Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-08-15-D-302 Carfilzomib

Stand: August 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Carfilzomib **zur Behandlung des multiplen Myeloms nach mindestens einer Vorbehandlung**	
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 • Pomalidomid – Beschluss vom 20. Februar 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Carfilzomib – Beschluss vom 2. Juni 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Carfilzomib – Beschluss vom 19. Januar 2017 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 • Daratumumab – 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
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:	
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).
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.
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.
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.
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

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Multiples Myelom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 20.06.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 565 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 25 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Behandlung erwachsener Patienten mit Multiplem Myelom, die bereits mindestens eine Therapie erhalten haben.

Abkürzungen:

AE	Adverse effects
ASCT	Autologous stem cell transplantation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
CR	Complete Response
DAHTA	Deutsche Agentur für Health Technology Assessment
ECOG-PS	Eastern cooperative oncology group (performance status)
EFS	Event free survival
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
ICTRP	International Clinical Trials Registry Platform
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MM	Multiple myeloma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
ORR	Objective response rate
PD	Progressive disease
PFS	Progression free survival
PLD	Pegylated liposomal doxorubicin
PR	Partial response
RCT	Randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TTP	Time to progression
TTR	Time to response
QoL	Quality of Life
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2016. [9]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel - Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Panobinostat vom 17. März 2016.	**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. Panobinostat ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 gilt der medizinische Zusatznutzen durch die Zulassung als belegt. Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß 5. Kapitel § 12 Absatz 1 Nummer 1 Satz 2 der Verfahrensordnung des G-BA (VerfO) das Ausmaß des Zusatznutzens für die Anzahl der Patienten und Patientengruppen, für die ein therapeutisch bedeutsamer Zusatznutzen besteht. Diese Quantifizierung des Zusatznutzens erfolgt am Maßstab der im 5. Kapitel § 5 Absatz 7 Nummer 1 bis 4 VerfO festgelegten Kriterien. **Ausmaß des Zusatznutzens:** nicht quantifizierbar
G-BA, 2016 [7]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel - Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Daratumumab vom 1. Dezember 2016	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 20.05.2016):** 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. Daratumumab 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. **Ausmaß des Zusatznutzens:** nicht quantifizierbar
G-BA, 2016 [5]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel - Richtlinie (AM-RL):	**I. Anlage XII wird wie folgt geändert:** 1. Die Angaben zu Pomalidomid in der Fassung des Beschlusses vom 20. Februar 2014 (BAnz AT 12.03.2014 B2) werden aufgehoben. 2. Anlage XII wird in alphabetischer Reihenfolge um den Wirkstoff Pomalidomid wie folgt ergänzt: **Zugelassenes Anwendungsgebiet:**

Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pomalidomid vom 17. März 2016	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. 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. **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.
G-BA, 2016 [8]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel - Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Elotuzumab vom	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 11.05.2016):** Empliciti ist in Kombination mit Lenalidomid und Dexamethason zur Behandlung des Multiplen Myeloms bei Erwachsenen indiziert, welche mindestens eine vorangegangene Therapie erhalten haben (siehe Abschnitt 4.2 und 5.1 der Fachinformation). **Zweckmäßige Vergleichstherapie:** Die zweckmäßige Vergleichstherapie für Empliciti in Kombination mit Lenalidomid und Dexamethason zur Behandlung des Multiplen Myeloms bei Erwachsenen, welche mindestens eine vorangegangene Therapie erhalten haben, ist: − Bortezomib als Monotherapie oder − Bortezomib in Kombination mit pegyliertem, liposomalen Doxorubicin oder − Bortezomib in Kombination mit Dexamethason

1. Dezember 2016**.**	oder − Lenalidomid in Kombination mit Dexamethason **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Lenalidomid in Kombination mit Dexamethason:** Anhaltspunkt für einen geringen Zusatznutzen
G-BA, 2016 [6]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel - Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Carfilzomib vom 2. Juni 2016.	**I. Die Anlage XII wird in alphabetischer Reihenfolge um den Wirkstoff Carfilzomib wie folgt ergänzt:** […] **Zugelassenes Anwendungsgebiet (laut Zulassung vom 19. November 2015):** Carfilzomib (Kyprolis®) ist in Kombination mit Lenalidomid und Dexamethason zur Behandlung von erwachsenen Patienten mit multiplem Myelom indiziert, die mindestens eine vorangegangene Therapie erhalten haben. Carfilzomib ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 gilt der medizinische Zusatznutzen durch die Zulassung als belegt. Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß 5. Kapitel § 12 Absatz 1 Nummer 1 Satz 2 der Verfahrensordnung des G-BA (VerfO) das Ausmaß des Zusatznutzens für die Anzahl der Patienten und Patientengruppen, für die ein therapeutisch bedeutsamer Zusatznutzen besteht. Diese Quantifizierung des Zusatznutzens erfolgt am Maßstab der im 5. Kapitel § 5 Absatz 7 Nummer 1 bis 4 VerfO festgelegten Kriterien. **Ausmaß des Zusatznutzens:** nicht quantifizierbar […] **III. Die Geltungsdauer des Beschlusses ist bis zum 31. Dezember 2017 befristet.**
G-BA, 2017 [11]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel - Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Carfilzomib vom 15. Juni 2017	**I. In Anlage XII werden die Regelungen unter Abschnitt II zur Geltungsdauer des Beschlusses über die Nutzenbewertung von Carfilzomib vom 2. Juni 2016 wie folgt geändert:** Die Angaben unter Abschnitt III werden aufgehoben. *(Aufhebung der Befristung des Carfilzomib-Beschlusses vom 2. Juni 2016)*
G-BA, 2017 [10]. Beschluss des	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 29. Juni 2016):** Kyprolis ® ist in Kombination mit Dexamethason allein zur Behandlung von erwachsenen Patienten mit multiplem Myelom indiziert, die mindestens

Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel - Richtlinie (AM -RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Carfilzomib (neues Anwendungsgebiet: in Kombination mit Dexamethason bei Multiplem Myelom) vom 19. Januar 2017	eine vorangegangene Therapie erhalten haben. Carfilzomib 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. Halbsatz 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 Absatz7 Nummer1 bis 4 VerfO festgelegten Kriterien. **Ausmaß des Zusatznutzens:** gering
G-BA, 2017 [4]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ixazomib vom 6. Juli 2017	**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. 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. **Ausmaß des Zusatznutzens:** nicht quantifizierbar

Systematische Reviews

Sun Z et al, 2017 [23]. Triplet versus doublet combination regimens for the treatment ofrelapsed or refractory multiple myeloma: A meta-analysis of phase III randomized controlled trials	1. Fragestellung To compare the efficacy and safety of triplet versus doublet combination therapies in RRMM.
	2. Methodik **Population:** patients with previously treated RRMM **Intervention:** triplet combination therapy **Komperator:** doublet combination therapy **Endpunkte:** OS, PFS, ORR,CR, Very good partial response (VGPR) and safety **Recherche/Suchzeitraum:** in Embase, Medline, the Cochrane Central Register of ControlledTrials, and the Cochrane Database of Systematic Reviews up to May 2016 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 RCTs **Qualitätsbewertung der Studien:** 5-item Jadad score including randomization, blinding, withdrawals
	3. Ergebnisse *Included studies*: *5 Phase III studies* 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

