Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-06-01-D-232 Elotuzumab

Stand: Mai 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Elotuzumab **zur Behandlung des Multiplen Myeloms**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt.*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss vom 20. Februar 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pomalidomid
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Elotuzumab N. N. Empliciti	Anwendungsgebiet: Empliciti ist in Kombination mit Lenalidomid und Dexamethason zur Behandlung des Multiplen Myeloms bei Erwachsenen indiziert, welche mindestens eine vorangegangene Therapie erhalten haben (siehe Abschnitt 4.2 und 5.1 der Fachinformation).
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 ist indiziert für die Behandlung von erwachsenen Patienten mit unbehandeltem multiplem Myelom, die nicht transplantierbar sind (siehe Abschnitt 4.2). 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. […]
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®	<u>Multiples Myelom</u> Als Erhaltungstherapie bei Patienten, die nach einer initialen Induktions-Chemotherapie eine objektive Remission erreichten (mehr als 50%ige Reduktion des Myelomproteins). Gegenwärtige klinische Erfahrungen zeigen, dass eine Erhaltungstherapie mit Interferon alfa- 2b die Plateauphase verlängert; jedoch wurden Effekte auf die Gesamtüberlebenszeit nicht endgültig bewiesen. […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

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Indikation für die Recherche bei Elotuzumab (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 der Fachinformation).

Berücksichtigte Wirkstoffe/Therapien:

s. Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

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 08.04.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), arztbibliothek.de (ÄZQ), NVL, AWMF, GIN, NGC, TRIP, NICE, DAHTA, NIHR HSC, BMJ Clinical Evidence. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, DGHO-Onkopedia, NCCN, NCI, ESMO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Es wurde keine Sprachrestriktion vorgenommen. Eine detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab insgesamt 385 Treffer, welche anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Die erste Durchsicht ergab 88 eingeschlossene Quellen, die anschließend im Volltext überprüft wurden. Daraus konnten 10 Referenzen, die in die synoptische Evidenz-Übersicht aufgenommen werden.

Abkürzungen

AE	Adverse effects
ASCT	Autologous stem cell transplantation
CR	Complete response
ECOG-PS	Eastern cooperative oncology group (performance status)
EFS	Event-free survival
EMA	European medicines agency
EORTC QLQ 30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Cancer
EORTC QLQ MY20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Multiple Myeloma
FDA	Food and Drug Administration
G-BA	Gemeinsamer bundesausschuss
MM	Multiple myelom
NCCN	National comprehensive cancer network
OS	Overall survival
ORR	Objective response rate
PD	Progressive disease
PFS	Progressionsfreies überleben
PLD	Pegylated liposomal doxorubicin
PR	Partial response
RCT	Randomized controlled trial
SAE	Serious adverse events
TTP	Time to progression
TTR	Time to response
UE	Unerwünschtes ereignis
QOL	Quality of life

IQWiG Berichte/ G-BA Beschlüsse

<table>
<tr>
<td>G-BA, 2015 [5]
Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Bewertung von Arzneimitteln für seltene Leiden nach § 35a Absatz 1 Satz 10 i.V.m. 5. Kapitel § 12 Nr. 1 Satz 2 VerfO: Wirkstoff: Pomalidomid

2. Dezember 2013</td>
<td>Zusammenfassung der Bewertung

Bei Pomalidomid handelt es sich um einen Wirkstoff aus der Gruppe der Immunmodulatoren, das in Kombination mit Dexamethason indiziert ist zur Behandlung von erwachsenen Patienten mit rezidivierten oder refraktären multiplen Myelom, die mindestens zwei vorausgegangene Therapien, darunter Lenalidomid und Bortezomib, erhalten haben und unter der letzten Therapie eine Progression gezeigt haben.

Die Unterlagen zum Nachweis des Ausmaßes des Zusatznutzens für Pomalidomid basieren auf der pivotalen Zulassungsstudie CC-4047-MM-003.

Ergebnisse aus der Zulassungsstudie CC-4047-MM-003

3.3. Zusammenfassende Darstellung der Ergebnisse

Die Ergebnisse der Studie werden in der folgenden Tabelle unter Berücksichtigung des Verzerrungspotentials zusammengefasst. Es wird dargestellt, ob sich unter Pomalidomid ein positiver Effekt bei hohem (↑) oder niedrigem (↑↑) Verzerrungspotential bzw. negativer Effekt bei hohem (↓) oder niedrigem (↓↓) Verzerrungspotential bzw. kein Unterschied (↔) gezeigt werden konnte. Bei den Nebenwirkungen werden die absoluten Häufigkeiten in der Interventionsgruppe dargestellt.

Tabelle 15: Studienergebnisse
<table>
<tr><th>Kategorie</th><th>Ergebnis</th></tr>
<tr><td>Gesamtüberleben</td><td></td></tr>
<tr><td>Gesamtüberleben</td><td>↑</td></tr>
<tr><td>Morbidität</td><td></td></tr>
<tr><td>Progressionsfreies Überleben</td><td>↑↑</td></tr>
<tr><td>Knochenschmerzen</td><td>↔</td></tr>
<tr><td>ECOG-PS</td><td>↑</td></tr>
<tr><td>Lebensqualität</td><td></td></tr>
<tr><td>EORTC QLQ-30</td><td>↔</td></tr>
<tr><td>EORTC QLQ-MY20</td><td>↔</td></tr>
<tr><td>EQ 5D</td><td>↔</td></tr>
<tr><td>Nebenwirkungen</td><td></td></tr>
<tr><td>Mindestens ein UE (IG/KG)[1)]</td><td>97 % / 93 %</td></tr>
<tr><td>Mindestens ein SUE (IG/KG)[1)]</td><td>51 % / 50 %</td></tr>
<tr><td>Mindestens ein UE CTC Grad 3 oder 4 (IG/KG)[1)]</td><td>78 % / 76 %</td></tr>
<tr><td>Abbruch aufgrund von UE (IG/KG)[1)]</td><td>10 % / 5 %</td></tr>
</table>
[1)] Interventionsgruppe/Kontrollgruppe</td>
</tr>
<tr>
<td>G-BA, 2014 [4]

