiers affected the NMA results. Specifically, these analyses involved stratification by previous LOT (one prior LOT vs. two or more prior LOTs), patients with/without prior bortezomib exposure, and patients with/without prior IMiD exposure

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 studies

Charakteristika der Studien

Table 2. Study and patient characteristics from RCTs included in the NMA.

Trial	Intervention (dosage); number of patients	Outcomes	Median (range) prior LOT at baseline	Prior treatment criteria	Prior treatment exposure at baseline (%)	Prior treatment patients relapsed on/were refractory to (%)
Base-case analyses						
CASTOR [11]	Daratumumab (16 mg/kg) + bortezomib (1.3 mg/m^2) + dexamethasone (20 mg) bortezomib (1.3 mg/m^2) + dexamethasone (20 mg)	PFS: HR[a] OS: HR[a] ORR: sCR + CR + VGPR + PR	≥1 Median: 2 (range: 1–10)	Include: Progression on last regimen Exclude: Bortezomib refractory; prior daratumumab, allogeneic SCT	Bortezomib: 65.5% Thalidomide: 49.4% Lenalidomide: 42.0% Dexamethasone: 90.6% Carfilzomib: 4.4% ASCT: 61.2%	Refractory to IMiD only: 32.9% Refractory to PI only: 1.4% Refractory to both PI and IMiD: 3.2% Lenalidomide-refractory: 28.3% Thalidomide-refractory: 11.2% Pomalidomide-refractory: 2.6% Ixazomib-refractory: 2.2% Carfilzomib-refractory: 1.8% Bortezomib-refractory: 0.6%
ENDEAVOR [9]	Carfilzomib (27 mg/m^2) + dexamethasone (20 mg) bortezomib (1.3 mg/m^2) + dexamethasone (20 mg)	PFS: HR, KM OS: HR[a] ORR: sCR + CR + VGPR + PR	1–3 Median: 2 (range: 1–4)	Exclude: Bortezomib or carfilzomib refractory	Bortezomib: 54% Thalidomide: 49% Lenalidomide: 38% Carfilzomib: <1%	NR
PANORAMA 1 [12]	Panobinostat (20 mg) + bortezomib (1.3 mg/m^2) + dexamethasone (20 mg) bortezomib (1.3 mg/m^2) + dexamethasone (20 mg)	PFS: HR, KM OS: HR, KM ORR: CR + PR	1–3 Median/mean NR	Exclude: Primary refractory; bortezomib refractory	Bortezomib: 43% Thalidomide: 51.2% Lenalidomide: 20.4% Dexamethasone: 81.1% Melphalan (oral): 28.6%	NR
VCD phase III [10]	Cyclophosphamide (50 mg) + bortezomib (1.3 mg/m^2) + dexamethasone (20 mg) bortezomib (1.3 mg/m^2) + dexamethasone (20 mg)	PFS[b] OS: HR[a,c] ORR: ≥PR	1–3 Median/mean NR	NR	Bortezomib: 14%	NR
Additional trials included in sensitivity analyses						
CA204-009 [13]	Elotuzumab (10 mg/kg) + bortezomib (1.3 mg/m^2) + dexamethasone (20 mg) bortezomib (1.3 mg/m^2) + dexamethasone (20 mg)	PFS: HR, KM OS: HR[a,c] ORR[d]	1–3 Median/mean NR	Include: Response to prior PI regimen; progression on last regimen Exclude: PI-refractory or intolerance	PI: 51%–53%	NR
MMVAR-Velcade [14]	Thalidomide (200 mg) + bortezomib (1.3 mg/m^2) + dexamethasone (20 mg)	PFS: HR, KM OS: KM ORR[d]	≥1 ASCT 1 prior ASCT: 53% ≥2 prior ASCT: 47%	Include: ≥1 ASCT Exclude: Allogeneic SCT	Bortezomib: 20%–21% Thalidomide: 6%–10%	NR
Nordic Myeloma Study [15]	bortezomib (1.3 mg/m^2) + dexamethasone (20 mg) Thalidomide (50 mg) + dexamethasone (20 mg) bortezomib (1.3 mg/m^2) + dexamethasone (20 mg)	PFS: KM OS: KM ORR[d]	NR (only required that patients were refractory to melphalan) Median/mean NR	Include: relapsed or refractory to melphalan Exclude: Prior bortezomib, lenalidomide, thalidomide	HDM: 49%–52%	NR

[a]Data not yet mature.
[b]Outcome not explored in study; time-to-progression reported and used in analysis.
[c]Can be calculated or or derived from KM curves.
[d]Outcome not explored in sensitivity analysis.
ASCT: autologous stem cell transplantation; CR: complete response; HDM: high-dose melphalan; HR: hazard ratio; KM: Kaplan–Meier; LOT: line of therapy; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PI: proteasome inhibitor; PR: partial response; sCR: stringent complete response; SCT: stem cell transplantation; VGPR: very good partial response.

Qualität der Studien:

- the base case trials were of low to moderate quality

Studienergebnisse:

Netzwerkgeometrie

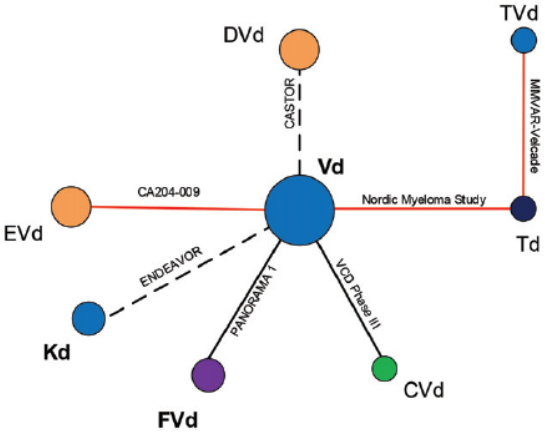


Figure 2. Network diagram. Blue: Proteasome inhibitor alone or in combination. Dark blue: Immunomodulators ± glucocorticoid; Orange: Monoclonal antibody alone or in combination; Purple: Histone deacetylase inhibitor + proteasome inhibitor; Green: Proteasome inhibitor + glucocorticoid ± alkylating agent; Bold text: licensed treatment (FDA and/or EMA); Regular text: unlicensed treatment; Dashed black line: Trial with incomplete or interim results; Solid red line: Trial was removed from the base-case NMA. CVd: cyclophosphamide + bortezomib + dexamethasone; DVd: daratumumab + bortezomib + dexamethasone; EVd: elotuzumab + bortezomib + dexamethasone; FVd: panobinostat + bortezomib + dexamethasone; Kd: carfilzomib + dexamethasone; Td: thalidomide + dexamethasone; TVd: thalidomide + bortezomib + dexamethasone; Vd: bortezomib + dexamethasone.

- The base-case network was composed of 4 trials that evaluated
  - carfilzomib plus dexamethasone (Kd)
  - cyclophosphamide plus Vd (CVd)
  - daratumumab plus Vd (DVd) and
  - panobinostat plus Vd (FVd)

  with Vd being the reference treatment.
- 3 trials excluded from the base case evaluated
  - elotuzumab plus Vd [13],
  - thalidomide plus Vd [14], and
  - thalidomide plus dexamethasone [15].
- They were excluded from the base case because, compared to the other 4 studies, they had clearly different treatment populations (e.g. different treatment history [i.e. autologous stem cell transplantation or melphalan]) or an irrelevant comparator not routinely used in clinical practice (e.g. elotuzumab in combination with Vd
- Of the 4 base-case studies, three included patients who had received 1-3 prior LOTs, while 1 trial included patients who had received at least 1 prior LOT with no upper limit. Also, all of the included base-case studies used similar dosing for Vd, with only slight differences in route of administration and treatment duration that were not considered significant enough to affect the validity of the NMA

Ergebnisse der direkten Vergleiche

Study (Comparison)	PFS [HR (95% CI)]	OS [HR (95% CI)]	ORR [OR (p-value)]
CASTOR (DVd vs. Vd)	0.33 (0.26 to 0.43)	0.63 (0.42 to 0.96)	84 vs. 63 (p<0.0001)
ENDEAVOR (Kd vs. Vd)	0.53 (0.44 to 0.65)	0.79 (0.58 to 1.08)	76.7 vs. 62.4 (p<0.0001)
PANORAMA 1 (FVd vs. Vd)	0.69 (0.58 to 0.83)	0.94 (0.78 to 1.14)	60.7 vs. 54.6 (p=0.09)
VCD Phase III (CVd vs. Vd)	TTP: 0.71 (0.43 to 1.19)*	0.85 (0.41 to 1.73)*	--

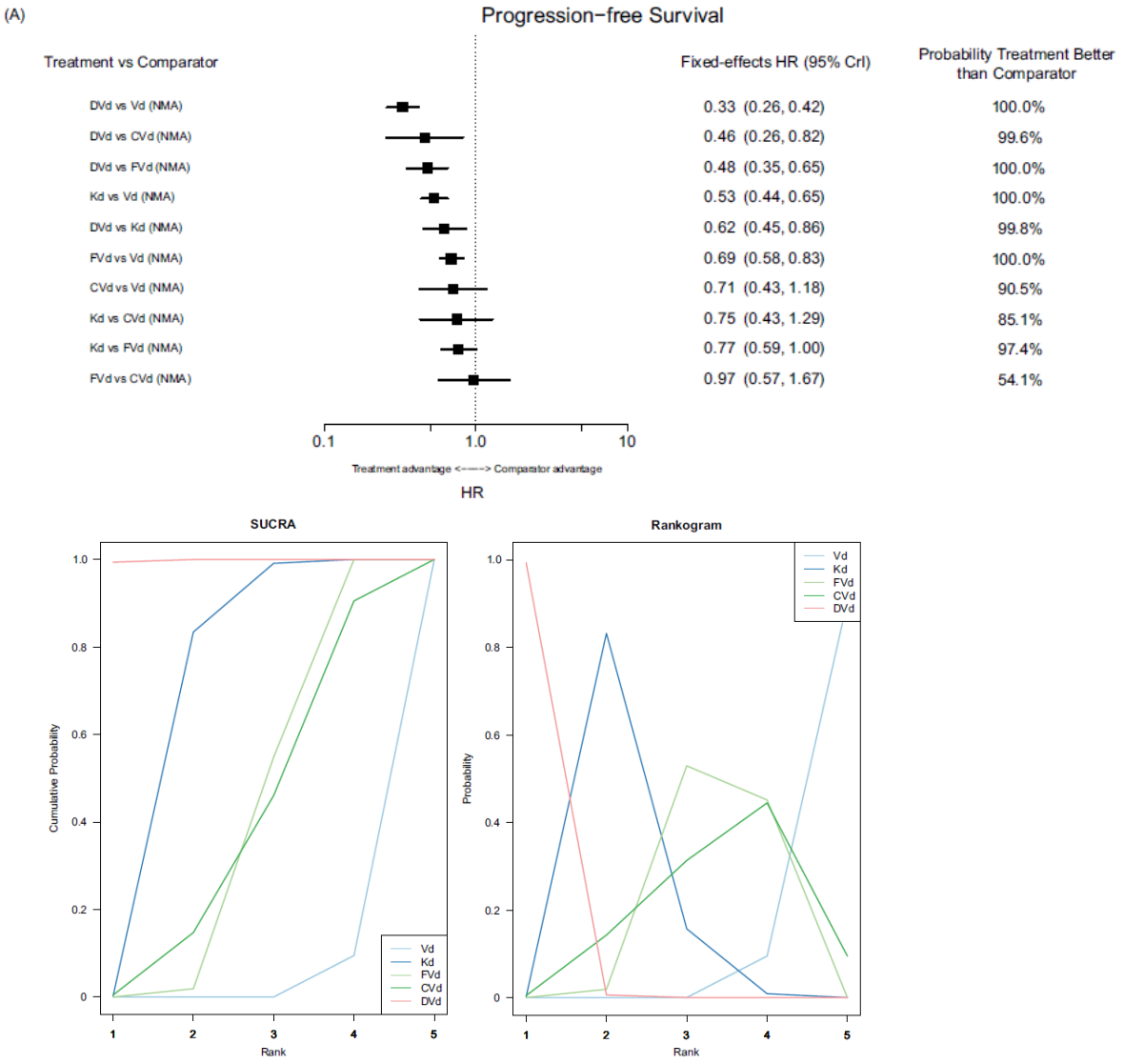
* HR value less than 1.0 favors Vd

Abbreviations: CI = confidence interval; CVd = cyclophosphamide + bortezomib + dexamethasone; DVd = daratumumab + bortezomib + dexamethasone; FVd = panobinostat + bortezomib + dexamethasone; HR =