Patient characteristics (prior therapies):

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) (ASPIRE)	Experimental	NR	NR	NR	Bortezomib (65.9%), lenalidomide (19.9%)	184 (46.5%)	211 (53.3%)	
	Control	NR	NR	NR	Bortezomib (65.7%), Lenalidomide (19.7%)	157 (39.6%)	238 (60.4%)	
Lonial et al. (2015) (ELOQUENT-2)	Experimental	113 (35.2%)	112 (34.9%)	96 (29.9%)	Bortezomib (68%), Melphalan (69%), lenalidomide (5%), thalidomide (48%)	151 (47%)	118 (37%)	52 (16%)
	Control	114 (35.1%)	128 (39.4%)	83 (25.5%)	Bortezomib (71%), Melphalan (61%) lenalidomide (6%), thalidomide (48%)	159 (49%)	114 (35%)	52 (16%)
San-Miguel et al. (2014) (PANORAMA1)	Experimental	134 (35%)	247 (64%)	6 (2%)	Bortezomib (44%), lenalidomide (19%), thalidomide (53%)	197 (51%)	124 (32%)	64 (17%)
	Control	141 (37%)	235 (62%)	5 (1%)	Bortezomib (42%), lenalidomide (22%) Thalidomide (49%)	198 (52%)	108 (28%)	75 (20%)
Garderet et al. (2012) (MMVAR)	Experimental	NR	NR	NR	Bortezomib (20%) and thalidomide (10%)	NR	NR	NR
	Control	NR	NR	NR	Bortezomib (21%) and thalidomide (6%)	NR	NR	NR

Abbreviations: NR, not reported.

Study quality:

- Moreau et al., 2016 (TOURMALINE) + San-Miguel et al., 2014

	(PANORAMA1): Jadad-Score=5 • Alle anderen: Jadad-Score=3 *Results* <u>Efficacy</u> **Ixazomib**+ lenalidomide + dexamethasone vs. Placebo + lenalidomide + dexamethasone (Moreau et al., 2016 [TOURMALINE] N=722) • OS: not reported • PFS: HR 0,74 (95%CI 0,586; 0,934 • ORR: n.s. • VGRP: n.s • CR: n.s. ➔ Vorteil Ixazomib nur für PFS gezeigt **Carfilzomib** + lenalidomide + dexamethasone vs. Lenalidomide + dexamethasone (Stewart et al.,2015 [ASPIPE], N=792) • OS: HR 0,79 (95%CI 0,63; 0,99) • PFS: HR 0,69 (95%CI 0,57; 0,83) • ORR: RR 1,31 (95%CI 1,21; 1,42) • VGRP: RR 1,73 (95%CI 1,51; 1,98) • CR: RR 3,41 (95% 2,43; 4,78) ➔ Vorteil Carfilzomib **Elotuzumab** + lenalidomide + dexamethasone vs. Lenalidomide + dexamethasone (Lonial et al., 2015 [ELOQUENT-2]; N=646) • OS: not reported • PFS: HR 0,70 (95%CI 0,57; 0,86) • ORR: RR 1,20 (95%CI 1,10; 1,32) • VGRP: n.s. • CR: n.s ➔ Vorteil Elotuzumb für PFS und ORR gezeigt **Panobinostat** + bortezomib + dexamethasone vs Placebo + bortezomib + dexamethasone (San-Miguel et al., 2014 [PANORAMA1], N=768) • OS: n.s. • PFS: HR 0,63 (95%CI 0,52; 0,76) • ORR: n.s • VGRP: RR 1,76 (95%CI 1,32; 2,33) • CR: RR 1,88 (95% 1,14; 3,10) ➔ Vorteil Panobinostat für PFS, VGRP, CR **Triplet vs. doublet** therapies - Pooled analyses of 5 studies • OS: HR 0.83 (95%CI: 0.71–0.94) (data from 3 studies) • PFS: HR (0.68, 95%CI: 0.62–0.74) • ORR: (1.19 (95%CI:1.10–1.27)

	• Very good partial response (VGPR) 1.44 (95%CI: 1.18–1.77), • and complete response (CR) 1.76 (95%CI: 1.04–2.97), <u>Safety (pooled analyses)</u> Grade 3 or 4 toxicities / No. of trials / RR, 95%CI / *P* value Overall 5 1.11 (1.05–1.18) 0.001 Infections 4 1.33 (0.97–1.83) 0.079 Thrombocytopenia 5 1.64 (1.13–2.38) 0.009 Neutropenia 5 1.13 (0.71–1.81) 0.60 Anemia 5 0.92 (0.78–1.08) 0.29 Fatal 4 1.00 (0.74–1.36) 0.99 ➔ Nachteil der Triplet-Therapien bzgl. Gesamt-AE Grad ≥ 3 und Thrombozytopenie Grad ≥ 3
	4. Anmerkungen/Fazit der Autoren Meta-analysis demonstrates that triplet regimens result in improved OS, PFS, ORR, VGPR, and CR compared to doublets, though the risk of grade 3 and 4 adverse events are higher with triplets. The pooled estimates of response and survival strongly favor triplets in the RRMM patients. More high-quality of phase III trials are needed to confirm our findings. 5. *Kommentar zu Review* • Inclusion of 2nd und 3rd line therapies • Safety data of individual trials not reported
Teh BW et al., 2016 [24]. Infection risk with immuno-modulatory and proteasome inhibitor-based therapies across treatment phases for multiple myeloma: A systematic review and meta-analysis.	1. Fragestellung To determine the impact of immunomodulatory drugs (IMiDs) and proteasome inhibitor (PI)based therapy on infection risk in patients with MM 3 treatment periods: • induction, • maintenance therapy and • relapse/refractory disease (RRMM).
	2. Methodik **Population:** Patienten, mit MM →Hier Population der RRMM relevant mit folgenden Interventionen: **Intervention:** IMiD or PI-based treatment regimens (single or multi agent combination) **Komparator:** high-dose corticosteroids **Endpunkt:** severe infection, febrile neutropaenia, pneumonia and deaths from infection **Recherche/Suchzeitraum** bis 2015 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 30, davon 5 RCT in RRMM **Qualitätsbewertung der Studien:** Cochrane risk of bias; GRADE for assessing overall quality of evidence

3. Ergebnisse

Included studies for the treatment of relapsed and refractory myeloma

Bortezomib vs. Dexamethasone

- Richardson et al, 2005:

Lenalidomide+ dexamethasone vs. dexamethasone

- Dimooulos et al., 2007
- Weber et al. 2007

Pomalidomide dexamethasone vs. dexamethasone

- San Migueal et al., 2013

Thalidomide

- Kropf et al. 2012

Results

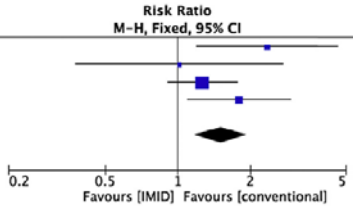
<u>IMiD-based therapy versus conventional therapy for relapsing and refractory myeloma</u>

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

d

Study or Subgroup	IMID Events	Total	Conventional Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dimopoulos et al 2007	26	176	11	175	12.6%	2.35 [1.20, 4.61]
Kropff et al 2012	15	373	5	126	8.5%	1.01 [0.38, 2.73]
San Miguel et al 2013	91	300	36	150	54.8%	1.26 [0.91, 1.76]
Weber et al 2007	38	177	21	176	24.0%	1.80 [1.10, 2.94]
Total (95% CI)		**1026**		**627**	**100.0%**	**1.51 [1.18, 1.93]**
Total events	170		73			

Heterogeneity: $Chi^2 = 3.87$, $df = 3$ ($P = 0.28$); $I^2 = 22\%$
Test for overall effect: $Z = 3.28$ ($P = 0.001$)



(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

<u>Subgroup: Lenalidomide versus conventional</u>

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

4. Fazit der Autoren

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

5. Hinweise zum Review

This study was supported by a grant from the Fight Cancer Foundation. The foundation had no input into the design, conduct or design of this study.

