Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-176 Carfilzomib

Stand: Oktober 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Carfilzomib **in Kombination mit Daratumumab und Dexamethason zur Behandlung von erwachsenen Patienten mit multiplem Myelom, die mindestens eine vorangegangene Therapie erhalten haben.**	
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	• Panobinostat – Beschluss vom 17. März 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Pomalidomid – Beschluss vom 17. März 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Elotuzumab – Beschluss vom 1. Dezember 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Ixazomib – Beschluss vom 6. Juli 2017 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Carfilzomib – Beschluss vom 15. Februar 2018 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Daratumumab – Beschluss vom 15. Februar 2018 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V
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:	
Carfilzomib L01XX45 Kyprolis®	<u>Zu bewertendes geplantes Anwendungsgebiet:</u> Kyprolis ist in Kombination mit entweder […] oder Daratumumab und Dexamethason [...] zur Behandlung von erwachsenen Patienten mit multiplem Myelom indiziert, die mindestens eine vorangegangene Therapie erhalten haben. <u>Bereits zugelassenes Anwendungsgebiet:</u> *siehe unten*
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 (Plasmozytom)
Doxorubicin L01DB01 Adrimedac®	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: […] – Fortgeschrittenes multiples Myelom Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Doxorubicin *(pegyliert liposomal)* L01DB Caelyx®	Caelyx ist indiziert: […] – 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®	Vincristinsulfat-Teva® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: […] – multiplem Myelom
Immunmodulatoren	
Lenalidomid L04AX04 Revlimid®	Multiples Myelom Revlimid ist in Kombination mit Dexamethason indiziert für die Behandlung des multiplen Myeloms bei erwachsenen Patienten, die mindestens eine vorausgegangene Therapie 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.
Proteasominhibitoren	
Bortezomib L01XX32 Velcade®	VELCADE als Monotherapie oder in Kombination mit pegyliertem, liposomalen Doxorubicin oder Dexamethason ist indiziert für die Behandlung erwachsener Patienten mit progressivem, multiplen Myelom, die mindestens 1 vorangehende Therapie durchlaufen haben und die sich bereits einer hämatopoetischen Stammzelltransplantation unterzogen haben oder für diese nicht geeignet sind. […]
Carfilzomib L01XX45 Kyprolis®	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 (siehe Abschnitt 5.1).
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.
Histon-Deacetylase-Inhibitoren	
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.
Antikörper	
Elotuzumab L01XC23 Empliciti®	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). 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 5.1).
Daratumumab	DARZALEX ist indiziert:

L01XC24 Darzalex®	• 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 Lenalidomid und Dexamethason oder Bortezomib und Dexamethason für die Behandlung erwachsener Patienten mit multiplem Myelom, die bereits mindestens eine Therapie erhalten haben. […]
Glucocorticoide	
Dexamethason H02AB02 Dexa-CT®	Onkologie Palliativtherapie maligner Tumoren Prophylaxe und Therapie von Zytostatikainduziertem Erbrechen im Rahmen antiemetischer Schemata
Prednisolon H02AB06 Decortin® H	Hämatologie/Onkologie: […] – akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, chronische lymphatische Leukämie, Morbus Waldenström, multiples Myelom (DS: e) […] – Palliativtherapie maligner Erkrankungen Hinweis: Prednisolon kann zur Symptomlinderung, z. B. bei Inappetenz, Anorexie und allgemeiner Schwäche bei fortgeschrittenen malignen Erkrankungen nach Ausschöpfung spezifischer Therapiemöglichkeiten angewendet werden. Einzelheiten sind der aktuellen Fachliteratur zu entnehmen.
Prednison H02AB07 Decortin®	Hämatologie/Onkologie: […] – akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, chronische lymphatische Leukämie, Morbus Waldenström, multiples Myelom (DS: e) […] – Palliativtherapie maligner Erkrankungen Hinweis: Prednison kann zur Symptomlinderung, z. B. bei Inappetenz, Anorexie und allgemeiner Schwäche bei fortgeschrittenenmalignen Erkrankungen nach Ausschöpfung spezifischer Therapiemöglichkeiten angewendet werden. Einzelheiten sind der aktuellen Fachliteratur zu entnehmen.
Immunstimulanzien	
Interferon alfa-2b L03A B05 IntronA®	Multiples Myelom 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: 2019-B-176 (Carfilzomib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	23. August 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	The Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
ERG	Evidence Review Group
ESMO	European society for medical oncology
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GoR	Grade of Recommendations
HDAC	histone deacetylase
HR	Hazard ratio
HRQoL	health-related quality of life
IMiDs	immunomodulatory imide drugs
IQWiG	Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
LoE	Level of Evidence
mAbs	monoclonal antibodies
MM	multiple myeloma
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NCCN	National Comprehensive Cancer Network
NMA	network meta-analysis
OR	Odds ratio
ORR	overall response rate
PFS	progression-free-survival
RRMM	relapsed/refractory multiplemyeloma
SIGN	Scottish Intercollegiate Guidelines Network
STA	single technology appraisal
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Indikation der Synopse: zur Behandlung von erwachsenen Patienten mit multiplem Myelom, die mindestens eine vorangegangene Therapie erhalten haben.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *multiples Myelom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 06.08.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 578 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 24 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2018 [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 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 [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 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, 2017 [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 6. Juli 2017 - Ixazomib

Indikation

Zugelassenes Anwendungsgebiet (laut Zulassung vom 21. November 2016):

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.

Vergleichstherapie

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.

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.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß des Zusatznutzens:

nicht quantifizierbar

G-BA, 2016 [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 1. Dezember 2016 - Elotuzumab

Indikation

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).

Vergleichstherapie

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 / Ergebnis

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

Anhaltspunkt für einen geringen Zusatznutzen

G-BA, 2016 [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 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.

Vergleichstherapie

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.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß des Zusatznutzens:

nicht quantifizierbar

G-BA, 2016 [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 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 [18].

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 of any age, gender or ethnic origin and with any diagnosis of multiple myeloma. We included patients 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 samebackground 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:

- Overall survival (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

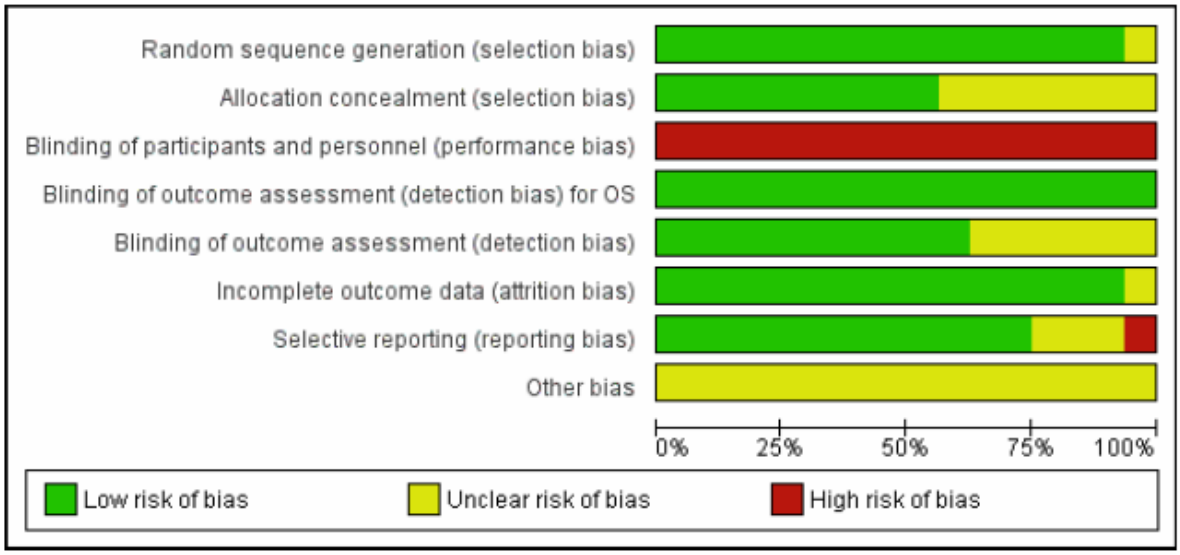
Ergebnisse

Anzahl eingeschlossener Studien:

- 6 relevant RCTs involving 5626 patients and included 12 trials
- All trials were randomised and open-label studies. Two trials were published in abstract form and therefore we were unable to assess potential risk of bias in full.

Qualität der Studien:

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

- There is moderate-quality evidence that bortezomib prolongs OS (four studies, 1586 patients; Peto OR 0.77, 95% CI 0.65 to 0.92) and PFS (five studies, 1855 patients; Peto OR 0.65, 95% CI 0.57 to 0.74) from analysing trials of bortezomib versus no bortezomib with the same background therapy in each arm.
- There is high-quality evidence that bortezomib prolongs OS (five studies, 2532 patients; Peto OR 0.76, 95% CI 0.67 to 0.88) but low-quality evidence for PFS (four studies, 2489 patients; Peto OR 0.67, 95% CI 0.61 to 0.75) from analysing trials of bortezomib versus no bortezomib with different background therapy in each arm or compared to other agent(s).
- We identified four trials in the meta-analysis that measured time to progression (TTP) and were able to extract and analyse PFS data for three of the studies, while in the case of one study, we included TTP data as PFS data were not available. We therefore did not analyse TTP separately in this review.
- Patients treated with bortezomib have increased risk of thrombocytopenia, neutropenia, gastro-intestinal toxicities, peripheral neuropathy, infection and fatigue with the quality of evidence highly variable.
- There is high-quality evidence for increased risk of cardiac disorders from analysing trials of bortezomib versus no bortezomib with different background therapy in each arm or versus other agents.
- The risk of TRD in either comparison group analysed is uncertain due to the low quality of the evidence.
- Only four trials analysed HRQoL and the data could not be meta-analysed.

Subgroup analysis - disease setting

- We considered three subgroups for myeloma disease setting: transplant eligible, transplant ineligible and relapsed/refractory disease and included 11 trials in this subgroup analysis (we did not include the All India Institute Study as the disease setting was unclear).
  - For OS, a statistically significant benefit with bortezomib treatment was observed in all groups, with the smallest benefit observed in the transplant eligible group. Considering this group alone, the benefit was not statistically significant with a Peto odds ratio (OR) of 0.86 (95% CI 0.73 to 1.02) (Analysis 2.1). For PFS, the observed benefit for bortezomib was lower in the transplant eligible group than the other two groups but still statistically significant (Analysis 2.2). There was evidence of heterogeneity between subgroups for PFS (P = 0.002, I^2 = 84.5%).

Subgroup analysis - therapy setting

- We considered three subgroups for myeloma therapy setting: induction, consolidation and maintenance and included six trials in the subgroup analysis for therapy setting.
  - A statistically significant benefit for bortezomib was observed in all outcomes and subgroups except for OS following consolidation therapy. Heterogeneity tests between subgroups were non-significant for all outcomes.

Anmerkung/Fazit der Autoren

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

Chen R et al., 2017 [4].

Effect of pomalidomide on relapsed/refractory multiple myeloma: a systematic review and meta-analysis

Fragestellung

To summarize the effect of pomalidomide for the treatment of patients with RRMM.

Methodik

Population:

- relapsed/refractory MM (RRMM)

Intervention:

- Pomalidomide

Komparator:

- Not specified

Endpunkte

- Not specified

Recherche/Suchzeitraum

- on September 20, 2016

Qualitätsbewertung der Studien:

- Cochrane tool for assessment of bias

Ergebnisse

Anzahl eingeschlossener Studien

- 8

Charakteristika der Population:

Table 1. Basic information and characteristics of included studies

Study (year)	Country	Period	Design	No. of patients	Median age, range	Disease characteristics
Lacy *et al.* (2009)[24]	US	November 2007 to August 2008	Phase 2	60	66(35-88)	At least one but no more than three prior regimens (lenalidomide, thalidomide, or bortezomib)
Lacy *et al.* (2010)[25]	US	November 2008 to April 2009	Phase 2	34	62(39-77)	Previously treated, symptomatic, histologically confirmed MM refractory to lenalidomide therapy
Lacy *et al.* (2011)[26]	US	May 2009 to November 2009	Phase 2	35 (2mg)	63(39-77)	Previously treated, symptomatic MM refractory to both lenalidomide and bortezomib therapy
		November 2009 to April 2010		35(4mg)	61(45-77)	
Leleu *et al.* (2013)[28]	France	October 2009 to August 2010	Randomized phase 2	43 (arm 21/28) 41 (arm 28/28)	60(45-81) 60(42-83)	Relapsed MM after at least one prior regimen of myeloma treatment, nonresponders to at least two cycles of either the last line of lenalidomide or bortezomib
San *et al.* (2013)[29]	Australia, Canada, Europe, Russia and the US	March 2011 to Aug 2012	Randomized phase 3	302*	64(35-84)	Refractory or relapsed and refractory MM, and had failed at least two previous treatments of bortezomib and lenalidomide
Richardson *et al.* (2014)[30]	US and Canada	December 2009 to April 1, 2011	Randomized phase 2	113(POM+LoDEX) 108(POM alone)	64(34-88) 61(37-88)	Aged ≥18 years, had RRMM, and had measurable M-paraprotein levels in serum or urine. All patients had received ≥2 prior antimyeloma therapies, including ≥2 cycles of lenalidomide and ≥2 cycles of bortezomib, given separately or in combination
Leleu *et al.* (2015)[27]	France	January 2012 to July 2013	Phase 2	50	59(30-80)	RRMM following at least 1 prior regimen of myeloma treatment. All patients had loss of 17p (46%) and/or t(4;14) (64%)
Baz *et al.* (2016)[31]	US	December 2011 to March 2014	Randomized phase 2	36(PomDex) 34(PomCyDex)	64(50-78) 65(47-80)	RRMM received ≥2 prior lines of therapies to include a prior immunomodulatory drug, and patients were required to be refractory to lenalidomide

*Another 153 patients in the study were received high-dose dexamethasone (40 mg/day on days 1–4, 9–12, and 17–20, orally)
MM, multiple myeloma; POM, pomalidomide; PomCyDex, pomalidomide, dexamethasone and cyclophosphamide; PomDex, pomalidomide and low-dose dexamethasone; POM+LoDEX, pomalidomide plus low-dose dexamethasone; RRMM, relapsed/refractory multiple myeloma.