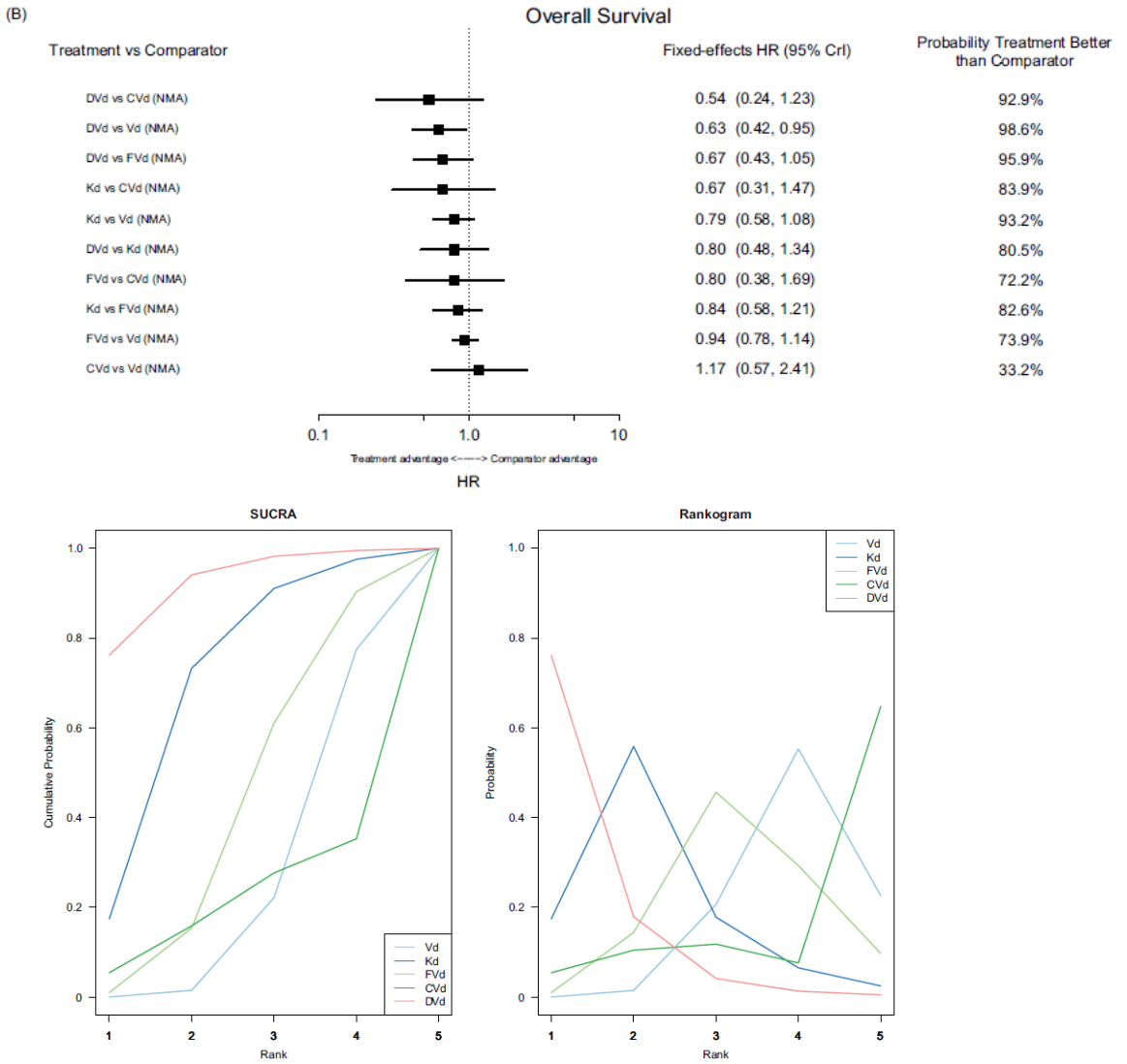
hazard ratio; Kd = carfilzomib + dexamethasone; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Vd = bortezomib + dexamethasone

Ergebnisse der NMA

PFS



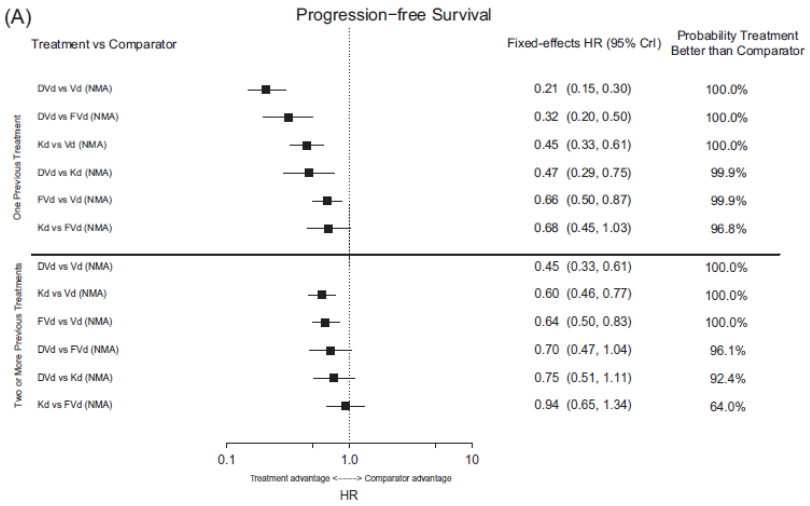
OS



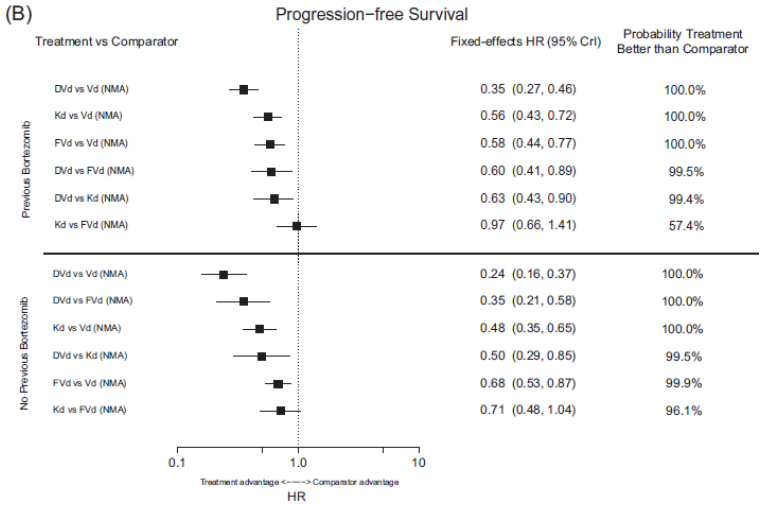
CrI: credible interval; CVd: cyclophosphamide + bortezomib + dexamethasone; DVd: daratumumab+ bortezomib+ dexamethasone; FVd: panobinostat + bortezomib + dexamethasone; HR: hazard ratio; Kd: carfilzomib+ dexamethasone; SUCRA: surface under the cumulative ranking; Vd: bortezomib + dexamethasone

Subgroup analyses for PFS.

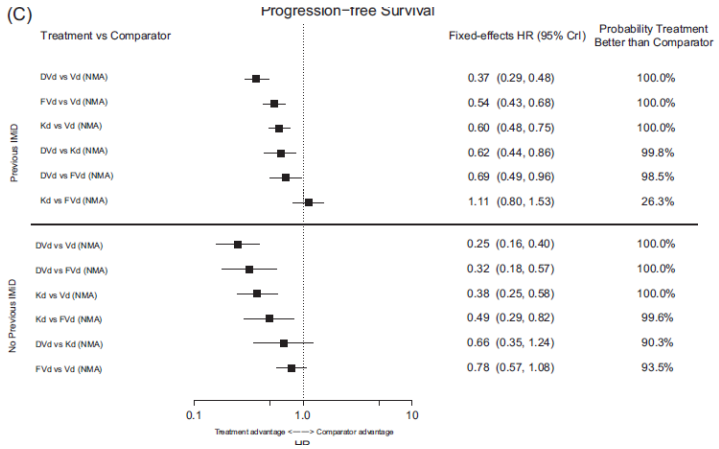
- Prior lines of therapies (Figure 4(A)).
  - In patients who had received 1 prior LOT, there was an additional statistical advantage for DVd in prolonging PFS compared with all other IMiD-free regimens, and for FVd or Kd compared with Vd
  - there were no added advantages in terms of HRs for PFS in patients who received 2 or more prior LOTs.



- prior bortezomib-use (Figure 4(B)).
  - In subgroup of patients who had not received prior bortezomib, there was an additional advantage for DVd compared with FVd and with Vd,
  - no further advantages were observed for other comparators or for patients who had received prior bortezomib



- prior IMiD exposure (Figure 4(C)).
  - For patients with no prior IMiD exposure, there was an increased advantage for DVd compared with FVd and Vd, and for Kd compared with Vd
  - patients who had received a prior IMiD continued to experience longer PFS when treated with DVd than with all other comparators



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Anmerkung/Fazit der Autoren

This NMA demonstrates the value of daratumumab as a treatment option in combination with Vd, with respect to treatment response and survival advantages over other relevant IMiD-free treatments.

Results from the subgroup analyses based on treatment history were largely consistent with the base case, with additional benefits being observed for patients treated with DVd who received one prior LOT.

Kommentare zum Review

- Detaillierte Informationen zum Bayes-Verfahren fehlen (u.a. keine Angabe zu verwendeten Priors)

Dimopoulos MA et al., 2018 [3].

A Comparison of the Efficacy of Immunomodulatory-containing Regimens in Relapsed/Refractory Multiple Myeloma: A Network Meta-analysis.

Fragestellung

To compare the clinical efficacy of immunomodulatory drug-containing regimens in patients with relapsed or refractory multiple myeloma.

Methodik

Population:

- Adult patients with primary diagnosis of RRMM

Intervention/Komparator:

- IMiD-based combination regimens
- Studies that compared ≥ 2 licensed treatments that were considered relevant comparators in RRMM, including treatments undergoing or being prepared for regulatory body prelicensing review, already licensed, or routinely used

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- In Medline + Embase + Cochrane Library from January 1, 1995 to November 3, 2016

Qualitätsbewertung der Studien:

The quality of the included full-text studies was assessed using the checklist described in the Centre for Reviews and Dissemination guidance document, with each trial assigned an overall quality rating of high, moderate, or low

NMA spezifische Angaben/ Überprüfung der NMA-Annahmen:

- NMA using Bayesian framework
- RCTs were included in the network only if they had >= 2 arms that allowed the formation of a network of IMiD-containing regimens, regardless of drug class or mechanism of action
- RCTs comparing different administration routes, doses, or schedules of a specific regimen were excluded
- assessment was undertaken to determine the feasibility of conducting an NMA of the efficacy outcomes in the identified RCTs. The feasibility assessment included a comparison of patient population similarity (eg, number of previous lines of therapy and previous treatment criteria) and intervention similarity (eg, treatment dosing and administration). This included eliciting views from key opinion leaders and clinical experts from North and South America and Europe using an advisory board meeting on the patient eligibility criteria across RCT
- Subgroup analyses for PFS were conducted to confirm the robustness of the results from the base-case analysis by exploring the effect of the clinically meaningful treatment-effect modifiers. The specific analyses included stratification by previous line of therapy (LOT; 1 previous LOT or ≥2 previous LOTs), patients with and without previous bortezomib exposure, and patients with and without previous lenalidomide exposure
- Because of the limitations of the network (ie, the presence of only 1 study per treatment comparison), only fixed-effects models were fitted. Because only 1 study was present per comparison, it was not possible to test for statistical heterogeneity or inconsistency in effects.

