Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-271 Elotuzumab

Stand: Februar 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Elotuzumab **zur Behandlung des rezidivierten und refraktären Multiplen Myeloms**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*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 prüfendes Arzneimittel:	
Elotuzumab L01XC23 Empliciti®	Geplantes Anwendungsgebiet: Empliciti ist in Kombination mit Pomalidomid und Dexamethason indiziert für die Behandlung des rezidivierten und refraktären Multiplen Myeloms bei erwachsenen Patienten, die mindestens zwei vorausgegangene Therapien, darunter Lenalidomid und einen Proteasom-Inhibitor, erhalten haben und unter der letzten Therapie eine Progression gezeigt haben.
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

Weitere antineoplastische Arzneimittel	
Lenalidomid L04AX04 Revlimid®	Multiples Myelom Revlimid als Monotherapie ist indiziert für die Erhaltungstherapie von erwachsenen Patienten mit neu diagnostiziertem multiplem Myelom nach einer autologen Stammzelltransplantation. Revlimid als Kombinationstherapie (siehe Abschnitt 4.2) ist indiziert für die Behandlung von erwachsenen Patienten mit unbehandeltem multiplem Myelom, die nicht transplantierbar sind. 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 Dexamethason indiziert für die Behandlung des rezidivierten oder 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.
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. VELCADE ist in Kombination mit Melphalan und Prednison für die Behandlung erwachsener Patienten mit bisher unbehandeltem multiplen Myelom indiziert, die für eine Hochdosis-Chemotherapie mit hämatopoetischer Stammzelltransplantation nicht geeignet sind. VELCADE ist in Kombination mit Dexamethason oder mit Dexamethason und Thalidomid für die Induktionsbehandlung erwachsener Patienten mit bisher unbehandeltem multiplen Myelom indiziert, die für eine Hochdosis-Chemotherapie mit hämatopoetischer Stammzelltransplantation geeignet sind. […]
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.
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).
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).
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.
Daratumumab L01XC24 Darzalex®	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. • 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: 2018-B-271 (Elotuzumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	8. Januar 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	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	Gemeinsamer Bundesausschuss
GoR	Grade of Recommendations
HDAC	histone deacetylase
HR	Hazard ratio
HRQoL	health-related quality of life
IMiDs	immunomodulatory imide drugs
IQWiG	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 für die Synopse:

- zur Behandlung von erwachsenen Patienten mit multiplem Myelom, die mindestens zwei vorherige Therapien, erhalten haben.
- zur Behandlung von erwachsenen Patienten mit multiplem Myelom, die mindestens drei vorherige Therapien, erhalten haben.

2 Systematische Recherche

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

Die Erstrecherche wurde am 20.06.2017 durchgeführt, die Folgerecherche am 15.10.2018. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 773 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 24 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2018 [9].

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

Anwendungsgebiet

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.

Zweckmäßige 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

Siehe auch: **[4], [3].**

Anwendungsgebiet

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

Zweckmäßige 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 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung der allogenen Stammzelltransplantation bei Multiplem Myelom jenseits der Erstlinientherapie

Vom 19. Januar 2017

Anwendungsgebiet

Patientinnen und Patienten mit einem Multiplen Myelom nach Progress oder Rezidiv des Tumors unter oder nach der Erstlinientherapie

In die Erprobungsstudie sollen nur Patientinnen und Patienten eingeschlossen werden, die sämtliche der folgenden Merkmale erfüllen:

- Diagnose Multiples Myelom,
- Rezidiv oder Progress des Multiplen Myeloms unter oder nach systemischer Erstlinientherapie,
- keine Vorbehandlung mit allogener SZT,
- nach Bewertung der behandelnden Ärztin oder des behandelnden Arztes für Behandlung mit allogener SZT geeignet (ohne Altersbeschränkung),
- unter Induktionschemotherapie zur Behandlung des Rezidivs oder Progresses des Multiplen Myeloms muss eine Remission oder stabile Erkrankung erreicht sein und
- Zustimmung der Patientin oder des Patienten zur Studienteilnahme nach Aufklärung

Zweckmäßige Vergleichstherapie

Zweitlinientherapie mit Hochdosischemotherapie und autologer SZT (Vergleichsintervention)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 19. Januar 2017 folgende Richtlinie zur Erprobung der allogenen Stammzelltransplantation bei Multiplem Myelom jenseits der Erstlinientherapie beschlossen:

I.

„Richtlinie des Gemeinsamen Bundesausschusses zur Erprobung der allogenen Stammzelltransplantation bei Multiplem Myelom jenseits der Erstlinientherapie

(Erprobungs-Richtlinie Stammzelltransplantation bei Multiplem Myelom; Erp-RL SZT MM)

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

Anwendungsgebiet

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.

Zweckmäßige 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

Anwendungsgebiet

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

Zweckmäßige Vergleichstherapie

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 [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 - Panobinostat

Anwendungsgebiet

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.

Zweckmäßige 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 [11].

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

Anwendungsgebiet

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.

Zweckmäßige 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

Es wurden keine relevanten Cochrane Reviews identifiziert

3.3 Systematic Reviews

Chen R et al., 2017 [2].

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

Research question

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

Methods

Population:

- relapsed/refractory MM (RRMM)

Intervention:

- Pomalidomide

Comparator:

- Not specified

Outcomes (e.g. primary/secondary outcomes):

- Not specified

Literature search:

- on September 20, 2016

Quality assessment of studies:

- Cochrane tool for assessment of bias

Results

Number of studies:

- 8

Characteristics of 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.

Quality of the studies:

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

Study results:

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)

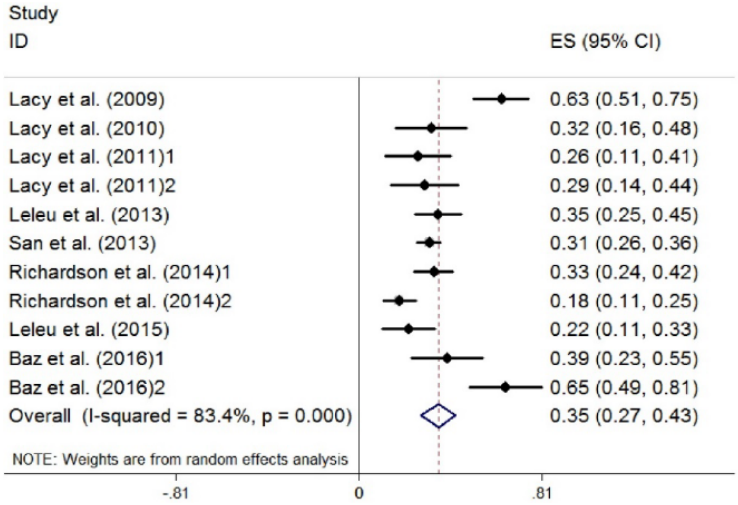


Figure 3. Complete response of pomalidomide treatment in patients with RRMM. (RRMM, relapsed/refractory multiple myeloma; ES, effect size)

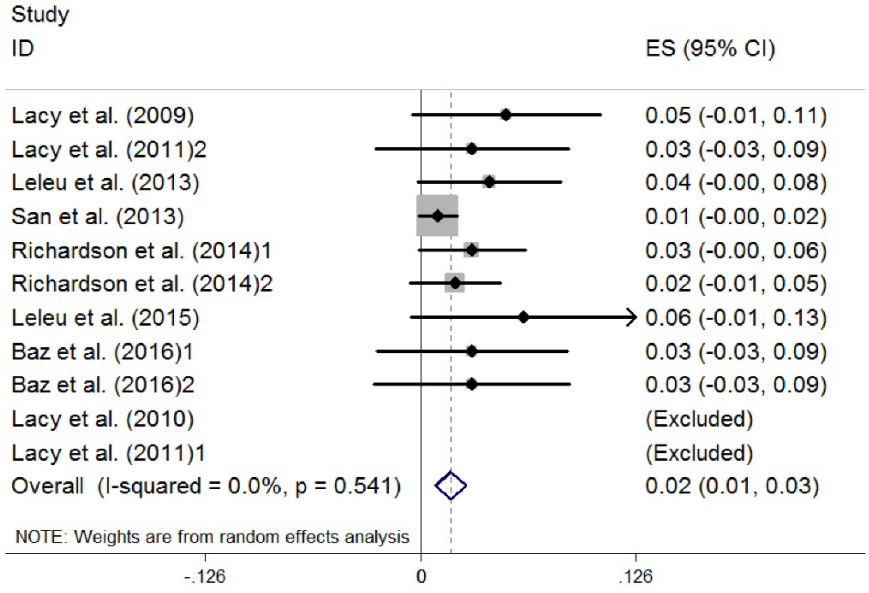


Table 5. Adverse effects of pomalidomide treatment

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

Authors' conclusions and comments

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.

Please Note

Limitations:

- 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.

Mushtaq A et al., 2018 [17].

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

Research question

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.

Methods

Population:

- relapsed and refractory multiple myeloma (RRMM)
- NDMM

Intervention:

- Carfilzomib (CFZ)

Comparator:

- Not specified

Outcomes (e.g. primary/secondary outcomes):

- 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]).