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung</td>
<td>Zugelassenes Anwendungsgebiet:

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.</td>
</tr>
</table>

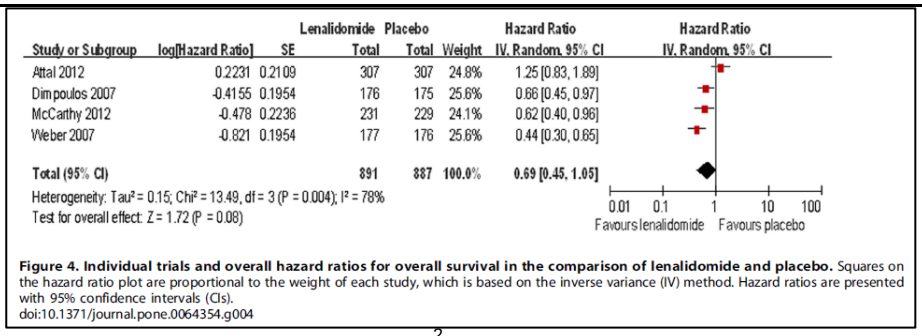
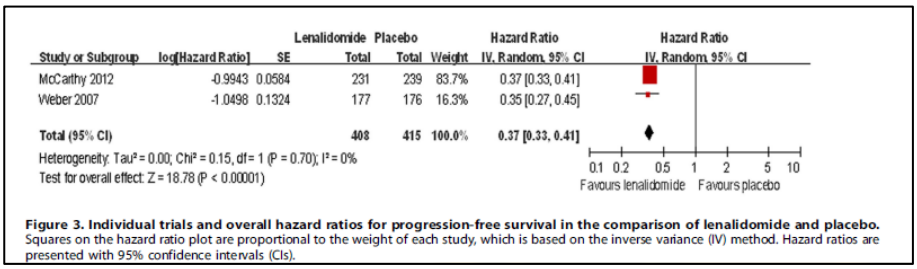
von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pomalidomid 20. Februar 2014	**Ausmaß des Zusatznutzens des Arzneimittels:** Pomalidomid ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 des Fünften Buches Sozialgesetzbuch (SGB V) gilt der medizinische Zusatznutzen durch die Zulassung als belegt. Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß Kapitel 5 § 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 Kapitel 5 § 5 Absatz 7 Nummer 1 bis 4 VerfO festgelegten Kriterien. **Ausmaß des Zusatznutzens: beträchtlich**

Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

Systematische Reviews

Yang, 2013 [10] Lenalidomide treatment for multiple myeloma: systematic review and meta-analysis of randomized controlled trials.	1. Fragestellung To gain a better, more complete understanding of the efficacy and safety of lenalidomide, we performed a meta-analysis of randomized controlled trials in which patients with MM received lenalidomide as initial or maintenance therapy.
	2. Methodik **Population:** Patienten, mit MM, die Lenalidomid erhalten **Intervention:** Lenalidomid (hier nur Darstellung von Lenalidomid als 2nd line) **Komparator:** andere Chemotherapie oder Placebo **Endpunkt:** OS, PFS **Suchzeitraum (Aktualität der Recherche):** bis Nov 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7, davon 4 (n=1778) Studien mit Lenalidomid als 2nd-line **Qualitätsbewertung der Studien:** ''risk of bias'' method recommended by the Cochrane Collaboration **Table 2.** Methodological quality assessment of included trial. | Author [Year] | Location | Allocation generation | Allocation concealment | Double blinding | Data analysis | Drop-out | Other risk of bias | |---|---|---|---|---|---|---|---| | **Second-line therapy** | | | | | | | | | Attal [2012] | France, Belgium, Switzerland | Unclear | Unclear | Double blinded | ITT | 7.0% | Early stopping lenalidomide maintenance therapy based on an increased incidence of second primary cancers | | Dimopoulos [2007] | Europe, Israel, Australia | Unclear | Unclear | Double blinded | ITT | N/A | Study designed and data analysis by manufacturer, early study data are unblended | | McCarthy [2012] | United States | Unclear | Unclear | Double blinded | ITT | N/A | Increase in time to progression led to early study unblinding and crossover | | Weber [2007] | United States, Canada | Computer generated | Unclear | Double blinded | ITT | N/A | Response rate and time to progression are based on data obtained before unblinding | ITT, intention-to-treat; PP, per-protocol; N/A, not available. doi:10.1371/journal.pone.0064354.t002
	3. Ergebnisdarstellung **Lenalidomid vs Placebo als 2nd line (insg. 4 Studien)** <u>Overall Survival (4 trials, n= 1778)</u> ⇒ there was a trend for increased overall survival with lenalidomide, our meta-analysis revealed that there was no statistically significant difference in overall survival between lenalidomide maintenance therapy and placebo (HR = 0.69; 95% CI: 0.41–1.05) →There was evidence of significant