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 studies

Charakteristika der Studien

Table 2 Study and Patient Characteristics From RCTs Included in NMA

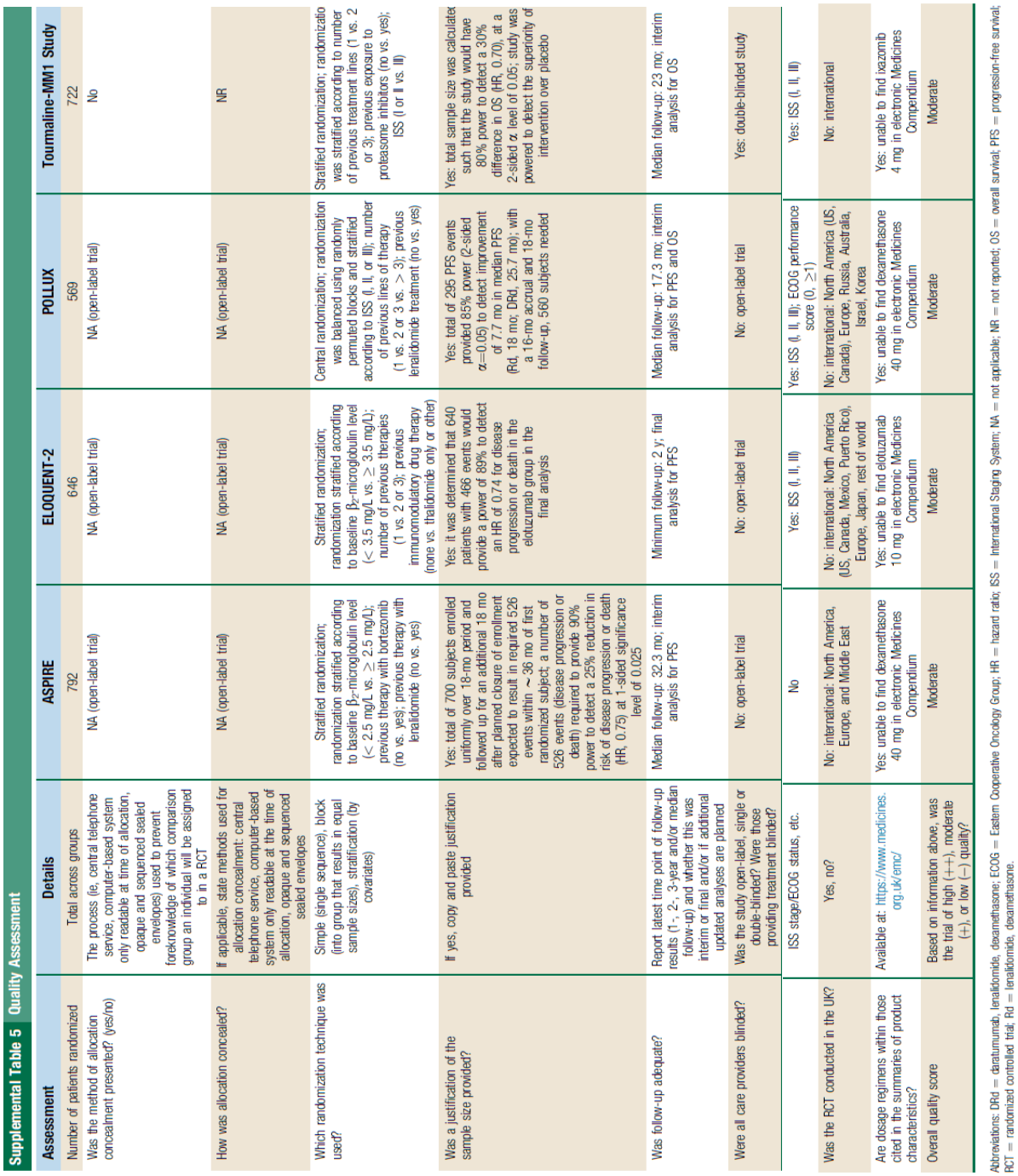
Trial	Intervention (Dosage); Patients, n	Outcomes	Median (Range) LOT at Baseline	Previous Treatment Criteria	Previous Treatment Exposure at Baseline	Relapsed/Refractory Status
Base-Case Analyses						
ASPIRE[15]	Carfilzomib (20-27 mg/m^2) + lenalidomide (25 mg) + dexamethasone (40 mg); 396	PFS: HR, KM; OS: HR, KM; ORR: sCR, CR, and VGPR	2 (1-3)	Excluding bortezomib or lenalidomide + dexamethasone refractory; previous carfilzomib	Bortezomib, 66%; lenalidomide, 20%; IMID, 59%; bortezomib + IMD, 37%	Bortezomib nonresponsive, 15%; lenalidomide refractory, 7%; IMID refractory, 22%; bortezomib nonresponsive and IMID refractory, 6%
	Lenalidomide (25 mg) + dexamethasone (40 mg); 396		2 (1-3)		Bortezomib: 66% lenalidomide: 20% IMD: 58% bortezomib + IMD: 35%	Bortezomib nonresponsive, 15%; lenalidomide refractory, 7%; IMID refractory, 22%; bortezomib nonresponsive and IMID refractory, 7%
ELOQUENT-2[17]	Elotuzumab (10 mg/kg) + lenalidomide (25 mg) + dexamethasone (40 mg); 321	PFS: HR, KM; OS: HR[a,b]; ORR: sCR, CR, VGPR, and PR	2 (1-4)	Including lenalidomide $\leq$ 10% of study sample; excluding lenalidomide refractory	Bortezomib, 68%; thalidomide, 48%; lenalidomide, 5%	Bortezomib refractory, 22%; thalidomide refractory, 9%
	Lenalidomide (25 mg) + dexamethasone (40 mg); 325		2 (1-4)		Bortezomib, 71%; thalidomide, 48%; lenalidomide, 6%	Bortezomib refractory, 21% thalidomide refractory: 11%
POLLUX[16]	Daratumumab (16 mg/kg) + lenalidomide (25 mg) + dexamethasone (40 mg); 286	PFS: HR[a]; OS: HR[a]; ORR: sCR, CR, VGPR, and PR	1 (1-11)	Excluding allogeneic SCT; lenalidomide refractory	PI, 86%; bortezomib, 84%; carfilzomib, 2%; IMID, 55%; lenalidomide, 18%; thalidomide, 43%	PI refractory, 16%; IMID refractory, 4%; PI + IMID refractory, 5%; bortezomib refractory, 21%; carfilzomib refractory; 1%; thalidomide refractory, 9%
	Lenalidomide (25 mg) + dexamethasone (40 mg); 283		1 (1-8)		PI, 86%; bortezomib, 84%; carfilzomib, 2%; IMID, 55%; lenalidomide, 18%; thalidomide, 44%	PI refractory, 20%; IMID refractory, 4%; PI + IMID refractory, 2%; bortezomib refractory, 21%; carfilzomib refractory, 1%; pomalidomide refractory, 0.7%; thalidomide refractory, 6%
Tourmaline-MM1[18]	Ixazomib (4 mg) + lenalidomide (25 mg) + dexamethasone (40 mg); 360	PFS: HR, KM[c]; OS: [a,d],; ORR: sCR, CR, VGPR, and PR	Mean, 1.5 (1-3)	Including thalidomide refractory; excluding PI, lenalidomide refractory	Bortezomib, 69%; carfilzomib, < 1%; lenalidomide, 12%; thalidomide, 44%	PI refractory, 1%; IMID refractory, 21%
	Lenalidomide (25 mg) + dexamethasone (40 mg); 362		Mean, 1.5 (1-3)		Bortezomib, 69%; carfilzomib, 1%; lenalidomide, 12%; thalidomide, 47%	PI refractory, 2%; IMID refractory, 25%
Sensitivity Analyses						
MM-003[13]	Pomalidomide (4 mg) + dexamethasone (40 mg); 302	PFS: HR, KM; OS: HR, KM; ORR: [e]	5 (2-17)	Including $\geq$ 2 cycles of lenalidomide and/or bortezomib; previous alkylator; excluding thalidomide, lenalidomide, dexamethasone hypersensitivity; high-dose dexamethasone resistance	ASCT, 69%-71%; bortezomib, 100%; dexamethasone, 98%-99%; lenalidomide, 100%; thalidomide, 57%-61%	Bortezomib refractory, 79%; lenalidomide refractory, 92%-95%; bortezomib and lenalidomide refractory, 74%-75%
	Dexamethasone (40 mg); 153					
MM-009[12,14]	Lenalidomide (25 mg) + dexamethasone (40 mg); 177	PFS: [f]; OS: HR, KM; ORR: [e]	1 previous LOT, 38%; $\geq$ 2 previous LOTs, 62%	NR	Bortezomib, 11%; SCT, 62%; thalidomide, 44%	NR
	Dexamethasone (40 mg); 176					

Table 2 Continued

Trial	Intervention (Dosage); Patients, n	Outcomes	Median (Range) LOT at Baseline	Previous Treatment Criteria	Previous Treatment Exposure at Baseline	Relapsed/Refractory Status
MM-010[12,14]	Lenalidomide (25 mg) + dexamethasone (40 mg); 176	PFS: [f]; OS: HR, KM; ORR: [e]	1 previous LOT, 32%; ≥ 2 previous LOTs, 68%	Excluding thalidomide or dexamethasone intolerance	Bortezomib, 4%; SCT, 55%; thalidomide, 34%	NR
	Dexamethasone (40 mg); 175					
PomCyDex phase II[11]	Pomalidomide (4 mg) + CP (400 mg) + dexamethasone (40 mg); 34	PFS: HR, KM; OS: HR, KM; ORR: [e]	4 (2-12)	Including previous IMiDs and refractory to lenalidomide	HDM/ASCT, 75%-82%; previous alkylating agent, 89%-94%	Bortezomib refractory, 71%-78%; carfilzomib refractory, 38%-44%; lenalidomide refractory, 100%
	Pomalidomide (4 mg) + dexamethasone (40 mg); 36					

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; CP = cyclophosphamide; HDM = high-dose melphalan; HR = hazard ratio; IMiD = immunomodulatory drug; KM = Kaplan-Meier; LOT = line of therapy; NMA = network meta-analysis; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI = proteasome inhibitor; PR = partial response; RCT = randomized controlled trial; sCR = stringent complete response; SCT = stem cell transplantation; VGPR = very good partial response.
[a]Data not yet mature.
[b]Can be calculated/derived from KM curves.
[c]Events reported in the KM curve were used to derive the HR.
[d]Outcome explored in study but relevant data required for analysis not provided.
[e]Outcome not explored in sensitivity analyses.
[f]Outcome not explored in study; time to progression reported and used in analysis.

Qualität der Studien:



Supplemental Table 5 Quality Assessment

Assessment	Details	ASPIRE	ELOQUENT-2	POLLUX	Tourmaline-MM1 Study
Number of patients randomized	Total across groups	792	646	569	722
Was the method of allocation concealment presented? (yes/no)	The process (ie, central telephone service, computer-based system only readable at time of allocation, opaque and sequenced sealed envelopes) used to prevent foreknowledge of which comparison group an individual will be assigned to in a RCT	NA (open-label trial)	NA (open-label trial)	NA (open-label trial)	No
How was allocation concealed?	If applicable, state methods used for allocation concealment: central telephone service, computer-based system only readable at the time of allocation, opaque and sequenced sealed envelopes	NA (open-label trial)	NA (open-label trial)	NA (open-label trial)	NR
Which randomization technique was used?	Simple (single sequence), block (into group that results in equal sample sizes), stratification (by covariates)	Stratified randomization; randomization stratified according to baseline β_2-microglobulin level (< 2.5 mg/L vs. ≥ 2.5 mg/L); previous therapy with bortezomib (no vs. yes); previous therapy with lenalidomide (no vs. yes)	Stratified randomization; randomization stratified according to baseline β_2-microglobulin level (< 3.5 mg/L vs. ≥ 3.5 mg/L); number of previous therapies (1 vs. 2 or 3); previous immunomodulatory drug therapy (none vs. thalidomide only or other)	Central randomization; randomization was balanced using randomly permuted blocks and stratified according to ISS (I, II, or III); number of previous lines of therapy (1 vs. 2 or 3 vs. > 3); previous lenalidomide treatment (no vs. yes)	Stratified randomization; randomizatio was stratified according to number of previous treatment lines (1 vs. 2 or 3); previous exposure to proteasome inhibitors (no vs. yes); ISS (I or II vs. III)
Was a justification of the sample size provided?	If yes, copy and paste justification provided	Yes: total of 700 subjects enrolled uniformly over 18-mo period and followed up for an additional 18 mo after planned closure of enrollment expected to result in required 526 events within ~ 36 mo of first randomized subject; a number of 526 events (disease progression or death) required to provide 90% power to detect a 25% reduction in risk of disease progression or death (HR, 0.75) at 1-sided significance level of 0.025	Yes: it was determined that 640 patients with 466 events would provide a power of 89% to detect an HR of 0.74 for disease progression or death in the elotuzumab group in the final analysis	Yes: total of 295 PFS events provided 85% power (2-sided α=0.05) to detect improvement of 7.7 mo in median PFS (Rd, 18 mo; DRd, 25.7 mo); with a 16-mo accrual and 18-mo follow-up, 560 subjects needed	Yes: total sample size was calculate such that the study would have 80% power to detect a 30% difference in OS (HR, 0.70), at a 2-sided α level of 0.05; study was powered to detect the superiority of intervention over placebo
Was follow-up adequate?	Report latest time point of follow-up results (1-, 2-, 3-year and/or median follow-up) and whether this was interim or final and/or if additional updated analyses are planned	Median follow-up: 32.3 mo; interim analysis for PFS	Minimum follow-up: 2 y; final analysis for PFS	Median follow-up: 17.3 mo; interim analysis for PFS and OS	Median follow-up: 23 mo; interim analysis for OS
Were all care providers blinded?	Was the study open-label, single or double-blinded? Were those providing treatment blinded?	No: open-label trial	No: open-label trial	No: open-label trial	Yes: double-blinded study
	ISS stage/ECOG status, etc.	No	Yes: ISS (I, II, III)	Yes: ISS (I, II, III); ECOG performance score (0, ≥1)	Yes: ISS (I, II, III)
Was the RCT conducted in the UK?	Yes, no?	No: international: North America, Europe, and Middle East	No: international: North America (US, Canada, Mexico, Puerto Rico), Europe, Japan, rest of world	No: international: North America (US, Canada), Europe, Russia, Australia, Israel, Korea	No: international
Are dosage regimens within those cited in the summaries of product characteristics?	Available at: https://www.medicines.org.uk/emc/	Yes: unable to find dexamethasone 40 mg in electronic Medicines Compendium	Yes: unable to find elotuzumab 10 mg in electronic Medicines Compendium	Yes: unable to find dexamethasone 40 mg in electronic Medicines Compendium	Yes: unable to find ixazomib 4 mg in electronic Medicines Compendium
Overall quality score	Based on information above, was the trial of high (++), moderate (+), or low (–) quality?	Moderate	Moderate	Moderate	Moderate

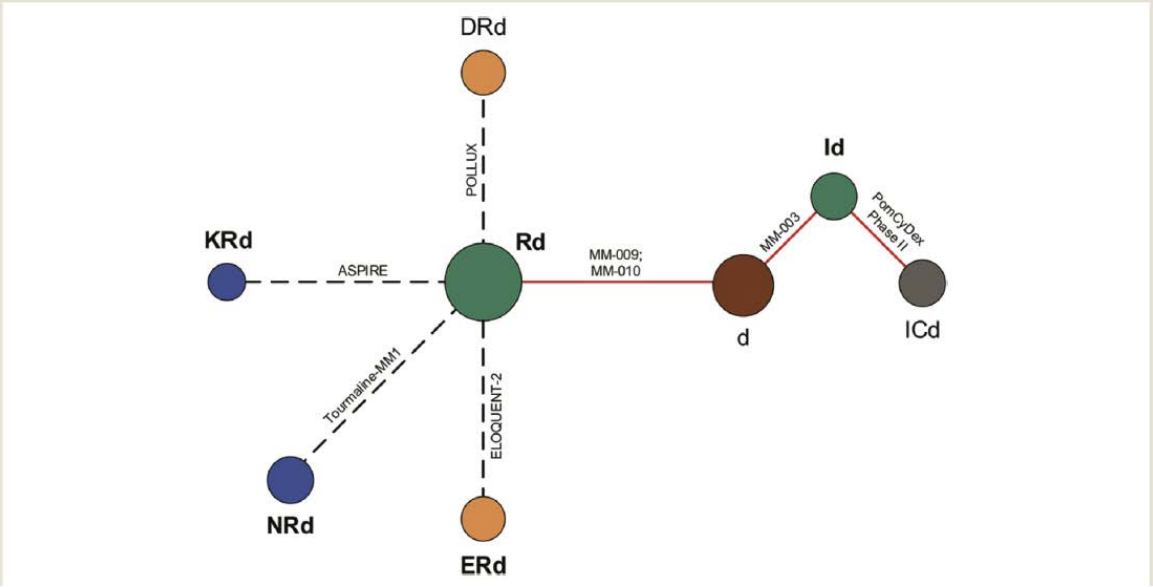
Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ISS = International Staging System; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; Rd = lenalidomide, dexamethasone.