Qualität der Studien:

Noncomparative studies						
Study (year)	Representativeness of study sample	Ascertainment of exposure	Demonstration outcome was not present at start	Detection bias minimized	Attribution bias minimized	Follow-up time appropriate
Lacy *et al.* (2009)[24]	Yes	Yes	Yes	Yes	Yes	Yes
Lacy *et al.* (2010)[25]	Yes	Yes	Yes	Yes	Yes	Yes
Lacy *et al.* (2011)[26]	Yes	Yes	Yes	Yes	Yes	Yes
Leleu *et al.* (2015)[27]	Yes	Yes	Yes	Yes	Yes	Yes
Randomized controlled trials						
Study	Random sequence generation	Allocation concealment	Performance bias	Detection bias	Attribution bias minimized	Reporting bias minimized
Leleu *et al.* (2013)[28]	Yes	Unclear	Unclear	Unclear	Yes	Unclear
San *et al.* (2013)[29]	Yes	Unclear	Unclear	Unclear	Yes	Unclear
Richardson *et al.* (2014)[30]	Yes	Unclear	Unclear	Unclear	Yes	Unclear
Baz *et al.* (2016)[31]	Yes	Unclear	Unclear	Unclear	Yes	Unclear

Studienergebnisse

Table 4. Efficacy of the treatment

Study (year)	Total no.	ORR(≥PR)	CR	VGPR	PR	Median TOR, months	Median OS, months	Median PFS, months	Median DOR, months
Lacy *et al.* (2009)[24]	60	38 (63%)	3 (5%)	17 (28%)	18 (30%)	-	Not reached	11.6	Not reached
Lacy *et al.* (2010)[25]	34	11(32%)	0	3(9%)	8(24%)	2	13.9	4.8	9.1
Lacy *et al.* (2011)[26]	35(2mg)	9(26%)	0	5(14%)	4(11%)	1	Not reached	6.5	Not reached
	35(4mg)	10(29%)	1(3%)	3(9%)	6(17%)	1.7	Not reached	3.2	3.9
Leleu *et al.* (2013)[28]	84	29(35%)	3(4%)	2(2%)	24 (29%)	5.4	14.9	4.	7.3
San *et al.* (2013)[29]	302	95 (31%)	3(1%)	14(5%)	78(26%)	-	13.1	4.0	7.5
Richardson *et al.* (2014)[30]	113(POM+LoDEX)	37(33%)	3(3%)	0	34(30%)	1.9	16.5	4.2	8.3
	108(POM alone)	19(18%)	2(2%)	0	17(16%)	4.3	13.6	2.7	10.7
Leleu *et al.* (2015)[27]	50	11(22%)	3(6%)	0	8(16%)	4.1	12	2.8	5.5
Baz *et al.* (2016)[31]	36(PomDex)	14(39%)	1(3%)	4(11%)	9(25%)	-	16.8	4.4	-
	34(PomCyDex)	22(65%)	1(3%)	3(9%)	18(53%)	-	Not reached	9.5	-

CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; POM, pomalidomide; PomCyDex , pomalidomide, dexamethasone and cyclophosphamide; PomDex, pomalidomide and low-dose dexamethasone; POM+LoDEX, pomalidomide plus low-dose dexamethasone; TOR, time to response; VGPR, very good partial response

Figure 2. Overall response of pomalidomide treatment in patients with RRMM. (RRMM, relapsed/refractory multiple myeloma; ES, effect size)

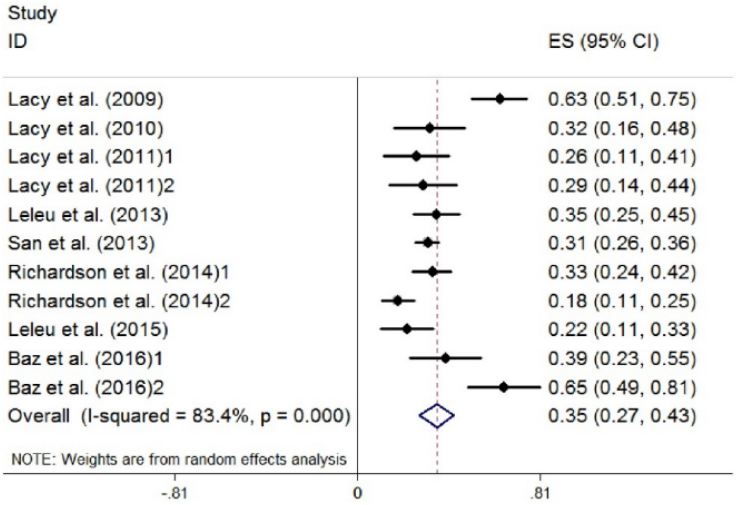


Figure 3. Complete response of pomalidomide treatment in patients with RRMM. (RRMM, relapsed/refractory multiple myeloma; ES, effect size)

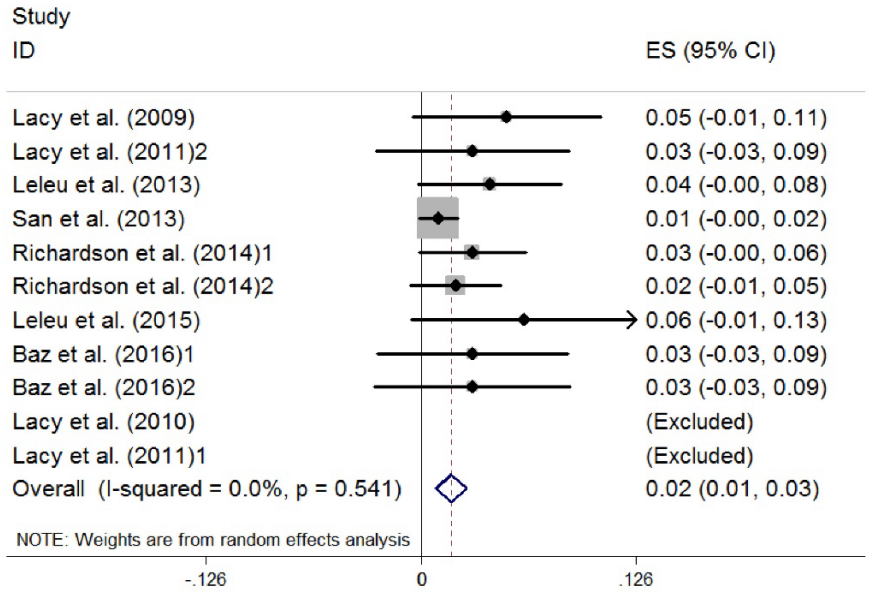


Table 5. Adverse effects of pomalidomide treatment

Study (year)	Treatment
Lacy *et al.* (2009)[24]	Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity occurred in 23 patients (38%) and consisted of anemia (5%), thrombocytopenia (3%), and neutropenia (32%).The most common grade 3 or 4 nonhematologic toxicities consisted of fatigue (17%) and pneumonia (8%).
Lacy *et al.* (2010)[25]	Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity occurred in 13 patients (38%) and consisted of anemia (12%), thrombocytopenia (9%) and neutropenia (29%). The most common grade 3/4 non-hematologic toxicity was fatigue (9%).
Lacy *et al.* (2011)[26]	Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity regardless of attribution occurred in 83% (2-mg cohort) and 80% (4-mg cohort) and at least possibly attributed to the regimen occurred in 71% (2-mg cohort) and 74% (4-mg cohort). Grade 3 or 4 neutropenia (regardless of attribution) was seen in 51% (2-mg cohort) and 66% (4-mg cohort). Grade 3 or 4 nonhematologic toxicity regardless of attribution occurred in 69% (2-mg cohort) and 54% (4-mg cohort) and at least possibly attributed to the regimen was seen in 26% (2-mg cohort) and 26% (4-mg cohort). The most common nonhematologic toxicity was fatigue (2-mg cohort: 88%; 4-mg cohort: 91%) with grade 3/4 fatigue occurring in 9% of patients in both cohorts.
Leleu *et al.* (2013)[28]	Grade 3 and 4 AEs that occurred in >10% of cases were neutropenia in 62%, anemia in 36%, thrombocytopenia in 27%, pneumonia in 13%, bone pain in 11%, renal failure in 11%, and dyspnea in 12%.
San *et al.* (2013)[29]	The most common grade 3-4 hematological AEs in the POM+LoDEX and HiDEX groups were neutropenia (143 [48%] of 300 vs 24 [16%] of 150, respectively), anemia (99 [33%] vs 55 [37%], respectively), and thrombocytopenia (67 [22%] vs 39 [26%], respectively). Grade 3-4 non-hematological adverse events in the POM+LoDEX and HiDEX groups included pneumonia (38 [13%] vs 12 [8%], respectively), bone pain (21 [7%] vs seven [5%], respectively), and fatigue (16 [5%] vs nine [6%], respectively).
Richardson *et al.* (2014)[30]	The most common grade 3-4 AE was neutropenia, which occurred in 41% of patients treated with POM+LoDEX and 48% of patients treated with POM alone. The incidence of grade 3-4 febrile neutropenia was low in the POM+LoDEX and POM alone groups (3% and 5%, respectively). The most common grade 3-4 nonhematologic AE was pneumonia (22% with POM+LoDEX and 15% with POM alone). In the POM1LoDEX group, 27% of the cases of any grade pneumonia were also associated with dyspnea (any grade).
Leleu *et al.* (2015)[27]	The toxicity profile of the Pom-Dex combination consisted primarily of myelosuppression, as previously reported, and appeared manageable in these fragile RRMM patients. A total of 49 patients (98%) experienced an AE, of which 44 (88%) were treatment related. The incidence rate of grade 3 and 4 AEs was 45 (90%), including hematologic AEs, and 32 (64%) experienced a serious adverse event (SAE).
Baz *et al.* (2016)[31]	Grade 3 and 4 anemia, neutropenia, and thrombocytopenia were noted in 11%, 31%, and 6% of arm B patients vs in 24%, 52%, and 15% of arm C patients, respectively. Gastrointestinal toxicity including nausea, vomiting, and diarrhea was also similar in the 2 treatment arms.

AEs, adeverse effects; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide

Anmerkung/Fazit der Autoren

Pomalidomide was generally well tolerated by patients reported in the studies. Further studies would be required to conduct more prospective randomized controlled trials (RCTs) with larger samples to assess the proper place of pomalidomide as single agent or combined with other agents for RRMM.

Kommentare zum Review

- Firstly, most of the studies we included had different treatment regimens and dosage, and it is hard to be uniformed. Also, the precision of pooled ES can be affected by the small sample size of some studies; therefore, we chose the random-effects model for the entire study to increase power and precision regardless of heterogeneity. Moreover, the effect of pomalidomide might vary by different ethnicities around the world, and it is difficult to summarize them.
- ASCT Erhalt unklar.

Mushtaq A et al., 2018 [16].

Efficacy and toxicity profile of carfilzomib based regimens for treatment of multiple myeloma: A systematic review

Fragestellung

The aim of our study is to conduct comprehensive literature search for efficacy, dosing and toxicity profile of CFZ in both newly diagnosed and relapsed setting. Our secondary aim is to analyze whether CFZ treatment can be extended to the frontline setting.

Methodik

Population:

- relapsed and refractory multiple myeloma (RRMM)

- NDMM

Intervention:

- Carfilzomib (CFZ)

Komparator:

- Not specified

Endpunkte

- efficacy outcomes (complete response [CR], near complete response [nCR], stringent complete response [sCR], very good partial response [VGPR], partial response [PR], overall response rate [ORR], overall survival [OS] and progression free survival [PFS]).

Recherche/Suchzeitraum

- A comprehensive literature search was performed on 6/5/2017

Qualitätsbewertung der Studien:

- Not specified

Ergebnisse

Anzahl der eingeschlossenen Studien:

- 26 articles met the inclusion criteria, 15 in NDMM group and 11 in RRMM group

Table 2
Carfilzomib based regimens for relapsed and refractory multiple myeloma.