Qiao SK et al., 2015 [22].

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

1. Fragestellung

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.

2. Methodik

Population: Patients with newly diagnosed or previously treated MM

Intervention: Lenalidomide‐containing regimens

Komperator: non-lenalidomide‐containing regimens

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

Recherche/Suchzeitraum: bis Mai 2013

Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 RCTs (→ davon 2 relapsed or refractory MM

Qualitätsbewertung der Studien: 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).

3. Ergebnisse (für das hier relevante AWG)

Relapsed or refractory multiple myeloma

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

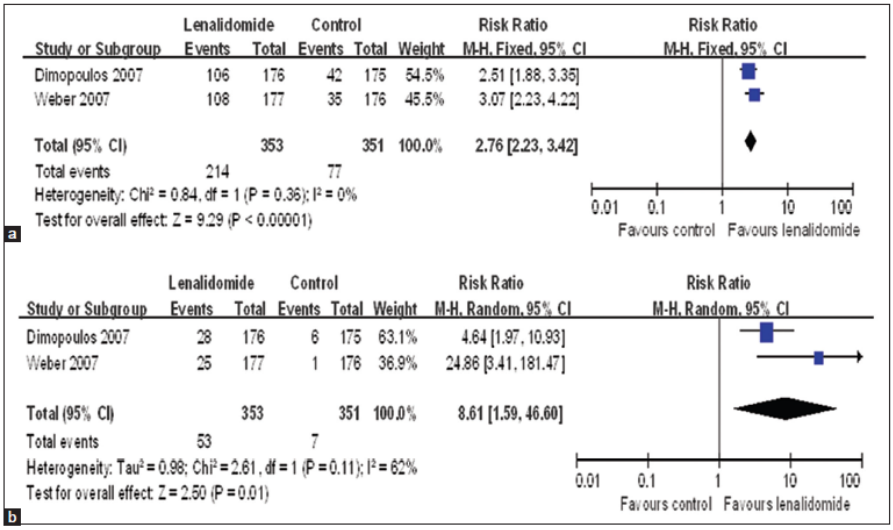


Figure 3: Forest plots of responses rate comparing lenalidomide with control for relapsed or refractory multiple myeloma. (a) Overall response; (b) Complete response.

- 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

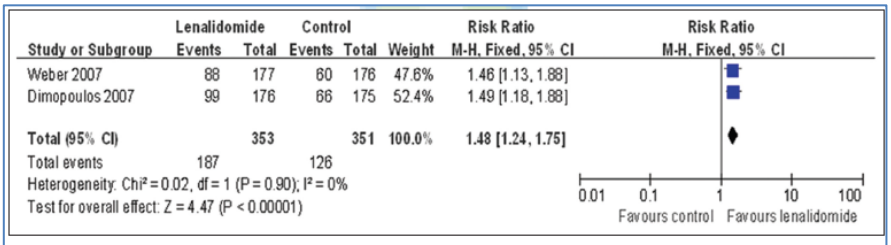


Figure 4: Forest plot of 3-year progression-free survival rate comparing lenalidomide with control for relapsed or refractory multiple myeloma.

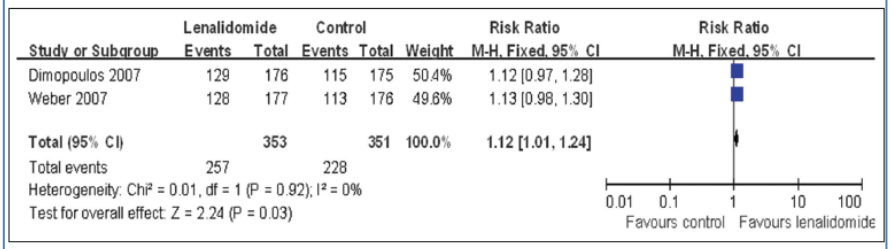


Figure 5: Forest plot of 3-year overall survival rate comparing lenalidomide with control for relapsed or refractory multiple myeloma.

4. Fazit der Autoren
   Lenalidomide+dex vs. Placebo+Dex: significantly increased OR, CR and showed statistically better PFS and OS.
5. *Hinweise zum Review*

Bezüglich der 2 relevanten Studien (Dimopoulos 2007, Weber 2007) werden Ergebnisse zur Sicherheit im SR von Yang et al. 2013 [25] analysiert

Yang B et al., 2013 [25].	1. Fragestellung To gain a better, more complete understanding of the efficacy and safety of lenalidomide, we performed a meta-analysis of randomized controlled

Lenalidomide treatment for multiple myeloma: systematic review and meta-analysis of randomized controlled trials.	trials in which patients with MM received lenalidomide as initial or maintenance therapy.
	2. Methodik **Population:** Patienten, mit MM **Intervention:** Lenalidomid (hier nur Darstellung von Lenalidomid als 2nd line) **Komparator:** Placebo **Endpunkt:** OS, PFS, AE **Recherche/Suchzeitraum** bis Nov 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7, davon 2 (n=353) Studien mit Lenalidomid als 2nd-line **Qualitätsbewertung der Studien:** ‘‘risk of bias’’ method recommended by the Cochrane Collaboration:
	3. Ergebnisse **Lenalidomid vs Placebo als 2nd line** (insg. 2 Studien: Dimopoulus 2007 und Weber 2007) Beide Studien: doppelblind, adequate ITT, unklar ob verdeckte Zuteilung, keine Angaben zu Studienabbrechern, Randomisierungmethode unklar bei Dimopoulus 2007, computergestützte Randomisierung bei Weber 2007 Dosierung von Lenalidomid und Dexamethason war gleich in beiden Studien: L 25 mg, on day 1 to 21 of a 28-day cycle + D 40 mg/d on day 1–4, 9– 12, and 17–20 for the first 4 cycles, after the 4th cycle, only on day 1– 4 *Dimopoulos M et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357(21):2123-2132.:* • Relapsed or refractory MM, at least one previous antimyeloma therapy • Intervention: Lenalidomid+Dexamethason (n=176) • Kontrolle: Placebo+Dexamethason (n=175) • OS: HR=0.66 (95% CI 0.45-0.97) • Time to progression: Len+Dex=11.3 Monate vs. Placebo+Dex=4,7 Monate, p<0.0001 • Neutropenie: HR=12,93 (4,78-34,97) *Weber DM et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357(21): 2133-2142.* • Patients who had received at least one previous therapy for MM • Intervention: Lenalidomid+Dexamethason (n=177) • Kontrolle: Placebo+Dexamethason (n=176) • OS: HR=0,44 (95% CI 0,30-0,65) • PFS: HR=0.35 (95% CI 0,27-0,45) • Neutropenie: HR=9,02 (4,48-18,16) • Anämie: HR=2,14 (1,12-4,11) • Tiefe Venenthrombose: HR=3,46 (1,43-8,37)