Studienergebnisse:

Netzwerkgeometrie

- 4 of 8 trials were excluded from subsequent base-case analyses because their patient populations differed substantially from those of the other studies (eg, different treatment history; ie, ≥ 2 previous LOTs) or had included an irrelevant comparator not routinely used in clinical practice (eg, dexamethasone monotherapy) → Figure 2

Figure 2 Network Diagram. Brown indicates glucocorticoid alone; blue, proteasome inhibitor alone or combined; green, immunomodulators with or without a glucocorticoid; gray, immunomodulators and glucocorticoid with or without an alkylating agent; orange, monoclonal antibody alone or combined; bold text, treatments licensed by the US Food and Drug Administration and/or European Medicines Agency; regular text, unlicensed treatments; black dashed lines, trials with incomplete or interim results; and solid red lines, trials removed from the base-case network meta-analysis



Abbreviations: d = dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; ICd = pomalidomide, cyclophosphamide, dexamethasone; Id = pomalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone.

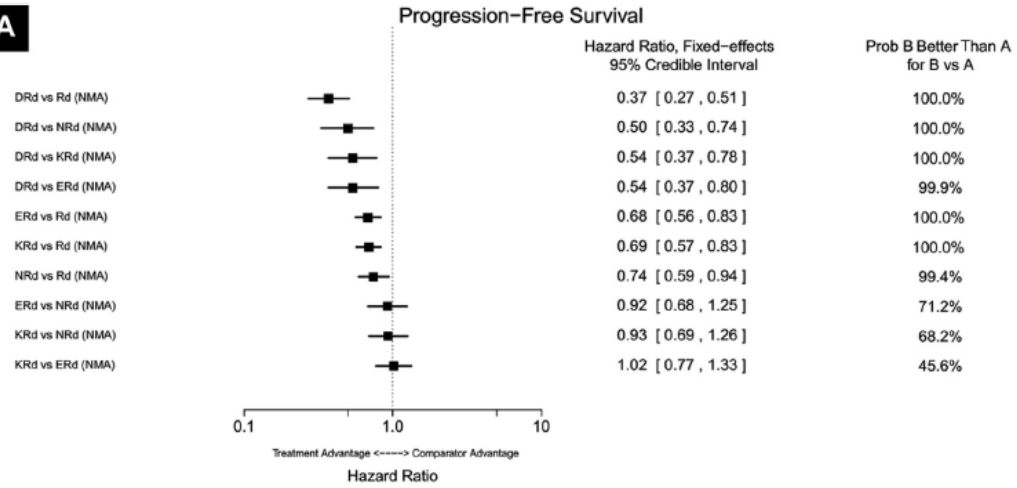
Ergebnisse der direkten Vergleiche

Study (Comparison)	PFS (HR; 95% CI)	OS (HR; 95% CI)
ASPIRE[15] (KRd vs. Rd)	0.69 (0.57-0.83)	0.79 (0.63-0.99)
ELOQUENT-2[17] (ERd vs. Rd)	0.70 (0.57-0.85)	0.77 (0.61-0.97)
POLLUX[16] (DRd vs. Rd)	0.37 (0.28-0.50)	0.63 (0.42-0.95)
Tourmaline-MM1[18] (NRd vs. Rd)	0.742 (0.587-0.939)	0.905 (0.62-1.32)

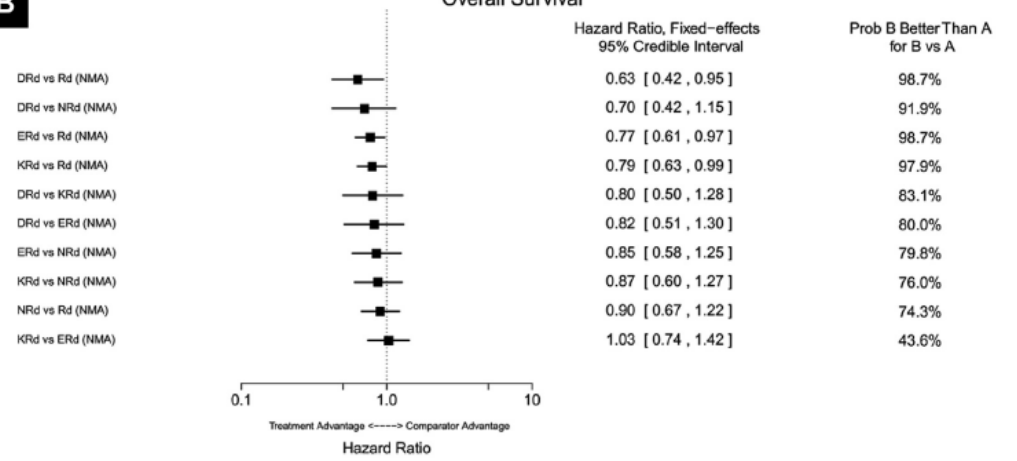
NMA-Ergebnisse

Figure 3 (A) Progression-Free Survival, (B) Overall Survival, and (C) Overall Response Rate With Immunomodulatory Drug (IMiD)-containing Regimens. Hazard ratios for a given treatment compared with another IMiD-containing regimen presented for (A) progression-free survival and (B) overall survival. (C) Comparisons for each treatment versus each of the other treatments; specifically, every combination of A versus B, where A is the treatment at the beginning of each row and B is the treatment at the top of each column. Odds ratios (ORs) > 1 indicate a numerical advantage for the treatment at the end of the row. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. The probability (prob) that the OR for A versus B is < 1 (ie, that regimen A is more Efficacious) is presented under the OR. Interventions with a significant advantage are shown in bold with green shading; interventions with a trend toward improving the overall response (eg, OR > 1.20 but credible intervals crossing 1.0) are shaded in orange. It is possible that 100% probability will appear to represent any value > 99.951%

A



B

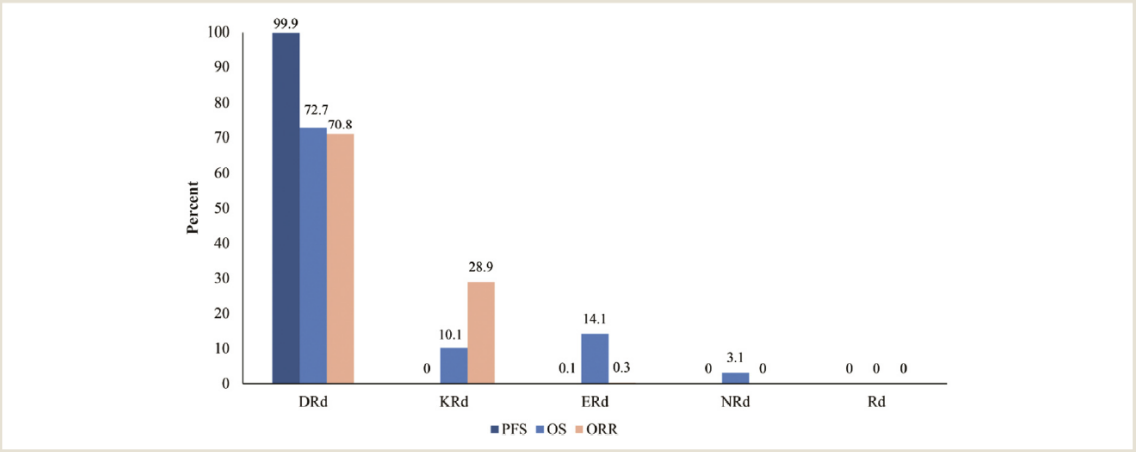


C

	Rd	KRd	ERd	NRd
DRd	**4.07 [2.42, 7.15]** 100%	1.20 [0.64, 2.33] 71%	**2.03 [1.06, 4.00]** 98.4%	**2.82 [1.52, 5.46]** 100%
NRd	**1.44 [1.03, 2.02]** 98.3%	0.42 [0.26, 0.69] 0.0%	0.72 [0.43, 1.21] 10.2%	
ERd	**2.00 [1.37, 2.98]** 100%	0.59 [0.35, 1.01] 2.6%		
KRd	**3.39 [2.38, 4.91]** 100%			

Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone.

Figure 4 Probability of Being the Best Treatment Across Survival and Response Outcomes



Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Rd = lenalidomide, dexamethasone.

Subgroup Analyses for PFS:

Results across all subgroup analyses were generally consistent with base-case analysis:

- For the patients who had received 1 previous LOT, the likelihood of prolonging PFS worsened for NRd compared with Rd, and the HRs improved in favor of DRd compared with ERd and NRd (Figure 5A).
- No significant HR changes were seen for patients who had received >= 2 previous LOTs. The HRs were improved in favor of DRd compared with Rd, KRd, and ERd for patients with no previous bortezomib therapy (Figure 5B).
- The HRs remained similar to the base-case analyses across all comparators for patients who had received previous bortezomib therapy and for all patients, regardless of whether they had previously received lenalidomide (Figure 5C).

Figure 5 Subgroup Analyses: Progression-Free Survival (PFS) of Patients With 1 Versus ≥ 2 Previous Lines of Therapy (LOTs; A), With and Without Previous Bortezomib Exposure (B), and With and Without Previous Lenalidomide Exposure (C). Tabular data represent comparisons for each treatment versus each of the other treatments. To obtain hazard ratios (HRs) for comparisons in the opposite direction, reciprocals should be taken. The probability that the HR is < 1 is presented under the HR. (A) For 1 previous LOT, HRs < 1 indicate a numerical advantage for the treatment at the top of the column. For ≥ 2 previous LOTs, HRs < 1 indicate a numerical advantage for the treatment at the beginning of the row. (B) For no previous bortezomib, HRs < 1 indicate a numerical Advantage for the treatment at the top of the column. For previous bortezomib, HRs < 1 indicate a numerical advantage for the treatment at the beginning of the row. (C) For no previous lenalidomide, HRs < 1 indicate a numerical advantage for the treatment at the top of the column. For previous lenalidomide, HRs < 1 indicate a numerical advantage for the treatment at the beginning of the row. It is possible that 100% probability will appear to represent any value > 99.951%. Interventions with a significant advantage are shown in bold with green shading; interventions with a trend toward improving PFS (eg, HR < 0.80 but credible intervals crossing 1.0) are shaded in orange

A

	Two or more prior LOT		
DRd	--	**0.58 [0.35 0.97]** 98.1%	**0.55 [0.34, 0.89]** 99.2%	**0.38 [0.25, 0.58]** 100%
0.43 [0.25, 0.74] 99.9%	**NRd**	--	--	--
0.48 [0.29, 0.80] 99.7%	1.11 [0.71, 1.72] 32.6%	**ERd**	0.95 [0.65, 1.37] 61.6%	**0.65 [0.49, 0.87]** 99.8%
0.52 [0.31, 0.86] 99.4%	1.20 [0.78, 1.84] 20.8%	1.08 [0.72, 1.61] 35.1%	**KRd**	**0.69 [0.54, 0.87]** 99.9%
0.36 [0.23, 0.55] 100%	0.83 [0.59, 1.16] 86.3%	0.75 [0.56, 1.00] 97.4%	**0.69 [0.53, 0.91]** 99.5%	**Rd**
One prior LOT				

B

	Prior bortezomib		
DRd	**0.58 [0.39, 0.85]** 99.7%	**0.56 [0.38, 0.83]** 99.8%	**0.39 [0.28, 0.54]** 100%
0.30 [0.12, 0.79] 99.3%	**ERd**	0.97 [0.71, 1.33] 57.1%	**0.68 [0.55, 0.85]** 100%
0.35 [0.13, 0.88] 98.7%	1.14 [0.69, 1.88] 30.5%	**KRd**	**0.70 [0.56, 0.88]** 99.9%
0.25 [0.10, 0.61] 99.9%	0.83 [0.57, 1.20] 84.1%	0.73 [0.52, 1.02] 96.7%	**Rd**
No prior bortezomib			

C

	Prior lenalidomide		
DRd	0.72 [0.22, 2.31] 70.9%	0.53 [0.22, 1.31] 91.4%	**0.42 [0.19, 0.94]** 98.2%
0.52 [0.35, 0.76] 100%	**ERd**	0.74 [0.28, 1.94] 73.2%	0.59 [0.25, 1.41] 88.5%
0.52 [0.35, 0.77] 100%	1.01 [0.75, 1.38] 46.2%	**KRd**	0.80 [0.52, 1.22] 84.7%
0.36 [0.26, 0.50] 100%	**0.70 [0.57, 0.87]** 100%	**0.69 [0.55, 0.86]** 100%	**Rd**
No prior lenalidomide			

Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone.