Author, year, study design	Number of patients	Median age	ISS staging: I/II/III/unknown (%)	Cytogenetics: High risk/Standard risk/unknown or missing (%)	CFZ (mg/m2) or control group dose	Median duration of treatment/Median number of cycles	CFZ or control group regimen	Median number of prior lines of therapy	CR/nCR/sCR (%)	VGPR/PR (%)	ORR (%)	OS (months)	PFS (months)
Trials on single agent carfilzomib													
Jagannath et al., 2012, phase II	46	63.5	NS	15.2/71.7/10.9	20	NS/≤ 12 cycles	CFZ alone	5	NS	NS/16.7	16.7	NS	3.5
Siegel et al., 2012a,b, phase II	266	63	29/38/31/2	28/60/12	20/27	3 months/Maximum number of 12 cycles	CFZ alone	5	0.4/NS/NS	5.1/18.3	23.7	15.6	3.7
Watanabe et al., 2016, Phase I/II	50	67	32/36/22/10	32/62/6	15/20, 20/27	NS	CFZ alone	5	0/NS/NS	4/16	20	Not reached	5.1
Vij et al., 2012a,b, phase II	129	65	73% had stage I or II/17% stage III/10% missing	14.7/79.8/5.4	20/27	NS/7	CFZ alone	2	2.4/NS/NS	20.6/24.6	47.6	NS	54.3% at 9 months
Hájek et al., 2017, phase III	CFZ group (n = 157)	63	17/20/42/21	14/43/43	20/27	16.3 weeks/NS	CFZ alone	5	1/NS/NS	3/15	19.1	10.2	3.7
	Control group (n = 158)	66	13/26/35/26	18/48/34	Cd[1]	10.7 weeks/NS	Cd[1]	5	0/NS/NS	3/8	11.4	10	3.3
Carfilzomib based doublet regimens													
Berdeja et al., 2015, Phase II	44	66	46/32/11/11	34[2]/39/27	20/45	NS/6	CFZ + P	5	NS	33(≥ VGPR)/33	67	67% at 24 months	7.7 at median follow up of 17 months
Berenson et al., 2014, Phase I/II	116	68.5	40/43/14/2	17/49/34	20/70	7.7/NS	Kd	1	11/NS/3	33/31	77	NS	12.6
Lendvai et al., 2014, Phase II	44	63	NS	45/52/2	20/56	NS	Kd	5	2/NS/NS	21/31	55	20.3	4.1
Dimopoulos et al., 2016a,b, phase III	464	65	44% stage I/56% stage II III	21/61/18	20/56	NS[x]	Kd	2	11/NS/2	42/22	77	*Immature* at interim analysis	18.7
	465	65	44% stage I/56% stage II III	24/63/13	1.3 mg/m2 bortezomib	NS[x]	Vd	2	4/NS/2	22/34	63		9.4
Carfilzomib based triplet regimens													
Wang et al., 2013, Phase I/II	52[3]	63	NS	21.2/76.9/1.9	20/27	NS/9.5 cycles	CRd	3	1.9/NS/3.8	36.5/34.6	76.9	NS	15.4
Stewart et al., 2014, Phase III	396	64	NS	12/37/50.8	20/27	88 weeks/NS	KRd	2	17.7/NS/14.1	69.9/NS	87	73% at 24m	26.3
	396	65		13/42.9/43.9	Rd[4]	57weeks/NS	Rd	2	5/NS/4.3	40.4/NS	66.7	65% at 24m	17.6

Abbreviations: [x]continued until disease progression, intolerbale toxicity or withdrwal of consent, [1]84 mg dexamethasone and optional cyclophosphamide (1400 mg), [2]mentioned as abnormal and not high risk, [3]Maximum planned dose cohort, [4] 25 mg lenalidomide, 40 mg dexamethasone, NS: not specified, P: panobinostat, CFZ: carfilzomib, m: months, N: number of patients, CR: complete response, nCR: near complete response, sCR: stringent complete response, VGPR: very good partial response, PR: partial response, ORR: overall response rate, OS: overall survival, PFS: progression free survival, Kd: carfilzomib + dexamethasone, KRd/CRd: carfilzomib + lenalidomide + dexamethasone, Vd: bortezomib + dexamethasone, Rd: lenalidomide + dexamethasone

Qualität der Studien:

- Not assessed

Studienergebnisse:

Group B: carfilzomib based regimens in relapsed and refractory multiple myeloma

- Single agent carfilzomib (5 studies, n=807)
- Carfilzomib based doublet regimens (3 studies, n=204); 5.2.2. Phase III (1 study, n=929)
- Carfilzomib based triplet regimens (2 studies, n=448)

- CFZ demonstrates comparable or even better efficacy to bortezomib with much favorable AE profile.
- Deep, rapid and sustainable response using KRd with safer toxicity profile supports extension of KRd therapy to frontline therapy for all risk categories of MM. High incidence of grade ≥3 HTN underscores the importance of serial BP monitoring.
- In RRMM, CFZ has documented efficacy with standard 20–27mg/m2 dose. Further large-scale trials are needed to study benefit-to-risk profile of 20–56 and 20–70 mg/ m2 dose of CFZ vs standard 20–27 mg/m2 dose in NDMM and RRMM.

Anmerkung/Fazit der Autoren

Our results suggest that CFZ demonstrates comparable efficacy to bortezomib with much favorable AE profile both in NDMM and RRMM. There are only two studies with head to head comparison of CFZ based regimens with bortezomib based regimens.(ClinicalTrials.gov, 2017a; Dimopoulos et al., 2016b) Cross-trial comparisons of studies on CFZ with studies on bortezomib can be imprecise due to significant heterogeneity in patient population, number of prior lines of therapy, dose and schedule of drug used and whether treatment was in conjunction with stem cell transplantation. KRd and Rd regimen have well documented efficacy for treatment of RRMM. Further large-scale trials are needed to study benefit-to-risk profile of 20–56 and 20–70 mg/m2 dose of CFZ vs standard 20–27 mg/m2 dose. Reported incidence (3%–25%) of grade ≥3 HTN with CFZ deserves attention and emphasizes the importance of serial BP monitoring before, during and after CFZ infusions. For patients with NDMM, data supporting KRd mainly comes from phase II trials. Deep, rapid and sustainable response using KRd with safer toxicity profile supports extension of KRd therapy to frontline therapy for all risk categories of MM. Role of conventional dose second consolidation after HDCT and autologous stem rescue needs further exploration for safety and efficacy in larger randomized trials. Data from randomized phase III trials is needed for head to head comparison of KRd vs RVd, and KRd vs daratumumab-KRd for NDMM patients.

Kommentare zum Review:

- Gemischte Patienten: Darunter Patienten die ASCT erhalten haben

Shah C et al., 2018 [19].

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.

  Vij *et al.* [23] enrolled and studied Bort naïve patients separately. ASPIRE study excluded patients who progressed during treatment with Bort [21]. Berenson *et al.* enrolled only those patients who relapsed within 12 weeks of receiving or were refractory to their most recent Bort-containing regimen [15].

Intervention:

- carfilzomib

Komparator:

- Not specified

Endpunkte

- overall response rate (ORR)
- overall clinical benefit rate (CBR) (ORR+MR)
  (minimal response = MR)

Recherche/Suchzeitraum

- Not mentioned

Qualitätsbewertung der Studien

Cochrane Collaboration's tools

Ergebnisse

Anzahl der Studien

- 14

Charakteristika der Population

- 2938

- Thirty-two patients were excluded from analysis due to various reasons such as incorrect enrollment (2), missing baseline and/ or post-baseline disease assessment (12), intolerance to maximum dose criteria of the study (12), self-withdrawal (1), reason not mentioned (5). The median age of the patients ranged between 61.5–68.5 years. Characteristics of patients with the response and long-term outcomes from different studies are summarized in Tables 1–3. There were three randomized controlled trials (RCTs) with 2036 enrolled patients, 1017 in Carf group and 1019 in control group [16, 17, 21]. A total of 7 clinical trials used Carf in combination with other agents, such as Dexa in four studies [12, 15, 16, 25], Len and Dexa in two studies [21, 24] and panobinostat in one study [13] as shown in Tables 1–3.

Table 1: Patient characteristics, response and long-term outcomes summary from phase III studies with control groups

Author, Year	Regimen used	Carf dosing (mg/m²)	Median age (years)	Patients analyzed, n	CR, *n* (%)	VGPR, n (%)	ORR, *n* (%)	CBR, *n* (%)	Median DOR (mos)	Median PFS (mos)	Median OS (mos)	Type of cardiac events
Dimopoulos MA *et al.*, 2016	Carf, Dexa	20 (Days 1, 2 of cycle 1) f/b 56	65	464	58 (13)	194 (42)	356 (77)	380 (82)	NA	18.7	47.6	Cardiac failure, Ischemic heart disease
(ENDEAVOR)	Bort, Dexa		65	465	29 (6)	104 (22)	290 (62)	343 (74)	NA	9.4	24.3	
Hajek R *et al.*, 2017 (FOCUS)	Carf	20 (Days 1, 2 of cycle 1) f/b 27	63	157	1 (1)	5 (3)	30 (19)	49 (31)	7.2	3.7	10.2	Cardiac failure
	Pred or Dexa		66	158	0 (0)	5 (3)	18 (11)	33 (21)	9.5	3.3	10	
Stewart AK *et al.*, 2015 (ASPIRE)	Carf, Len, Dexa	20 (Days 1, 2 of cycle 1) f/b 27	64	396	126 (31.8)	277 (69.9)	344 (87.1)	359 (91)	28.6	26.3	NA	cardiac failure, ischemic heart disease
	Len, Dexa		65	396	37 (9.3)	160 (40.4)	264 (66.7)	302 (76.3)	21.2	17.6	NA	

Abbreviations: Carf, carfilzomib; CR, complete response; VGPR, very good partial response; ORR, overall response rate; CBR, clinical benefit rate; PFS, progression free survival; OS, overall survival, Pred, prednisone; Dexa, dexamethasone; Len, lenalidomide; Bort, bortezomib; NA, not available; f/b, followed by; mos, months; MI, myocardial infarction; CHF, congestive heart failure; CAD, coronary artery disease;

Table 2: Patient characteristics, response and long-term outcomes summary from phase II studies

Author, Year	Regimen used	Carf dosing (mg/m²)	Median age (years)	Pts analyzed, *n*	CR, *n* (%)	VGPR, *n* (%)	ORR, *n* (%)	CBR, *n* (%)	Median DOR (mos)	Median PFS (mos)	Median OS (mos)	Type of cardiac events
Lendvai N *et al.*, 2014	Carf	20 (Days 1, 2 of cycle 1) f/b 56	63	42	1 (2)	9 (21)	23 (55)	25 (60)	11.7	4.1	20.3	Heart failure
Siegel DS *et al.*, 2012	Carf	20 (Days 1, 2 of cycle 1) f/b 27	63	257	1 (0.4)	13 (5.1)	61 (23.7)	95 (37)	7.8	3.7	15.6	Cardiac failure, cardiac arrest, MI
Jagannath S *et al.*, 2012	Carf	20 (Days 1, 2, 8, 9, 15, 16)	63.5	46	NA	NA	7 (16.7)	10 (24)	7.2	3.5	NA	Cardiac failure
Wang M *et al.*, 2013	Carf, Len, Dexa	20 (Days 1, 2 of cycle 1) f/b 27	61.5	84	1 (1.2)	30 (35.7)	58 (69.0)	64 (76)	18.8	11.8	NA	MI, sick-sinus syndrome, CAD
Vij R *et al.*, 2012	Carf	20 (Days 1, 2 of cycle 1) f/b 27	63	35	1 (2.9)	1 (2.9)	6 (17.1)	11 (31.4)	NA	4.6	29.9	CHF
Vij R *et al.*,2012	Carf	20 (Days 1, 2 of cycle 1) f/b 27	66	126	3 (2.4)	26 (20.6)	60 (47.6)	78 (62)	NA	NA	NA	CHF
Badros AZ *et al.*, 2013	Carf, Dexa	15 (cycle 1) f/b 20 (cycle 2) f/b 27	64	47	0	0	12 (25.5)	15 (32)	7.9	NA	NA	CHF

Abbreviations: See Table 1.

Table 3: Patient characteristics, response, and long-term outcomes summary from phase I/II trials

Author, Year	Regimen used	Carf dosing (mg/m²)	Median age (years)	Pts analyzed, *n*	CR, *n* (%)	VGPR, *n* (%)	ORR, *n* (%)	CBR, *n* (%)	MedianDOR (mos)	Median PFS (mos)	Median OS (mos)	Type of cardiac events
Watanabe T *et al.*, 2016	Carf, Dexa	20 (Days 1, 2 of cycle 1) f/b 27	67	50	0	2 (4)	10 (20)	14 (28)	9.5	5.1	23.4	CHF, atrioventricular block, cardiomyopathy
Berenson JR *et al.*, 2016	Carf, Dexa	20 (Days 1 of cycle 1) f/b 45 or 56 or 70 or 88 (once weekly)	68.5	104	11 (11)	34 (33)	77 (77)	84 (84)	NA	12.6	NA	MI, atrial fibrillation, cardiorespiratory arrest, CHF
Berdeja JG *et al.*, 2015	Carf, Pano	20 (Days 1, 2 of cycle 1) f/b 27 or 36 or 45 [€]	66	42	NA	14 (33)	28 (67%)	33 (79)	11.6	7.7	NA	CHF
Berenson JR *et al.*, 2014	Carf[#]	20 (cycle 1) f/b 27 (cycle 2) f/b 36 (cycle 3) f/b 45 (cycle 4)[*]	67	37	3 (8.1)	6 (16.2)	16 (43.2)	23 (62.2)	9.9	8.3	15.8	Tachyarrhythmia, CHF

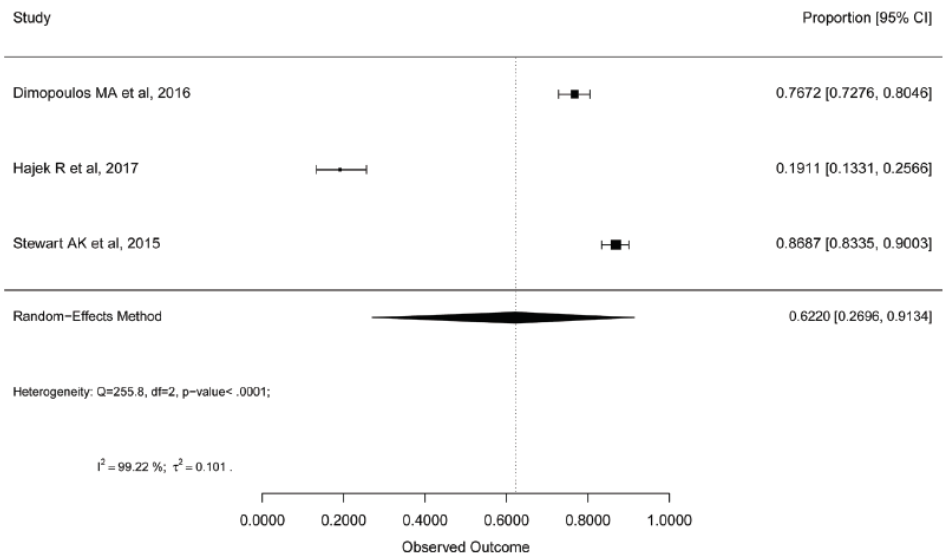
Abbreviations: See Table 1
[#]in various combinations with immunomodulatory drug (Thal or Len), pegylated liposomal doxorubicin, glucocorticoids, cyclophosphamide, methylprednisone, bendamustine
[€]4 (9.5%) out 42 patients had maximum carfilzomib dose ≤ 27 mg/m².
[*]10 (27%) out 37 patients had maximum carfilzomib dose ≤ 27 mg/m².