	• Infektionen: HR=1,79 (1,10-2,92)
	4. Anmerkungen/Fazit der Autoren Lenalidomide is an effective treatment for MM; however, treatment-related adverse events must be considered and appropriate adjustments and/or prophylactic treatment should be initiated where possible. *5. Hinweise zum Review* Die dargestellten Studien sind mit den relevanten Studien im SR von Qiao 2015 [22] identisch.
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.	1. Fragestellung 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.
	2. Methodik **Population:** patients with relapsed or refractory MM **Intervention:** targeted agents alone (monotherapy) **Komperator:** combinations of targeted agents with other types of agents (combined therapy) **Endpunkt:** 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. **Suchzeitraum (Aktualität der Recherche):** bis Mai 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 (n=997), davon 1 relevant Studie in der 2. Therapielinie, 1 relevante Studie in der 3. Therapielinie **Qualitätsbewertung der Studien:** Jadad scale
	3. Ergebnisse Relevante eingeschlossene Vergleiche: • pomalidomide vs. pomalidomide plus dexamethasone, • bortezomib vs. bortezomib plus PLD

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

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.

Methodological quality of studies: moderate (Jadad:2)

Orlowski RZ 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(25):3892-3901.

- Phase III: RCT, open
- Patients with MM who progressed after a response to ≥1 line of therapy or refractory to initial therapy (lenalidomide or thalidomide), N= 646
- Bortezomib vs. bortezomib plus pegylated liposomal doxorubicin (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)
- Results: Bortezomib vs. bortezomib plus PDL
    - OS: HR=1,41, (95% CI 1.002–1.97) P=0.0476 zugunsten der Kombitherapie
    - PFS: significantly longer in combined therapy group compared with monotherapy group; HR=1,69 [1.32–2.16], P = 0.0003
    - TTP: significantly prolonged when compared to monotherapy group; HR=1,82 (95% CI 1,41-2,35) (P = 0.000004).
    - the risk of grade 3-4 AEs was significantly smaller (P < 0.05) in the monotherapy group than in combined therapy group (RR 0,81 [CI 0,73;0,89])
    - SAE: kein stat. sign. Unterschied

NCT00833833 (2013) MTD, safety, and efficacy of pomalidomide (CC-4047) alone or with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma:

- Phase III-Studie
- Patients with relapsed or refractory multiple myeloma who received prior treatment that includes lenalidomide and bortezomib, N =221
- Results: pomalidomide vs. pomalidomide plus dexamethasone
    - combined therapy significantly prolonged PFS (HR 0,73 [95%CI 0,54; 0,99]), significantly more patients achieved PR,

	significantly less patients experienced PD. o No other significant differences were demonstrated (OS, TTR, and DR) o AE Grad 3-4: kein stat. sign. Unterschied o Risk of SAE was significantly smaller (P < 0.05) in the monotherapy group than in combined therapy group
	4. Anmerkungen/Fazit der Autoren • bortezomib and PLD compared to bortezomib monotherapy seems to be the most effective in terms of significantly prolonged TTP, PFS, DR, and even OS • In general, combined therapy is superior to monotherapy only in some end points and it is less tolerated in patients with relapsed/refractory MM. *5. Hinweise zum Review* The manuscript was self-financed by the authors.
Kouroukis TC et al., 2014 [14]. Bortezomib in multiple myeloma: systematic review and clinical considerations	Fragestellung The systematic review addresses these questions: • In patients with MM, what is the efficacy of bortezomib alone or in combination, as measured by survival, quality of life (QOL), disease control [for example, time to progression (TTP)], response duration, or response rate? • What is the toxicity associated with the use of bortezomib? • Which patients are more or less likely to benefit from treatment with bortezomib?
	Methodik **Population:** adult patients with mm and evaluating bortezomib as a single agent or in combination with other regimens **Intervention:** bortezomib as a single agent or in combination with other regimens **Komperator:** any agent, any combination of agents, or placebo **Endpunkt:** efficacy as measured by survival, quality of life (qol), disease control [for example, time to progression (ttp)], response duration, or response rate **Suchzeitraum (Aktualität der Recherche):** to August 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 19 RCTs, 1 Network meta analysis, 6 Systematic Reviews; davon 2 Primärstudien relevant **Qualitätsbewertung der Studien:** For the evaluation of the quality of included rcts, discrete parameters such as reporting of the sample-size calculation for the study, the randomization method, allocation

	concealment, blinding, intention-to-treat analysis, final analysis, early termination, losses to follow-up, and ethics approval were considered.
	Ergebnisse 7 RCTs beschäftigen sich mit refraktärem oder rezidiviertem MM, davon 2 RCT mit relevanten Interventionen: *Bortezomib vs. bortezomib plus PLD* • 1 open label RCT in patients with MM who progressed after response to ≥1 line of therapy or refractory to initial therapy, N=646 ; (Orlowski RZ et al. J Clin Oncol 2007;25(25):3892-3901.) • Results: →siehe auch SR von Lopuch 2015 o PFS: sign. improved in combined therapy group compared with monotherapy group; HR=1,69, P = 0.0003 o TTP: significantly prolonged in combination group (HR=1,82,P=0.000004). o OS: 65% vs. 76%, p = 0.03 zugunsten der Kombitherapie o Response Rate: no difference o AE gesamt kein stat. sign. Unterschied o increased incidence of neutropenia, diarrhea, and nausea in a bortezomib–pld group than in a bortezomib-alone group (7% vs. 4%, p = 0.034, and 2% vs. <1%, p = 0.0241, respectively). *Bortezomib (n=333) vs. Hochdosis-Dexamethason (n=336)* • 1 RCT in patients with relapsed MM with 1-3 prior therapies (=APEX): Richardson PG et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352(24):2487-2498. • > 60% der Studienpopulation mit mehr als 1 Vortherapie • Results o Time to progression: HR=0.55; P<0.001 zugunsten von Bortezomib o OS after one year: bortezomib had a higher rate of overall survival (80%) than those who received dexamethasone (66%, P=0.003): HR=0.57; P=0.001 zugunsten von Bortezomib o higher incidence of hematologic events and peripheral neuropathy o significantly higher incidence of diarrhea and nausea (7% vs. 2% and 2% vs. 0% respectively, p < 0.01), in patients who received bortezomib than in those who received dexamethasone
	Anmerkungen/Fazit der Autoren • In relapsed and refractory mm, bortezomib monotherapy and combination therapy with pld are both effective approaches. However, compared with bortezomib alone, the combination with pld improves ttp, pfs, and os significantly • In patients with relapsed or refractory mm, the combination of pld plus bortezomib is a more effective treatment option than is bortezomib alone.