Anmerkung/Fazit der Autoren

In patients with RRMM who are suitable for an IMiD-containing regimen, DRd showed clear advantages in survival and response outcomes compared with other IMiD-containing regimens.

Kommentare zum Review

- Detaillierte Informationen zum Bayes-Verfahren fehlen (u.a. keine Angabe zu den verwendeten Priors)

Sun Z et al., 2017 [18].

Triplet versus doublet combination regimens for the treatment of relapsed or refractory multiple myeloma: A meta-analysis of phase III randomized controlled trials

Fragestellung

To compare the efficacy and safety of triplet versus doublet combination therapies in RRMM.

Methodik

Population:

- patients with previously treated RRMM

Intervention:

- triplet combination therapy

Komparator:

- doublet combination therapy

Endpunkte:

- OS, PFS, ORR, CR, Very good partial response (VGPR) and safety

Recherche/Suchzeitraum:

- 05/2016

Qualitätsbewertung der Studien:

- 5-item Jadad score including randomization, blinding, withdrawals

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs

Charakteristika der Studien

Moreau et al., 2016 (TOURMALINE; N=722)

- Intervention: **Ixazomib** 4mg + lenalidomide 25mg + dexamethasone 40mg
- Control: Placebo + lenalidomide 25mg + dexamethasone 40mg

Stewart et al.,2015 (ASPIRE, N=792)

- Intervention: **Carfilzomib** 20mg/m^2 + lenalidomide 25mg + dexamethasone 40mg
- Control: Lenalidomide 25mg + dexamethasone 40mg

Lonial et al., 2015 (ELOQUENT-2; N=646)

- Intervention**: Elotuzumab** 10 mg/kg + lenalidomide 25 mg + dexamethasone 40 mg
- Control: Lenalidomide 25 mg + dexamethasone 40 mg

San-Miguel et al., 2014 (PANORAMA1, N=768)

- Intervention: **Panobinostat** 20mg + bortezomib 1.3mg/m^2 + dexamethasone 20mg
- Control: Placebo + bortezomib 1.3mg/m^2 + dexamethasone 20mg

Garderet et al., 2012 (MMVAR, N=269)

- Intervention: Bortezomib 1.3mg/m^2 + thalidomide 200mg + dexamethasone 40mg
- Control: Thalidomide 200mg + dexamethasone 40mg

Patientencharakteristika

he patients' characteristics of the included trials.

Author/year	Treatment group	Disease status			Prior therapy agents	No. of prior therapies		
		Relapsed	refractory	Others		1	2	3 or more
Moreau et al. (2016) (TOURMALINE)	Experimental	276 (77%)	42 (12%)	24 (7%)	Bortezomib (69%), Carfilzomib (<1%)	224 (62%)	97 (27%)	39 (11%)
	Control	280 (77%)	40 (11%)	22 (6%)	Bortezomib (69%), Carfilzomib (1%)	217 (60%)	111 (31%)	34 (9%)
Stewart et al. (2015) (ASPIPE)	Experimental	NR	NR	NR	Bortezomib (65.9%), lenalidomide (19.9%)	184 (46.5%)	211 (53.3%)	
	Control	NR	NR	NR	Bortezomib (65.7%), Lenalidomide (19.7%)	157 (39.6%)	238 (60.4%)	
Lonial et al. (2015) (ELOQUENT-2)	Experimental	113 (35.2%)	112 (34.9%)	96 (29.9%)	Bortezomib (68%), Melphalan (69%), lenalidomide (5%), thalidomide (48%)	151 (47%)	118 (37%)	52 (16%)
	Control	114 (35.1%)	128 (39.4%)	83 (25.5%)	Bortezomib (71%), Melphalan (61%) lenalidomide (6%), thalidomide (48%)	159 (49%)	114 (35%)	52 (16%)
San-Miguel et al. (2014) (PANORAMA1)	Experimental	134 (35%)	247 (64%)	6 (2%)	Bortezomib (44%), lenalidomide (19%), thalidomide (53%)	197 (51%)	124 (32%)	64 (17%)
	Control	141 (37%)	235 (62%)	5 (1%)	Bortezomib (42%), lenalidomide (22%) Thalidomide (49%)	198 (52%)	108 (28%)	75 (20%)
Garderet et al. (2012) (MMVAR)	Experimental	NR	NR	NR	Bortezomib (20%) and thalidomide (10%)	NR	NR	NR
	Control	NR	NR	NR	Bortezomib (21%) and thalidomide (6%)	NR	NR	NR

Abbreviations: NR, not reported.

Qualität der Studien:

- Moreau et al., 2016 (TOURMALINE) + San-Miguel et al., 2014 (PANORAMA1): Jadad-Score=5
- Other studies: Jadad-Score=3

Studienergebnisse:

Ixazomib+ lenalidomide + dexamethasone vs. Placebo + lenalidomide + dexamethasone (Moreau et al., 2016 [TOURMALINE] N=722)

- OS: not reported
- PFS: HR 0,74 (95%CI 0,586; 0,934
- ORR: n.s.
- VGRP: n.s
- CR: n.s.

➔ Vorteil Ixazomib nur für PFS gezeigt

Carfilzomib + lenalidomide + dexamethasone vs. Lenalidomide + dexamethasone (Stewart et al.,2015 [ASPIPE], N=792)

- OS: HR 0,79 (95%CI 0,63; 0,99)
- PFS: HR 0,69 (95%CI 0,57; 0,83)
- ORR: RR 1,31 (95%CI 1,21; 1,42)
- VGRP: RR 1,73 (95%CI 1,51; 1,98)
- CR: RR 3,41 (95% 2,43; 4,78)

➔ Vorteil Carfilzomib

Elotuzumab + lenalidomide + dexamethasone vs. Lenalidomide + dexamethasone (Lonial et al., 2015 [ELOQUENT-2]; N=646)

- OS: not reported
- PFS: HR 0,70 (95%CI 0,57; 0,86)
- ORR: RR 1,20 (95%CI 1,10; 1,32)
- VGRP: n.s.

- CR: n.s

➔ Vorteil Elotuzumb für PFS und ORR gezeigt

Panobinostat + bortezomib + dexamethasone vs Placebo + bortezomib + dexamethasone (San-Miguel et al., 2014 [PANORAMA1], N=768)

- OS: n.s.
- PFS: HR 0,63 (95%CI 0,52; 0,76)
- ORR: n.s
- VGRP: RR 1,76 (95%CI 1,32; 2,33)
- CR: RR 1,88 (95% 1,14; 3,10)

➔ Vorteil Panobinostat für PFS, VGRP, CR

Triplet vs. doublet therapies - Pooled analyses of 5 studies

- OS: HR 0.83 (95%CI: 0.71–0.94; I^2=0%) (data from 3 studies)
- PFS: HR (0.68, 95%CI: 0.62–0.74, I^2=0%)
- ORR: (1.19 (95%CI:1.10–1.27; (I^2= 61.4%,)
- Very good partial response (VGPR) 1.44 (95%CI: 1.18–1.77),
- and complete response (CR) 1.76 (95%CI: 1.04–2.97),

Safety (pooled analyses)

Grade 3 or 4 toxicities	No. of trials	RR, 95%CI	*P* value
Overall	5	1.11 (1.05–1.18)	0.001
Infections	4	1.33 (0.97–1.83)	0.079
Thrombocytopenia	5	1.64 (1.13–2.38)	0.009
Neutropenia	5	1.13 (0.71–1.81)	0.60
Anemia	5	0.92 (0.78–1.08)	0.29
Fatal	4	1.00 (0.74–1.36)	0.99

Disadvantage of Triplet-therapies in AE Grade ≥ 3 and Thrombozytopenie Grade ≥ 3

Anmerkung/Fazit der Autoren

Meta-analysis demonstrates that triplet regimens result in improved OS, PFS, ORR, VGPR, and CR compared to doublets, though the risk of grade 3 and 4 adverse events are higher with triplets. The pooled estimates of response and survival strongly favor triplets in the RRMM patients. More high-quality of phase III trials are needed to confirm our findings

Kommentare zum Review

- Inclusion of 2nd und 3rd line therapies
- Safety data of individual trials not reported

Shah et al., 2018 [17].

Efficacy and safety of carfilzomib in relapsed and/or refractory multiple myeloma: systematic review and meta-analysis of 14 trials.

Fragestellung

We analysed efficacy of Carf in RRMM patients and performed various subgroup analyses to understand effects of different doses of Carf (high vs. standard) and regimens (monotherapy vs. combination) into response rates as well as adverse events. We also performed subgroup analyses to evaluate efficacy of Carf in high risk cytogenetics and different ISS stages. Furthermore, we analyzed commonly reported adverse events including cardiotoxicity with respect to different doses of Carf.

Methodik

Population:

- patients who relapsed after receiving ≥ 1 previous lines of therapy which usually included Bort, Len and/or Thal.

Intervention:

- carfilzomib

Komparator:

- nicht spezifiziert

Endpunkte

- OS,
- PFS, the median duration of treatment, median time to overall response, the median duration of overall response
- Adverse events

Recherche/Suchzeitraum:

- search of PubMed, Web of Science, and clinical trial registry, keine expliziten Angaben zum Suchzeitraum
- We also searched abstracts from American Society of Clinical Oncology and American Society of Hematology conferences.
- included only prospective trials published prior to January 2017

Qualitätsbewertung der Studien

- Cochrane Collaboration's tools

Ergebnisse

Anzahl an Studien:

- 14 (3 RCT with 2036 enrolled patients; 11 single-arm studies)

Charakteristika der Studien

Hier Darstellung auf RCTs beschränkt

Author, Year	Regimen used	Carf dosing (mg/m²)	Median age (years)	Patients analyzed, n
Dimopoulos MA *et al.*, 2016	Carf, Dexa	20 (Days 1, 2 of cycle 1) f/b 56	65	464
(ENDEAVOR)	Bort, Dexa		65	465
Hajek R *et al.*, 2017 (FOCUS)	Carf	20 (Days 1, 2 of cycle 1) f/b 27	63	157
	Pred or Dexa		66	158
Stewart AK *et al.*, 2015 (ASPIRE)	Carf, Len, Dexa	20 (Days 1, 2 of cycle 1) f/b 27	64	396
	Len, Dexa		65	396

Qualität der Studien:

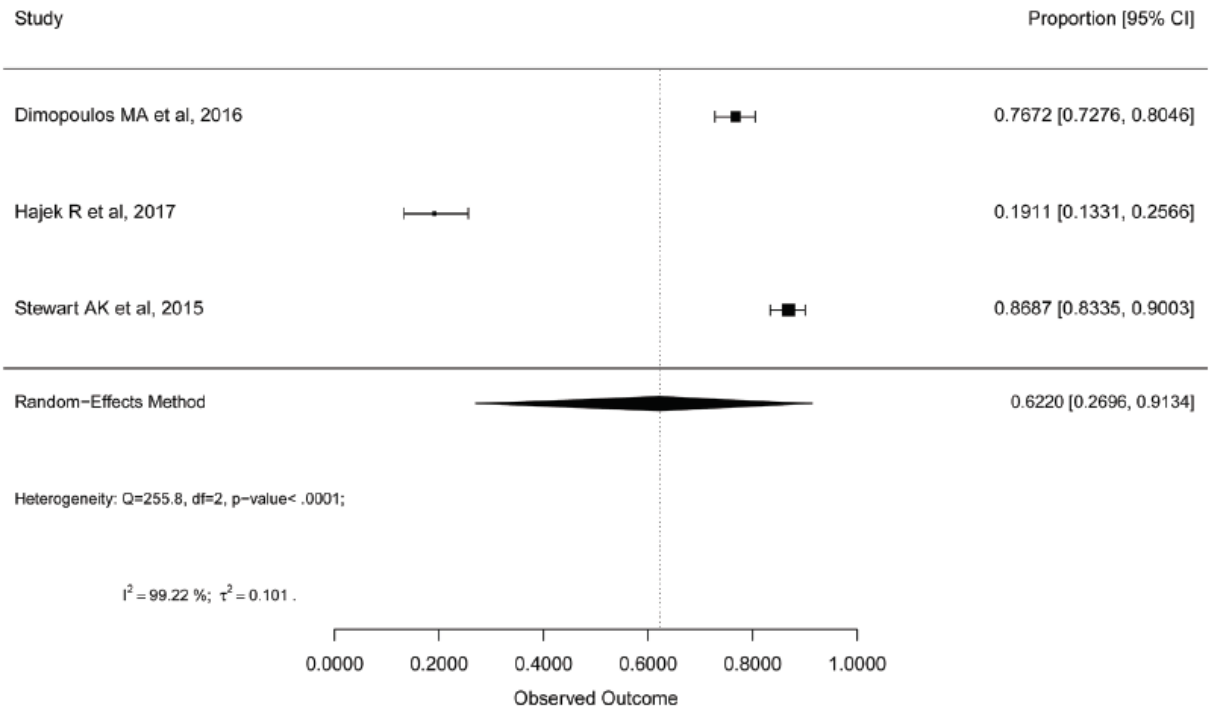
- Among the RCTs, the risk of selection bias and attrition bias were low while performance bias, detection bias, and reporting bias were unclear as per Cochrane Collaboration's tools.