	 **Figure 4. Individual trials and overall hazard ratios for overall survival in the comparison of lenalidomide and placebo.** Squares on the hazard ratio plot are proportional to the weight of each study, which is based on the inverse variance (IV) method. Hazard ratios are presented with 95% confidence intervals (CIs). doi:10.1371/journal.pone.0064354.g004 ⇒ heterogeneity among the trials (I^2 = 78%). <u>PFS (2 trials, n= 823)</u> ⇒ A random-effects statistical model revealed that lenalidomide therapy was associated with increased progression-free survival compared with placebo (HR = 0.37; 95% CI: 0.33–0.41) → There was no evidence of significant heterogeneity among the trials (I^2 = 0%).  **Figure 3. Individual trials and overall hazard ratios for progression-free survival in the comparison of lenalidomide and placebo.** Squares on the hazard ratio plot are proportional to the weight of each study, which is based on the inverse variance (IV) method. Hazard ratios are presented with 95% confidence intervals (CIs). 4. Anmerkungen/Fazit der Autoren ⇒ Population characteristics, crossover designs with the probable risk of inadequate washout period, differing lenalidomide schedules and dosages, and use of concomitant drugs may have resulted in a somewhat speculative interpretation of our analysis. ⇒ Separate subgroup analysis should be done for older vs. younger adults, but the data needed to conduct subgroup analysis could not be extracted from the studies. ⇒ In summary, the findings from our meta-analysis indicate that lenalidomide therapy significantly improves response rates and increases progression-free survival in patients with newly diagnosed MM, and those receiving previous antimyeloma therapy, but it is associated with an increased risk of a number of adverse events. 5. Hinweis FBMed ⇒ Die eingeschlossenen RCT als 2nd-line untersuchen Lenalidomid sowohl nach ASCT als auch im Rezidiv ohne ASCT.
Lopuch, 2015 [8] Effectiveness of targeted therapy as monotherapy or combined therapy in	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.

patients with relapsed or refractory multiple myeloma: A systematic review and meta-analysis.	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:** overall response rate (ORR), complete response (CR), partial response (PR), progressive disease (PD), progression-free survival (PFS), event-free survival (EFS), time to progression (TTP), time to response (TTR) or OS, incidents of death (overall and caused by adverse events, AEs), and discontinuation of the intervention from any cause, any AEs, any serious adverse events (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) **Qualitätsbewertung der Studien:** Jadad scale
	3. Ergebnisdarstellung **Eingeschlossene Vergleiche:** ⇒ pomalidomide vs. pomalidomide plus dexamethasone, ⇒ bortezomib vs. bortezomib plus PLD ⇒ bortezomib vs. bortezomib plus bevacizumab ⇒ thalidomide vs. thalidomide plus interferon alfa (IFNα)

Table 1 Characteristics of the included randomized controlled trials

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

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

White (2013) & Chlou (2007) = Phase II-Studien

NCT00833833 (2014) & Orlowski (2007)= Phase III-Studien

Monotherapy vs. Combined Therapy

⇒ The meta-analysis of four RCTs comparing monotherapy to combined therapy showed that the **risk of discontinuation** of the intervention was similar in both groups (P = 0.27) → significant between-study heterogeneity was observed (P = 0.06, I^2 = 58.5%).

⇒ There were not statistically significant differences between monotherapy and combined therapy in each individual trial (P > 0.05)

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

End points	No. of trials	Group of patients		RB/RR/HR (95% CI), *P*	Test of heterogeneity Cochran Q, df, *P*, I^2	References
		Monotherapy (*N*)	Combined therapy (*N*)			
		n/*N*				
PFS	2	161	162	HR = 0.73 [0.53–0.93], *P* < 0.0001	Cochran *Q* = 0.002, df = 1, *P* = 0.97	31,33
	1	322	324	HR = 1.69 [1.32–2.16], *P* = 0.0003		32
EFS	1	12	16	*P* = 0.0193		26
TTP	1	322	324	HR = 1.82 [1.41–2.35], *P* = 0.000004		32
TTR	2	143	178	HR = 1,04 [0.46–1.62], *P* > 0.05	Cochran *Q* = 16.32, df = 1, *P* = 0.003, I^2 = 87.7%	31,32
OS	3	161	162	HR = 0.80 [0.48–1.11] *P* > 0.05	Cochran *Q* = 0.34, df = 1, *P* = 0.84, I^2 = 0%	26,31,33
	1	322	324	HR = 1,41 [1.002–1.97], *P* = 0.0476		32
		n/*N*	*n*/*N*			
Discontinuation	4	354/495	330/502	RR = 1.06 [0.96–1.17], *P* = 0.27	Cochran *Q* = 7.23, df = 3, *P* = 0.06, I^2 = 58,5%	26,31,32,33
ORR	3	158/387	175/389	RB = 0.90 [0.77–1.06], *P* = 0.22	Cochran *Q* = 1.15, df = 2, *P* = 0.56, I^2 = 0%	26,32,33
CR	4	9/495	16/502	RB = 0.58 [0.27–1.27], *P* = 0.17	Cochran *Q* = 0.24, df = 3, *P* = 0.97, I^2 = 0%	26,31,32,33
PR	4	155/495	179/502	RB = 0.78 [0.42–1.45], *P* = 0.44	Cochran *Q* = 12.45, df = 3, *P* = 0.01, I^2 = 75,9%	26,31,32,33
PD	2	23/120	10/129	RR = 2.58 [1.29–5.12], *P* = 0.007	Cochran *Q* = 0.004, df = 1, *P* = 0.95	26,31
Death	4	62/495	44/502	RR = 1.38 [0.96–1.99], *P* = 0.08	Cochran *Q* = 0.16, df = 3, *P* = 0.98, I^2 = 0%	26,31,32,33
Discontinuation due to AEs	4	94/491	226/496	RR = 0.74 [0.28–1.94], *P* = 0.54	Cochran *Q* = 14.00, df = 3, *P* = 0.0029, I^2 = 78,6%	26,31,32,33
AEs	3	457/475	472/480	RR = 0.98 [0.96–1.001], *P* = 0.58	Cochran *Q* = 0.80, df = 2, *P* = 0.67, I^2 = 0%	31,32,33
SAEs	2	148/425	184/430	RR = 0.82 [0.69–0.97], *P* = 0.02	Cochran *Q* = 0.48, df = 1, *P* = 0.49	31,32
Grade 3/4 AEs	3	328/475	393/480	RR = 0.87 [0.76–0.98], *P* = 0.03	Cochran *Q* = 5.70, df = 2, *P* = 0.06, I^2 = 64.9%	31,32,33
AEs leading to death	2	14/368	14/368	RR = 1.00 [0.48–2.07], *P* = 0.999	Cochran *Q* = 1.11, df = 1, *P* = 0.29	32,33

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

4. Anmerkungen/Fazit der Autoren

⇒ The main results of the meta-analyses showed that combined therapy significantly increased the risk of SAEs and grade 3/4 AEs. On the contrary, combined therapy significantly improved the efficacy outcomes such as PFS and decreased the risk of PD.