	• For individuals who cannot access or tolerate this therapy, treatment with bortezomib alone is recommended. Consideration should be given to the use of antiviral prophylaxis against herpes zoster (shingles), because that condition is now recognized to occur more frequently during bortezomib therapy

Leitlinien

NICE, 2016 [16]. Myeloma: diagnosis and management. NICE Guideline 35. Full guideline February 2016	Fragestellung: Diagnostik und Management von MM
	Methodik: **Grundlage der Leitlinie:** 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 **Suchzeitraum:** re-run 6–8 weeks before the guideline was submitted to, literature published before 8th June 2015 considered **LoE und GoR:** 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.
	Ergebnisse: **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 [18] based on APEX trial: *Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352(24):2487-2498.* **11.2 second autologous stem cell transplant** (keine relevante Therapieoption im Anwendungsgebiet **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 [19] *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 *Hinweis: TA338 nicht mehr aktuell, wurde ersetzt durch TA427*
NCCN, 2017 [17]. Multiple Myeloma. NCCN Clinical Practice Guidelines in Oncology, Version 03.2017	Guideline of National Comprehensive Cancer Network (NCCN)
	Methodik: **Grundlage der Leitlinie:** syst. Literaturrecherche (Update-Recherche) der PubMed-Datenbank **Suchzeitraum des Updates:** bis 04/2016 **LoE & GoR:** **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.** Empfehlungen sind mit Literatur verknüpft *Hinweise zur LL: Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt. Es fehlen Darstellungen zur Literaturrecherche, GoR und Konsensusfindung*
	Empfehlungen

MYELOMA THERAPY[1-4, 11]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

Therapy for Previously Treated Multiple Myeloma	
Preferred Regimens:	**Other Regimens:**
• Repeat primary induction therapy (if relapse at >6 mo)	• Bendamustine
• Bortezomib/dexamethasone (category 1)[6]	• Bendamustine/bortezomib/dexamethasone
• Bortezomib/cyclophosphamide/dexamethasone	• Bendamustine/lenalidomide/dexamethasone
• Bortezomib/lenalidomide/dexamethasone	• Bortezomib/liposomal doxorubicin (category 1)[6]
• Carfilzomib[10]/dexamethasone (category 1)[6,]	• Cyclophosphamide/lenalidomide/dexamethasone
• Carfilzomib[10]/lenalidomide/dexamethasone (category 1)[12]	• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[19]
• Daratumumab[13,14]	• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/ etoposide (DT-PACE) ± bortezomib (VTD-PACE)[19]
• Daratumumab[14]/bortezomib/dexamethasone (category 1)	• Elotuzumab/bortezomib/dexamethasone
• Daratumumab[14]/lenalidomide/dexamethasone (category 1)	• High-dose cyclophosphamide
• Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[12]	• Ixazomib[16]/dexamethasone[6]
• Ixazomib[16]/lenalidomide/dexamethasone (category 1)[12]	• Panobinostat[20]/bortezomib/dexamethasone (category 1)
• Lenalidomide/dexamethasone[17] (category 1)[6]	• Panobinostat[20]/carfilzomib[6,10]
• Pomalidomide[18]/dexamethasone[17] (category 1)[6]	• Pomalidomide[18]/cyclophosphamide/dexamethasone
• Pomalidomide[18]/bortezomib/dexamethasone	
• Pomalidomide[18]/carfilzomib[10]/dexamethasone	

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.
[3]Subcutaneous bortezomib is the preferred method of administration for patients with pre-existing or high-risk peripheral neuropathy.
[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[6]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.
[11]Consideration for appropriate regimen is based on the context of clinical relapse.
[10]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[12]Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[13]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.
[14]May interfere with serological testing and cause false-positive indirect Coombs test.
[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 one prior therapy.
[17]Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.
[18]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.
[19]Generally reserved for the treatment of aggressive multiple myeloma.
[20]Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.

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

MYEL-D

Kouroukis CT et al., 2013 [13]. Bortezomib in Multiple Myeloma and Lymphoma Siehe auch **Kouroukis CT et al., 2014 [12].**	Fragestellung 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. **Fragen:** **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?
	Methodik: Grundlage der Leitlinie: syst. Literaturrecherche Suchzeitraum: Update-Recherche (2004 through August 2012) LoE & GoR: keine allgemeinen Kategorien Qualität der Studien: quality of included RCTs, following parameters were considered: • reporting of the sample-size calculation for the study, • randomization method, • allocation concealment, • blinding, • intention-to-treat (ITT) analysis, final analysis, • early termination, • losses to follow-up, and • ethical approval. Tabellen zur Qualitätsbewertung in der Langversion der LL einsehbar. Empfehlungen sind mit Literatur verknüpft *Hinweis zur LL: Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt. Es fehlen Angaben/Kriterien zum GoR und Konsensusfindung.*
	Ergebnisse **<u>Efficacy of bortezomib</u>**

	Relapsed or refractory patients: The combination of bortezomib and pegylated liposomal doxorubicin (PLD) is a recommended treatment option for patients with MM 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 three to five seconds on days 1, 4, 8, and 11 of an every-21-days cycle. PLD 30 mg/m2 is administered as a one-hour 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 (CR) (as determined by negative electrophoresis and immunofixation). *Key Evidence* *One RCT compared bortezomib plus PLD (n=324) to bortezomib alone (n=322) in patients with relapsed or refractory MM (23) and reported that overall survival at 15 months was superior for the combination compared to bortezomib monotherapy (76% vs. 65%; p=0.03). The median time-to-progression was also significantly higher in the PLD plus bortezomib arm (9.3 months vs. 6.5 months, respectively; HR, 1.82; 95% confidence interval [CI], 1.41 to 2.35; p=0.000004). The Hematology Disease Site Group (DSG) opinion is that the treatment can be discontinued two to four cycles after the achievement of CR* *Ref. 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.* **Relapsed or refractory Patients not suitable for Bortezomib + PLD:** For patients with MM 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 three to five seconds on days 1, 4, 8, and 11 for eight three-week cycles, and then on days 1, 8, 15, and 22 for three five-week maintenance cycles.

Key Evidence

One RCT compared bortezomib monotherapy (n=333) to dexamethasone (n=336) in patients with relapsed or refractory MM (21, 22) and reported that the median overall survival was significantly higher for patients who received bortezomib (29.8 months vs. 23.7 months; HR, 0.77; p=0.027). The median time-to-progression was also significantly higher in the bortezomib arm (HR, 0.55; p<0.001). Of note, grade 3 adverse events were more common in the bortezomib arm (61% vs. 44%; p<0.01).

Ref. 21 und 22:

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

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.

Toxicity:

Key evidence:

Multiple myeloma: In all patients, bortezomib drug combinations were associated with an increased incidence of peripheral neuropathy and hematologic events, as well as nausea and diarrhea, in contrast to non-bortezomib-containing regimens (8,15, 16, 21, 23). The subcutaneous route has been shown to be as effective as the intravenous route [30]. The HDSG opinion is that blood count, blood chemistries and creatinine levels should be monitored on days 1 and 8 of each cycle.

References:

[8] San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906e917.

[15] Harousseau J-L, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol 2010;28:4621e4629.

[16] Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010;376:2075e2085.

[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.

[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.