Literature search:

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

Quality assessment of studies:

- Not specified

Results

Number of studies:

- 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

Quality of the studies:

- Not assessed

Study results:

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.

Authors' conclusions and comments

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.

Shah C et al., 2018 [21].

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

Research question

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.

Methods

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

Intervention:

- carfilzomib

Comparator:

- Not specified

Outcomes (e.g. primary/secondary outcomes):

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

Literature search:

- Not mentioned

Quality assessment of studies:

Cochrane Collaboration's tools

Results

Number of studies:

- 14

Characteristics of 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 (ENDEAVOR)	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
	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.

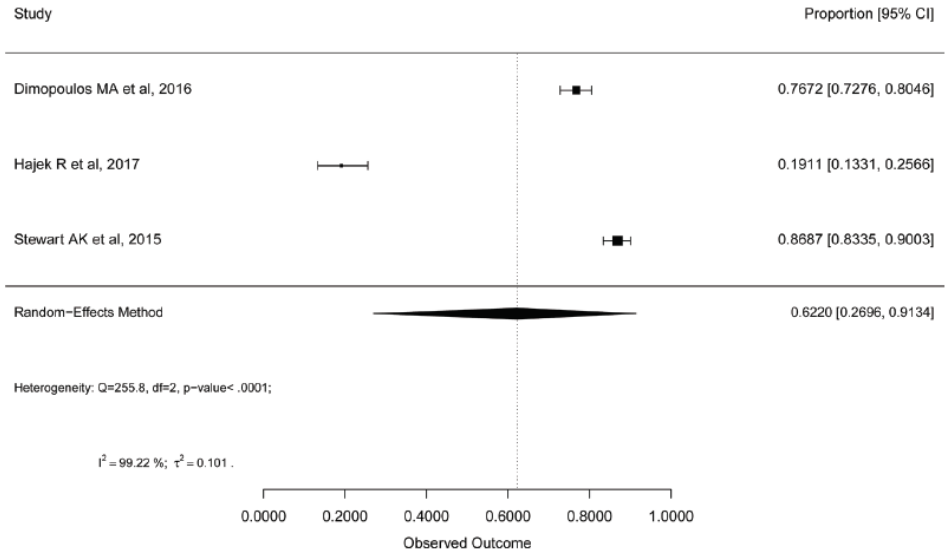
[•]10 (27%) out 37 patients had maximum carfilzomib dose ≤ 27 mg/m².

Quality of the studies:

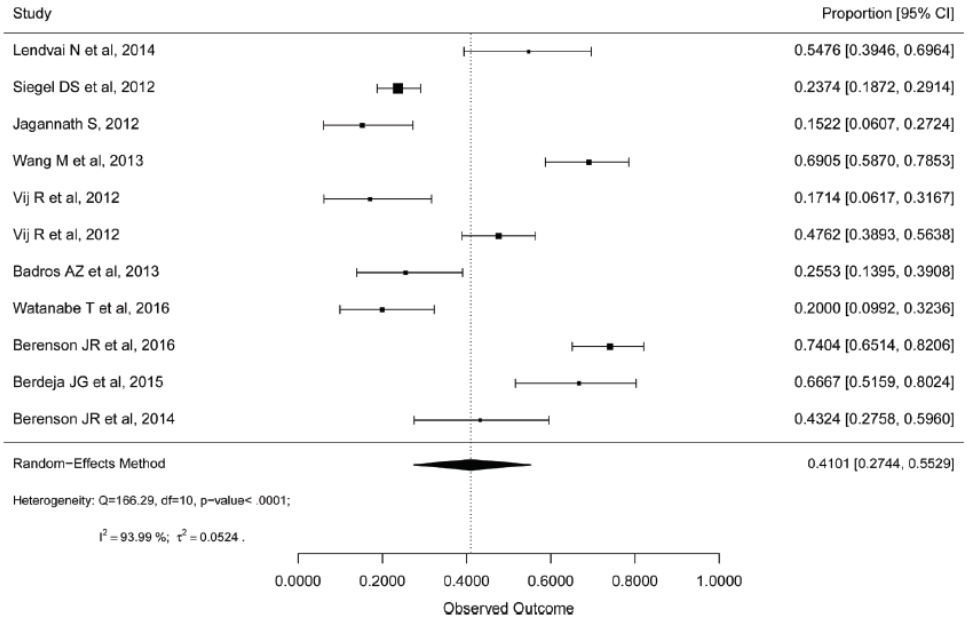
- No publication bias was detected by visual inspection of funnel plots and by Egger's tests.
- Study quality and risks of biases were assessed using the Cochrane Collaboration's tools. Among the RCTs, the risk of selection bias and attrition bias were low while performance bias, detection bias, and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

Study results:

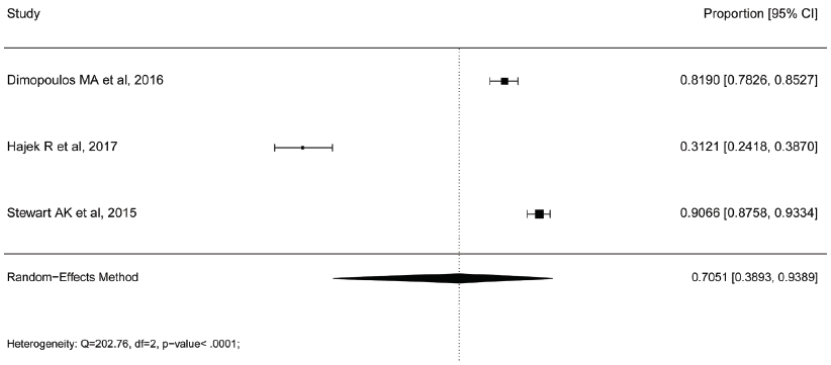
- ORR (phase III only)

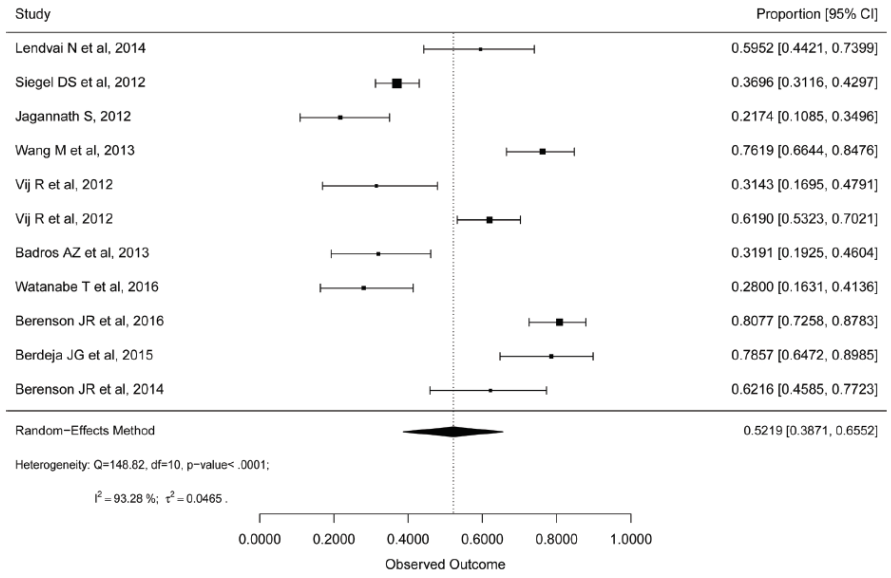


- ORR (phase III excluded)



Clivical benefit rate (phase III only)





Authors' conclusions and comments

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.

Maiese EM et al., 2018 [16].

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

Research question

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

Methods

Population:

- patients with previously treated MM (ie,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.

Comparator:

- Not specified

Outcomes (e.g. primary/secondary outcomes):

- PFS
- ORR

Literature search:

- To September 1, 2016

Quality assessment of studies:

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.