⇒ The above results indicate that combined therapy is superior to monotherapy only in limited range, improving only some of the end points,

	but it is also less tolerated. ⇒ Moreover, there is also limited possibility to compare head-to-head particular agents. The results of RCTs included in this review indicate that bortezomib is more effective than pomalidomide and thalidomide (IMiDs) in terms of efficacy outcomes (OS, PFS, ORR) as well as safety outcomes (≥1 AEs, ≥1 SAEs, grade 3/4 AEs). ⇒ This paper also demonstrated that there is very limited number of RCTs conducted on large patient populations and assessing different therapeutic options for relapsed or refractory MM.
	5. Hinweis FBMed ⇒ The manuscript was self-financed by the authors.
Kouroukis et al., 2014 [7] Bortezomib in multiple myeloma: systematic review and clinical considerations	1. Fragestellung The systematic review addresses these questions: I. 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? II. What is the toxicity associated with the use of bortezomib? III. Which patients are more or less likely to benefit from treatment with bortezomib?
	2. 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 **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.
	3. Ergebnisdarstellung Ausschließlich 7 RCTs beschäftigen sich mit refraktärem oder rezidiviertem MM → nur **4 von 7 Studien** beschäftigen sich mit den in Dtl. zugelassenen Arzneimitteln)

	⇒ **2 von 4 Studien** included only bortezomib-naïve patients (20,23) ⇒ **2 von 4 Studien** included patients who had previously received treatment for mm, including bortezomib (17,22) **Efficacy** ⇒ **TTP:** Bortezomib monotherapy improved TTP statistically significantly more than did dexamethasone alone (hr: 0.55; $p < 0.001$)[23]. Compared with bortezomib monotherapy, the combination of bortezomib with pegylated liposomal doxorubicin (PLD) significantly improved ttp (hr: 1.82; $p = 0.000004$)[20] ⇒ **OS:** Bortezomib in combination with PLD was found to significantly improve os (65% vs. 76%, $p = 0.03$)[20]. Bortezomib monotherapy improved OS significantly more than did dexamethasone (hr: 0.77, $p = 0.003$)[23.] ⇒ **PFS:** Bortezomib in combination with PDL (compared with bortezomib alone) was found to significantly improve PFS (hr: 1.69, $p = 0.000026$)[20]. ⇒ **Response Rate:** No significant difference in OR or CR was detected between bortezomib monotherapy and bortezomib plus PLD[20]. **Toxicity** ⇒ One study showed an 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)[20]. ⇒ Adverse events leading to discontinuation of treatment occurred in 37% of a bortezomib group compared with 29% of a dexamethasone group (reported by Richardson et al. 23). ⇒ A corollary report from the apex study[23] by Chanan–Khan[35] examined the incidence of herpes zoster events in patients treated with bortezomib. The authors found that a significantly higher incidence of herpes zoster was associated with bortezomib than with the control [17] Lonial S, Kaufman J, Tighiouart M, et al. A phase i/ii trial combining high-dose melphalan and autologous transplant with bortezomib for multiple myeloma: a dose- and schedulefinding study. Clin Cancer Res 2010;16:5079–86. [20] 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;25:3892–901. [22] Reece DE, Sullivan D, Lonial S, et al. Pharmacokinetic and pharmacodynamic study of two doses of bortezomib in patients with relapsed multiple myeloma. Cancer Chemother Pharmacol 2011;67:57–67. [23] Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487–98.
	4. 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 ⇒ The magnitude of the benefit for the combination of bortezomib and pld is

	identical to that seen for bortezomib alone compared with dexamethasone in the original pivotal trial of bortezomib, the apex trial ⇒ 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
	5. Hinweise FB Med ⇒ The authors of this report disclosed potential conflicts. One author (DER) was the principal investigator or the local investigator and received research funding for four trials.
Gao et al., 2014 [3] Lenalidomide after stem-cell transplantation for multiple myeloma: a meta-analysis of randomized controlled trials	1. Fragestellung We then performed a combined analysis of these trials in an attempt to clarify the relative benefits and risks of lenalidomide maintenance therapy after ASCT in patients with MM.
	2. Methodik **Population:** patients with MM after ASCT **Intervention:** Lenalidomide maintenance therapy **Komparator:** Placebo maintenance therapy **Endpunkte:** progression-free survival (PFS), overall survival (OS), Adverse events **Suchzeitraum:** bis März 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 2 RCTs (n = 1074) **Qualitätsbewertung der Studien:** The quality of trials was evaluated by two independent reviewers by examining the adequacy
	3. Ergebnisdarstellung **PFS** ⇒ 1053 patients were evaluable for PFS → the pooled OR of PFS was 2.50 (95% CI = 1.93 to 3.24, P < 0.00001), showing marked benefit of lenalidomide maintenance for improving PFS, with no statistically significant heterogeneity (P = 0.54, I^2 = 0%) **OS** ⇒ Although there was a trend toward increased OS with lenalidomide, a random-effects statistical model revealed that there was no statistically significant difference in OS between lenalidomide maintenance therapy arm and placebo maintenance therapy arm (OR = 1.21, 95% CI = 0.65 to 2.24, P = 0.54). Significant heterogeneity existed between the two trials (P = 0.04, I^2 = 76%)

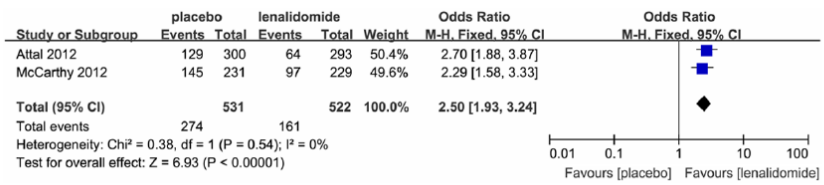


Figure 2. Pooled odd ratios of progression-free survival in the comparison of lenalidomide maintenance therapy arm and placebo maintenance therapy arm.