Patient subgroups that are more or less likely to benefit from

	the use of bortezomib. Treatment with bortezomib combinations (i.e. bortezomib with melphalan and prednisone for newly diagnosed patients or either bortezomib and dexamethasone or bortezomib and PLD for those with relapsed or refractory disease) is recommended for all patient subgroups (i.e. patients who are older, patients with impaired renal function, patients with a high risk cytogenetic profile, patients exposed to multiple previous lines of therapy and ASCT and patients with an elevated level of b2-microglobulin). *Key evidence:* *In refractory multiple myeloma patients, bortezomib and dexamethasone has been shown to be superior to dexamethasone alone in patients 65 years or older (response rate P = 0.0004; TTP P = 0.002) and patients with International Staging System stage II and III disease (response rate P < 0.0004; TTP P = 0.0002) and patients refractory to the most recent therapy or patients who have previously received greater than one previous line of therapy (response rate P<0.0001 and TTP P<0.0001 for both subgroups) [31], as well as in patients with renal impairment [32]. Bortezomib plus PLD was also more efficacious than bortezomib alone in most subgroups analysed [23,33]. An advantage of bortezomib and PLD compared with bortezomib alone was observed in patients with cytogenetic abnormalities, except for deletion 13q [23].* *References:* *[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.* *[31] Richardson PG, Sonneveld P, Schuster MW, et al. Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed multiple myeloma. Br J Haematol 2007;137:429e435.* *[32] San-Miguel JF, Richardson PG, Sonneveld P, et al. Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study. Leukemia 2008;22:842e849.* *[33] Sonneveld P, Hajek R, Nagler A, et al. Combined pegylated liposomal doxorubicin and bortezomib is highly effective in patients with recurrent or refractory multiple myeloma who received prior thalidomide/lenalidomide therapy. Cancer 2008;112:1529e1537.*
	Hinweise zur LL The working group members for this topic and the Chair of the Hematology DSG disclosed potential conflicts of interest relating to the topic of this evidence-based series
Barosi G et al., 2012 [1]. SIE, SIES, GITMO evidence-based guidelines on novel agents (thalidomide,	Fragestellung In this project, we produced drug-specific recommendations targeting the use of new agents for multiple myeloma (MM).
	Methodik

bortezomib, and lenalidomide) in the treatment of multiple myeloma	**Grundlage der Leitlinie:** systematische Literaturrecherche innerhalb eines strukturierten Konsensusprozess (conceptual framework elements of the NIH Consensus Development Program) • Bildung eines Advisory Council (AC) • Systematischer Literaturreview • Grading the evidence (GRADE) • Evidence tables, with short comments on all the predefined dimensions of quality (i.e., study design, quality, consistency, and directness); quantitative summaries of effect for each outcome • The panel members received the material by mail, and they were asked to individually drafting recommendation by agreeing on benefit/risk ratio profile for each intervention. • Using a modified Delphi process [8], the list of produced statements was circulated electronically to all participants through two iterations. Participants voted on which statements they felt warranted discussion at the meeting, and provided comments on the wording of the statements which were progressively finalized. • Final adjudication of the recommendation(s) was made through three face-to-face meetings • The nominal group technique was used to solve any residual disagreement on the selected items. • Recommendations were both classified into four mutually exclusive categories — do it, probably do it, probably don't do it, don't do it — according to GRADE suggestions, and were provided in more detailed form with suggestions and comments derived from consensus of the panel. **Suchzeitraum**: English-language publications edited after 2005 until 15.12.2011 **Datenbanken:** PubMed, the Cochrane Register of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and ISI Web of Knowledge, EMBASE, Conference proceedings **LoE/GoR:** GRADE
	Ergebnisse **Is the use of new agents recommended in patients refractory to or relapsing after first line therapy?** <u>Recommendation:</u> The Panel claimed that from the evidence so far obtained, <u>both bortezomib in combination with pegylated liposomal doxorubicin and lenalidomide dexamethasone combination should be recommended</u> in patients with refractory or relapsing MM. The decision on what is the best treatment in refractory or relapsed

	patients according their previous therapy and time from end of therapy to progression cannot be taken on the basis of the available evidence. The Panel consensually recommended that patients who have a late relapse (relapsing after 12 months from the end of therapy) after a bortezomib-containing regimen should be re-challenged with bortezomib. Early relapsing or refractory to bortezomib should receive lenalidomide with dexamethasone. **Fazit:** Use it, weak positive for bortezomib/ pegylated liposomal doxorubicin combination and lenalidomide/dex combination *Evidence:* Thalidomide single agent: no RCT available Bortezomib single agent: APEX-trial: The quality of evidence was judged weak for the low generalizability and weak directness of the results. The panel judged the benefit of single agent bortezomib overcome the risk (weak positive). *References:* *52. Richardson PG, Sonneveld P, Schuster MW et al (2005) Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352:2487–2498* *53. Richardson PG, Sonneveld P, Schuster M et al (2007) Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood 110:3557–3560* Bortezomib–pegylated liposomal doxorubicin (PLD) combination therapy Orlowsky et al. randomized MM patients with progressive disease after response to one or more lines of therapy or refractory to initial treatment to bortezomib and PLD or bortezomib monotherapy (DOXIL-MMY-3001): The panel judged the benefit of bortezomib/PLD combination therapy overcome the risks. The strength of the evidence was judged weak for poor generalizability of the results. *Referenz: 55. Orlowski RZ, Nagler A, Sonneveld P et al (2007) 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 28:3892–3901* Lenalidomide–dexamethasone (len/dex) combination: comparison with with high-dose dexamethasone in two RCTs of identical design but different locations. The quality of evidence was judged high. *References:* *57. Weber D, Chen C, Niesvizky R et al (2007) Lenalidomide plus Dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 357:2133–2142* *58. Dimopoulos M, Spencer A, Attal M et al (2007) Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 357:2123–2132* *59. Dimopoulos MA, Chen C, Spencer A et al (2009) Long-term followup on overall survival from theMM-009 andMM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 23:2147–2152*

Chen C et al., 2012 [3]. Lenalidomide in Multiple Myeloma: Guideline Recommendations Report Date: May 30, 2012 Siehe auch **Chen C et al., 2013 [2]** .	Fragestellung The purpose of this guideline is to provide recommendations for the use of lenalidomide alone or in combination with other agents in patients with previously untreated **or relapsed/refractory multiple myeloma**. **Fragen:** a) Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with relapsed or refractory (relapsed/refractory) multiple myeloma compared with non-lenalidomide–containing treatments? b) Which multiple myeloma patients, both in the previously untreated and relapsed or refractory groups, are more or less likely to benefit from treatment with lenalidomide?
	Methodik Grundlage der Leitlinie: • syst. Literaturrecherche in medline, embase, and the Cochrane Library, meeting proceedings and relevant websites • Suchzeitraum: Januar 2000 bis Feb.2012 • Study selection criteria defined • Selelction of studies; screened independently by the methodologist and by two clinician members of the Working Group • Hematology dsg developed draft recommendations based both on consensus and on evidence from the systematic review • Internal and External Review LoE & GoR: keine allgemeinen Kategorien; Bewertung und Empfehlungen werden narrativ vorgenommen Empfehlungen sind mit Literatur verknüpft *Sonstige methodische Hinweise:* Status der Leitline = „im Review“ → This document will be reviewed in 3 years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best-available evidence. Four guideline authors declared they had no conflicts. CC declared receiving trial support from Celgene, and MC declared being a site investigator on a lenalidomide clinical trial (MM-020) sponsored by Celgene. Among the members of the Hematology DSG, RM declared that he received research funding from Celgene; AS declared that he was a principal investigator (PI) in a lenalidomide trial funded by Celgene; DR declared he received funding and was a PI in trials sponsored by Celgene, BMS, Janssen, Johnson & Johnson, Otsuka, Novartis, and Merk; the other