Qualität der Studien

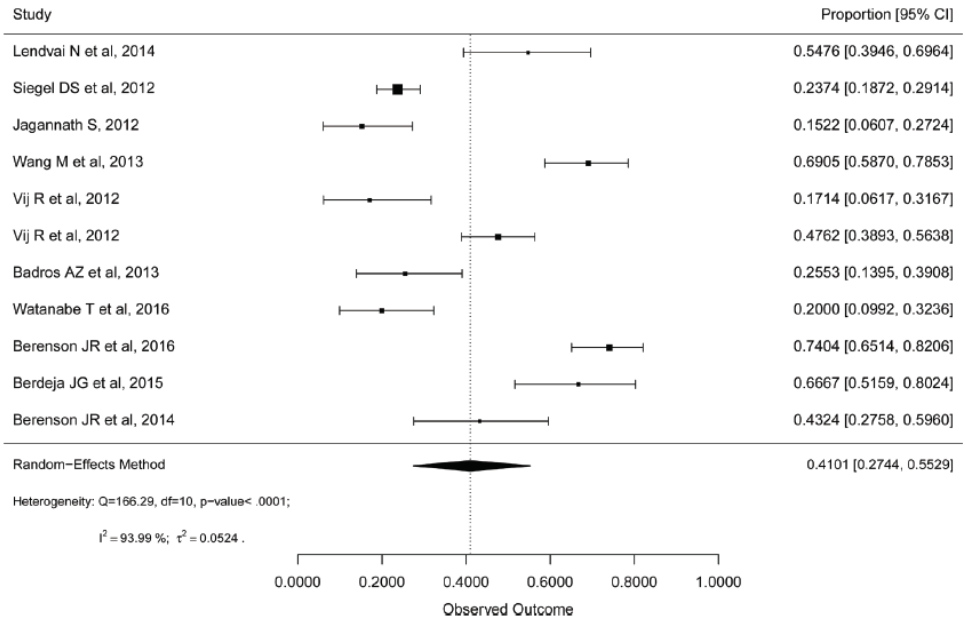
- No publication bias was detected by visual inspection of funnel plots and by Egger's tests.
- Study quality and risks of biases were assessed using the Cochrane Collaboration's tools. Among the RCTs, the risk of selection bias and attrition bias were low while performance bias, detection bias, and reporting bias were unclear as per Cochrane Collaboration's tools. Among non-randomized trials, the overall risks of biases were low

Studienergebnisse

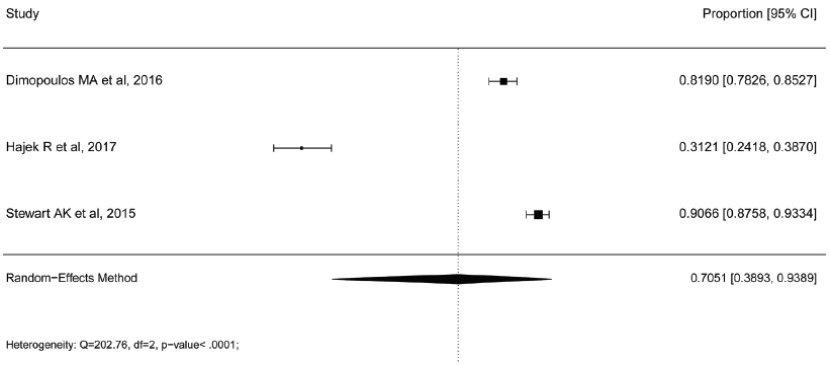
- ORR (phase III only)

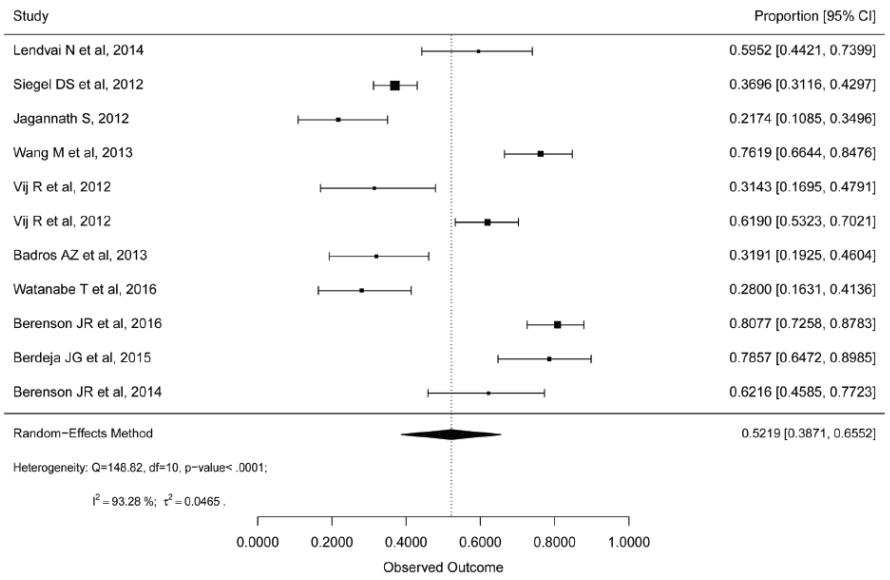


- ORR (phase III excluded)



Clivical benefit rate (phase III only)





Anmerkung/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:

- ASCT Erhalt unklar.

Maiese EM et al., 2018 [13].

Comparative Efficacy of Treatments for Previously Treated Multiple Myeloma: A Systematic Literature Review and Network Meta-analysis

Fragestellung

A systematic literature review was conducted to identify all available clinical evidence for treatment of patients with previously treated MM (i.e. relapsed/ refractory multiple myeloma [RRMM]). Results were synthesized by using network meta-analysis methods to assess the relative efficacy, including PFS and overall response rate (ORR), of daratumumab in combination with lenalidomide and dexamethasone and daratumumab in combination with bortezomib and dexamethasone versus other RRMM therapies.

Methodik

Population:

- patients with previously treated MM (i.e. relapsed/ refractory multiple myeloma[RRMM])

Intervention:

- For the systematic literature review were any of the following monotherapy orcombinationtherapies, either FDA approved or being investigated, in the MM indication:
- bortezomib(V), carfilzomib (K), daratumumab (D), elotuzumab (E), filanesib, isatuximab, ixazomib (I), lenalidomide (R), marizomib, oprozomib, panobinostat (Pa), pomalidomide (Po), ricolinostat, thalidomide (T), and vorinostat (Vo). In addition, trials investigating dexamethasone, doxorubicin, and cyclophosphamide were allowed into the analysis to further enable connections in the evidence base.

Komparator:

- Not specified

Endpunkte

- PFS
- ORR

Recherche/Suchzeitraum

- To September 1, 2016

Qualitätsbewertung der Studien

- To assess the quality of the included studies, a risk of bias assessment, as set out in the National Institute for Health and Care Excellence's specification for manufacturers, was applied to each study.

Ergebnisse

Anzahl der Studien

- 27 RCTs in the NMA

Charakteristika der Population

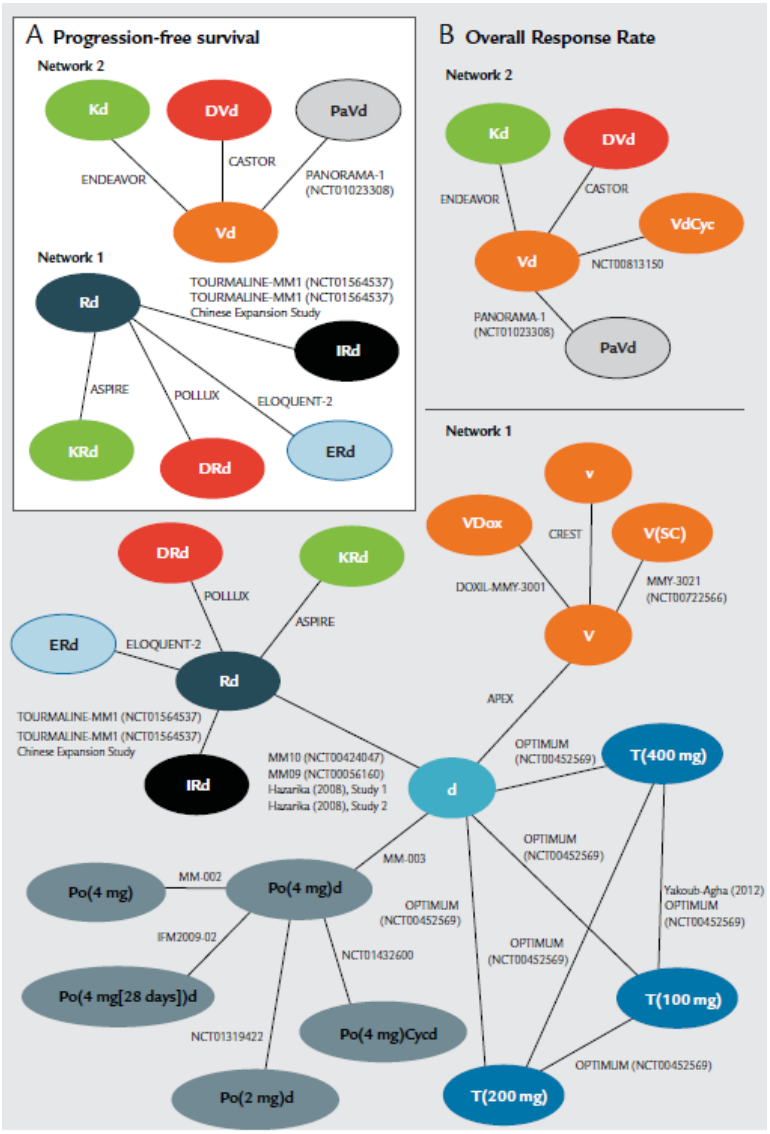
- Nineteen trials were conducted in multiple countries, and 8 trials were conducted in 1 country. The median age of patients ranged from 56.5 to 71.0 years; 42.6% to 68.7% of patients were male; and patients received a median of 2 prior lines of treatment (range,1–17).

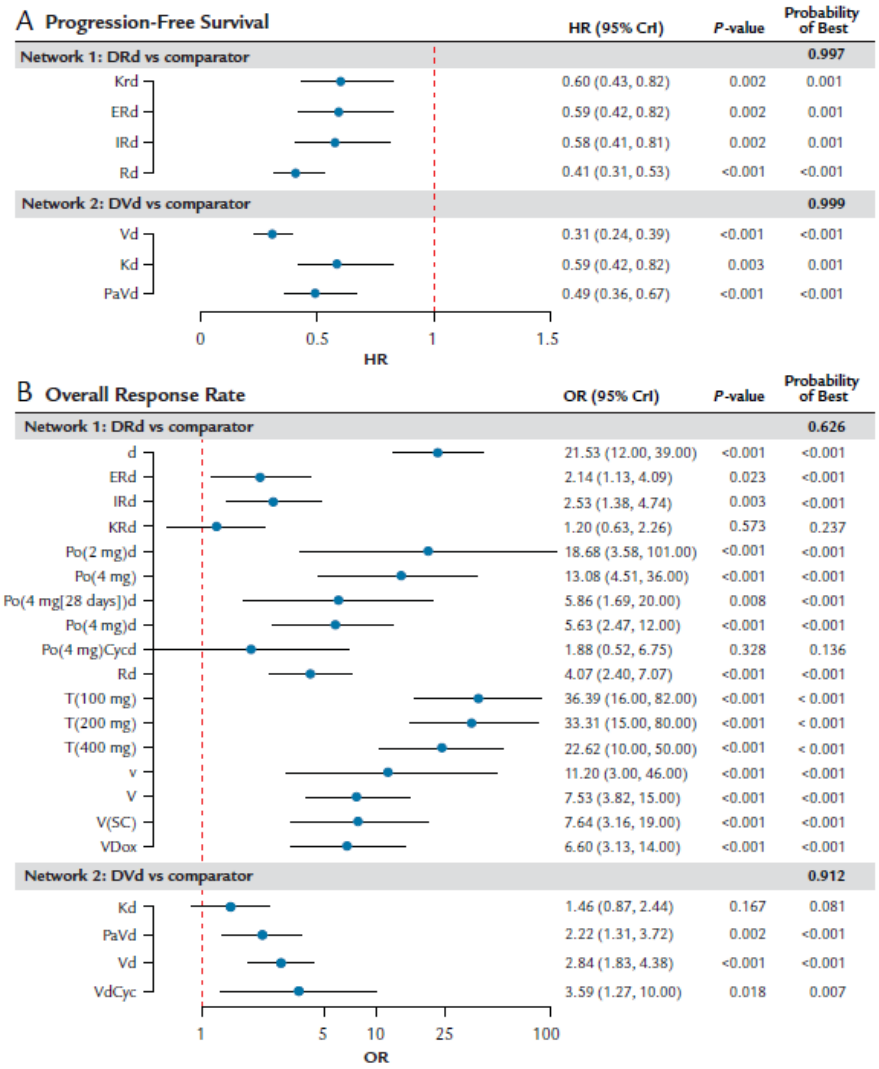
Qualität der Studien

- Blinding was applied in a double-blind fashion in 9 trials, whereas 13 were open-label; information on blinding was not clear for the other studies.