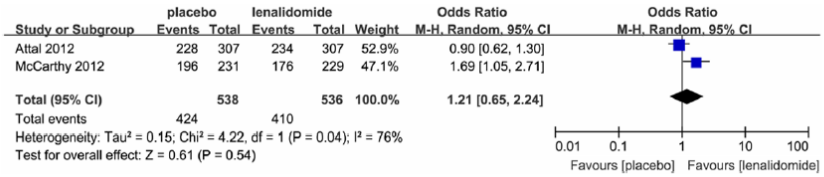


Figure 3. Pooled odd ratios of overall survival in the comparison of lenalidomide maintenance therapy arm and placebo maintenance therapy arm

Adverse effects

⇒ we found significant differences between lenalidomide and placebo arms, with more patients in the lenalidomide arm experiencing greater incidence of neutropenia (OR = 4.88, 95% CI = 3.67 to 6.50), infection (OR = 2.82, 95% CI = 1.67 to 4.73), hematologic cancers (OR = 3.31, 95% CI = 1.30 to 8.41), and solid tumors (OR = 2.24, 95% CI = 1.01 to 4.98)

⇒ No significant differences between lenalidomide and placebo arms were seen with deep vein thrombosis (OR = 2.15, 95% CI = 0.92 to 5.06), peripheral neuropathy (OR = 1.50, 95% CI = 0.53 to 4.25), thrombocytopenia (OR = 1.05, 95% CI = 0.12 to 9.54), or anemia (OR = 1.36, 95% CI = 0.02 to 83.86).

⇒ Among all the adverse events, significant heterogeneity was seen only with thrombocytopenia ($P < 0.0001$, $I^2 = 93\%$) and anemia ($P = 0.0001$, $I^2 = 93\%$).

4. Anmerkungen/Fazit der Autoren

⇒ In summary, we showed that lenalidomide maintenance therapy for patients with MM after ASCT improved PFS. However, treatment-related adverse events must be closely monitored and longer follow-up and additional high quality RCTs were needed to evaluate the effects of lenalidomide maintenance on OS.

5. Hinweise FB Med:

Leitlinien

NCCN, 2015 [9] Multiple Myeloma Version 4.2015	1. Fragestellung k.A.
	2. Methodik: **Grundlage der Leitlinie:** syst. Literaturrecherche (Update-Recherche) **Suchzeitraum:** Juli 2013 – Oktober 2014 **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.** **Eingeschlossene Studiendesigns:** Klinische Phase II-, III-& IV-Studien, Leitlinien, RCTs. Meta-Analysen, Systematische Übersichtsarbeiten, Validierungsstudien
	3. Ergebnisse ⇒ Die Therapie für Patienten mit einem mit refraktärem oder rezidiviertem MM ist abhängig von der klinischen Situation: a. Patients with relapsed disease after ASCT b. Patients with primary PD after initial ASCT c. Patients ineligible for ASCT for ASCT with progressive or relapsing disease after initial primary therapy 1. Bortezomib als Monotherapie für Patienten mit einem mit refraktärem oder rezidiviertem MM **(Category 1)** The phase III APEX trial compared bortezomib versus high-dose dexamethasone as therapy for relapsed disease.[69] Among the 669 participants, patients randomized to bortezomib had a combined CR and PR rate 38% vs. 18% for those receiving dexamethasone), improved median time to progression (6.22 vs 3.49 months) and one-year survival (80% vs. 66%). In an updated efficacy analysis,[196] the response rate was 43% with bortezomib versus 18% for dexamethasone ($P < .0001$). A CR or near-CR was observed in 16% versus 0% of relapsed patients, respectively. Median OS was 29.8 months with bortezomib and 23.7 months with dexamethasone, despite nearly two thirds of patients' crossing over to bortezomib. Survival rates after one year were 80% and 67%, respectively ($P = .00002$). Patients 2. Bortezomib mit PLD für Patienten mit einem mit refraktärem oder rezidiviertem MM **(Category 1)**

Bortezomib with PLD was approved by the FDA as a treatment option for patients with MM who have not previously received bortezomib and have received at least 1 prior therapy. The approval was based on a priority review of data from an international phase III trial (n = 646) showing that use of the combination significantly extended the median time to disease progression compared with bortezomib alone (9.3 vs. 6.5 months).[200] Median duration of response was increased from 7.0 months to 10.2 months with the combination therapy. Based on these

3. Bortezomib und Dexamethason für Patienten mit einem mit refraktärem oder rezidiviertem MM **(Category 2A)**

Addition of dexamethasone to bortezomib in patients with relapsed/ refractory myeloma who had PD during bortezomib monotherapy resulted in improvement of response in 18% to 34% of patients.[201-203] The NCCN Multiple Myeloma Panel Members have included the bortezomib and dexamethasone regimen as an option for patients with relapsed/refractory myeloma (category 2A).