Studienergebnisse: (nur RCTs)

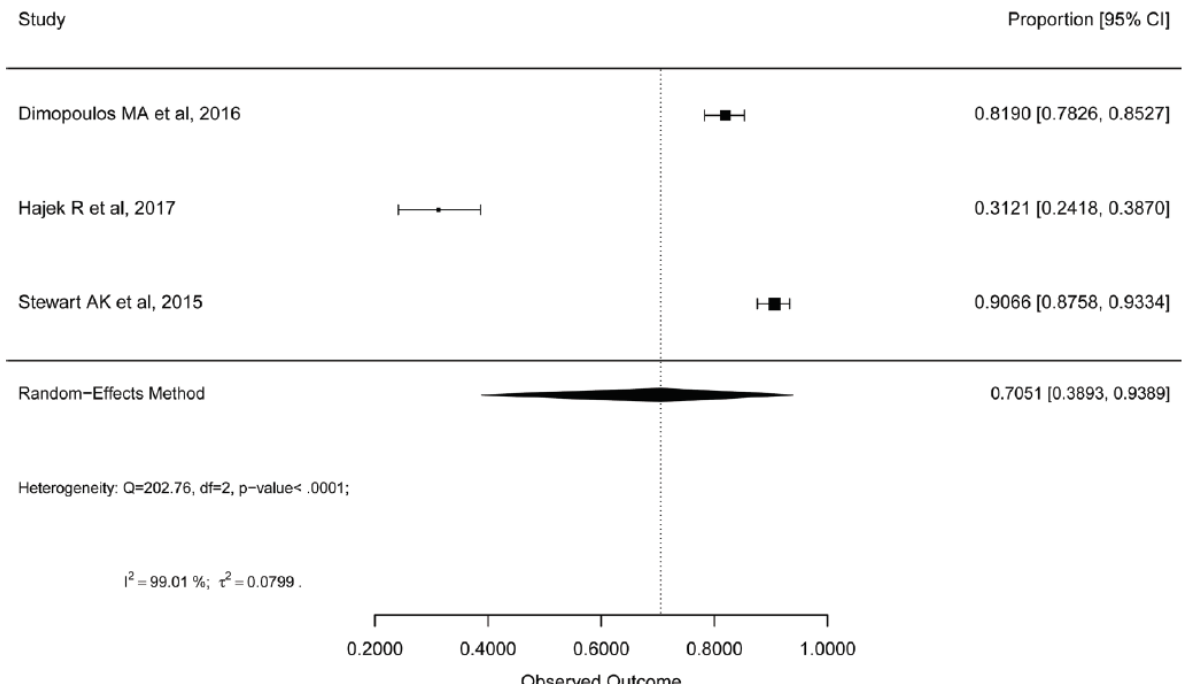
- OS: median OS in Carf groups varied from 10–47.6 months

Author, Year	Median OS (mos)
Dimopoulos MA *et al.*, 2016	47.6
(ENDEAVOR)	24.3
Hajek R *et al.*, 2017 (FOCUS)	10.2
	10
Stewart AK *et al.*, 2015 (ASPIRE)	NA
	NA

- ORR



- Clinical benefit rate (nur RCTs)



- AE

Table 5: Odds ratio (OR) calculations for common adverse events comparing events in Carf versus control groups from phase III trials

Adverse events	No. of trials	Total events, *N*	Total pts, *N*	I^2 statistics	OR (95% CI)	*P*-value
Hematological						
Anemia	3	336	2036	55.78	1.12 (0.78–1.62)	0.53
Thrombocytopenia	3	267	2036	8.72	1.16 (0.88–1.53)	0.28
Neutropenia	2	250	1107	60.47	0.93 (0.50–1.74)	0.81
Non-hematological						
Neuropathy	3	70	2036	65.46	0.54 (0.18–1.65)	0.28
Renal toxicity	3	90	2036	56.46	1.85 (0.93–3.67)	0.07
Fatigue	2	112	1721	25.82	0.97 (0.62–1.51)	0.87
Diarrhea	2	80	1721	51.76	0.64 (0.33–1.27)	0.20
Nausea	2	13	1244	0	1.60 (0.51–4.99)	0.41
Upper respiratory infection	2	23	1721	0	2.28 (0.93–5.61)	0.07
Pyrexia	3	28	2036	0	4.13 (1.61–10.58)	0.001
Pneumonia	1	29	315	0	0.50 (0.22–1.11)	0.08
Cardiotoxicity	3	61	2036	0	2.04 (1.31–3.17)	0.002
Hypertension	3	64	2036	0	3.33 (1.98–5.60)	<0.0001

Abbreviations: OR, odds ratio; CI, confidence interval

Fazit der Autoren

Carf produces significantly better responses with acceptable safety profile in RRMM patients. Combination regimens and higher dose Carf offers better response with no significant extra toxicity. Its efficacy is regardless of cytogenetics or disease stage. Incidences of cardiotoxicity and hypertension seem higher with Carf

Kommentare zum Review

- Ergebnisdarstellung für die Synopse auf RCTs (n=3) beschränkt.
- Keine Informationen zur Anzahl an Vortherapien im Review berichtet
- Effektschätzer nur für Response-Endpunkte berichtet, Daten zu OS nur deskriptiv berichtet
- Klinische Heterogenität bzgl. Intervention und Kontrolle zw. den Studien; Sehr hohe stat. Heterogenität zwischen den Studien; gepoolte Effektschätzer nicht vertrauenswürdig, Betrachtung der Einzelstudienergebnisse

3.4 Leitlinien

Mikhael J et al., 2019 [14].

Treatment of multiple myeloma: ASCO and CCO Joint Clinical Practice Guideline.

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit: CoI-Mangagement entsprechend der ASCO Conflict of Interest Policy; All funding for the administration of the project was provided by ASCO
- Systematische Suche, Auswahl und Bewertung der Evidenz durchgeführt
- Konsensusprozess: informal consensus
- Externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität geplant

Recherche/Suchzeitraum:

- from 2005 through 2018

LoE/GoR

- Strength of evidence: The quality of the total body of evidence used to inform a given recommendation is assessed to evaluate its validity, reliability, and consistency. This assessment considers the individual study quality ratings, the overall risk of bias, and the overall validity and reliability of the total body of evidence. The summary rating is an indication of the Expert Panel's confidence in the available evidence.
- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment is primarily based on the strength of the available evidence for each recommendation and it is an indication of the Expert Panel's confidence in its guidance or recommendation. However, where evidence is lacking, it also affords panels the opportunity to comment on the strength of their conviction and uniformity of their agreement that the recommendation represents the best possible current guidance.

Recommendations

TRANSPLANT-ELIGIBLE POPULATION

Clinical Question 1: What criteria are used to assess eligibility for ASCT?

- Recommendation 1.1. Patients should be referred to a transplant center to determine transplant eligibility (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate)

- Recommendation 1.2. Chronologic age and renal function should not be the sole criteria used to determine eligibility for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Clinical Question 2 What are the options for initial therapy before transplant?

- Recommendation 2.1. The optimal regimen and number of cycles remain unproven. However, at least three to four cycles of induction therapy including an immunomodulatory drug, proteasome inhibitor (PI), and steroids are advised prior to stem-cell collection (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.2. Up-front transplant should be offered to all transplant-eligible patients. Delayed initial SCT may be considered in select patients (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 2.3. Agents associated with stem-cell toxicity, such as melphalan and/or prolonged immunomodulatory drugs exposure (more than four cycles), should be avoided in patients who are potential candidates for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.4. Ample stem-cell collection (sufficient for more than one SCT) should be considered up front, due to concern for limited ability for future stem-cell collection after prolonged treatment exposure (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.5. The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy; patients should be referred for SCT independent of depth of response (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.6. High-dose melphalan is the recommended conditioning regimen for ASCT (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 2.7. Tandem ASCT should not be routinely recommended (Type: evidence based; Evidence quality: intermediate, benefit equals harm; Strength of recommendation: strong).
- Recommendation 2.8. Salvage or delayed SCT may be used as consolidation at first relapse for those not choosing to proceed to transplant initially (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.9. Allogeneic transplant for multiple myeloma is not routinely recommended but may be considered in select high-risk patients or in the context of a clinical trial (Type: evidence based; Evidence quality: intermediate, harm outweighs benefit; Strength of recommendation: strong).

Clinical Question 3: What post-transplant therapy should be recommended?

- Recommendation 3.1. Consolidation therapy is not routinely recommended but may be considered in the context of a clinical trial. For patients ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least two cycles may be considered

(Type: evidence based; evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

- Recommendation 3.2. Lenalidomide maintenance therapy should be routinely offered to standard-risk patients starting at approximately day 90 to 110 at 10 to 15 mg daily until progression. A minimum of 2 years of maintenance therapy is associated with improved survival, and efforts to maintain therapy for at least this duration are recommended (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 3.3. For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered (Type: informal consensus/ evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation:moderate).
- Recommendation 3.4. For high-risk patients, maintenance therapy with a PI with or without lenalidomide may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate)
- Recommendation 3.5. There is insufficient evidence to make modifications to maintenance therapy based on depth of response, including MRD status (Type: informal consensus/evidence based; Evidence quality: low/ intermediate, benefit outweighs harm; Strength of recommendation:moderate)

<u>TRANSPLANT-INELIGIBLE POPULATION</u>

Clinical Question 5: What are the options for initial therapy in transplant ineligible patients?

- Recommendation 5.1. Initial treatment recommendations for patients with multiple myeloma who are transplant ineligible should be individualized based on shared decision making between physicians and patients. Multiple factors should be considered; disease-specific factors such as stage and cytogenetic abnormalities, and patient-specific factors including age, comorbidities, functional status, frailty status, and patient preferences should also be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 5.2. Initial treatment of patients with multiple myeloma who are transplant ineligible should include t minimum a novel agent (immunomodulatory drugs or PI) and a steroid if possible (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 5.3. Triplet therapies for patients with multiple myeloma who are transplant ineligible, including bortezomib, lenalidomide, and dexamethasone, should be considered. Daratumumab plus bortezomib plus melphalan plus prednisone may also be considered (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 5.4. Physicians/patients should balance the potential improvement in response and disease control with a possible increase in toxicity. Initial dosing should be individualized based on patient age, renal function, comorbidities, functional status, and frailty status. Subsequent dosing may be tailored based on initial response and tolerability (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 5.5. Continuous therapy should be offered over fixed-duration therapy when initiating an immunomodulatory drugs or PI-based regimen (Type:

evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

RELAPSED DISEASE

(Anmerkung: auch Evidenz zur Behandlung refraktärer Patienten berücksichtigt)

Clinical Question 7: What factors influence choice of first relapse therapy?

- Recommendation 7.1. Treatment of biochemically relapsed myeloma should be individualized. Factors to consider include patient's tolerance of prior treatment, rate of rise of myeloma markers, cytogenetic risk, presence of comorbidities (ie, renal insufficiency), frailty, and patient preference. High-risk patients as defined by high-risk cytogenetics and early relapse post-transplant/initial therapy should be treated immediately. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse (Type: informal consensus/evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 7.2. All clinically relapsed patients with symptoms due to myeloma should be treated immediately (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 7.3. Triplet therapy should be administered on first relapse, though the patient's tolerance for increased toxicity should be considered. A triplet is defined as a regimen with two novel agents (PIs, immunomodulatory drugs, or monoclonal antibodies) in combination with a steroid (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong),

  Hintergrundinformationen : siehe Anhang
- Recommendation 7.4. Treatment of relapsed multiple myeloma may be continued until disease progression. There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD) (Type: evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 7.5. Prior therapies should be taken into consideration when selecting the treatment at first relapse. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. Triplet regimens are preferred based on tolerability and comorbidities (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

  Hintergrundinformationen: siehe Anhang
- Recommendation 7.6. ASCT, if not received after primary induction therapy, should be offered to transplant eligible patients with relapsed multiple myeloma. Repeat SCT may be considered in relapsed multiple myeloma if progression-free survival after first transplant is 18 months or greater (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Clinical Question 8: How does risk status influence therapy in myeloma (newly diagnosed and relapse)?

- Recommendation 8.1. The risk status of the patients should be assessed using the Revised International Staging System for all patients at the time of diagnosis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong). Recommendation

- 8.2. Repeat risk assessment at the time of relapse should be performed and should include bone marrow with fluorescence in situ hybridization for myeloma abnormalities seen with progression, including 17p and 1q abnormalities. Fluorescence in situ hybridization for primary abnormalities (translocations and trisomies), if seen in the initial diagnostic marrow, does not need to be repeated (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.3. Assessment of other risk factors such as renal insufficiency, age, presence of plasma cell leukemia/circulating plasma cells, extramedullary disease, and frailty, should also be considered/ performed (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.4. In patients with genetic high-risk disease, a triplet combination of PI, immunomodulatory drug, and a steroid should be the initial treatment, followed by one or two ASCTs, followed by a PI based maintenance until progression (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong). Recommendation
- 8.5. In patients with renal insufficiency, drugs should be modified based on renal clearance (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.6. In patients with plasma cell leukemia or extramedullary disease, cytotoxic chemotherapy may have a role (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

National Collaborating Centre for Cancer, 2016 (last updated: 2018) [15].