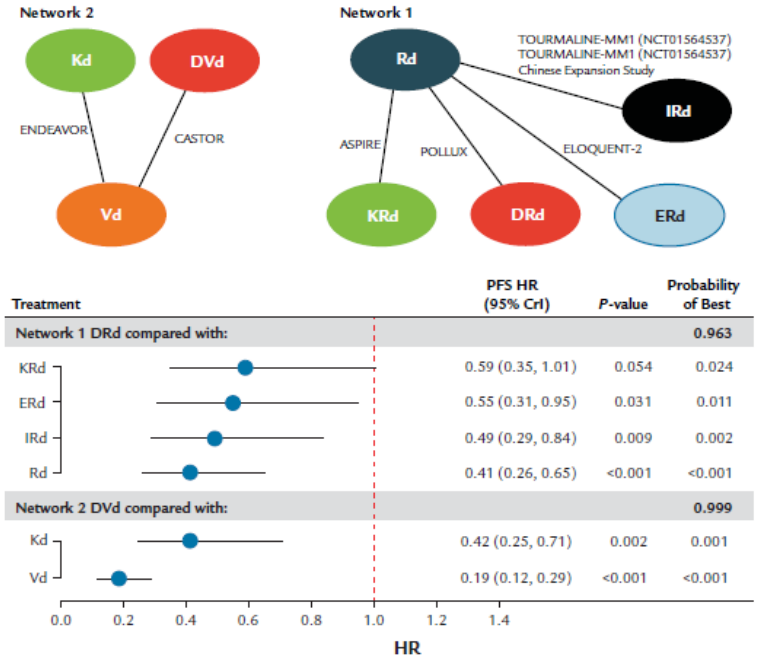
Studienergebnisse

- Efficacy of Treatments in Overall Population


A Progression-free survival
Network 2
Kd
DVd
PaVd
ENDEAVOR
CASTOR
PANORAMA-1 (NCT01023308)
Vd
Network 1
Rd
TOURMALINE-MM1 (NCT01564537)
TOURMALINE-MM1 (NCT01564537)
Chinese Expansion Study
IRd
ASPIRE
POLLUX
ELOQUENT-2
KRd
DRd
ERd
B Overall Response Rate
Network 2
Kd
DVd
ENDEAVOR
CASTOR
VdCyc
Vd
NCT00813150
PANORAMA-1 (NCT01023308)
PaVd
Network 1
v
VDox
CREST
V(SC)
DOXIL-MMY-3001
MMY-3021 (NCT00722566)
V
APEX
DRd
KRd
POLLUX
ASPIRE
ERd
ELOQUENT-2
Rd
TOURMALINE-MM1 (NCT01564537)
TOURMALINE-MM1 (NCT01564537)
Chinese Expansion Study
IRd
MM10 (NCT00424047)
MM09 (NCT00056160)
Hazarika (2008), Study 1
Hazarika (2008), Study 2
d
OPTIMUM (NCT00452569)
T(400 mg)
OPTIMUM (NCT00452569)
MM-003
Po(4 mg)
MM-002
Po(4 mg)d
OPTIMUM (NCT00452569)
Yakoub-Agha (2012)
OPTIMUM (NCT00452569)
IFM2009-02
NCT01432600
OPTIMUM (NCT00452569)
Po(4 mg[28 days])d
T(100 mg)
NCT01319422
Po(4 mg)Cycd
OPTIMUM (NCT00452569)
Po(2 mg)d
T(200 mg)



- Efficacy of Treatments in Patients with only 1 prior Line of treatment



In the subgroup of patients with only 1 prior line of treatment, insufficient evidence was available for ORR for both networks. Therefore, the ORR data in this subgroup were not analyzed.

Anmerkung/Fazit der Autoren

The NMA suggests that, compared with other approved MM treatments in the United States, DRd and DVd have a higher probability of providing the longest PFS in patients who have received at least 1 prior therapy and inpatients who have received only 1 prior therapy.

Kommentare zum Review

- Vermutlich lediglich eine Studie mit Patienten die ASCT erhalten haben
- There are not shown any AE / safety data.
- This study was conducted by RTI Health Solutions under the direction of Janssen Scientific Affairs LLC.
- It is not possible to asses the risk of bias of the NMA.

Zheng Y et al., 2018 [24].

Monoclonal Antibodies versus Histone Deacetylase Inhibitors in Combination with Bortezomib or Lenalidomide plus Dexamethasone for the Treatment of Relapsed or Refractory Multiple Myeloma: An Indirect-Comparison Meta-Analysis of Randomized Controlled Trials

Fragestellung

We thus conducted this meta-analysis to compare indirectly the efficacy and safety of MAbs and HDACis in combination with lenalidomide or bortezomib plus dexamethasone.

Methodik

Population:

- relapsed or refractory multiple myeloma

Intervention:

- MAbs and HDACis in combination with lenalidomide or bortezomib plus dexamethasone

Komparator:

- either placebo control or blank control was qualified in the control group

Endpunkte

- time to progression (TTP), progression-free survival (PFS), and overall survival (OS)
- grade 3 or higher treatment-related adverse events were the safety outcomes including haematological toxicities and common nonhematological adverse events

Recherche/Suchzeitraum

- on December 9, 2017

Qualitätsbewertung der Studien

- Jadad scale (randomization method, doubleblinding, and outcomes of follow-up)

Ergebnisse

Anzahl der Studien

- 6 RCTs

Charakteristika der Population

- N= 3270

Table 2: Patients' baseline characteristics and disease-related demographics of included studies.

Study	CASTOR		POLLUX		ELOQUENT-2		NCT01478048		PANORAMA1		VANTAGE088	
	E	C	E	C	E	C	E	C	E	C	E	C
Number of patients	251	247	286	283	321	325	77	75	387	381	317	320
Median age (year)	64	64	65	65	67	66	65	65	63	63	61	63
ECOG performance status												
0	NA	NA	139 (48.6)	150 (53.0)	NA	NA	38 (49.4)	46 (61.3)	175 (45.2)	162 (42.5)	126 (39.7)	119 (37.2)
1	NA	NA	1 o r2:	1 or 2:	NA	NA	35 (45.5)	23 (30.7)	191 (49.4)	186 (48.8)	164 (51.7)	167 (52.2)
2	NA	NA	147 (51.4)	133 (47.0)	NA	NA	2 (0.03)	6 (8.0)	19 (4.9)	29 (7.6)	24 (7.6)	34 (10.6)
ISS disease staging												
I	98 (39.0)	96 (38.9)	137 (47.9)	140 (49.5)	141 (43.9)	138 (42.5)	26 (33.8)	19 (25.3)	156 (40.3)	152 (39.9)	95 (30.0)	80 (25.0)
II	94 (37.5)	100 (40.5)	93 (32.5)	86 (30.4)	102 (31.8)	105 (32.3)	23 (29.9)	20 (26.7)	104 (26.9)	92 (24.1)	98 (30.9)	99 (30.9)
III	59 (23.5)	51 (20.6)	56 (19.6)	57 (20.1)	66 (20.6)	68 (20.9)	11 (14.3)	16 (21.3)	77 (19.9)	86 (22.6)	87 (27.4)	82 (25.6)
Not assessed					12 (0.04)	14 (0.04)	17 (22.1)	20 (26.7)	50 (12.9)	51 (13.4)	37 (11.7)	59 (18.4)
Previous lines of therapy												
1	122 (48.6)	113 (45.7)	149 (52.1)	146 (51.6)	151 (47.0)	159 (48.9)	50 (64.9)	51 (68.0)	197 (50.9)	198 (52.0)	143 (45.1)	127 (39.7)
2	70 (27.9)	74 (30.0)	85 (29.7)	80 (28.3)	118 (36.8)	114 (35.1)	2 or more: 27	2 or more: 24	124 (32.0)	108 (28.3)	105 (33.1)	134 (41.9)
3 or more	59 (23.5)	60 (24.3)	52 (18.2)	57 (20.1)	52 (16.2)	52 (16.0)	(35.1)	(32.0)	64 (16.5)	75 (19.7)	69 (21.8)	59 (18.4)
Previous stem-cell transplantation												
Yes	156 (62.2)	149 (60.3)	180 (62.9)	180 (63.6)	167 (52.0)	185 (56.9)	39 (50.6)	41 (54.7)	215 (55.6)	224 (58.8)	113 (35.6)	115 (35.9)
No	95 (37.8)	98 (39.7)	106 (37.1)	103 (36.4)	154 (48.0)	140 (43.1)	38 (49.4)	34 (45.3)	172 (44.4)	157 (41.2)	204 (64.4)	205 (64.1)
Drugs used in previous treatment												
Proteasome inhibitors	179 (71.3)	198 (80.2)	245 (85.7)	242 (85.5)	219 (68.2)	231 (71.1)	39 (50.6)	40 (53.3)	169 (43.7)	161 (42.3)	79 (24.9)	73 (22.8)
Immunomodulatory drugs	169 (67.3)	172 (69.6)	158 (55.2)	156 (55.1)	169 (52.6)	178 (54.8)	55 (71.4)	58 (77.3)	277 (71.6)	273 (71.7)	192 (60.6)	208 (65.0)
Alkylating agents	240 (95.6)	224 (90.7)	268 (93.7)	270 (95.4)	220 (68.5)	197 (60.6)	NA	NA	300 (77.5)	268 (70.3)	NA	NA

NA: not available; E: experimental group; C: control group.

Qualität der Studien:

Table 3: Quality assessment of included studies according to Jadad scale.

Study	Randomization	Blinding	Withdrawal or lost to follow-up	Total Jadad score
Palumbo et al. (2016)	2	0	1	3
Dimopoulos et al. (2016)	2	0	1	3
Lonial et al. (2015)	2	0	1	3
Jakubowiak et al. (2016)	2	0	1	3
San-Miguel et al. (2014)	2	2	1	5
Dimopoulos et al. (2013)	2	2	1	5

Studienergebnisse:

Table 4: Meta-analysis outcome of efficacy comparing monoclonal antibodies and HDACi.

	Number of trials included	Risk ratio (95% CI)			Tests for publication bias	
		MAb group versus control group	HDACi group versus control group	MAb group versus HDACi group (indirect comparison)	Egger's test (*P* value)	Begg's test (*P* value)
PFS	6 (trials 1, 2, 3, 4, 5, and 6)	HR 0.52 (0.36–0.75)	HR 0.70 (0.57–0.85)	HR 0.83 (0.66–0.98)	0.18	0.45
OS	4 (trials 3, 4, 5, and 6)	HR 0.75 (0.60–0.93)	HR 0.87 (0.72–1.05)	HR 0.87 (0.65–1.15)	0.39	0.73
CR	6 (trials 1, 2, 3, 4, 5, and 6)	1.42 (0.75–2.69)	1.71 (1.17–2.51)	0.85 (0.23–3.12)	0.17	0.02
VGPR	5 (trials 1, 2, 3, 4, and 5)	1.57 (1.23–2.00)	1.76 (1.32–2.33)	0.83 (0.44–1.57)	0.67	0.46
OR	6 (trials 1, 2, 3, 4, 5, and 6)	1.22 (1.16–1.29)	1.22 (1.10–1.34)	1.04(0.91–1.18)	0.89	1.00
PD + SD	6 (trials 1, 2, 3, 4, 5, and 6)	0.55 (0.38–0.78)	0.73 (0.62–0.87)	0.80 (0.65–0.94)	0.32	0.26

MAb: monoclonal antibody; HDACi: histone deacetylase inhibitor; PFS: progression-free survival; OS: overall survival; OR: overall response; CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease; HR: hazard ratio. Trials included: trial 1 represents Palumbo et al. (2016); trial 2 represents Dimopoulos et al. (2016); trial 3 represents Lonial et al. (2015); trial 4 represents Jakubowiak et al. (2016); trial 5 represents San-Miguel et al. (2014); trial 6 represents Dimopoulos et al. (2013).

Table 5: Meta-analysis outcome of efficacy comparing daratumumab and HDACi.