Results

Number of studies:

- 27 RCTs in the NMA

Characteristics of population:

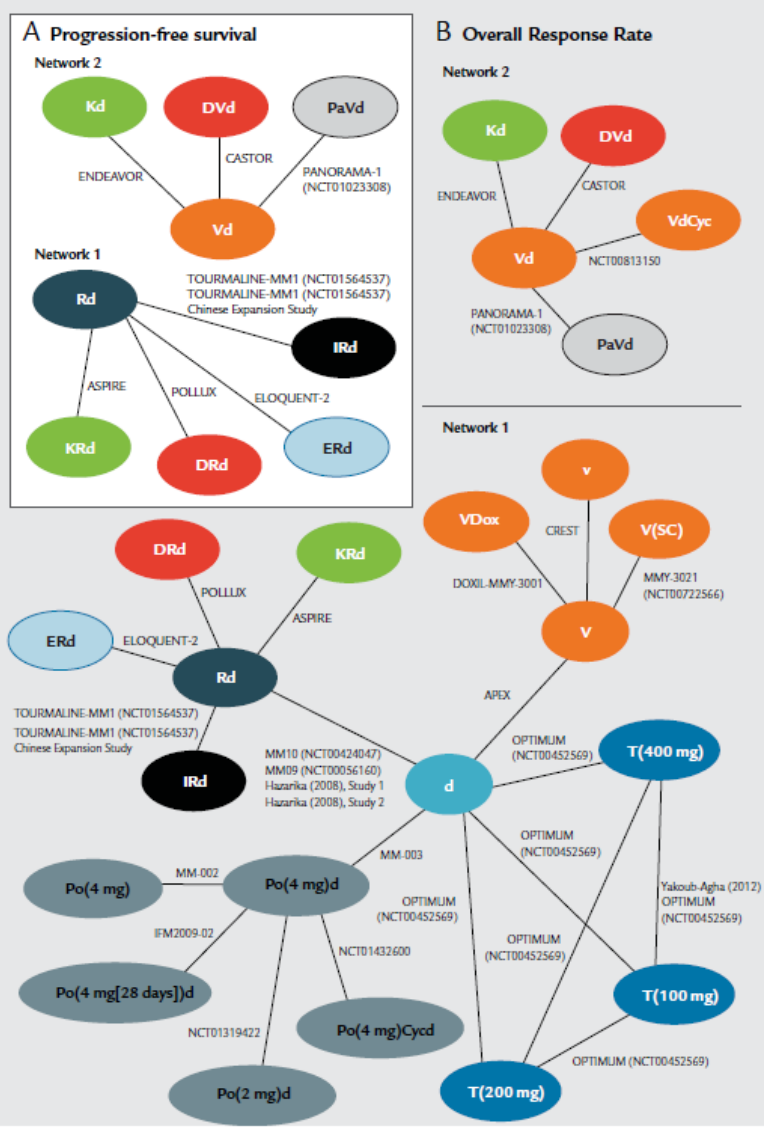
Nineteen trials were conducte dinmultiple countries, and8 trials were conducted in1 country (UnitedStates, 5;France,1; Germany, 1;and China,1).The median age of patients ranged from 56.5 to 71.0 years; 42.6% to 68.7% of patients were male;and patients received a median of 2 prior lines of treatment (range,1–17).

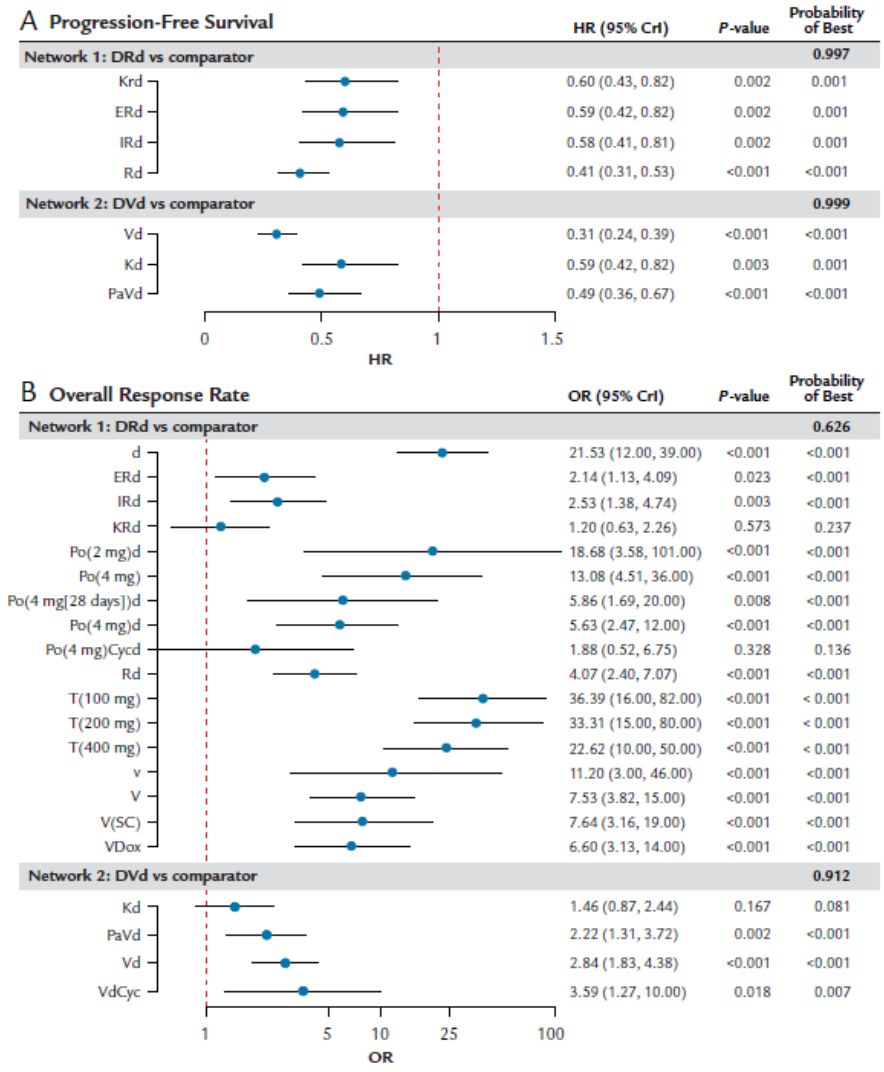
Quality of the studies:

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.

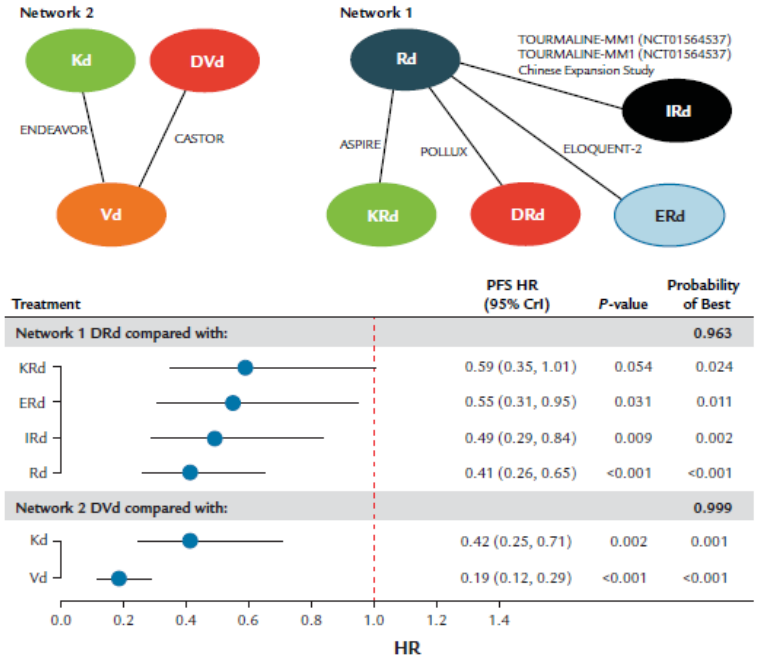
Study results:

- 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.

Authors' conclusions and comments

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.

Please Note

- 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

Research question

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.

Methods

Population:

- relapsed or refractory multiple myeloma

Intervention:

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

Comparator:

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

Outcomes (e.g. primary/secondary outcomes):

- 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

Literature search:

- on December 9, 2017

Quality assessment of studies:

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

Results

Number of studies:

- 6 RCTs

Characteristics of population:

- N= 3270

Table 1: Baseline characteristics of the included studies.

Study/reference	Phase	Number of patients	Treatment regimens	Median follow-up (months)	Primary endpoint	Median PFS (months)	1-year PFS rate (%)	Median OS (months)	1-year OS rate (%)
Palumbo et al. (2016) (CASTOR)	III	498	E: daratumumab 16 mg/kg + bortezomib 1.3 mg/m2 + dexamethasone 20 mg C: bortezomib 1.3 mg/m2 + dexamethasone 20 mg	E: 7.4 C: 7.4	PFS	E: NA C: 7.2	E: 60.7% C: 26.9%	E: NA C: NA	E: NA C: NA
Dimopoulos et al. (2016) (POLLUX)	III	569	E: daratumumab 16 mg/kg + lenalidomide 25 mg + dexamethasone 40 mg C: lenalidomide 25 mg + dexamethasone 40 mg	E: 13.5 C: 13.5	PFS	E: NA C: 18.4	E: 83.2% C: 60.1%	E: NA C: NA	E: 92.1% C: 86.8%
Lonial et al. (2015) (ELOQUENT-2) Dimopoulos et al. (2017) (ELOQUENT-2 follow-up)	III	646	E: elotuzumab 10 mg/kg + lenalidomide 25 mg + dexamethasone 40 mg C: lenalidomide 25 mg + dexamethasone 40 mg	E: 24.5 C: 24.5	PFS	E: 19.4 C: 14.9	E: 1-year PFS rate 68%; 2-year PFS rate 41% C: 1-year PFS rate 57% 2-year PFS rate 27%	E: 43.7 C: 39.6	E: 1-year OS rate 91%; 2-year OS rate 73% C: 1-year OS rate 83% 2-year OS rate 69%
Jakubowiak et al. (2016) (NCT01478048)	II	152	E: elotuzumab 10 mg/kg + bortezomib 1.3 mg/m2 + dexamethasone 20 mg C: bortezomib 1.3 mg/m2 + dexamethasone 20 mg	E: 15.9 C: 11.7	PFS	E: 9.7 C: 6.9	E: 1-year PFS rate 39%; 2-year PFS rate 18% C: 1-year PFS rate 33% 2-year PFS rate 11%	E: NA C: NA	E: 1-year OS rate 85%; 2-year OS rate 73% C: 1-year OS rate 74% 2-year OS rate 66%
San-Miguel et al. (2014) (PANORAMA1) San-Miguel et al. (2016) (PANORAMA1 follow-up)	III	768	E: panobinostat 20 mg + bortezomib 1.3 mg/m2 + dexamethasone 20 mg C: placebo + bortezomib 1.3 mg/m2 + dexamethasone 20 mg	E: 6.47 C: 5.59	PFS	E: 11.99 C: 8.08	E: 2-year PFS rate 20.6% C: 2-year PFS rate 8.4%	E: 40.3 C: 35.8	E: NA C: NA
Dimopoulos et al. (2013) (VANTAGE088)	III	637	E: vorinostat 400 mg + bortezomib 1.3 mg/m2 C: placebo + bortezomib 1.3 mg/m2	E: 14.2 C: 14.2	PFS	E: 7.63 C: 6.83	E: NA C: NA	E: NA C: 28.07	E: NA C: NA