4. Lenalidomide plus Dexamethason für Patienten mit einem mit refraktärem oder rezidiviertem MM **(Category 1)**

Lenalidomide combined with dexamethasone received approval from the FDA as a treatment option for patients with MM who had received at least one prior treatment. This was based on the results of two studies of a total of 692 patients randomized to receive dexamethasone either with or without lenalidomide. The primary efficacy endpoint in both studies was time to progression. A pre-planned interim analysis of both studies reported that the median time to progression was significantly longer in the lenalidomide arm compared to the control group.[204,205] The updated clinical data from the pivotal North American phase III trial (MM-009) in 353 previously treated patients with MM reported increased OS and median time to disease progression in patients receiving lenalidomide plus dexamethasone compared to patients receiving dexamethasone plus placebo.[205] Similar results were seen in the international trial MM-010.[204] Patients in both of these trials had been heavily treated before enrollment. Many had three or more prior lines of therapies with other agents and more than 50% of patients having undergone SCT.[204,205] Most adverse events and Grade 3/4 adverse events were more frequent in patients with MM who received the combination of lenalidomide/ dexamethasone compared to placebo and dexamethasone. Thrombocytopenia (61.5%) and neutropenia (58.8%) were the most frequently reported adverse events observed.

5. Bortezomib, Lenalidomid und Dexamethason für Patienten mit einem mit refraktärem oder rezidiviertem MM **(Category 2A)**

Data from preclinical studies showed lenalidomide sensitizes myeloma cells to bortezomib and dexamethasone. The results of phase I and phase II studies show that bortezomib, lenalidomide, and dexamethasone is well-tolerated and active, with durable responses in heavily pretreated patients with relapsed and/or refractory MM, including patients who have had prior lenalidomide, bortezomib, thalidomide, and SCT.[207,208] The updated data after over 2 years of follow-up report a median PFS of 9.5 months and median OS of 26 months, with 12- and 24-month OS rates of 86% and 55%, respectively.[209] The NCCN Multiple Myeloma Panel Members have included bortezomib, lenalidomide, and dexamethasone as a category 2A option for relapsed/refractory MM.

6. Cyclophosphamid & Dexamethason plus Lenalidomid oder Bortezomib für Patienten mit einem mit refraktärem oder rezidiviertem MM **(Category k.A.)**

The effects of adding of an alkylating agent (such as cyclophosphamide) and a novel agent (such as lenalidomide or bortezomib) to dexamethasone have been investigated for patients with relapsed/refractory MM. A retrospective analysis to assess the efficacy of lenalidomide in combination with cyclophosphamide and dexamethasone showed that this regimen is effective in heavily pre-treated patients with manageable adverse effects.[210] The combination of bortezomib, dexamethasone, and cyclophosphamide was found to be effective in patients with relapsed/refractory myeloma with an acceptable toxicity profile.[211,212] The NCCN Multiple Myeloma Panel Members have included cyclophosphamide, and dexamethasone in combination with either lenalidomide or bortezomib, to the list of options for relapsed/refractory MM.

7. Promalidomid plus Dexamethason für Patienten mit einem mit refraktärem oder rezidiviertem MM, die zuletzt zwei vorangegangene Therapie bekommen haben (immunomodulatory agent and Bortezomib. Have demonstrated disease progression on or within 60 days of completion of the last therapy **(Category 2A).**

Pomalidomide, like lenalidomide, is an analogue of thalidomide. It possesses potent immunomodulatory and significant anti-myeloma properties.[234] The results of a phase I study of pomalidomide (4 mg orally on days 1– 21 of each 28-day cycle), with or without dexamethasone (40 mg/week), showed encouraging activity with manageable toxicity in patients with relapsed refractory MM, including those refractory to both lenalidomide and bortezomib.[235] A subsequent phase II randomized, open-label study evaluated the combination of pomalidomide and low-dose dexamethasone versus single-agent pomalidomide in patients with relapsed, refractory MM who had received a trial of lenalidomide and bortezomib.[236] Of the 221 patients who were evaluated after a median follow-up of 14.2 months, the median PFS was 4.2 months in patients treated with pomalidomide plus low-dose dexamethasone compared with 2.7 months in patients

treated with pomalidomide (HR, 0.68; $P = .003$).[237] The median OS was 16.5 months compared to 13.6 months with pomalidomide alone.[237] Grade 3 to 4 neutropenia occurred in 41% of patients treated with pomalidomide plus low-dose dexamethasone versus 48% of patients treated with pomalidomide monotherapy. No grade 3 to 4 peripheral neuropathy was reported.

A phase III, multicenter, randomized, open-label study conducted in Europe compared the efficacy and safety of pomalidomide and low-dose dexamethasone (n=302) versus high-dose dexamethasone (n=153) in patients with relapsed MM who were refractory to both lenalidomide and bortezomib.[238] After a median follow-up of 10 months, PFS, the primary endpoint of the study, was significantly longer in patients who received pomalidomide and low-dose dexamethasone compared with those who received high-dose dexamethasone (4.0 vs. 1.9 months; HR, 0.45; $P < .0001$).[239] The most common hematologic grade 3 and 4 adverse effects found higher with the low-dose dexamethasone compared with the high-dose were neutropenia and pneumonia.[239] Other phase III studies of pomalidomide plus low-dose dexamethasone in combination with other agents (eg, bortezomib) are currently ongoing (Clinical Trial ID: NCT01734928).

4. Anmerkung FbMed

⇒ Zusammenfassung der Empfehlungen siehe Anhang (Abb. 1)

Kouroukis et al., 2013 [6] Bortezomib in Multiple Myeloma and Lymphoma	1. 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. **Frage:** **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? **III.** Which patients are more or less likely to benefit from treatment with bortezomib?
	2. Methodik: ⇒ The systematic review is a convenient and up-to-date source of the best available evidence on the role of bortezomib in the treatment of adult patients with MM and lymphoma. Grundlage der Leitlinie: syst. Literaturrecherche Suchzeitraum: Update-Recherche (2004 through August 2012) LoE & GoR: keine allgemeinen Kategorien; Bewertung und Empfehlungen werden narrativ vorgenommen Qualität der Studien: For the evaluation of the quality of included RCTs, we considered discrete parameters such as the 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. We did not perform quality assessments of single-arm phase II studies.
	3. Ergebnisse ⇒ In that report, the Hematology DSG recommended bortezomib monotherapy for patients with MM refractory to or relapsing within one year of the conclusion of initial or subsequent treatment(s) and who are candidates for further therapy. This recommendation was made based on the benefit in overall survival and TTP observed in the APEX trial ⇒ In relapsed and refractory myeloma, both bortezomib monotherapy and combination therapy with PLD are effective approaches. ⇒ the use of bortezomib alone for relapsed/refractory disease is recommended by the DSG. ⇒ In patients who are eligible for ASCT, bortezomib-based induction prior to transplantation is a recommended option. ⇒ the Hematology DSG does not recommend that bortezomib be used as first-line therapy outside the setting of a clinical trial. ⇒ For patients with myeloma refractory to or relapsing within one year of the