	Number of trials included	Risk ratio (95% CI)			Tests for publication bias	
		Daratumumab group versus control group	HDACi group versus control group	Daratumumab group versus HDACi group (indirect comparison)	Egger's test (*P* value)	Begg's test (*P* value)
PFS	4 (trials 1, 2, 5, and 6)	HR 0.38 (0.30–0.48)	HR 0.70 (0.57–0.85)	HR 0.55 (0.40–0.74)	0.06	0.31
CR	4 (trials1, 2, 5, and 6)	2.21 (1.74–2.81)	1.71 (1.17–2.51)	1.71 (0.72–4.06)	0.15	0.09
VGPR	3 (trials 1, 2, and 5)	1.83 (1.61–2.07)	1.76 (1.32–2.33)	1.03 (0.60–1.79)	0.66	1.00
ORR	4 (trials1, 2, 5, and 6)	1.25 (1.18–1.34)	1.22 (1.10–1.34)	1.06 (0.92–1.22)	0.64	0.73
PD + SD	4 (trials 1, 2, 5, and 6)	0.41 (0.30–0.58)	0.73 (0.62–0.87)	0.73 (0.60–0.88)	0.31	0.09

HDACi: histone deacetylase inhibitor; PFS: progression-free survival; OS: overall survival; ORR: overall response rate; CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease; HR: hazard ratio. Trials included: trial 1 represents Palumbo et al. (2016); trial 2 represents Dimopoulos et al. (2016); trial 3 represents Lonial et al (2015); trial 4 represents Jakubowiak et al. (2016); trial 5 represents San-Miguel et al. (2014); trial 6 represents Dimopoulos et al. (2013).

Table 6: Meta-analysis outcome of common at least grade 3 adverse events comparing monoclonal antibodies versus HDACis.

	Number of trials included	Risk ratio (95% CI)			Tests for publication bias	
		MAb group versus control group	HDACi group versus control group	MAb group versus HDACi group (indirect comparison)	Egger's test (*P* value)	Begg's test (*P* value)
Hematological adverse events						
Anemia	6 (trials 1, 2, 3, 4, 5, and 6)	0.81 (0.66–1.00)	1.07 (0.84–1.35)	0.79 (0.59–1.07)	0.95	1.00
Neutropenia	5 (trials 1, 2, 3, 5, and 6)	1.36 (0.77–2.41)	1.83 (0.70–4.81)	0.70 (0.51–0.96)	0.30	0.46
Thrombocytopenia	6 (trials 1, 2, 3, 4, 5, and 6)	1.02 (0.75–1.39)	2.05 (1.79–2.34)	0.35 (0.23–0.53)	0.03	0.26
Nonhematological adverse events						
Nausea or vomiting	4 (trials 2, 4, 5, and 6)	2.57 (0.66–9.99)	3.43 (0.91–12.91)	0.28 (0–398.63)	0.76	1.00
Peripheral neuropathy	4 (trials 1, 4, 5, and 6)	0.71 (0.40–1.27)	1.16 (0.85–1.58)	0.63 (0.35–1.14)	0.14	1.00
Upper respiratory tract infection	4 (trials 1, 2, 5, and 6)	1.38 (0.44–4.32)	2.56 (1.08–6.07)	0.71 (0.04–11.47)	0.31	0.40
Pyrexia	6 (trials 1, 2, 3, 4, 5, and 6)	0.89 (0.46–1.70)	0.91 (0.39–2.12)	1.02 (0.32–3.22)	0.47	1.00
Fatigue	6 (trials 1, 2, 3, 4, 5, and 6)	1.39 (0.95–2.04)	2.29 (1.74–3.02)	0.37 (0.17–0.82)	0.97	1.00
Constipation	6 (trials 1, 2, 3, 4, 5, and 6)	1.49 (0.53–4.16)	1.43 (0.55–3.73)	0.70 (0.05–10.53)	0.78	0.71
Diarrhea	6 (trials 1, 2, 3, 4, 5, and 6)	1.63 (1.03–2.58)	2.56 (1.93–3.41)	0.42 (0.15–1.19)	0.47	1.00

MAb: monoclonal antibody; HDACi: histone deacetylase inhibitor. Trials included: trial 1 represents Palumbo et al. (2016); trial 2 represents Dimopoulos et al. (2016); trial 3 represents Lonial et al. (2015); trial 4 represents Jakubowiak et al. (2016); trial 5 represents San-Miguel et al. (2014); trial 6 represents Dimopoulos et al. (2013).

Anmerkung/Fazit der Autoren

Treatment with MAbs in combination with bortezomib or lenalidomide plus dexamethasone resulted in longer PFS (HR 0.83, 95% CI: 0.66–0.98), fewer incidences of at least grade 3 thrombocytopenia (RR 0.35, 95% CI: 0.23–0.53), neutropenia (RR 0.70, 95% CI: 0.51–0.96), and sense of fatigue (RR 0.37, 95% CI: 0.17–0.82) than HDACis. The daratumumab plus bortezomib or lenalidomide and dexamethasone might significantly improve PFS in comparison with HDACis plus bortezomib or lenalidomide and dexamethasone (HR 0.55, 95% CI: 0.40–0.74). In conclusion, MAbs may be superior to HDACis in achieving longer PFS and may be better tolerated when in combination therapy with bortezomib or lenalidomide plus dexamethasone.

In other words, MAb is superior to HDACi when combined with bortezomib or lenalidomide plus dexamethasone from perspectives of both efficacy and safety. However, it remains still pivotal to conduct randomized controlled phase III trials to acquire head-to-head comparison evidence, further validating our findings.

Komentare zum Review

- Results don't show results according different numbers of treatment lines separately.

Teh BW et al., 2016 [21].

Infection risk with immunomodulatory and proteasome inhibitor-based therapies across treatment phases for multiple myeloma: A systematic review and meta-analysis.

Fragestellung

To determine the impact of immunomodulatory drugs (IMiDs) and proteasome inhibitor (PI) based therapy on infection risk in patients with MM 3 treatment periods:

- (…)
- maintenance therapy and
- relapse/ refractory disease (RRMM).

Methodik

Population:

- MM

Intervention:

- IMiD or PI-based treatment regimens (single or multi agent combination)

Komparator:

- high-dose corticosteroids

Endpunkte:

severe infection, febrile neutropaenia, pneumonia and deaths from infection

Recherche/Suchzeitraum:

- to 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias; GRADE for assessing overall quality of evidenc

Ergebnisse

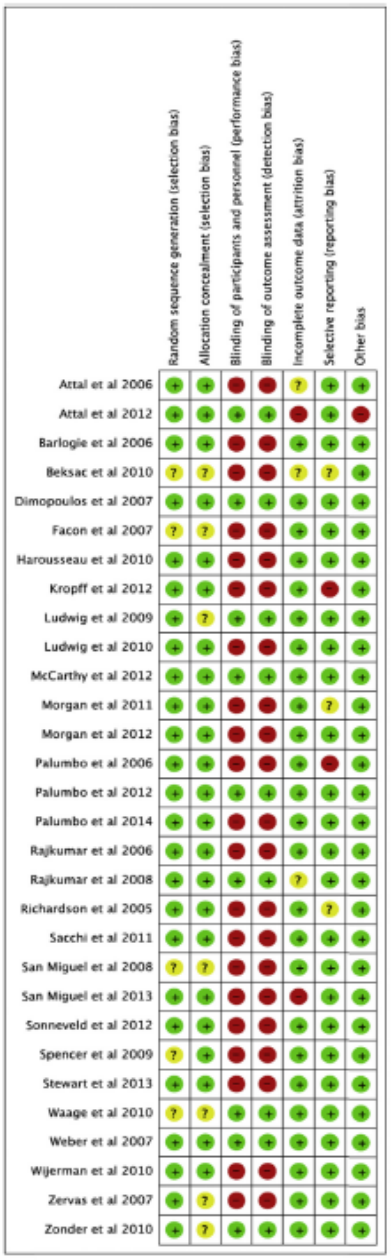
Anzahl der Studien:

- 30. Included studies for the treatment of relapsed and refractory myeloma

Charakteristika der Population:

(…) 7 were studies of maintenance therapy. The remaining studies covered both induction and maintenance (IMiD) (n=1) and patients with relapsed/refractory myeloma (n=5).

Qualität der Studien:



'+' low risk, '-' high risk, '?' unclear risk of bias

Studienergebnisse:

- (…) IMiDs or PI-based therapies versus high-dose corticosteroids for relapse and refractory disease
  - Overall rates of severe infection: The rate of severe infection in previously treated patients with relapse or refractory disease managed with IMiD-based therapy was 170 of 1026 patients (16.6%). The rate of febrile neutropaenia in a metaanalysis of the same group of patients was 4.0%. There was a single study of 669 evaluating the role of bortezomib, which reported a rate of all grade infections of 23.3%. Two IMiD-based studies had further data on the rate of severe pneumonia, which was 12.6%.

- For the treatment of RRMM, analysis of four studies of IMiD-based therapy versus high-dose dexamethasone demonstrated a RR of 1.51 (95% CI: 1.18-1.93; p < 0.01) for severe infection (RR = 13.57 (95% CI: 3.30-55.72; p < 0.01) for febrile neutropaenia and RR = 1.63 (95% CI: 1.04-2.55; p = 0.03) for pneumonia with no significant heterogeneity.

Anmerkung/Fazit der Autoren

(…) Thalidomide was associated with half the risk of severe infection when used as induction therapy in transplant-eligible patients and for maintenance therapy, when compared to bortezomib and lenalidomide, respectively. The addition of IMiDs to corticosteroids for relapse and refractory MM is associated with higher risk of severe infection. Ultimately, the choice of therapeutic agent will depend on the evaluation of its risk and benefit for the specific patient. Further studies are required to determine the immune determinants leading to increased infection risk.

Kommentare zum Review:

- Unklar Anteil Patienten mit ASCT
- The number of prior therapies are not known.
- Results are shown here are just selected from RRMM trials.

Sun Z et al., 2017 [20].

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 der Studien:

- 5 RCTs

Charakteristika der Population:

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

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

Stewart et al.,2015 (ASPIPE, 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

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

bbreviations: 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:

Efficacy

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) (data from 3 studies)
- PFS: HR (0.68, 95%CI: 0.62–0.74)
- ORR: (1.19 (95%CI:1.10–1.27)
- 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),

<u>Safety (pooled analyses)</u>

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 concerning 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:

- Unklar ob Patienten eine ASCT erhalten haben
- Inclusion of 2nd und 3rd line therapies
- Safety data of individual trials not reported.

Chen M et al., 2018 [3].

Immunomodulatory drugs and the risk of serious infection in multiple myeloma: systematic review and meta-analysis of randomized and observational studies.

Fragestellung

to assess the risk of serious infection at different treatment status (induction therapy, maintenance therapy, and relapse and refractory therapy) and help in guiding decisions on the treatment in patients with MM.

Methodik

Population:

- patients with MM

Intervention/Komparator:

- patients with MM initiating a new immunomodulatory therapy regimen including thalidomide, lenalidomide, or pomalidomide

Endpunkte:

- one or more adverse events about infection

Recherche/Suchzeitraum:

- Medline, Web of Science, China National Knowledge Infrastructure, and the Cochrane Central Register of Controlled Trials from inception to 20 May 2017.

Qualitätsbewertung der Studien:

- Jadad scale & GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 92 studies involving 19,876 patients
- 45 RCTs, representing 16,291 patients, and 47 cohort studies, involving 3285 patients. IMiDs used in MM included thalidomide in 55 studies, lenalidomide in 30 studies, and pomalidomide in 7 studies.

Qualität der Studien:

- Siehe Ergebnisteil

Studienergebnisse:

- A total of 810 episodes of serious infection occurred in 5940 patients treated with thalidomide-based regimens and the incidence of treatment on induction (ASCT eligible), induction (non- ASCT eligible), maintenance, and relapsed or refractory were 14.80, 11.00, 10.70, and 7.00%, respectively.
- Fifteen trials reported overall 440 serious infection events in 5293 MM patients who used lenalidomide-based regimens for treatment. The rates of serious infection on induction, maintenance, and relapsed or refractory therapy were 12.30, 8.20, and 7.20%.
- There were 10 of 384 patients who received pomalidomide-based regimen therapy experiencing serious infection. Pomalidomide-based regimens were used

Table 3 Rates of serious infection in patients with MM from RCTs

IMiDs	Treatment status	Pooled incidence	95% CI	I^2	Model
Thalidomide	Induction (ASCT eligible)	14.80%	6.40–23.10%	98.20%	Random-effect
	Induction (ASCT ineligible)	11.00%	7.90–14.20%	79.5%	Random-effect
	Maintenance	10.70%	5.90–15.50%	81.90%	Random-effect
	Relapsed and refractory	7.00%	2.00–11.90%	77.20%	Random-effect
Lenalidomide	Induction (ASCT ineligible)	12.30%	9.90–14.60%	57.00%	Random-effect
	Maintenance	8.20%	4.90–11.40%	68.40%	Random-effect
	Relapsed and refractory	7.20%	3.90–10.50%	96.20%	Random-effect
Pomalidomide	Relapsed and refractory	23.00%	3.90–42.20%	94.50%	Random-effect

MM multiple myeloma, *IMiDs* immunomodulatory drugs, *CI* confidence interval

Relative risk of serious infection

- (…) IMiD-based maintenance therapy statistically significantly increased the rate of serious infection in patients with MM (RR = 1.59, 95% CI 1.26–2.01, p < 0.01). Using GRADE, we rated the quality of identified studies as moderate, due to risk of bias. Subgroup analysis showed that lenalidomide-based maintenance therapy significantly increased risk of serious infection (RR = 2.45, 95% CI 1.57–3.83, p < 0.01).
- However, thalidomide-based maintenance therapy did not show a significant increase of risk of serious infection (RR = 1.30, 95% CI 0.98–1.71, p = 0.068). We graded the results as low because of risk of bias and imprecision.

- (…) Four studies involving 1652 patients were included for the analysis of serious infection in patients with relapsed and refractory MM. Patients using IMiDs for therapy demonstrated a significantly increased risk for serious infection compared to non-IMiD therapy (RR = 1.38, 95% CI 1.08–1.78, p = 0.011).