PFS: progression-free survival; OS: overall survival; E: experimental group; C: control group; NA: not available.

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.

Quality of the studies:

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

Study results:

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).

Authors' conclusions and comments

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.

Please Note

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

Teh BW et al., 2016 [23].

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

Research question

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

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

Methods

Population:

- MM

Intervention:

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

Comparator:

high-dose corticosteroids

Outcomes (e.g. primary/secondary outcomes):

severe infection, febrile neutropaenia, pneumonia and deaths from infection

Literature search:

- to 2015

Quality assessment of studies:

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

Results

Number of studies:

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

Characteristics of population:

There were 29 phase III studies and 1 phase II study. Of these studies, 11 evaluated the use of IMiD or PI-based induction therapy for newly diagnosed non-transplant-eligible patients], 6

evaluated newly diagnosed transplant-eligible patients , whilst a further 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) [38-42].

RRMM:

[38] 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; 24:2487-98.

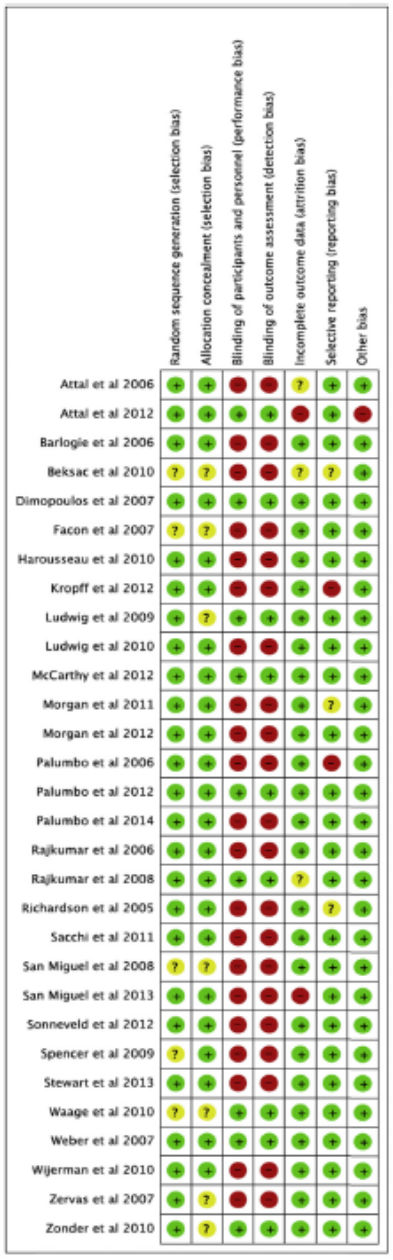
[39] Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007; 357(21):2123-32.

[40] 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):2133-42.

[41] Kropff M, Baylon HG, Hillengass J, Roba T, Hajek R, Liebisch P, et al. Thalidomide versus dexamethasone for the treatment of relapsed and/or refractory multiple myeloma: results from optimum, a randomized trial. Haematologica 2012;97(5): 784-90.

[42] San Miguel J, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus highdose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14(11):1055-66.

Quality of the studies:



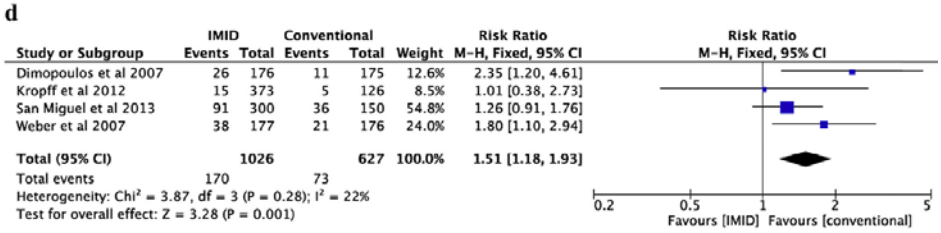
'+' low risk, '-' high risk, '?' unclear risk of bias

Study results:

IMiD-based therapy versus conventional therapy for relapsing and refractory myeloma

- All grade 3/4 infection: (Kropff et al. 2012 nicht relevant)

d



(Moderate quality of evidence)

- febrile neutropaenia (gleiche RCT wie bei all grade3 /4 infection): RR 13.57 (95% CI: 3.30-55.72; p < 0.01), no significant heterogeneity; low quality of evidence
- pneumonia (2 Studien: Weber, San Miguel) RR 1.63 (95% CI: 1.04-2.55; p <0.03) with no significant heterogeneity; moderate quality of evidence

Subgroup: Lenalidomide versus conventional

All grade 3/4 infection (2 RCT: Dimopoulos, Weber): RR 1.99 (1.34 -2.96) <0.01, moderate quality of evidence

Authors' conclusions and comments

The addition of IMiDs to corticosteroids for relapse and refractory MM is associated with higher risk of severe infection

Please Note

The number of prior therapies are not known.

Results are shown here are just selected from RRMM trials.

Sun Z et al., 2017 [22].

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

Research question

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

Methods

Population:

- patients with previously treated RRMM

Intervention:

- triplet combination therapy

Comparator:

- doublet combination therapy

Outcomes (e.g. primary/secondary outcomes):

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

Literature search:

- 05/2016

Quality assessment of studies:

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

Results

Number of studies:

- 5 RCTs

Characteristics of 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.

Quality of the studies:

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

Study results:

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),

Safety (pooled analyses)

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

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

Authors' conclusions and comments

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.

Please Note

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

Qiao SK et al., 2015 [20].

Efficacy and Safety of Lenalidomide in the Treatment of Multiple Myeloma: A Systematic Review and Meta‐analysis of Randomized controlled Trials

Research question

To assess the efficacy and safety of lenalidomide in the treatment of patients with MM and specifically to elucidate whether lenalidomide‐containing regimens offer a survival advantage over nonlenalidomide‐containing regimens

Methods

Population:

- Patients with newly diagnosed or previously treated MM

Intervention:

- Lenalidomide‐containing regimens

Comparator:

- non-lenalidomide‐containing regimens

Outcomes (e.g. primary/secondary outcomes):

overall response (OR), complete response (CR), PFS, OS, and Grade 3 or 4 toxicities

Literature search:

- to May 2013

Quality assessment of studies:

modified Jadad quality score including the presence of randomization, allocation concealment, blinding, and withdrawal/dropout A general quality score was assigned to each study as follows: Non‐RCTs (0), low quality studies (1–3), and high quality studies (4–7)

Results

Number of studies:

- 7 RCTs (relapsed or refractory MM: n=2)

Characteristics of population:

Table 1: Characteristics of included studies in the meta-analysis

Study, year	Study design	Patient details	Intervention	Number of patients	Ages (years)	Outcomes	Jadad score
Dimopoulos *et al.* 2007	RCT	Relapsed or refractory	Experiment: L-DEX	176	63 (33–84)	OS, PFS, AEs	5
			Control: P-DEX	175	64 (40–82)		
Weber *et al.* 2007	RCT	Relapsed	Experiment: L-DEX	177	64 (36–86)	OS, PFS, AEs	6
			Control: P-DEX	176	62 (37–85)		
Zonder *et al.* 2010	RCT	Newly diagnosed	Experiment: R-DEX	97	48	OS, PFS, AEs	6
			Control: P-DEX	95	45		
Kumar *et al.* 2012	RCT	Previously untreated	Experiment: VDCR	48	61.5 (41–81)	OS, PFS, AEs	5
			Control: VDC	33	62 (40–75)		
Palumbo *et al.* 2012	RCT	Newly diagnosed	Experiment: MPR + R	152	71 (65–87)	OS, PFS, AEs	6
			Control: MP + P	154	72 (65–91)		
Attal *et al.* 2012	RCT	ASCT	Experiment: L	307	55 (22–67)	OS, PFS, AEs	6
			Control: P	307	55 (32–66)		
McCarthy *et al.* 2012	RCT	ASCT	Experiment: L	231	59 (29–71)	OS, PFS, AEs	6
			Control: P	229	58 (40–71)		

RCT: Randomized clinical trial; ASCT: Autologous stem cell transplantation; OS: Overall survival; PFS: Progression-free survival; AEs: Adverse events.