Institute for Health and Care Excellence (NICE)

Myeloma: diagnosis and management. NICE Guideline 35. Full guideline February 2016.

Leitlinienorganisation/Fragestellung:

This guideline covers the diagnosing and managing of myeloma (including smouldering myeloma and primary plasma cell leukaemia) in people aged 16 and over. It aims to improve care for people with myeloma by promoting the most effective tests and treatments for myeloma and its complications.

Methodik

<u>Grundlage der Leitlinie:</u>

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz durchgeführt;
- 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.

<u>Recherche/Suchzeitraum:</u>

- Up to 8th June 2015

Level of Evidence (LoE) / Strength of Recommendation (SoR):

- For each outcome, an overall assessment of both the quality of the evidence as a whole (very low, low, moderate or high) as well as an estimate of the size of effect is given.

GoR:

- 'Offer' – for the vast majority of patients, an intervention will do more good than harm
- 'Do not offer' – the intervention will not be of benefit for most patients
- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Table 3: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2012).

Sonstige methodische Hinweise:

Die LL enthält zudem Empfehlungen aus NICE technology appraisals (TA), die nicht im Rahmen der LL-Entwicklung abgeleitet wurden. Sie wurden in Übereinstimmung mit den NICE-Guidelines zur Entwicklung klinischer Leitlinien in diese Leitlinie aufgenommen Die TA unterliegen einer regelmäßigen Aktualisierung.

Recommendations

Please note: NICE has a suite of technology appraisal guidance on myeloma either published or in development. These published technology appraisals (TA)cover NICE's position in relation to primary disease treatment, salvage therapy for relapsed myeloma and consolidation/maintenance therapy after primary management. The recommendations in this guideline complement the existing technology appraisals, giving further guidance in addition to the technology appraisals where myeloma-related subgroups are not included.

6.1.1 First autologous stem cell transplantation

- Consider using frailty and performance status measures that include comorbidities to assess the suitability of people with myeloma for first autologous stem cell transplant.
- Do not use age or the level of renal impairment alone to assess the suitability of people with myeloma for first autologous stem cell transplant.

Evidence: low-moderate quality of evidence

6.1.2 Allogeneic stem cell transplantation

- Take into account that only a small number of people with myeloma are suitable for allogeneic stem cell transplantation.
- When assessing whether people with myeloma are suitable for an allogeneic stem cell transplant, take into account:

- whether the person has chemosensitive disease
- how many previous lines of treatment they have had
- whether a fully human leukocyte antigen (HLA) matched donor is available
- how graft-versus-host disease (GvHD) and other complications may get worse with age
- the risk of higher transplant-related mortality and morbidity, versus the potential for long-term disease-free survival
- improving outcomes with other newer treatments
- the person's understanding of the procedure and its risks and benefits.

- Consider allogeneic stem cell transplantation as part of a clinical trial if one is available

Evidence:
The Guideline Committee considered the outcomes of overall survival, progression free survival, health-related quality of life, treatment related mortality and morbidity, patient/carer/family acceptability, adverse events and patient reported outcome measures to be the most relevant in determining whether allogeneic stem cell transplant was effective in specific subgroups of patients.
No evidence was identified for the outcomes treatment related morbidity, health-related quality of life, adverse events, patient reported outcome measures and patient/carer/family acceptability
When drafting the recommendations the Guideline Committee considered overall survival and progression free survival to be the most important quality of the evidence was very low to low for all outcomes

11 Managing relapsed myeloma

11.1 first relapse

- **Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:**
  - **the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) […]**
- **People currently receiving bortezomib monotherapy who do not meet the criteria in the recommendation above should have the option to continue therapy until they and their clinicians consider it appropriate to stop.**

Evidence: see TA 129 Bortezomib, NICE 2007 (www.nice.org.uk/TA129), based on APEX trial: Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352(24):2487-2498

11.2 Second autologous stem cell transplant

- Offer a second autologous stem cell transplant to people with relapsed myeloma who are suitable and who have:
  - completed re-induction therapy without disease progression and
  - had a response duration of more than 24 months after their first autologous stem cell transplant.
- Consider a second autologous stem cell transplant for people with relapsed myeloma who are suitable and who have:

- completed reinduction therapy without disease progression and
- had a response duration of between 12 and 24 months after their first autologous stem cell transplant.

- Be aware that people with relapsed myeloma are more likely to be suitable for a second autologous stem cell transplant if they have:
  - had a good response to the first autologous stem cell transplant
  - a lower International Staging System (ISS) stage
  - not had many prior treatments
  - good overall fitness, based on resilience, frailty and performance status
  - no adverse fluorescence in-situ hybridisation (FISH) results.

Evidence:

The Guideline Committee considered the outcomes of overall survival, progression-free survival, health-related quality of life, treatment related mortality and morbidity, patient/carer/family acceptability, adverse events and patient reported outcome measures to be the most relevant in determining whether second autologous stem cell transplant was effective in specific subgroups of patients with relapsed/refractory myeloma.

Of these, evidence was identified for overall survival and progression-free survival. Evidence was also reported for time to progression in one study. When drafting the recommendations the Guideline Committee considered overall survival and progression-free survival to be the most important as these are most clinically meaningful.

There was moderate quality evidence for time to progression and very low to moderate quality evidence for overall survival and progression free survival.

11.3 Subsequent therapy

- Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies

  Evidence: based on TA 171 Lenalidomid, NICE 2009; www.nice.org.uk/TA171

- People currently receiving lenalidomide for the treatment of multiple myeloma, but who have not received two or more prior therapies, should have the option to continue therapy until they and their clinicians consider it appropriate to stop.
- Pomalidomide, in combination with dexamethasone, is not recommended within its marketing authorisation for treating relapsed and refractory multiple myeloma in adults who have had at least 2 previous treatments, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy

  Based on NICE TA 338 (www.nice.org.uk/TA338)

  Please Note: guidanceTA338 has been updated and replaced by NICE technology appraisal guidance 427. (https://www.nice.org.uk/guidance/ta427):

- Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme.

Information regarding genetic abnormalities

- ***FISH:*** *Thirty four studies were identified that investigated the prognostic value of FISH. Thirty one studies examined genetic abnormalities in newly diagnosed myeloma patients*

and determined the prognostic impact of these genetic abnormalities on patient survival (PFS and/or OS) and three studies examined genetic abnormalities in smouldering myeloma patients and determined the prognostic impact of these genetic abnormalities on time to progression to active myeloma.

The most common genetic abnormalities assessed were: t(11;14), t(4;14), t(14;16), del(17p), del(13q), del(1p), 1q gains, del(p53) and hyperdiploidy.

(…) The Guideline Committee noted that the evidence had shown the standard risk abnormalities t(11;14) and hyperdiploidy were markers of not having high-risk disease. Because they indicate standard as opposed to high-risk disease, the group made a recommendation to consider the use of FISH to identify these markers as knowing this information can be helpful in discussing prognosis with patients.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2021) am 11.03.2021

#	Suchfrage
1	[mh “Multiple Myeloma”]
2	(multiple OR (plasma NEXT cell)):ti,ab,kw
3	(myeloma OR myelomas):ti,ab,kw
4	#2 AND #3
5	((Kahler NEXT disease*) OR myelomatos*s):ti,ab,kw
6	{OR #1, #4-#5}
7	#6 with Cochrane Library publication date from March 2016 to present

Systematic Reviews in Medline (PubMed) am 11.03.2021

#	Suchfrage
1	Multiple Myeloma[mj]
2	((multiple[tiab]) OR plasma-cell[tiab]) OR "plasma cells"[tiab]
3	(myeloma[tiab]) OR myelomas[tiab]
4	#2 AND #3
5	(("Kahler Disease*"[tiab]) OR myelomatosis[tiab]) OR myelomatoses[tiab]
6	#1 OR #4 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR

	bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	((#7) AND ("2016/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMedam 11.03.2021

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[tiab]) OR plasma-cell[tiab]) OR "plasma cells"[tiab]
3	(myeloma[tiab]) OR myelomas[tiab]
4	#2 AND #3
5	(("Kahler Disease*"[tiab]) OR myelomatosis[tiab]) OR myelomatoses[tiab]
6	#1 OR #4 OR #5
7	(#6) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
8	(((#7) AND ("2016/03/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Mikhael J et al (2019) [14] Treatment of multiple myeloma: ASCO and CCO Joint Clinical Practice Guideline.

Hintergrundinformationen

- zu Recommendation 7.3. “Triplet therapy should be administered on first relapse, though the patient’s tolerance for increased toxicity should be considered. A triplet is defined as a regimen with two novel agents (PIs, immunomodulatory drugs, or monoclonal antibodies) in combination with a steroid.”:

Literature review and clinical interpretation. The treatment of relapsed multiple myeloma is complex and does not have a simple algorithm. When available, clinical trials are preferred and should be considered at every phase of treatment.

On first relapse, the choice of therapy should take into account patient-related, disease-related, as well as treatment-related factors. For patients who are fit, triplet is generally recommended over doublet therapy due to improved clinical outcomes. Triplet therapy is defined as containing two novel agents plus steroids. Novel agents include immunomodulatory drugs such as lenalidomide, pomalidomide, or thalidomide; PI such as ixazomib, bortezomib, or carfilzomib; and monoclonal antibodies such as daratumumab and elotuzumab. Doublet therapy is defined as one novel agent with steroids. Multiple randomized studies[53,55,58,95,107,112] as well as meta-analyses[10,17,21,26,31] have shown that triplets are more effective than doublet combinations in improving PFS, overall response rate, and/or OS, even in older adult patients.[58] In fact, the US Food and Drug Administration (FDA) approval of multiple recent drugs such as daratumumab,[55,107] elotuzumab,[53] carfilzomib,[58] ixazomib,[95] and panobinostat[112] have been based on the improved PFS of these drugs used in triplet combinations versus doublets in relapsed and/or refractory myeloma. Data suggest that even the use of alkylating agents as part of triplet therapy yields better outcomes than doublets.[75] Although triplet therapy offers better clinical outcomes, toxicity appears increased in triple versus doublet therapy,[17,21,26,31,58] and this must be considered when selecting therapy. For some patients, prior toxicity may result in the selection of doublet versus triplet therapy. The ENDEAVOR trial (ClinicalTrialos.gov identifier: NCT01568866) demonstrated the superiority of the doublet carfilzomib plus dexamethasone to bortezomib plus dexamethasone in both PFS and OS[52] in relapsed multiple myeloma. In subgroup analyses, carfilzomib, dexamethasone was superior to bortezomib, dexamethasone regardless of cytogenetic risk,[44] number of prior therapy lines,[94] or prior exposure to bortezomib or lenalidomide.[94] Overall, the selection of doublet versus triplet therapy should be individualized.

The best triplet or how to sequence triplet or doublet therapy in the relapse or refractory setting remains unclear. Published RCTs in relapsed myeloma comparing individual triplets or novel agents in triplet combination are lacking. Several network meta-analyses have been performed to ascertain which combination or type of novel agent was more efficacious, with variable results and no obvious conclusion.[9,10,24,31,60] Because the optimal sequence of therapies is unknown and most patients receive between two to more than 10 lines of therapy for relapsed disease, the general strategy has been to use all approved drugs in rational sequential combinations (ie, immunomodulatory drug plus PI plus steroid followed by second-generation immunomodulatory drug plus monoclonal antibody plus steroid followed by second-generation PI plus alkylator plus steroid, and so on).

Although clinical trials are preferred at all treatment time points, as patients become multiply relapsed and resistance develops to immunomodulatory dugs, PI, and antibodies, referral for a novel clinical trial can be considered. In addition, the use of chemotherapeutic agents such as cyclophosphamide, melphalan, or panobinostat[112] may also be considered.

- Zu Recommendation 7.5. “Prior therapies should be taken into consideration when selecting the treatment at first relapse. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. Triplet regimens are preferred based on tolerability and comorbidities.”:

Literature review and clinical interpretation. In the past decade, there has been tremendous progress in the treatment of multiple myeloma, with a number of agents/combinations being approved by the FDA, including monoclonal antibodies (daratumumab, elotuzumab), histone deacetylase inhibitors (panobinostat), PIs (bortezomib, carfilzomib, ixazomib), and immunomodulatory drugs (lenalidomide, thalidomide, pomalidomide) along with historical alkylators and anthracyclines. This wealth of treatment options makes it challenging for the treating clinician to select which drugs to use, as well as when to use them and in what order.

In general, these regimens are tried sequentially based on many factors, including availability, prior therapy, and toxicity profile, as there are no randomized trials available to guide specific treatment sequences.

In the 2017 Journal of Clinical Oncology article by van Beurden-Tan et al,[9] they aimed to synthesize all efficacy evidence, enabling a comparison of all current treatments for relapsed multiple myeloma. They combined evidence from 17 phase III RCTs, including 16 treatments. Of 16 treatment options, the combination of daratumumab, lenalidomide, and dexamethasone was the best option in terms of both ranking and probability of being the best treatment. All three best-treatment options are triple-combination regimens, and all are in combination with lenalidomide and dexamethasone (with daratumumab, carfilzomib, or elotuzumab). This is in line with earlier observations that triplet combinations are better than doublets[9] and are preferred if tolerated as outlined above.