	conclusion of initial or subsequent treatment(s) (including autologous stem cell transplantation), who are candidates for further chemotherapy, bortezomib is recommended as the preferred treatment option. Bortezomib is also a reasonable option for patients relapsing at least one year after autologous stem cell transplantation. ⇒ For patients with myeloma refractory to or relapsing within one year of the conclusion of initial or subsequent treatment(s) (including autologous stem cell transplantation) who are candidates for further chemotherapy, bortezomib is recommended as the preferred treatment option. ⇒ Bortezomib is also a reasonable option for patients relapsing at least one year after autologous stem cell transplantation. The DSG is aware that thalidomide, alkylating agents, or repeat transplantation may also be options for these patients. However, evaluation of these other options is beyond the scope of this Practice Guideline. ⇒ For patients with myeloma relapsing at least one year after the conclusion of alkylating agent-based chemotherapy who are candidates for further chemotherapy, further treatment with alkylating agent-based chemotherapy is recommended. ⇒ 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 ⇒ 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.
	4. Anmerkung FbMed ⇒ Status der Leitline = „im Review“ ⇒ 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 et al., 2012 [1] SIE, SIES, GITMO evidence-based guidelines on novel agents (thalidomide, bortezomib, and lenalidomide) in the treatment of multiple	1. Fragestellung In this project, we produced drug-specific recommendations targeting the use of new agents for multiple myeloma (MM).
	2. Methodik **Grundlage der Leitlinie:** systematische Literaturrecherche innerhalb eines strukturierten Konsensusprozess (conceptual framework elements of the NIH Consensus Development Program)

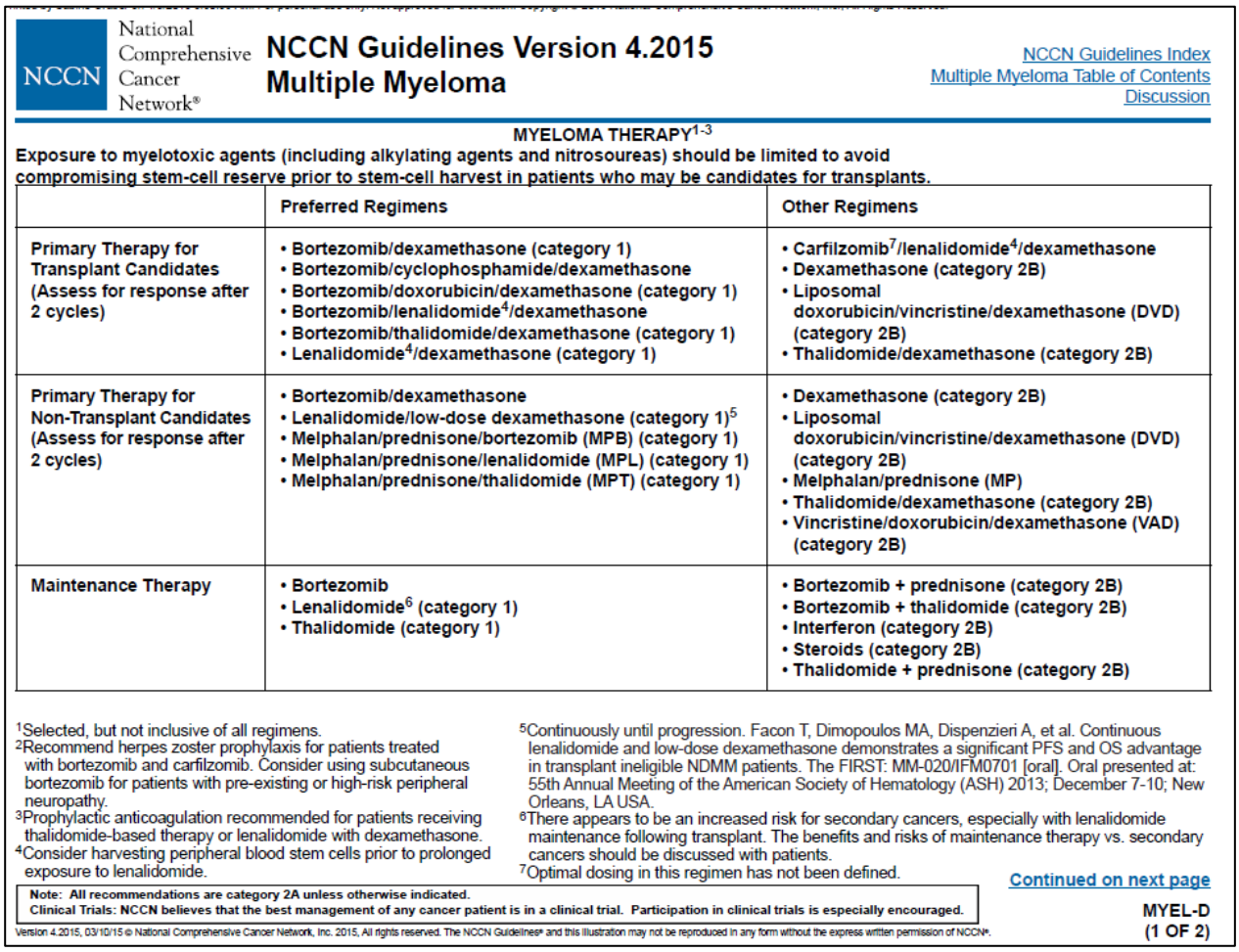
myeloma	**Table 1** Definition of project's objectives Presentation to panel members of the GRADE system Definition of the clinical questions Discussion of all the relevant outcomes and individual rating of the importance (relevance) of each outcome Systematic literature search and preparation of the evidence and summary of findings tables for each relevant outcome Individual rating of the quality of evidence for each relevant outcome and overall Individual rating of the balance of benefits and harms for each relevant outcome and overall Drafting of recommendations by individual panel's members, and individual rating of the strength of the recommendations Meetings to reach the final version of the recommendations by group discussion **Suchzeitraum**: bis 2011 (als Update einer Recherche aus 2005) **GoR:** We used the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system 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.
	3. Ergebnisse **Is the use of new agents recommended in patients refractory to or relapsing after first line therapy?** ⇒ The Panel claimed that from the evidence so far obtained, both bortezomib in combination with pegylated liposomal doxorubicin and lenalidomide dexamethasone combination should be recommended 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.
Chen et al., 2012 [2] Lenalidomide in Multiple Myeloma: Guideline Recommendations Report Date: May 30, 2012	1. 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:** **I.** 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? **II.** 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?
	2. Methodik Grundlage der Leitlinie: syst. Literaturrecherche Suchzeitraum: bis Feb.2012 LoE & GoR: keine allgemeinen Kategorien; Bewertung und Empfehlungen werden narrativ vorgenommen
	3. Ergebnisse **I.** Relapsed or refractory multiple myeloma. a) **Single-agent lenalidomide:** Lenalidomide alone for first-line therapy in myeloma cannot be recommended for standard use for patients with relapsed/refractory multiple myeloma b) **Lenalidomide and dexamethasone:** Lenalidomide plus dexamethasone is recommended for myeloma patients who have received at least one prior line of therapy. The recommended dose is lenalidomide 25 mg/day on days 1-21 plus dexamethasone, either low-dose 40 mg/day on days 1,8,15, and 22 or high-dose at 40 mg/day on days 1-4, 9-12, and 17-20, with either being given on a 28-day cycle. c) **Other lenalidomide combinations:** The combination of lenalidomide with other drugs is not recommended in this setting. **II.** Subgroups of patients most likely to benefit from treatment with lenalidomide. For patients with relapsed/refractory multiple myeloma, lenalidomide plus dexamethasone is a reasonable treatment option for the following patient subgroups: d) **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. e) Patients who have received prior thalidomide or autologous stem cell transplantation (ASCT). f) **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. g) **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. h) Patients with IgA subtype, pre-existing peripheral neuropathy, and different levels of Eastern Cooperative Oncology Group (ECOG) performance status.
	4. Anmerkung FbMed ⇒ Status der Leitline = „im Review“ → This document will be reviewed in three 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.