Included studies: 2 RCTs (comparing lenalidomide+dexamethasone vs placebo+dexamethasone) reported on 704 patients with relapsed or refractory MM, who had received at least 1 previous antimyeloma treatment :

- Dimopoulos 2007
- Weber 2007

Study, year	Study design	Patient details	Intervention	Number of patients	Ages (years)	Outcomes	Jadad score
Dimopoulos *et al.* 2007	RCT	Relapsed or refractory	Experiment: L-DEX	176	63 (33–84)	OS, PFS, AEs	5
			Control: P-DEX	175	64 (40–82)		
Weber *et al.* 2007	RCT	Relapsed	Experiment: L-DEX	177	64 (36–86)	OS, PFS, AEs	6
			Control: P-DEX	176	62 (37–85)		

Quality of the studies:

See: results (Table 1)

Study results:

Relapsed or refractory multiple myeloma

Table 1: Characteristics of included studies in the meta-analysis

Study, year	Study design	Patient details	Intervention	Number of patients	Ages (years)	Outcomes	Jadad score
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			Control: P-DEX	175	64 (40–82)		
Weber *et al.* 2007	RCT	Relapsed	Experiment: L-DEX	177	64 (36–86)	OS, PFS, AEs	6
			Control: P-DEX	176	62 (37–85)		
Zonder *et al.* 2010	RCT	Newly diagnosed	Experiment: R-DEX	97	48	OS, PFS, AEs	6
			Control: P-DEX	95	45		
Kumar *et al.* 2012	RCT	Previously untreated	Experiment: VDCR	48	61.5 (41–81)	OS, PFS, AEs	5
			Control: VDC	33	62 (40–75)		
Palumbo *et al.* 2012	RCT	Newly diagnosed	Experiment: MPR + R	152	71 (65–87)	OS, PFS, AEs	6
			Control: MP + P	154	72 (65–91)		
Attal *et al.* 2012	RCT	ASCT	Experiment: L	307	55 (22–67)	OS, PFS, AEs	6
			Control: P	307	55 (32–66)		
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			Control: P	229	58 (40–71)		

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Included studies

- 2 RCTs (comparing lenalidomide+dexamethasone vs placebo+dexamethasone) reported on 704 patients with relapsed or refractory MM, who had received at least 1 previous antimyeloma treatment
    - Dimopoulos 2007
    - Weber 2007

Study, year	Study design	Patient details	Intervention	Number of patients	Ages (years)	Outcomes	Jadad score
Dimopoulos *et al.* 2007	RCT	Relapsed or refractory	Experiment: L-DEX	176	63 (33–84)	OS, PFS, AEs	5
			Control: P-DEX	175	64 (40–82)		
Weber *et al.* 2007	RCT	Relapsed	Experiment: L-DEX	177	64 (36–86)	OS, PFS, AEs	6
			Control: P-DEX	176	62 (37–85)		

Results for Len+Dex vs. Placebo+Dex:

- statistically significant higher OR rates (pooled RR: 2.76; 95% CI: 2.23–3.42; P < 0.00001; incidence, 60.6% vs. 21.9%) and CR rates (pooled RR: 8.61; 95% CI: 1.59–46.60; P = 0.01; incidence, 15.0% vs. 2.0%)
- Heterogenität: I^2=62% für komplettes Ansprechen

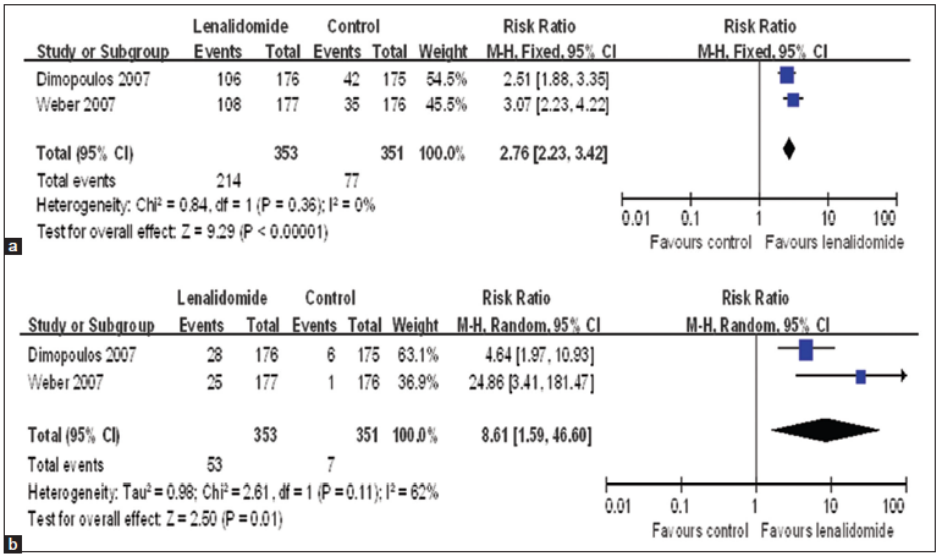

Figure 3: Forest plots of responses rate comparing lenalidomide with control for relapsed or refractory multiple myeloma. (a) Overall response; (b) Complete response.

- PFS: Len+Dex significantly longer 3-year PFS than Placebo+Dex (pooled RR: 1.48; 95% CI: 1.24–1.75; P < 0.00001)
- OS: 3-year OS (pooled RR: 1.12; 95% CI: 1.01–1.24; P = 0.03) in favour for Len+Dex

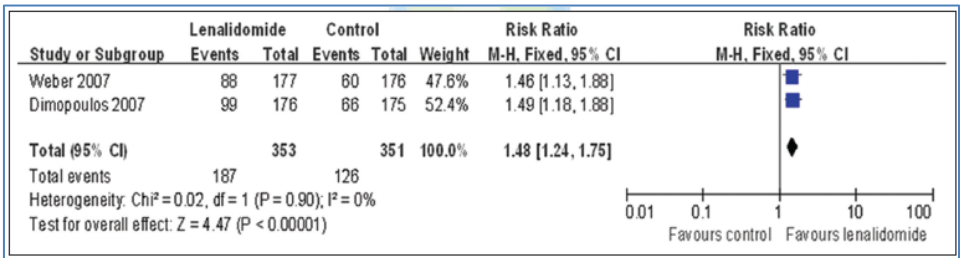

Figure 4: Forest plot of 3-year progression-free survival rate comparing lenalidomide with control for relapsed or refractory multiple myeloma.

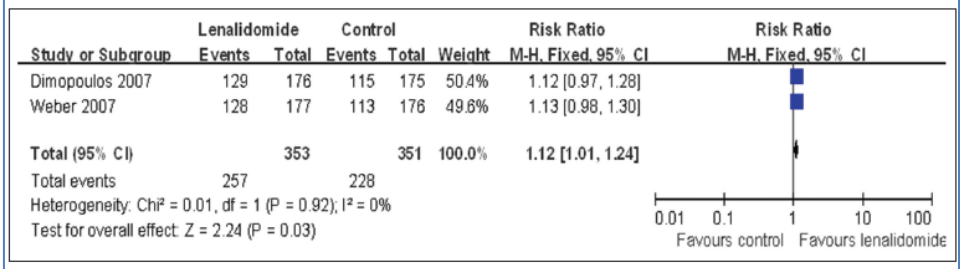

Figure 5: Forest plot of 3-year overall survival rate comparing lenalidomide with control for relapsed or refractory multiple myeloma.

Relapsed or refractory multiple myeloma

Two RCTs reported the data of a total of 704 patients with relapsed or refractory MM, who had received at least one previous antimyeloma treatment.

Lenalidomide‐containing regimens achieved a statistically significant higher OR rates (pooled RR: 2.76; 95% CI: 2.23–3.42; P < 0.00001; incidence, 60.6% vs. 21.9%; Figure 3a) and CR rates (pooled RR: 8.61; 95% CI: 1.59–46.60; P = 0.01; incidence, 15.0% vs. 2.0%; Figure 3b) compared with the no lenalidomide‐containing group. There was no significant heterogeneity among the reported OR ($P_{heterogeneity}$ = 0.36; I2 = 0%), but heterogeneity was found with respect to the reported CR ($P_{heterogeneity}$ = 0.11; I2 = 62%), and hence the random‐effects model was used. In terms of PFS and OS, patients treated with the lenalidomide‐containing regimens had significantly longer 3‐year PFS (pooled RR: 1.48; 95% CI: 1.24–1.75; P < 0.00001; Figure 4) and 3‐year OS (pooled RR: 1.12; 95% CI: 1.01–1.24; P = 0.03; Figure 5) than no lenalidomide‐containing regimens. There was no significant heterogeneity between the reported 3‐year PFS ($P_{heterogeneity}$ = 0.90; I2 = 0%) and 3‐year OS ($P_{heterogeneity}$ = 0.92; I2 = 0%), and the fixed effects model was used.