Prior treatments are important in deciding which regimen will be used. Patients who relapse more than 1 year after their treatment will likely respond to a repeat course of the previous therapy. If patients relapse during therapy or within 1 year of completing therapy, they are considered less sensitive to these agents and should be treated accordingly. For example, in patients progressing on lenalidomide maintenance therapy, salvage therapy with bortezomib and a monoclonal antibody can be considered. In bortezomib-refractory cases, lenalidomide with monoclonal antibody can be used. In double-refractory cases, pomalidomide combinations with monoclonal antibodies[172] or cyclophosphamide[173] are reasonable options.

This is particularly important in high-risk patients. Lui et al[209] performed a meta-analysis in relapsed multiple myeloma including patients with del(17p). Thirteen prospective studies were evaluated involving 3,187 patients with multiple myeloma and 685 with del (17p). The authors concluded that combined therapy (triplets and doublets) with second-generation PIs, monoclonal antibodies, and immunomodulatory drugs are associated with improved outcomes in patients with del (17p).

Evidenztabellen im Supplement der Publikation abgebildet

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

Kontaktdaten

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Indikation gemäß Beratungsantrag

Behandlung des Multiplen Myeloms bei erwachsenen Patienten

- die bereits mit den drei Hauptwirkstoffklassen behandelt wurden (mindestens ein immunmodulatorisches Arzneimittel, ein Proteasom-Inhibitor und ein Anti-CD38-Antikörper) und refraktär gegenüber der letzten Therapielinie sind

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Das Multiple Myelom (MM) ist eine seltene, biologisch ausgesprochen heterogene Krebserkrankung. Erstes Ziel der Behandlung eines symptomatischen Myelompatienten ist das Erreichen einer bestmöglichen Remission mit rascher Symptomkontrolle und Normalisierung myelombedingter Komplikationen bzw. der Vermeidung des Entstehens neuer Krankheitsfolgen. Dies erfolgt unter Berücksichtigung der individuellen Krankheits- und Lebenssituation, und unter weitestmöglicher Vermeidung kurz- und langfristig belastender Nebenwirkungen der Therapie. Bislang ist das MM meist eine inkurable Erkrankung, die Therapie ist überwiegend eine kontinuierliche Therapie.

Das Kollektiv der Patienten, die mindestens drei vorherige Therapien einschl. einem Proteasom-Inhibitor, einem Immunmodulator und einem Anti-CD38-Antikörper erhalten haben, ist heterogen. Das ist zum einen durch die biologische und klinische Vielfalt der Grundkrankheit, zum anderen durch die Erfahrungen aus den vorherigen Therapien bedingt.

Grundsätzlich ist die Prognose der Patienten trotz der Fortschritte, die in den vergangenen Jahren in der Behandlung erzielt wurden, eingeschränkt. Patienten, die gegen einen Anti-CD38 Antikörper, einen Proteasominhibitor und einen Immunmodulator refraktär sind, haben eine Überlebensprognose von unter 10 Monaten. Es besteht weiterhin ein großer, ungedeckter medizinischer Bedarf für diese Patientengruppe.

Standard ist eine Therapie nach Maßgabe des behandelnden Arztes unter Berücksichtigung der neuen Arzneimittel (Belantamab Mafodotin, Elotuzumab, Isatuximab, Ixazomib, Panobinostat, Selinexor). Bei fortgeschrittenen Rezidiven können auch konventionelle Zytostatika (Bendamustin, liposomales Doxorubicin) unter Abwägung von Nutzen und Nebenwirkungen erwogen werden.

Fragestellung

Der therapeutische Standard hat sich seit unserer letzten Stellungnahme zu diesem Thema nicht grundlegend geändert.

Stand des Wissens

Das Multiple Myelom (MM) ist eine seltene, biologisch sehr heterogene Krebserkrankung. Das klinische Spektrum reicht von asymptomatischen, inzidentell diagnostizierten Krankheitsbildern bis zu akuten Verläufen mit hämatopoetischer Insuffizienz, Nierenfunktionseinschränkung und/oder ausgeprägter Osteodestruktion. Vorstufe ist die monoklonale Gammopathie unklarer Signifikanz [1]. Die Diagnostik hat sich in den letzten Jahren erweitert und führt zu einer früheren Therapieeinleitung. So beinhaltet die Diagnostik jetzt radiologische Schnittbildverfahren zur Identifikation fokaler Läsionen, die MR-tomographisch noch vor dem Entstehen der klassischen Osteolysen detektierbar sind und sich in der Folge in solche entwickeln. Die Behandlung des Multiplen Myeloms erfolgt vor allem medikamentös. In den letzten 15 Jahren wurden zahlreiche neue Arzneimittel zugelassen, die in klinischen Studien gegenüber dem bisherigen Standard, in Kombinationen und in Sequenzen getestet wurden [1, 2]. Jährlich werden ungefähr 3.600 Neuerkrankungsfälle bei Männern und ca. 2.900 Neuerkrankungsfälle bei Frauen in Deutschland diagnostiziert.

Die Einleitung einer Therapie ist bei symptomatischem Multiplem Myelom nach den Kriterien der International Myeloma Working Group (IMWG) indiziert. Bestandteil der Definition sind die sogenannten CRAB-Kriterien, erweitert durch zyto-/histologische, radiologische und serologische Parameter [3, 4].

Erstes Ziel der Behandlung eines symptomatischen Myelompatienten ist das Erreichen einer bestmöglichen Remission mit rascher Symptomkontrolle und Normalisierung myelombedingter Komplikationen, unter Berücksichtigung der individuellen Krankheits- und Lebenssituation, und unter weitestmöglicher Vermeidung kurz- und langfristig belastender Nebenwirkungen der Therapie. Langfristiges Ziel ist die Verlängerung der progressionsfreien und der Gesamtüberlebenszeit.

Das Patientenkollektiv in fortgeschrittenen Therapielinien ist noch inhomogener aufgrund der zusätzlichen Ergebnisse und möglichen Folgeerscheinungen der Erstlinientherapie. und dem ständigen Wandel bzw. der ständigen Modifikation der Erst- und Zweitlinientherapie. Die Rezidivpopulation reicht somit von Patienten, die möglicherweise aufgrund eines langjährigen und eher spät rezidivierenden Verlaufes andere Vortherapien und wenige neue Substanzen erhalten haben, bis hin zu Patienten, die im Bereich von Monaten vor Eintritt der Rezidivtherapie bereits mit den neuen zugelassenen Standardtherapien behandelt wurden. Dies betrifft vor allem die Etablierung der immunmodulatorischen Substanzen in der Erstlinienbehandlung und nun auch die rasche Implementierung von Daratumumab in der ersten Therapielinie.

Da dies bis vor in jüngster Zeit die Schlüsselsubstanzen der Rezidivtherapie waren, hat deren Anwendung in der Erstlinientherapie für die Gestaltung der Rezidivbehandlung besondere Bedeutung.

Darüber hinaus hat sich die Nomenklatur aktuell geändert: Noch vor 2 Jahren wurde eine Therapie nach Bortezomib und einem Immunmodulator als Drittlinientherapie bezeichnet. Durch die Integration der Kombinationen Bortezomib/Lenalidomid/Dexamethason und Bortezomib/Thalidomid/Dexamethason in den Standard der Erstlinientherapie muss die frühere Drittlinientherapie jetzt als Zweitlinientherapie bezeichnet werden. Transparenter ist hier eine Beschreibung der Art der Vortherapien bzw. ihre Definition anhand der Substanzklassen anstelle einer formalen Definition.

Die Wahl der Arzneimittel richtet sich neben den Zulassungsbedingungen auch nach der Wirksamkeit der vorhergehenden Therapie, dem phänotypischen Bild des Rezidivs, der Verträglichkeit bzw. Komorbiditäten. Bei guter Wirksamkeit und Verträglichkeit der vorherigen Therapie kann bei der Zweit- oder Drittlinientherapie zwischen Arzneimitteln aus einer anderen oder der derselben Substanzklasse gewählt werden. Bei geringer Wirksamkeit und/oder schlechter Verträglichkeit ist ein Wechsel der Substanzklasse indiziert. Die neuen Arzneimittel sowie die möglichen Kombinationen sind sehr vielfältig und erlauben auch eine Sequenztherapie. Diese wird an das Krankheitsbild, die Vortherapie(n) und Komorbiditäten angepasst.

Dreifachkombinationen mit einem oder zwei der neuen Arzneimittel sind in der Regel wirksamer als Zweifachkombinationen. Aktuell stehen mehrere gleichwertige, in der Regel in randomisierten Phase III Studien etablierte Kombinationstherapien zur Verfügung. Durch die uneinheitliche Erstlinientherapie ergeben sich unterschiedliche Konstellationen. Wesentliche Kriterien bei der Wahl der Zweitlinientherapie sind die Zusammensetzung und das Ansprechen auf die Erstlinientherapie, i. e. Dauer und Tiefe der Remission sowie Verträglichkeit.

Wichtig ist auch die Berücksichtigung der Einschlusskriterien der Studien und die Tiefe der bisherigen Informationen. So gibt es bisher keine ausreichende Evidenz für die erneute Wirksamkeit von Daratumumab nach Vortherapie mit Daratumumab oder von Isatuximab nach Daratumumab. Auch gibt es Hinweise auf eine eingeschränkte Wirksamkeit von Lenalidomid in den verschiedenen Kombination nach einer Lenalidomid-haltigen Vortherapie.

Die aktuellen Daten für wirksame Therapien nach Vorbehandlung mit einer immunmodulierenden Substanz, einem Proteasom-Inhibitor und einem Anti-CD38-Antikörper können folgendermaßen zusammengefasst werden (alphabetische Reihenfolge):

- Immunmodulierende Substanzen können in einer späteren Therapielinie erneut eingesetzt werden, präferenziell ein anderes Präparat, z. B. Pomalidomid.
- Proteasom-Inhibitoren können ebenfalls in einer späteren Therapielinie erneut eingesetzt werden, präferenziell ein anderes Präparat, z. B. Carfilzomib oder Ixazomib.
- Wiederholung der Induktions- und Konsolidierungstherapie aus der Erstlinientherapie bei Patienten mit langer, tiefer Remission und guter Verträglichkeit; als Orientierung ist eine Remissionsdauer von >2 Jahren geeignet.

Neue, in dieser Indikation zugelassene Substanzen und Kombinationen sind (alphabetische Reihenfolge):

- Belantamab Mafodotin führte in einer Phase-II-Studie bei Patient*innen mit Refraktärität auf mindestens einen Proteasom-Inhibitor, eine immunmodulierende Substanz und einen Anti-CD38-Antikörper zu einer Remissionsrate von 32% mit einer medianen Remissionsdauer von 11 Monaten [5].

- Elotuzumab/Pomalidomid/Dexamethason führte gegenüber Pomalidomid/Dexamethason zu einer signifikanten Steigerung der Remissionsrate, zur Verlängerung der progressionsfreien Überlebenszeit und der Gesamtüberlebenszeit [6].
- Isatuximab führte bei Patient*innen mit mindestens zwei Vorbehandlungen, darunter einem Proteason-Inhibitor und einem Immunmodulator, in Kombination mit Pomalidomid und Dexamethason gegenüber Pomalidomid/Dexamethason zur Verlängerung der progressionsfreien Überlebenszeit [7].
- Ixazomib/Lenalidomid/Dexamethason führte gegenüber Lenalidomid/Dexamethason zu einer Erhöhung der Remissionsrate, der Rate tiefer Remissionen und zur Verlängerung des progressionsfreien Überlebens, nicht zur Verlängerung der Gesamtüberlebenszeit [8].
- Panobinostat führte in Kombination mit Bortezomib/Dexamethason gegenüber Bortezomib/Dexamethason zu einer Verlängerung der progressionsfreien, nicht der Gesamtüberlebenszeit [9].
- Pomalidomid führte in Kombination mit niedrigdosiertem Dexamethason gegenüber einer hochdosierten Dexamethason-Therapie zur Verlängerung der progressionsfreien und der Gesamtüberlebenszeit sowie zu einer Steigerung der Remissionsrate [10]. Die zusätzliche Kombination mit Cyclophosphamid steigert die Ansprechrate, aber auch die hämatologische Toxizität.
- Selinexor führte bei Patient*innen nach mindestens 4 Vortherapien zu einer Remissionsrate von 25,3% und einem Median der Remissionsdauer von 4 Monaten [11].
- Selinexor/Bortezomib/Dexamethason führte bei Patient*innen nach mindestens 4 Vortherapien zu einer Remissionsrate von 25,3% und einem Median der Remissionsdauer von 4 Monaten [12].
- Zytostatika: Wirksame ‚klassische' Zytostatika sind Bendamustin [13], Cyclophosphamid, Doxorubicin [14] und Melphalan, jeweils als Monotherapie oder in Kombinationen. Dazu gehören auch Therapieregime wie z.B. Bendamustin + Velcade/Bendamustin + Carfilzomib, VDT PACE oder DCTP, vor allem bei extramedullärer Manifestation.

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

Ja

Die unterschiedlichen Behandlungsentscheidungen sind im Vorschlag einer Therapie nach Maßgabe des behandelnden Arztes abgebildet.

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