Anhang

Abb.1 Therapy for previously treated MM *(NCCN 2015)*



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Discussion

MYELOMA THERAPY[1-3]

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.

	Preferred Regimens	Other Regimens
Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide[4]/dexamethasone • Bortezomib/thalidomide/dexamethasone (category 1) • Lenalidomide[4]/dexamethasone (category 1)	• Carfilzomib[7]/lenalidomide[4]/dexamethasone • Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Thalidomide/dexamethasone (category 2B)
Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone • Lenalidomide/low-dose dexamethasone (category 1)[5] • Melphalan/prednisone/bortezomib (MPB) (category 1) • Melphalan/prednisone/lenalidomide (MPL) (category 1) • Melphalan/prednisone/thalidomide (MPT) (category 1)	• Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Melphalan/prednisone (MP) • Thalidomide/dexamethasone (category 2B) • Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
Maintenance Therapy	• Bortezomib • Lenalidomide[6] (category 1) • Thalidomide (category 1)	• Bortezomib + prednisone (category 2B) • Bortezomib + thalidomide (category 2B) • Interferon (category 2B) • Steroids (category 2B) • Thalidomide + prednisone (category 2B)

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
[3]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
[4]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[5]Continuously until progression. Facon T, Dimopoulos MA, Dispenzieri A, et al. Continuous lenalidomide and low-dose dexamethasone demonstrates a significant PFS and OS advantage in transplant ineligible NDMM patients. The FIRST: MM-020/IFM0701 [oral]. Oral presented at: 55th Annual Meeting of the American Society of Hematology (ASH) 2013; December 7-10; New Orleans, LA USA.
[6]There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.
[7]Optimal dosing in this regimen has not been defined.

Continued on next page

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

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MYEL-D
(1 OF 2)

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 08.04.2015**

#	Suchfrage
#1	MeSH descriptor: [Multiple Myeloma] explode all trees
#2	multiple or (plasma cell) or plasma-cell:ti
#3	myeloma or myelomas:ti
#4	#2 next #3
#5	multiple or (plasma cell) or plasma-cell:ab
#6	myeloma or myelomas:ab
#7	#5 next #6
#8	#1 or #4 or #7
#9	"Kahler Disease":ti or Myelomatosis:ti or Myelomatoses:ti
#10	"Kahler Disease":ab or Myelomatosis:ab or Myelomatoses:ab
#11	#8 or #9 or #10
#12	#11 from 2010 to 2015

SR, HTAs in Medline (PubMed) am 08.04.2015

#	Suchfrage
#1	Multiple Myeloma[MeSH Terms]
#2	Search ((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	(((((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	(#6 AND #7)
#9	#6 Filters: Meta-Analysis; Systematic Reviews; Technical Report
#10	(#8 OR #9)
#11	(#8 OR #9) Filters: published in the last 5 years

Leitlinien in PubMed (Medline) am 08.04.2015

#	Suchfrage
#1	Multiple Myeloma[MeSH Terms]
#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	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title])
#8	(#6 AND #7)
#9	(#6 AND #7) Filters: published in the last 5 years

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