Authors' conclusions and comments

Lenalidomide+dex vs. Placebo+Dex: significantly increased OR, CR and showed statistically better PFS and OS.

Lopuch S et al., 2015 [15].

Effectiveness of targeted therapy as monotherapy or combined therapy in patients with relapsed or refractory multiple myeloma: A systematic review and meta-analysis

Research question

We performed a systematic review with meta-analysis to assess the balance between benefits and harms resulting from monotherapy and combined therapy in patients with relapsed or refractory MM treated with targeted agents approved in this indication by the FDA and/or the EMA.

Methods

Population:

- patients with relapsed or refractory MM

Intervention:

- targeted agents alone (monotherapy)

Comparator:

- combinations of targeted agents with other types of agents (combined therapy)

Outcomes (e.g. primary/secondary outcomes):

- ORR, CR, PR, progressive disease (PD), PFS, event-free survival (EFS), time to progression (TTP), time to response (TTR) or OS, incidents of death (overall and caused by AEs), and discontinuation of the intervention from any cause, any AEs, any SAEs, grade 3/4 AEs, AEs leading to death or incidents of discontinuation the intervention due to AEs

Literature search:

- To May 2013

Quality assessment of studies:

- Jadad scale

Results

Number of studies:

- 4

Characteristics of population:

- N= 997

Table 1 Characteristics of the included randomized controlled trials

References	Type of study	Treatment regimen	Population	Trial endpoints	Median follow-up
NCT00833833[31]	RCT, open	Pomalidomide vs. pomalidomide plus dexamethasone 4 mg pomalidomide was given once per day on days 1–21 of each 28-day cycle, dexamethasone was given on days 1, 8, 15, and 2 of each 28-day cycle (20 mg dexamethasone for participants who were ≥75 years and 40 mg dexamethasone for participants who were ≤75 years)	Patients with relapsed or refractory multiple myeloma who received prior treatment that includes lenalidomide and bortezomib, $N = 221$	Primary: PFS; secondary: AEs, CR, PR, MR, SD, PD, DR, TTR, OS	70 weeks
Orlowski (2007)[32]	RCT, open	Bortezomib vs. bortezomib plus PLD 1.3 mg/m^2 bortezomib was given on days 1, 4, 8, and 11 of each 21-day cycle, 30 mg/m^2 PLD was given on day 4 of each 21-day cycle	Patients with multiple myeloma who progressed after a response to ≥1 line of therapy or refractory to initial therapy (lenalidomide or thalidomide), $N = 646$	Primary: TTP; secondary: PFS, OS, CR, PR, AEs	7.2 months
White (2013)[33]	RCT, DB	Bortezomib vs. bortezomib plus bevacizumab 1.3 mg/m^2 bortezomib was given on days 1, 4, 8, and 11 of each 21-day cycle, 15 mg/kg bevacizumab was given on day 1 of each 21-day	Patients with relapsed or refractory multiple myeloma who progressed after 1–3 prior treatment regimens, $N = 102$	Primary: PFS; secondary: ORR, CR, PR, VGPR, DR, OS, AEs	13.3 months
Chiou (2007)[26]	RCT, open	Thalidomide vs. thalidomide plus INFα, thalidomide was given at a dose of 200 mg per day, a dose increased by 200 mg each 2 weeks to the maximal daily dose of 800 mg, 3 MIU/m^2 of INFα-2b was given 3 times weekly	Patients with relapsed or refractory multiple myeloma who relapsed or failed initial therapy, $N = 28$	Primary: ORR; secondary: TTR, DR, TTP, EFS, OS, CR, PR, MR, PD, AEs	Not reported

AEs, adverse events; CR, complete response; DB, double blind; EFS, event-free survival; INFα, interferon alfa; DR, duration of response; MIU, million international units; MR, minimal response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, partial response; RCT, randomised controlled trial; SD, stable disease; TTP, time to progression; TTR, time to response; VGPR, very good partial response.

Quality of the studies:

The methodological quality of the included RCTs was evaluated as moderate (two trials31,32 scored two points and two trials26,33 scored three points). All eligible trials were randomized,26,31–33 but only one trial33 was double blind and only one trial26 included description of the randomization method. All included trials were published in English as peer-reviewed articles.

Study results:

The results of the comparison of monotherapy with combined therapy in patients with relapsed or refractory MM are shown in Table 2.

Table 2 Summary of the efficacy and safety outcomes of the included studies

End points	No. of trials	Group of patients		RB/RR/HR (95% CI), P	Test of heterogeneity Cochran Q, df, P, I^2	References
		Monotherapy	Combined therapy			
		N	*N*			
PFS	2	161	162	HR = 0.73 [0.53–0.93], P < 0.0001	Cochran Q = 0.002, df = 1, P = 0.97	31,33
	1	322	324	HR = 1.69 [1.32–2.16], P = 0.0003		32
EFS	1	12	16	P = 0.0193		26
TTP	1	322	324	HR = 1.82 [1.41–2.35], P = 0.000004		32
TTR	2	143	178	HR = 1.04 [0.46–1.62], P > 0.05	Cochran Q = 16.32, df = 1, P = 0.003, I^2 = 87.7%	31,32
OS	3	161	162	HR = 0.80 [0.48–1.11] P > 0.05	Cochran Q = 0.34, df = 1, P = 0.84, I^2 = 0%	26,31,33
	1	322	324	HR = 1.41 [1.002–1.97], P = 0.0476		32
		n/*N*	*n*/*N*			
Discontinuation	4	354/495	330/502	RR = 1.06 [0.96–1.17], P = 0.27	Cochran Q = 7.23, df = 3, P = 0.06, I^2 = 58,5%	26,31,32,33
ORR	3	158/387	175/389	RB = 0.90 [0.77–1.06], P = 0.22	Cochran Q = 1.15, df = 2, P = 0.56, I^2 = 0%	26,32,33
CR	4	9/495	16/502	RB = 0.58 [0.27–1.27], P = 0.17	Cochran Q = 0.24, df = 3, P = 0.97, I^2 = 0%	26,31,32,33
PR	4	155/495	179/502	RB = 0.78 [0.42–1.45], P = 0.44	Cochran Q = 12.45, df = 3, P = 0.01, I^2 = 75,9%	26,31,32,33
PD	2	23/120	10/129	RR = 2.58 [1.29–5.12], P = 0.007	Cochran Q = 0.004, df = 1, P = 0.95	26,31
Death	4	62/495	44/502	RR = 1.38 [0.96–1.99], P = 0.08	Cochran Q = 0.16, df = 3, P = 0.98, I^2 = 0%	26,31,32,33
Discontinuation due to AEs	4	94/491	226/496	RR = 0.74 [0.28–1.94], P = 0.54	Cochran Q = 14.00, df = 3, P = 0.0029, I^2 = 78,6%	26,31,32,33
AEs	3	457/475	472/480	RR = 0.98 [0.96–1.001], P = 0.58	Cochran Q = 0.80, df = 2, P = 0.67, I^2 = 0%	31,32,33
SAEs	2	148/425	184/430	RR = 0.82 [0.69–0.97], P = 0.02	Cochran Q = 0.48, df = 1, P = 0.49	31,32
Grade 3/4 AEs	3	328/475	393/480	RR = 0.87 [0.76–0.98], P = 0.03	Cochran Q = 5.70, df = 2, P = 0.06, I^2 = 64.9%	31,32,33
AEs leading to death	2	14/368	14/368	RR = 1.00 [0.48–2.07], P = 0.999	Cochran Q = 1.11, df = 1, P = 0.29	32,33

AEs, adverse events; EFS, event-free survival; CR, complete response; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RB, relative benefit; RR, relative risk; SAEs, serious adverse events; TTP, time to progression; TTR, time to response. There was not possibility to perform meta-analysis of HRs for PFS and OS reported in three trials[31–33] because in two trials[31,33] HR was calculated relative to monotherapy and in the third trial[32] HR was calculated relative to combined therapy.

OS

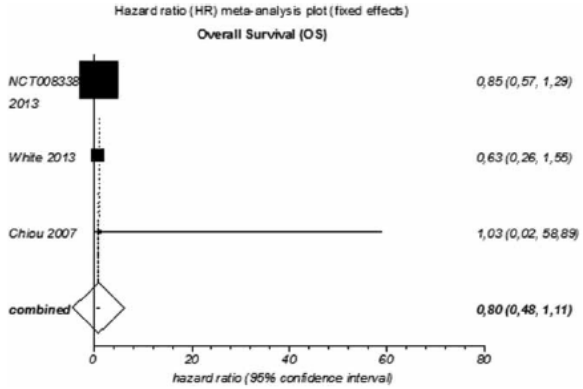

Figure 3 Meta-analysis of overall survival (OS) for targeted agents used as monotherapy or combined therapy in patients with relapsed or refractory MM.