	members of the Hematology DSG declared that they had no conflicts of interest. The internal reviewer and the three RAP members declared that they had no conflicts of interest. Of the four targeted peer reviewers, one declared having received honoraria that exceeded CAD$5,000 in one year to act as a consultant for Celgene, Roche, and Janssen Ortho and also declared being the PI in a phase 3 lenalidomide trial. *Hinweis zur LL: Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt. Es fehlen es fehlen Angaben/Kriterien zum LoE und Konsensusfindung.*
	Ergebnisse **<u>Relapsed or refractory multiple myeloma.</u>** **Recommendations** <u>Single-Agent Lenalidomide:</u> Lenalidomide alone <u>cannot be recommended</u> for standard use in the relapsed or refractory setting. <u>Lenalidomide and Dexamethasone:</u> The combination of lenalidomide and dexamethasone <u>is recommended</u> 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. <u>Other Lenalidomide Combinations</u>: No other combinations can be recommended. *Key Evidence:* Two seminal studies (1,2): ttp for lenalidomide plus dexamethasone compared with dexamethasone plus placebo. Meta-analysis of those two studies: 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). low-dose weekly dexamethasone with lenalidomide appears less toxic [than high dose] when used in the first line (10). From a safety perspective, the Hematology dsg considers low-dose dexamethasone a reasonable option for the relapsed or refractory setting. No rcts of lenalidomide in combination with other agents in this setting were identified. *References:* *1. Weber DM 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 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.

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

Subgroups most likely to benefit from treatment with lenalidomide

Recommendation:

For patients with relapsed/refractory multiple myeloma, lenalidomide plus dexamethasone is a reasonable treatment option for the following patient subgroups:

- **Patients with at least one prior line of therapy:** Those patients who are less heavily treated (only one prior line of therapy vs. two or more) appear to benefit the most.
- Patients who have received prior thalidomide or autologous stem cell transplantation (ASCT).
- **Younger or older patients:** Advanced age should not be an absolute contraindication for the use of lenalidomide, as long as any adverse events are carefully monitored.
- **Patients with mild-to-moderate renal failure (creatinine clearance ≥30 mL/min and ≤60 mL/min):** For patients with severe renal failure (creatinine clearance <30 mL/min), the Hematology DSG cautions against the use of lenalidomide until additional evidence for its use in this subgroup becomes available.
- Patients with IgA subtype, pre-existing peripheral neuropathy, and different levels of Eastern Cooperative Oncology Group (ECOG) performance status.

Key Evidence:
The subgroup analyses of data are derived primarily from the Rajkumar study10 in the first-line setting and from pooled data from the Weber and Dimopoulos studies1,2,10,18,34,35,39 in the relapsed or refractory setting. These data have been integrated with the clinical expertise of the Hematology dsg to provide support for the recommendations. Evidence to recommend lenalidomide in specific subgroups of previously untreated patients is limited. All subgroup analyses upon which the recommendations are based are retrospective post hoc analyses. In isolation, they represent a weak evidence base and therefore have been integrated with the expert opinion and clinical experience of the Hematology dsg.

References:

1. Weber DM 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.

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Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2017 [21]. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib Technology appraisal guidance 427	1.1 Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse ; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme. 1.2 This guidance is not intended to affect the position of patients whose treatment with pomalidomide was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. *Committee discussion* Treatment pathway 4.3 The committee considered the likely position of pomalidomide with dexamethasone in the treatment pathway for relapsed and refractory multiple myeloma, noting that its marketing authorisation specified that it should only be used after at least 2 previous treatment regimens, including both lenalidomide and bortezomib. The committee was aware that NICE currently recommends lenalidomide as third-line treatment, and it asked the experts if this reflects clinical practice. The clinical experts confirmed that for most patients, lenalidomide is offered at third line, after thalidomide then bortezomib (they clarified that a small proportion of people had received lenalidomide at second line through the Cancer Drugs Fund). The experts agreed that the evidence for pomalidomide with dexamethasone in this indication was largely for patients whose disease was heavily pre-treated, which was consistent with using it after 3 or more previous therapies. The committee concluded that the appropriate positioning of pomalidomide, in line with clinical practice and the evidence base was after third or subsequent relapse (that is, after 3 previous treatments including both lenalidomide and bortezomib) and that this positioning would be the focus of its considerations. […] Summary of appraisal committee's key conclusions Evidence for clinical effectiveness: The company presented evidence from MM-003, a phase III, open-label trial that compared pomalidomide plus low-dose dexamethasone with high-dose dexamethasone alone. The committee agreed that high-dose dexamethasone was a reasonable proxy for the clinical effectiveness of conventional chemotherapy. Because there was no direct evidence other than for conventional chemotherapy, the company selected individual treatment arms from available studies and ran separate analyses comparing pomalidomide and low-dose dexamethasone with each of the comparators. Estimate of the size of the clinical effectiveness: Pomalidomide and low-dose dexamethasone compared with high-dose dexamethasone: • Progression-free survival gain of 1.8 months in favour of pomalidomide. • Overall survival gain between 4.6 months and 7.0 months in favour of pomalidomide. Pomalidomide and low-dose dexamethasone compared with bendamustine: • Progression-free survival benefit of 4.2 months compared with 3.3 months in favour of pomalidomide. • Overall survival gain of 16.5-month compared with 8.1 months in favour of pomalidomide. Pomalidomide and low-dose dexamethasone compared with panobinostat: • Progression-free survival benefit of 4.1 months compared with 5.3 months for panobinostat. • Overall survival benefit of 12.4 months compared with 17.5 months for panobinostat. Evidence for cost effectiveness: […] Key conclusion: […] The committee acknowledged that the indirect comparisons were associated with considerable uncertainty but recognised that the company had presented the best evidence available. The most plausible ICERs for pomalidomide with low-dose dexamethasone compared with conventional chemotherapy and bendamustine with thalidomide and dexamethasone were below £50,000 per QALY gained, and the committee concluded that pomalidomide meets the end-of-life criteria compared with bendamustine and conventional chemotherapy. The end-of-life criterion for an additional 3 months survival gain was not met for the comparison with panobinostat with bortezomib and dexamethasone and the ICERs reflected 'savings perQALY lost'; that is, pomalidomide was less effective but less costly. The committee noted its conclusion in section 4.15 that the savings per QALY lost for pomalidomide compared with panobinostat were high enough for it to be considered a cost-effective use of NHS resources without applying the end-of-life criteria.