Anmerkung/Fazit der Autoren

In conclusions, our systematic review and meta-analysis showed that the incidence and risk of serious infection were high in MM patients treated with IMiDs. Pomalidomide was associated with the highest rate of serious infection in patients with relapsed and refractory MM. So, preventive and therapeutic management are essential for MM patients receiving IMiDs.

Kommentare zum Review

- Ergebnisdarstellung fokussiert auf Ergebnissen der RCTs.

Weisel K et al., 2019 [23].

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

Fragestellung

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

Intervention/Komparator:

- Studies that compared two or more active IMiD-free regimens

Endpunkte:

- PFS, OS, ORR

Recherche/Suchzeitraum:

- between 1 January 1995 and 3 November 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.

Ergebnisse

Anzahl eingeschlossener Studien:

- 52 articles identified, from which four trials were ultimately included in the base-case NMA

Charakteristika der Population:

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]	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 primary publications of the base case trials were of low to moderate quality

Studienergebnisse:

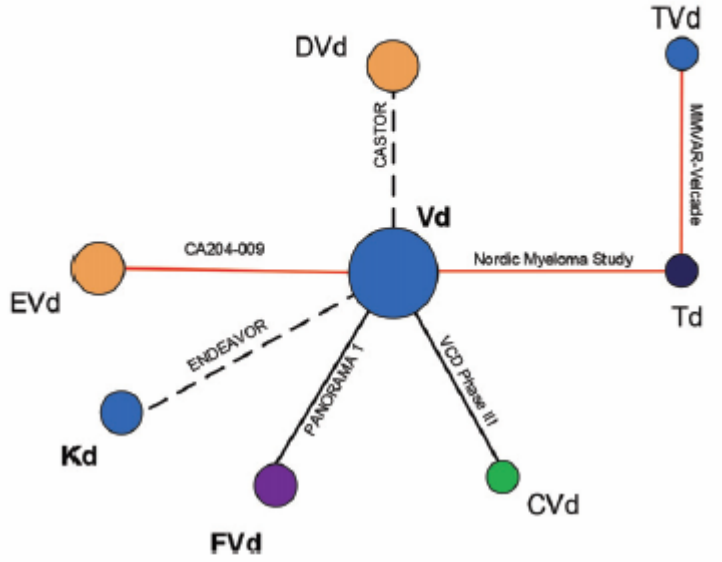


Figure 2. Network diagram. Blue: Proteasome inhibitor alone or in combination. Dark blue: Immunomodulators ± glucocorticoid; Orange: Monoclonal antibody alone or in combination; Purple: Histone deacetylase inhibitor + proteasome inhibitor; Green: Proteasome inhibitor + glucocorticoid ± alkylating agent; 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.

- PFS
  - Fixed-effects analyses showed that, in patients with RRMM, DVd prolonged PFS (i.e. demonstrated a statistical advantage, with an HR less than 0.80 and CrIs not crossing 1.0), when compared with other IMiD-free regimens (such as Kd, FVd, CVd, and Vd).
  - FVd and Kd demonstrated a statistical advantage in improving PFS compared with Vd, and CVd demonstrated a trend to improve PFS, but with a CrI that crossed 1.0. There was also a trend for Kd to improve PFS compared with FVd.
  - Results were inconclusive for the comparisons of CVd to Kd and to FVd, respectively.
  - The cumulative rank probability shows that DVd had a nearly 100% probability of being the best treatment for prolonging PFS among all regimens included in the NMA.
- OS:
  - In terms of OS, fixed-effects analyses showed that DVd had a statistical advantage in improving the outcome compared with Vd, and a trend toward improvement compared with Kd, FVd, and CVd.

- CVd and FVd did not demonstrate any advantages against other comparators. There was a slight trend for Kd to improve OS when compared with Vd.
- As shown in the cumulative rank probability graph, DVd had the highest probability of being the best treatment in improving OS, compared to other IMiDfree regimens.

- OR:
  - When assessing overall response, patients with RRMM who received DVd were more likely to achieve such an outcome (i.e. demonstrated a statistical advantage with an OR greater than 1.25 and with CrIs not crossing 1.0) compared with those who received Vd or FVd.
  - A similar trend was seen for patients treated with DVd were compared with those given Kd or CVd. Kd demonstrated a statistical advantage in achieving overall response compared with Vd, while there was a trend for CVd and FVd to improve ORR. Patients treated with CVd were less likely than those treated with Kd or FVd to achieve overall response, although the CrI in each case crossed 1.0.
- Subgroup analyses:
  - The results of the subgroup analyses were generally consistent with those of the base-case analysis for PFS. In patients who had received one 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. However, there were no added advantages in terms of HRs for PFS in patients who received two or more prior LOTs.
  - In the subgroup of patients who had not received prior bortezomib, there was an additional advantage for DVd compared with FVd and with Vd, while no further advantages were observed for other comparators or for patients who had received prior bortezomib.
  - 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. Also, patients who had received a prior IMiD continued to experience longer PFS when treated with DVd than with all other comparators.

Anmerkung/Fazit der Autoren

These findings provide policy-makers and clinicians with important evidence regarding the comparative effectiveness of different IMiD-free treatment regimens in patients with RRMM who have received at least one prior LOT. 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. This review includes the most comprehensive evidence base available; therefore, the results can be considered generalizable to the broader RRMM population for whom an IMiD-free regimen is suitable.

Kommentare zum Review:

- Siehe auch Dimopoulos MA et al. 2018 [5]

Luo XW et al., 2018 [12].

Treatment options for refractory/relapsed multiple myeloma: an updated evidence synthesis by network meta-analysis.

Fragestellung

an updated NMA of RCTs related to RRMM treatment

Methodik

Population:

- RRMM patients

Intervention/Komparator:

- Siehe Ergebnisteil

  Note: The dexamethasone monotherapy was set as the common reference regimen.

Endpunkte:

- nonresponse rate (NRR), time to progression (TTP), progression-free survival (PFS) and OS

Recherche/Suchzeitraum:

- January 1, 2000 and June 30, 2017

Qualitätsbewertung der Studien:

- Cochrane approach (siehe Botta C. et al. 2017 [2])

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 RCTs with a total of 10,853 subjects and 21 different regimens.
- Compared with the inclusion results by Botta et al. an additional seven references were included, among which four were newly identified studies and three were updated study results.

Charakteristika der Population:

Table 1 Basic information of included RCT reports

Authors	Year	Trial Identification	Arm 1	Arm 2	N	Outcome
Richardson et al[11]	2005	APEX	BOR	DEX	627	NRR, TTP, OS
Richardson et al[12]	2007	APEX	BOR	DEX	627	NRR, TTP, OS
Dimopoulos et al[13]	2007	MM-010	LEN + DEX	DEX	351	NRR, TTP, OS
Orlowski et al[14]	2007	DOXIL-MMY-3001	BOR + pIDOX	BOR + DEX	646	NRR, TTP, PFS, OS
Weber et al[15]	2007	MM-009	LEN + DEX	DEX	353	NRR, TTP, OS
Chanan-Khan et al[16]	2009	GMY302	OBL + DEX	DEX	224	NRR, TTP
Dimopoulos et al[17]	2009	MM-009 & MM-010	LEN + DEX	DEX	704	PFS, OS
Garderet et al[18]	2012	MMVAR/IFM 2005-04	BOR + THA + DEX	THA + DEX	244	NRR, TTP, PFS, OS
Hjorth et al[19]	2012	NCT00602511	THA + DEX	BOR + DEX	131	NRR, PFS, OS
Kropff et al[20]	2012	OPTIMUM	THA	DEX	499	NRR, TTP, PFS, OS
Dimopoulos et al[21]	2013	VANTAGE 088	VOR + BOR	BOR	635	NRR, TTP, PFS, OS
San-Miguel et al[4]	2013	MM-003	POM + DEX	DEX	455	NRR, TTP, PFS, OS
White et al.[22]	2013	AMBER	BEV + BOR	BOR	102	NRR, PFS, OS
Morgan et al[6]	2014	MM-003	POM + DEX	DEX	455	OS
Richardson et al[5]	2014	MM-002	POM + DEX	POM	221	NRR, PFS, OS
San-Miguel et al[23]	2014	PANORAMA1	PAN + BOR + DEX	BOR + DEX	768	NRR, TTP, PFS, OS
Lonial et al[24]	2015	ELOQUENT-2	ELO + LEN + DEX	LEN + DEX	646	NRR, PFS
Orlowski et al[25]	2015	NCT00401843	SIL + BOR	BOR	268	NRR, TTP, PFS, OS
Stewart et al[26]	2015	ASPIRE	CAR + LEN + DEX	LEN + DEX	792	NRR, PFS, OS
Dimopoulos et al[27]	2016	POLLUX	DAR + LEN + DEX	LEN + DEX	557	NRR, TTP, PFS, OS
Dimopoulos et al[28]	2016	ENDEAVOR	CAR + DEX	BOR + DEX	929	NRR, PFS, OS
Jakubowiak et al[29]	2016	NCT01478048	ELO + BOR + DEX	BOR + DEX	152	NRR, PFS, OS
Moreau et al[30]	2016	TOURMALINE-MM1	IXA + LEN + DEX	LEN + DEX	722	NRR, TTP, PFS
Orlowski et al[31]	2016	DOXIL-MMY-3001	BOR + pIDOX	BOR + DEX	646	OS
Palumbo et al[32]	2016	CASTOR	DAR + BOR + DEX	BOR + DEX	474	NRR, TTP, PFS, OS
San-Miguel et al[7]	2016	PANORAMA 1	PAN + BOR + DEX	BOR + DEX	768	OS
Dimopoulos et al[8]	2017	ELOQUENT-2	ELO + LEN + DEX	LEN + DEX	646	PFS, OS
Hou et al[10]	2017	NCT01564537	IXA + LEN + DEX	LEN + DEX	115	NRR, TTP, PFS, OS
Hajek et al[9]	2017	FOCUS	CAR	DEX	315	NRR, PFS, OS

Abbreviations: BOR, bortezomib; BEV, bevacizumab; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; pIDOX, Pegylated liposomal doxorubicin; ELO, elotumumab; IXA, ixazomib; LEN, lenalidomide; OBL, oblimersen; POM, pomalidomide; SIL, siltuximab; THA, thalidomide; NRR, non-response rate; PAN, panobinostat; PFS, progression-free survival; TTP, time to progression; OS, overall survival; N, number of patients; VOR, vorinostat.

Studienergebnisse:

- According to the result, the combination of daratumumab, lenalidomide, and dexamethasone showed better efficacy than other regimens in terms of NRR, TTP, and PFS (NRR: odds ratio [OR] =0.046, 95% credible interval [CrI]= [0.024, 0.085]; TTP: hazard ratio [HR] =0.14, 95% CrI= [0.092, 0.2]; PFS: HR =0.12, 95% CrI= [0.077, 0.18], compared with dexamethasone singlet).
- The combination of ixazomib, lenalidomide, and dexamethasone showed better efficacy than other regimens in terms of OS (HR =0.30, 95% CrI= [0.17, 0.54], compared with dexamethasone).
- The combination of daratumumab, lenalidomide, and dexamethasone ranked first in terms of overall efficacy (weighted average of SUCRAs =0.920).

Anmerkung/Fazit der Autoren

In conclusion, the combination of daratumumab, lenalidomide, and dexamethasone may currently be the most effective regimen in the population of RRMM patients. Triplet regimens containing daratumumab, ixazomib, carfilzomib, or elotumumab plus lenalidomide and dexamethasone can be recommended as the first-line therapies for RRMM patients.

Kommentare zum Review

- Unklar ob Patienten ASCT erhalten haben
- Siehe auch: Botta C. et al. 2017 [2] & van Beurden-Tan CHY et al. 2017 [22]

3.4 Leitlinien

National Collaborating Centre for Cancer, 2016 [17].

Institute for Health and Care Excellence (NICE)

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

Leitlinienorganisation/Fragestellung:

Diagnosis and management of MM

Methodik

Grundlage der Leitlinie:

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

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

- re-run 6–8 weeks before the guideline was submitted to, literature published before 8th June 2015 considered
- 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).

Recommendations

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) […]

  Evidence: see TA 129 Bortezomib, NICE 2007 [16] 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

11.3 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: see TA 171 Lenalidomid, NICE 2009 [17]

  Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357(21):2123-2132.

  Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357(21):2133-2142

- 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

  Please Note: meanwhile TA338 is replaced with TA427

Moreau P et al., 2017 [15].

European Society for Medical Oncology (ESMO)

Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Leitlinienorganisation/Fragestellung

Treatment recommendations for MM.

Methodik

<u>Grundlage der Leitlinie</u>

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

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,. . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [49].

- Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

Recommendations

Treatment of relapsed/refractory disease

- The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).
- Until 2015, the EMA had approved, at the time of first relapse and beyond, lenalidomide in combination with dexamethasone [I, A] and bortezomib, either alone as single-agent or in

combination with PEGylated doxorubicin [I, A]. Nevertheless, bortezomib is mostly used in combination with dexamethasone in the relapse setting.