PFS

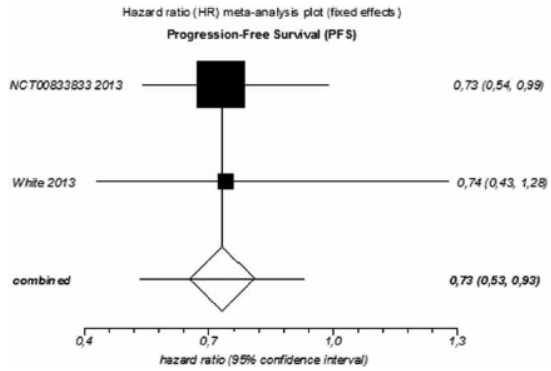

Figure 2 Meta-analysis of progression-free survival (PFS) for targeted agents used as monotherapy or combined therapy in patients with relapsed or refractory MM.

AE

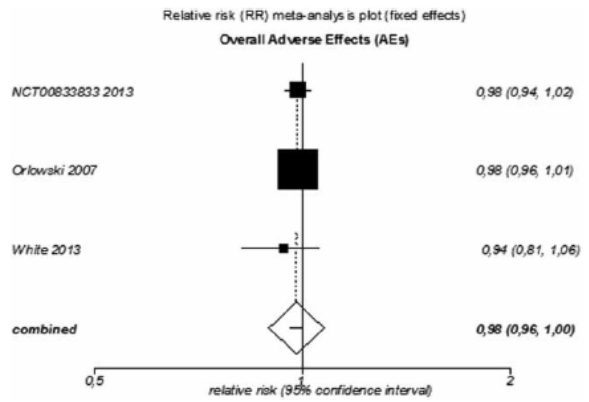

Figure 4 Meta-analysis of any adverse events (AEs) for targeted agents used as monotherapy or combined therapy in patients with relapsed or refractory MM.

Authors' conclusions and comments

The results of this meta-analysis showed that combined therapy is superior to monotherapy only in some end points and it is less tolerated in patients with relapsed/refractory MM. Thus, the overall superiority of complex therapy to monotherapy depends on the combination of the targeted agents.

3.4 Leitlinien

Kumar SK et al., 2018 [14].

NCCN Guidelines Insights: Multiple Myeloma, Version 3.2018

Siehe auch**: [19].**

Aim/Research question

This activity is designed to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with cancer.

Upon completion of this activity, participants will be able to:

• Integrate into professional practice the updates to the NCCN Guidelines for Multiple Myeloma

• Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Multiple Myeloma

Methods

Basis of guideline development:

The guidelines list regimens recommended by the NCCN MM Panel for newly diagnosed transplant- eligible and non–transplant-eligible candidates, maintenance therapy, and previously treated myeloma (MYEL-D, 1–3; pages 13–15). The panel notes that this list is a selected one and not inclusive of all regimens used for the management of MM.

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

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Recommendations

MYELOMA THERAPY[1-4,12]

Therapy for Previously Treated Multiple Myeloma (assess for response after each cycle)

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)[8]/dexamethasone (category 1)[9]
- Carfilzomib[8]/lenalidomide/dexamethasone (category 1)[13]
- Daratumumab[14]/bortezomib/dexamethasone (category 1)
- Daratumumab[14]/lenalidomide/dexamethasone (category 1)
- Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[13]
- Ixazomib[17]/lenalidomide/dexamethasone (category 1)[13]

Other Recommended Regimens

- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib[8]/cyclophosphamide/dexamethasone
- Carfilzomib (weekly)[8]/dexamethasone[9]
- Cyclophosphamide/lenalidomide/dexamethasone
- Bortezomib/dexamethasone (category 1)[9]
- Daratumumab[14,16]
- Daratumumab[14]/pomalidomide[20]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib[17]/dexamethasone[9]
- Ixazomib/pomalidomide[20]/dexamethasone
- Lenalidomide/dexamethasone[18] (category 1)[9]
- Panobinostat[19]/bortezomib/dexamethasone (category 1)
- Panobinostat[19]/carfilzomib[8,9]
- Panobinostat[19]/lenalidomide/dexamethasone
- Pomalidomide[20]/cyclophosphamide/dexamethasone
- Pomalidomide[20]/dexamethasone[18] (category 1)[9]
- Pomalidomide[20]/bortezomib/dexamethasone
- Pomalidomide[20]/carfilzomib[8]/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[21]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[21] ± bortezomib (VTD-PACE)[21]
- High-dose cyclophosphamide

[1]Selected, but not inclusive of all regimens.
[2]Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[3]Subcutaneous bortezomib is the preferred method of administration.
[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[8]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[9]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.
[12]Consideration for appropriate regimen is based on the context of clinical relapse.
[13]Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[14]May interfere with serological testing and cause false-positive indirect Coombs test.(See MYEL-E)
[15]Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[16]Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[17]Indicated for the treatment of patients who have received at least one prior therapy.
[18]Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.
[19]Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.
[20]Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
[21]Generally reserved for the treatment of aggressive multiple myeloma.

ACTIVE (SYMPTOMATIC) MYELOMA → **ADDITIONAL TREATMENT (FOR PATIENTS TREATED WITH OR WITHOUT A PRIOR TRANSPLANT)**

Relapse[i] or Progressive disease[i] → Therapy for previously treated myeloma[k] or Clinical trial or Autologous stem cell transplant[m,r] or Allogeneic stem cell transplant[o,r] → Refractory disease and lack of treatment options → Palliative care (See NCCN Guidelines for Palliative Care)

EVIDENCE BLOCKS FOR THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA

Preferred Regimens	
Bortezomib/lenalidomide/dexamethasone	
Carfilzomib (twice weekly)/dexamethasone	
Carfilzomib/lenalidomide/dexamethasone	
Daratumumab/bortezomib/dexamethasone	
Daratumumab/lenalidomide/dexamethasone	
Elotuzumab/lenalidomide/dexamethasone	
Ixazomib/lenalidomide/dexamethasone	

Useful in Certain Circumstances	
Bendamustine	
Dexamethasone/cyclophosphamide/ etoposide/cisplatin (DCEP)	
Dexamethasone/thalidomide/cisplatin/ doxorubicin/cyclophosphamide/etoposide (DT-PACE)	
Dexamethasone/thalidomide/cisplatin/ doxorubicin/cyclophosphamide/etoposide/ bortezomib (VTD-PACE)	
High-dose cyclophosphamide	

Other Regimens			
Bendamustine/bortezomib/ dexamethasone		Ixazomib/dexamethasone	
Bendamustine/lenalidomide/ dexamethasone		Ixazomib/pomalidomide/ dexamethasone	
Bortezomib/liposomal doxorubicin/dexamethasone		Lenalidomide/dexamethasone	
Bortezomib/cyclophosphamide/ dexamethasone		Panobinostat/bortezomib/ dexamethasone	
Carfilzomib/cyclophosphamide/ dexamethasone		Panobinostat/carfilzomib	
Carfilzomib (weekly)/ dexamethasone		Panobinostat/lenalidomide/ dexamethasone	
Cyclophosphamide/ lenalidomide/dexamethasone		Pomalidomide/cyclophosphamide/ dexamethasone	
Bortezomib/dexamethasone		Pomalidomide/dexamethasone	
Daratumumab		Pomalidomide/bortezomib/ dexamethasone	
Daratumumab/pomalidomide/ dexamethasone		Pomalidomide/carfilzomib/ dexamethasone	
Elotuzumab/bortezomib/ dexamethasone			

Please Note

- This activity is supported by educational grants from AstraZeneca, Celldex Therapeutics, Celgene Corporation, Genentech, Jazz Pharmaceuticals, Inc., Novartis Pharmaceuticals Corporation, and Seattle Genetics, Inc. This activity is supported by independent educational grants from AbbVie, Merck & Co., Inc. and NOVOCURE.
- The methodology of this guideline is not transparently. For example the connections between evidence and recommendation are not clear. Because of the small numbers of guidelines, the NCCN guideline is extracted and shown here.

National Collaborating Centre for Cancer, 2016 [18].

Institute for Health and Care Excellence (NICE)

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

Aim/Research question:

Diagnosis and management of MM

Methods

Basis of guideline development:

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2012).
A team of health professionals, lay representatives and technical experts known as the Guideline Committee (GC) with support from the NCC-C staff, undertook the development of this clinical guideline.
Following basic steps were taken:
• using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline

- forming the GC
- developing clinical questions (PICO-format)
- identifying the health economic priorities
- developing the review protocols explaining how the review was to be carried out, developing a plan of how to review the evidence and limiting the introduction of bias
- systematically searching for the evidence:
  - o key words and terms were agreed within GC; use of search filters, no language restriction
  - o Databases: The Cochrane Library, Medline and Premedline, Excerpta Medica (Embase), Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, Amed
- critically appraising the evidence:
  - o title and abstract screening by one researcher,
  - o extracting information in evidence tables: GRADE for interventional questions,
  - o Quality elements of GRADE: limitations, inconsistency, indirectness, imprecision, publication bias
- incorporating health economic evidence
- distilling + synthesising the evidence; writing recommendations
- agreeing the recommendations: For each clinical question the GC were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. The GC derived their guideline recommendations from this information. Recommendations are based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.
- structuring and writing the guideline
- consultation and validation

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

11 Managing relapsed myeloma

11.1 first relapse

- Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:
- • the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) […]

  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

Kouroukis CT et al., 2014 [12].