NICE, 2016 [20]. Panobinostat for treating multiple myeloma after at least 2 previous treatments. NICE technology appraisal guidance 380.	1.1 Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, as an option for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' when the company provides panobinostat with the discount agreed in the patient access scheme. *Committee discussion* Key conclusion […] The Committee accepted that the results from the PANORAMA-1 trial used in the post hoc subgroup analysis demonstrated that panobinostat plus bortezomib and dexamethasone was clinically more effective than bortezomib plus dexamethasone based on the interim and final overall survival data. The Committee considered the company's matching adjusted indirect comparison of panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone. The Committee noted the limitations of the company's comparison but accepted that the hazard ratio results suggested that panobinostat plus bortezomib and dexamethasone had a similar level of clinical effectiveness to lenalidomide plus dexamethasone. Considering all of the new cost-effectiveness evidence available for this comparison, which included the updated patient access scheme, the Committee agreed that the ICER was likely to be no higher than £25,000 per QALY gained and therefore within the range that would normally be considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).
NICE, 2007 [18]. Bortezomib monotherapy for relapsed multiple myeloma NICE technology appraisal guidance; Band 129	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) and • the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above). **The manufacturer's submission** The manufacturer's submission approached the decision problem by comparing the clinical effectiveness of bortezomib with that of high-dose dexamethasone (HDD), based on the results of the APEX (Assessment of Proteasome Inhibition for Extending Remissions) randomised controlled trial (RCT). The population considered was people with multiple myeloma at first or subsequent relapse; however, the manufacturer's submission placed emphasis on patients at first relapse. In an interim analysis of the APEX trial (median follow-up of 8.3 months), it was found that people receiving bortezomib had a statistically significantly longer median time to disease progression compared with people receiving HDD (6.2 months compared with 3.5 months, hazard ratio 0.55, 95% confidence interval 0.44 to 0.69; $p < 0.001$). They also had a significantly improved overall survival (hazard ratio 0.57, 95% confidence interval 0.40 to 0.81; $p = 0.001$) and a significantly higher overall (complete or partial) response rate (38% compared with 18%; $p < 0.001$). Updated analyses were performed at 15.8 months and 22 months of follow-up. At 22 months follow-up, the median overall length of survival in the intention to treat population was 29.8 months in the bortezomib arm compared with 23.7 months in the HDD arm. **Consideration of the evidence** The Committee understood that bortezomib has a novel mechanism of action and that the APEX trial has established bortezomib as an evidence based treatment for relapsed multiple myeloma. It concluded that bortezomib is considered a clinically important treatment for patients with multiple myeloma at both first and subsequent relapse.

	Clinical effectiveness The Committee discussed the methods and results of the APEX study and considered the issues raised about the study in the ERG report. Taking all issues into account, the Committee concluded that the APEX study constitutes clear evidence that bortezomib monotherapy is more clinically effective than HDD monotherapy for the treatment of relapsed multiple myeloma.
NICE, 2009 [19]. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy NICE technology appraisal guidance; Band 171	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, with the following condition: • The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer. **The manufacturer's submission** The manufacturer produced an analysis of the clinical and cost effectiveness of lenalidomide for the treatment of multiple myeloma in people who had received at least one prior therapy. This included people at first and subsequent relapse and people who had progressive disease after two or more cycles of antimyeloma treatment. Two randomised controlled trials (RCTs), of identical design but differing in their locations (MM-009 and MM-010), compared treatment with lenalidomide plus dexamethasone (len/dex) with dexamethasone alone for patients with multiple myeloma who had received at least one prior therapy. The trials enrolled 353 and 351 patients, respectively (n = 704). For the pooled trials, the subgroup of patients who had received one prior therapy had a median survival of 169.1 weeks in the len/dex arm compared with 145.4 weeks in the dexamethasone arm. Indirect comparison: Bortezomib vs. Lenalidomid and Dexamethason: An indirect comparison was undertaken to compare len/dex with bortezomib monotherapy because there were no head-to-head trials. The results of the trials for len/dex were compared with the results of the Assessment of Proteasome Inhibition for Extending Remissions (APEX) RCT. The APEX study compared bortezomib with high-dose dexamethasone. For median TTP, len/dex had a 34-week advantage over bortezomib for people who had received one prior therapy only, and there were no statistically significant differences for the secondary outcomes of complete response, partial response and progressive disease. However, this analysis is limited by the small number of data points. In addition, the common comparator (high-dose dexamethasone) was an active treatment and was not used in the same dose across the trials, and the definition of response differed between the trials. **Consideration of the evidence:** The Committee heard from clinical specialists and patient experts that lenalidomide is an important advance in the treatment of multiple myeloma and could be considered as an alternative to bortezomib (currently recommended as a treatment option in NICE technology appraisal guidance 129) at first relapse. The Committee noted the importance that patients, their carers and physicians placed on having effective options to treat multiple myeloma at presentation and at subsequent relapses. However, it understood that the optimal sequence of agents to use is as yet unclear and depends on several factors, including a person's treatment history, comorbidities and disease characteristics. The Committee concluded that the len/dex combination improved outcomes in people with relapsed multiple myeloma when compared with dexamethasone. This included people who had received either one or two or more prior therapies, and when prior therapies included the use of thalidomide. The Committee next discussed the relative effectiveness of len/dex compared with bortezomib. It noted that the evidence for the effectiveness of len/dex compared with bortezomib monotherapy was derived from an indirect comparison via the common comparator of high-dose dexamethasone. It considered that there was uncertainty in the results of the indirect comparison because of heterogeneity between the studies, such as differences in the regimen of dexamethasone and the definition of response. The Committee noted that there was additional uncertainty in interpreting the context of current practice, as it understood that bortezomib is usually used in combination with dexamethasone in clinical practice.

	The Committee discussed the adverse effects associated with lenalidomide. It noted that from the patients' viewpoint lenalidomide is associated with a more favourable adverse effect profile than most other regimens and agents used in the management of relapsed multiple myeloma. It heard from clinical specialists and patient experts that lenalidomide might be particularly useful for people with pre-existing peripheral neuropathy, in whom the use of bortezomib at first relapse is restricted. However, the Committee noted that lenalidomide is associated with a statistically significant increased risk of venous thrombosis and embolism. It heard from clinical specialists that this risk is usually managed with prophylaxis in the form of low-dose aspirin in people with multiple myeloma. However, in people with a history of venous thromboembolism or other relevant risk factors, the use of warfarin or low-molecular-weight heparin would be considered. The Committee heard that with such prophylaxis the risk would return to baseline levels. Hinweis Die Empfehlung von Lenalidomid + Dexamethason nach zwei vorangegangenen Therapien fußt teils auf ökonomischen Aspekten. Hier ist vorrangig die Evidenz für die Anwendung von Lenalidomid + Dexamethason nach einer vorangegangenen Therapie dargestellt.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 20.06.2017

#	Suchfrage
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	multiple or (plasma cell) or plasma-cell:ti,ab,kw
3	myeloma or myelomas:ti,ab,kw
4	#2 next #3
5	''Kahler Disease*'' or Myelomatosis or Myelomatoses:ti,ab,kw
6	#1 or #4 or #5
7	#6 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 20.06.2017

#	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 ("2012/06/01"[PDAT] : "2017/06/30"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))
9	(#8) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 20.06.2017

#	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 ("2012/06/01"[PDAT] : "2017/06/30"[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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