- In 2015 and 2016, based on the results of phase III prospective randomised trials, new triplet combinations were approved by the EMA. Panobinostat, a panHDAC inhibitor, in combination with bortezomib and dexamethasone, is now indicated for the treatment of patients with relapsed/refractory MM who have received at least two prior regimens including bortezomib and an immunomodulatory agent [II, C].
- Carfilzomib, the second-in-class proteasome inhibitor, has also been approved at the dose of 27 mg/m2 in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least one prior therapy [II, A]. Carfilzomib has also been approved at the dose of 56 mg/m2 in combination with dexamethasone alone in patients with at least one line of prior therapy [II, A].
- Elotuzumab, a monoclonal antibody targeting SLAM-F7, has also been approved in combination with lenalidomide and dexamethasone for the treatment ofMMin patients who have received at least one prior therapy [II, B].
- Ixazomib, the first oral proteasome inhibitor, in combination with lenalidomide and dexamethasone was also approved by the EMA in 2016 in patients who have received at least one prior line of therapy [II, A].
- In very advanced-stage disease, two other drugs are EMA approved for the treatment of relapsed MM. Pomalidomide, the third-in-class IMiD, in combination with low-dose dexamethasone, is approved in patients who have received at least two prior therapies, including both lenalidomide and bortezomib, and whose disease progressed after treatment with these medicines II, A].
- Daratumumab, a monoclonal antibody targeting CD38, was also recently approved for the treatment of adults with relapsed/refractoryMMwhose previous treatment included a proteasome inhibitor and an immunomodulatory agent and whose disease worsened after treatment [II, A]. Daratumumab has also shown significant efficacy at earlier stages of the disease, first relapse and beyond in combination with bortezomib-dexamethasone [II, A] or lenalidomide-dexamethasone [II, A] in two randomised phase III clinical trials. These two new triplet combinations may be considered in the near future as standards of care, in the case of regulatory approval.
- In young patients, a second ASCT may be considered, provided that the patient responded well to the previous ASCT and had a PFS of more than 24 months. In the relapse setting, allogeneic SCT should only be carried out in the context of a clinical trial.
- When possible, patients should be offered participation in clinical trials.

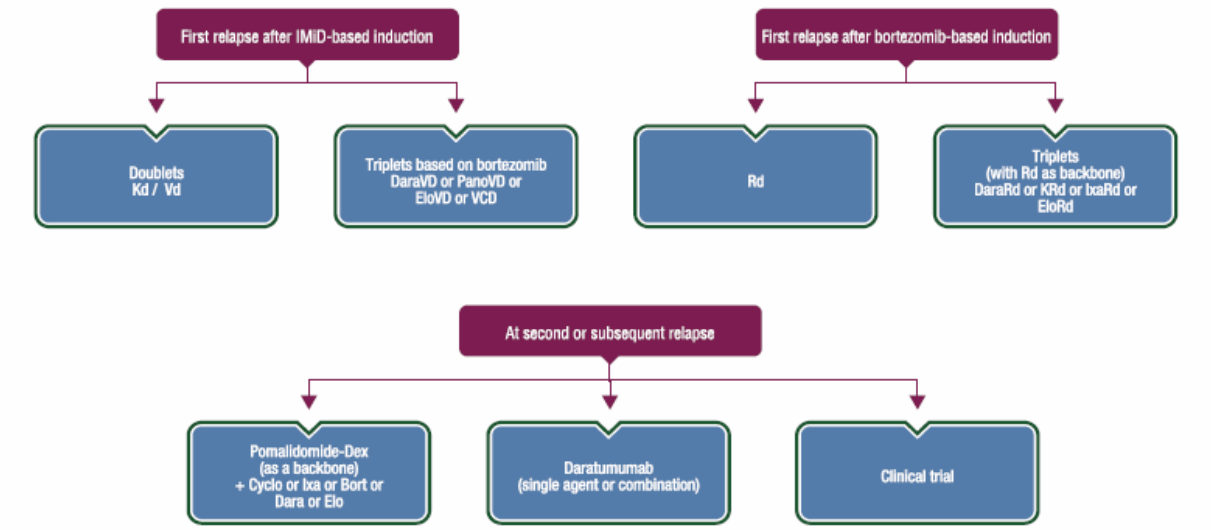


Figure 2. Treatment of relapse.
Bort, bortezomib; Cyclo, cyclophosphamide; Dara, daratumumab; DaraRd, daratumumab, lenalidomide, low dose dexamethasone; DaraVD, daratumumab, bortezomib, dexamethasone; Dex, dexamethasone; Elo, elotuzumab; EloRd, elotuzumab, lenalidomide, low dose dexamethasone; EloVD, elotuzumab, bortezomib, dexamethasone; IMiD, immunomodulatory drug; Ixa, izaxomib; IxaRd, izaxomib, lenalidomide, low dose dexamethasone; Kd, carfilzomib, low dose dexamethasone; KRd, carfilzomib, lenalidomide, low dose dexamethasone; PanoVD, panobinostat, bortezomib, dexamethasone; Rd, lenalidomide, low-dose dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; Vd, bortezomib, low dose dexamethasone.

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

Recherche/Suchzeitraum:

- from 2005 through 2018

LoE/GoR

- 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

Relapsed Disease

- Recommendation 7.1. Treatment of biochemically relapsed myeloma should be individualized. Factors to consider include patient's tolerance of prior treatment, rate of rise of myeloma markers, cytogenetic risk, presence of comorbidities (ie, renal insufficiency), frailty, and patient preference. High-risk patients as defined by high-risk cytogenetics and early relapse post-transplant/initial therapy should be treated immediately. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse (Type: informal consensus/evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 7.2. All clinically relapsed patients with symptoms due to myeloma should be treated immediately (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 7.3. Triplet therapy should be administered on first relapse, though the patient's tolerance for increased toxicity should be considered. A triplet is defined as a regimen with two novel agents (PIs, immunomodulatory drugs, or monoclonal antibodies) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 7.4. Treatment of relapsed multiple myeloma may be continued until disease progression. There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD) (Type: evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 7.5. Prior therapies should be taken into consideration when selecting the treatment at first relapse. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. Triplet regimens are preferred based on tolerability and comorbidities (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 7.6. ASCT, if not received after primary induction therapy, should be offered to transplanteligible patients with relapsed multiple myeloma. Repeat SCT may be considered in relapsed multiple myeloma if progression-free survival after first transplant is 18 months or greater (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).
- Recommendation 8.1. The risk status of the patients should be assessed using the Revised International Staging System for all patients at the time of diagnosis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong). Recommendation

- 8.2. Repeat risk assessment at the time of relapse should be performed and should include bone marrow with fluorescence in situ hybridization for myeloma abnormalities seen with progression, including 17p and 1q abnormalities. Fluorescence in situ hybridization for primary abnormalities (translocations and trisomies), if seen in the initial diagnostic marrow, does not need to be repeated (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.3. Assessment of other risk factors such as renal insufficiency, age, presence of plasma cell leukemia/circulating plasma cells, extramedullary disease, and frailty, should also be considered/ performed (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.4. In patients with genetic high-risk disease, a triplet combination of PI, immunomodulatory drug, and a steroid should be the initial treatment, followed by one or two ASCTs, followed by a PIbased maintenance until progression (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong). Recommendation
- 8.5. In patients with renal insufficiency, drugs should be modified based on renal clearance (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 8.6. In patients with plasma cell leukemia or extramedullary disease, cytotoxic chemotherapy may have a role (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 9.1. The IMWG revised response criteria should be used for response assessment (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 9.2. All measurable parameters need to be followed, including light and heavy chain analysis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 9.3. All responses excluding marrow and imaging should be confirmed as per IMWG criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 9.4. Response assessment should be performed after one cycle of therapy, and once a response trend is observed, it may be done every other cycle and less frequently once patient is in a plateau (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Alberta Provincial Hematology Tumour Team, 2015 [1].

Alberta Provincial Hematology Tumour Team

Multiple Myeloma

Leitlinienorganisation/Fragestellung

(…) What are the most suitable management strategies of multiple myeloma and related disorders?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The MEDLINE (1966 through July 2012), PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews databases were searched. In addition, the ASCO and ASH Abstracts and Proceedings databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials.

LoE/GoR

- kein Graduierungssystem (Formulierungen im Text)

Recommendations

Treatment Guidelines for Relapsed and Refractory Multiple Myeloma

- Whenever possible, patients with relapsed multiple myeloma should be considered for a clinical trial. In the absence of a suitable trial, treatment of relapsed disease should be determined on individual basis depending on timing of relapse, age, prior therapy, bone marrow function, co-morbidities, and patient preference.
- Repeat bone-marrow examination with cytogenetic testing should be performed at relapse as high-risk features frequently develop as the disease evolves, and may affect the choice of therapy. A short duration of last response is also a high risk feature, with poor long term prognosis for those with initial remission lasting less than 1 year.
- The choice of the salvage therapy is mostly guided by the preference of the patient and the treating physician. The following guidelines can help guide treatment decisions:
  - 1. Renal failure: Lenalidomide dose adjustment is required for patients in renal failure or on hemodialysis in order to minimize the risk of cytopenia. No such adjustment is required for bortezomib.
  - 2. Peripheral neuropathy: Bortezomib is neurotoxic and should not be the first choice of salvage therapy in patients with grade 2 sensory neuropathy, or grade 1 with pain.
  - 3. Prior exposure to thalidomide: Prior exposure to thalidomide does not preclude patients from responding to lenalidomide. While a shorter TTP was reported in the MM009 and MM010 studies in patients previously exposed to thalidomide, their mTTP was 8.6 months.78, 79
  - 4. Prior history of DVT: IMIDs are known to have a prothrombotic effect. Risk of thrombosis with thalidomide and lenalidomide varies between 10-15% and can be as high as 25% when these drugs are used with erythropoietin. Prophylaxis of DVT with aspirin or therapeutic Coumadin or LMWH is mandatory. Bortezomib is the agent of

choice over IMIDs for patients with prior life threatening thrombotic events. If IMIDs are to be used, patients should receive prophylactic LMWH.

- 5. Distance from hospital: IMIDs offer the advantage of being orally administered and therefore require less frequent visits to the hospital. Nevertheless, in non-compliant patients bortezomib is preferable.

- Autologous Stem Cell Transplant: A second high dose chemotherapy treatment with autologous stem cell transplantation for those patients who have had a disease free interval of > 2 years following their initial high dose therapy is a reasonable consideration. The median time to progression after a salvage second autologous stem cell transplant is typically 1-2 years95-99. Re-induction may increase the efficacy of the procedure but prospective data does not exist. The transplant related mortality (TRM) varies between 2 and 10%100. No data currently exists on the role of maintenance or post-ASCT consolidation after a second transplant. When a patient with relapsed myeloma is being considered for a salvage second transplant, the TRM and the activity of novel agents should be clearly discussed and reviewed with the patient.

Non-transplant based options:

- The majority of patients relapsing with myeloma will not be candidates for high dose chemotherapy and autologous stem cell transplant. Standard approaches generally incorporate a novel-agent containing regimen.
- Bortezomib: Bortezomib has long been accepted as a standard for the treatment of relapsed disease101. It is widely available in Canada and approved for use in this setting in Alberta. Based on the design of the initial phase III trials in this setting treatment should be continued to progression or intolerance. Although the initial trials generally examined bortezomib naïve patients, it is important to note that the majority of patients will now have been exposed to this agent in the upfront setting. Thus, the decision to pursue retreatment will be influenced on the response during prior exposure to the drug. When at all possible treatment with a triplet based combination should be considered.
- Immunomodulatory drugs:
  - Thalidomide The bulk of the evidence for the use of thalidomide in the relapse setting is phase II data Minimal phase III data to guide its use in the relapse setting. There is minimal monotherapy activity and thus is best used in conjunction with other agents in a doublet or triplet combination when other IMIDs are contraindicated (ex VTD or CTD). While neuropathy continues to be the major limiting side-effect its advantage is that there is minimal myelosuppression.
  - Lenalidomide Initial trials examined its use in combination with dexamethasone showing improved activity compared with dexamethasone alone and should be delivered as continuous therapy. Durable responses can be achieved and continuous therapy is generaly well tolerated. Phase II data supports the use of additional agents such as bortezomib (RVD) or alkylator especially if initial responses with steroid based doublet regimens are sub-optimal.
  - Pomalidomide This third generation immunomodulatory agent is indicated for use in patients with previous exposure to bortezomib and lenalidomide. At present, it is funded through a drug company sponsored compassionate access program. Inclusion in the provincial formulary is pending review. Phase III date supports its use over single agent

dexamethasone. Similar to other IMIDs pomalidomide should be combined with dexamethasone and continued to progression.

- IMIDs (thalidomide, lenalidomide, pomolidomide) and proteasome inhibitors (bortezomib, carfilzomib), either as single agents or combination with other drugs (dexamethasone, prednisone, melphalan, cyclophosphamide), have been shown to be active in the treatment of relapsed and refractory myeloma.
- When lenalidomide and dexamethasone are used for relapsed or refractory myeloma, treatment should continue until disease progression
- Pomolidomide (4mg for 21/28 days every 4 weeks) with dexamethasone 40mg weekly can be considered for myeloma that is refractory to both lenalidomide and bortezomib.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 8 of 12, August 2019) am 06.08.2019

#	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 myelomatosis OR myelomatoses):ti,ab,kw
6	{OR #1, #4-#5}
7	#6 with Cochrane Library publication date from Aug 2014 to present

Systematic Reviews in Medline (PubMed) am 06.08.2019

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[tiab]) OR Plasma-Cell[tiab]) OR "Plasma Cell"[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 studies[pt] OR validation studies[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-

#	Suchfrage
	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 ("2014/08/01"[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[ptyp]

Leitlinien in Medline (PubMed) am 06.08.2019

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[tiab]) OR Plasma-Cell[tiab]) OR "Plasma Cell"[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 guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
8	(((#7) AND ("2014/08/01"[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[ptyp]

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