Cancer Centre, Hamilton, Ontario, Canada

Bortezomib in multiple myeloma: a practice guideline

Siehe auch: [13].

Aim/Research question:

The purpose of this guideline is to provide recommendations for the use of bortezomib alone or in combination with other agents in patients with multiple myeloma, or lymphoma, including Waldenström's macroglobulinemia.

I. In patients with multiple myeloma (MM), or lymphoma, including Waldenström's macroglobulinemia (WM), what is the efficacy of bortezomib alone or in combination as

measured by survival, quality of life, disease control (e.g., time-to-progression (TTP)), response duration, or response rate?

II. What is the toxicity associated with the use of bortezomib?

Which patients are more or less likely to benefit from treatment with bortezomib?

Methods

Basis of guideline development:

A systematic review was conducted searching MEDLINE, EMBASE, the Cochrane Library and relevant meeting abstracts. Outcomes of interest were survival, disease control, response rate, response duration, quality of life and adverse effects. Members of the Cancer Care Ontario Hematology Disease Site Group (CCO HDSG), comprising physicians with content expertise, epidemiologists and consumers, developed a guideline through a systematic process that involved assessment of the best available evidence, consensus interpretation of the evidence and a validation process involving practitioners across the province.

searched from 2004 to August 2012

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

- No graduations

Recommendations

Patients with Relapsed/Refractory Disease

- The combination of bortezomib and pegylated liposomal doxorubicin (PLD) is a recommended treatment option for patients with multiple myeloma that has relapsed or is refractory to previous treatment who are candidates for further chemotherapy; who have no clinically significant cardiac disease; who have received less than 240 mg/m2, or the equivalent cumulative dose of doxorubicin; who have a left ventricular ejection fraction in the normal range; and who would be expected to tolerate the myelosuppression of combination therapy. The recommended dose and schedule of bortezomib is 1.3 mg/m2 given as a rapid intravenous bolus over 3-5 s on days 1, 4, 8 and 11 of an every 21 days cycle. PLD 30 mg/m2 is given as a 1 h infusion on day 4 of each cycle.

  Treatment should be continued for eight cycles unless disease progression or unacceptable treatment-related toxicity occurs. Patients who are still responding and who are tolerating therapy well may continue until the criteria of progressive myeloma are met, i.e. at least a 25% increase in the serum monoclonal protein level (which must be an absolute minimum increase of 5 g/l). The treatment can be discontinued two to four cycles after the achievement of complete remission (as determined by negative electrophoresis and immunofixation).

Key Evidence

One RCT compared bortezomib plus PLD (n = 324) with bortezomib alone (n = 322) in patients with relapsed or refractory multiple myeloma [23] and reported that overall survival at 15 months was superior for the combination compared with bortezomib monotherapy (76% versus 65%; P = 0.03). The median TTP was also significantly higher in the PLD plus bortezomib arm (9.3 months versus 6.5 months, respectively; hazard ratio 1.82; 95% confidence interval 1.41e2.35; P ¼ 0.000004). The HDSG opinion is that the treatment can be discontinued two to four cycles after the achievement of complete remission.

[23] Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol 2007;25:3892e3901

- For patients with multiple myeloma refractory or relapsed to previous treatment, who are candidates for further chemotherapy but are not candidates for the combination of bortezomib and PLD, bortezomib monotherapy is recommended as a preferred treatment option. The recommended dose and schedule of bortezomib is 1.3 mg/m2, given as a rapid intravenous bolus over 3e5 s on days 1, 4, 8 and 11 for eight 3-week cycles, and then on days 1, 8, 15 and 22 for three 5- week maintenance cycles.

Key Evidence

One RCTcompared bortezomib monotherapy (n=333) to dexamethasone (n = 336) in patients with relapsed or refractory multiple myeloma [21,22] and reported that the median overall survival was significantly higher for patients who received bortezomib (29.8 months versus 23.7 months; hazard ratio 0.77; P = 0.027). The median TTP was also significantly higher in the bortezomib arm (hazard ratio 0.55; P < 0.001). Of note, grade 3 adverse events were more common in the bortezomib arm (61% versus 44%; P < 0.01).

[21] Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487e2498.

[22] Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood 2007;110:3557e3560

Chen C et al., 2013 [1].

Cancer Care Ontario

Lenalidomide in multiple myeloma — a practice guideline

Aim/Research question:

We describe the process of creating a provincial guideline for the use of lenalidomide, alone or in combination with other drugs, in relapsed, refractory, or newly diagnosed disease (including smoldering and symptomatic patients, and candidates and non-candidates for transplant) and in maintenance treatment (after transplant or non-transplant therapy); and for strategies to manage lenalidomide-related toxicities.

Methods

Basis of guideline development:

- Outcomes of interest included overall survival, event-free survival, progression-free survival, time to progression, time to next treatment, response rate, and incidence of serious toxicity. The medline, embase, and Cochrane Library databases, as well as meeting abstracts and the Web sites of relevant organizations, were systematically searched for relevant literature.
- Recommendations were developed using the evidence from published studies and the clinical expertise of the working group and of the Cancer Care Ontario Hematology Disease Site Group.

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

The Hematology dsg developed draft recommendations based both on consensus and on evidence from the systematic review.

Recommendations

3.3 Question 2—Patients with Relapsed or Refractory Multiple Myeloma

Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with relapsed or refractory multiple myeloma compared with non-lenalidomide-containing treatments?

- Single-Agent Lenalidomide: Lenalidomide alone cannot be recommended for standard use in the relapsed or refractory setting.
- Lenalidomide and Dexamethasone: The combination of lenalidomide and dexamethasone is recommended for myeloma patients who have received at least 1 prior line of therapy. The recommended dosing is lenalidomide 25 mg daily on days 1–21, plus dexamethasone (either low-dose 40 mg daily on days 1,8,15, and 22, or high-dose 40 mg daily on days 1–4, 9–12, and 17–20) in a 28-day cycle,
- Other Lenalidomide Combinations: No other combinations can be recommended

Key Evidence

No randomized trials that compared lenalidomide as a single agent with a non-lenalidomide regimen in previously treated patients were located. Two seminal studies1,2 showed an improved ttp for lenalidomide plus dexamethasone compared with dexamethasone plus placebo. Our meta-analysis of those two studies showed that, compared with a non-lenalidomide regimen, lenalidomide improved ttp [hazard ratio (hr): 0.35; 95% confidence interval (ci): 0.29 to 0.42; $p < 0.00001$], os (hr: 0.54; 95% ci: 0.36 to 0.80; $p < 0.002$), and overall response (hr: 0.50; 95% ci: 0.44 to 0.58; $p < 0.00001$). Although high-dose dexamethasone in combination with lenalidomide was used in the two pivotal rcts of relapsed or refractory myeloma, low-dose weekly dexamethasone with lenalidomide appears less toxic when used in the first line10. From a safety perspective, the Hematology dsg considers low-dose dexamethasone a reasonable option for the relapsed or refractory setting. Again, select subgroups with acute myeloma complications may benefit from the greater response rates achievable with high-dose dexamethasone. No rcts of lenalidomide in combination with other agents in this setting were identified.

1. Weber DM, Chen C, Niesvizky R, et al. on behalf of the Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133–42.

2. Dimopoulos M, Spencer A, Attal M, et al. on behalf of the Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123–32.

Qualifying Statements

Both of the seminal studies1,2 were stopped at the first preplanned interim analysis for benefit and were funded by the drug's manufacturer. However, the studies enrolled more than 300 patients before stopping and had a large number of events. The recommendation to use low-dose dexamethasone with lenalidomide in the relapsed or refractory setting is generalized from the first-line Rajkumar study10 and is based primarily on improved safety. No comparative studies have evaluated low-dose dexamethasone dosing in the relapsed or refractory setting.

10. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29–37.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2018) am 15.10.2018

#	Suchfrage
1	MeSH descriptor: [Multiple Myeloma] explode all trees
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	#1 or #4 or #5
7	#6 with Cochrane Library publication date between Oct 2013 and Oct 2018

Systematic Reviews in Medline (PubMed) am 15.10.2018

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[Title/Abstract]) OR Plasma-Cell[Title/Abstract]) OR "Plasma Cell"[Title/Abstract]
3	(myeloma[Title/Abstract]) OR myelomas[Title/Abstract]
4	#2 AND #3
5	(("Kahler Disease"[Title/Abstract]) OR Myelomatosis[Title/Abstract]) OR Myelomatoses[Title/Abstract]
6	#1 OR #4 OR #5
7	(#6) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	((#7) AND ("2013/10/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 15.10.2018

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[Title/Abstract]) OR Plasma-Cell[Title/Abstract]) OR "Plasma Cell"[Title/Abstract]
3	(myeloma[Title/Abstract]) OR myelomas[Title/Abstract]
4	#2 AND #3
5	(("Kahler Disease"[Title/Abstract]) OR Myelomatosis[Title/Abstract]) OR Myelomatoses[Title/Abstract]
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*[Title])
8	(((#7) AND ("2013/10/01"[PDAT] : "3000"[PDAT])) NOT ((comment[Publication Type]) OR letter[Publication Type])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal]))

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