Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-10-01-D-193 Pomalidomid

Stand: Juni 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pomalidomid 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:	
Pomalidomid L04AX06 IMNOVID®	Zugelassenes Anwendungsgebiet: IMNOVID® ist in Kombination mit Dexamethason indiziert für die Behandlung des rezidivierten und refraktären Multiplen Myeloms (MM) bei erwachsenen Patienten, die mindestens zwei vorausgegangene Therapien, darunter Lenalidomid und Bortezomib, erhalten haben und unter der letzten Therapie eine Progression gezeigt haben.
Chemotherapien	
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: […] – Remissionsinduktion bei Plasmozytom (auch in Kombination mit Prednison)
Melphalan L01AA03 Alkeran®	Multiples Myelom (Plasmozytom)
Doxorubicin L01DB01 Adrimedac®	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: […] – Fortgeschrittenes multiples Myelom Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Doxorubicin *(pegyliert liposomal)* L01DB Caelyx®	Caelyx ist indiziert: […] – In Kombination mit Bortezomib zur Behandlung des progressiven multiplen Myeloms bei Patienten, die zumindest eine vorangegangene Therapie erhalten haben, und die sich bereits einer Knochenmarkstransplantation unterzogen haben bzw. dafür ungeeignet sind.
Carmustin L01AD01 Carmubris®	CARMUBRIS ist zur unterstützenden Behandlung chirurgischer Operationen und Bestrahlungen, oder als Kombinationsbehandlung mit anderen Substanzen bei folgenden Gewebsneubildungen angezeigt: […] Multiples Myelom: in Kombination mit anderen Zytostatika und einem Nebennierenrindenhormon, besonders Prednison.
Vincristin L01CA02 Vincristinsulfat-Teva®	Vincristinsulfat-Teva ® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: […] – multiplem Myelom

Weitere antineoplastische Arzneimittel	
Lenalidomid L04AX04 Revlimid®	Multiples Myelom Revlimid 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.
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®	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 nach § 35a SGB V

Inhalt

Indikation für die Recherche bei 2015-B-046 Pomalidomid: 5
Berücksichtigte Wirkstoffe/Therapien: 5
Systematische Recherche: 6
IQWiG Berichte/ G-BA Beschlüsse 8
Cochrane Reviews 9
Systematische Reviews 9
Leitlinien 12
Detaillierte Darstellung der Recherchestrategie: 20
Literatur 22
Anhang 23

Indikation für die Recherche bei 2015-B-046 Pomalidomid:

in Kombination mit Dexamethason indiziert für die Behandlung des rezidivierten und refraktären Multiplen Myeloms (MM) bei erwachsenen Patienten, die mindestens zwei vorausgegangene Therapien, darunter Lenalidomid und Bortezomib, erhalten haben und unter der letzten Therapie eine Progression gezeigt haben

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle 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 08.05.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), NVL (ÄZQ), 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, 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 418 Treffer, welche anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Die erste Durchsicht ergab 105 eingeschlossene Quellen, die anschließend im Volltext überprüft wurden. Daraus konnten 8 Referenzen in die synoptische Evidenz-Übersicht aufgenommen werden.

Abkürzungen

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
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
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
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MM	Multiple myelom
NCCN	National comprehensive cancer network
NCI	U.S. National Cancer Institute
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NVL	Nationale VersorgungsLeitlinien
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
TRIP	Turn Research into Practice Database
TTP	Time to progression
TTR	Time to response
UE	Unerwünschtes ereignis
QOL	Quality of life
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2014: [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 – Pomalidomid
20. Februar 2014

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.

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

Studienergebnisse nach Endpunkten[1,2]:

Interventionsgruppe (Pomalidomid + niedrig-dosiertes Dexamethason) N=302[3]		Kontrollgruppe (hoch-dosiertes Dexamethason) N=153[3]		Intervention vs. Kontrolle
Mortalität				
Gesamtüberleben (OS)				
Nach medianer Nachbeobachtungszeit von 18,1 Wochen[4]				
Todesfälle n (%)	OS in Wochen Median [95% KI]	Todesfälle n (%)	OS in Wochen Median [95% KI]	HR [95% KI] p-Wert
76 (25,2%)	n.e. [48,1;n.e.]	58 (37,9%)	34,0 [23,4;39,9]	0,53 [0,37;0,74] p<0,001
Nach medianer Nachbeobachtungszeit von 10,0 Monaten[5]				
OS in Monaten Median [95% KI]		OS in Monaten Median [95% KI]		HR [95% KI] p-Wert AD
12,7 [10,4;15,5]		8,1 [6,9;10,8]		HR=0,74 [0,56;0,97] p=0,0285 AD: 4,6 Monate
Morbidität				
Progressionsfreies Überleben (PFS)				
Progress/Tod n (%)	Wochen Median [95% KI]	Progress/Tod n (%)	Wochen Median [95% KI]	HR [95% KI] p-Wert AD
164 (54,3%)	15,7 [13,0;20,1]	103 (67,3%)	8,0 [7,0;9,0]	0,45 [0,35;0,59] p<0,001 AD: 7,7 Wochen
Gesundheitsbezogene Lebensqualität[6]				
EORTC QLQ-30: Keine signifikanten Unterschiede bei 13 von 15 Subskalen. Bei Subskala "Physische Funktion" Unterschied zugunsten von Pomalidomid, bei Subskala "Übelkeit und Erbrechen" zuungunsten von Pomalidomid. EORTC QLQ-MY20 und EQ 5D: keine signifikanten Unterschiede.				

Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

Systematische Reviews

Knopf et al., 2014: [5] Meta-Analysis of the Efficacy and Safety of Bortezomib Re-Treatment in Patients With Multiple Myeloma	1. Fragestellung Here we report a systematic literature review and meta-analysis that assesses the efficacy and safety of bortezomib-based retreatment in patients with relapsed and/or refractory MM with previous exposure to bortezomib.
	2. Methodik **Population:** Bortezomib-based therapy in patients with relapsed and/or refractory MM **Intervention:** Bortezomib **Komparator:** bortezomib with or without dexamethasone or combination therapy **Endpunkte:** efficacy and safety (ORR; partial response or better), adverse events (AEs), time to progression (TTP), progression-free survival (PFS), and overall survival (OS). **Suchzeitraum:** bis Mai 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 studies (Berücksichtigung unterschiedlicher Studiendesigns) **Qualitätsbewertung der Studien:** k.A.
	3. Ergebnisdarstellung ⇒ Patients who were defined as bortezomib-refractory after their initial bortezomib treatment were included **in 11 studies**, in which they comprised between 10% and 100% of the patient population. ⇒ Retreatment comprised bortezomib with or without dexamethasone in 4 studies and combination therapy in 19 studies. ⇒ Six studies included only patients whose disease had relapsed after their initial bortezomib treatment. ⇒ In the remaining 6 studies, data were not available on the refractory status of patients after initial bortezomib therapy

Table 2 Pooled, Weighted Average ORR and Pooled, Weighted Average Median TTP and OS (Overall and by Stratified Univariate Analysis of Prognostic Factors)

Patient Groups	ORR, % (95% CI)	Median TTP, Months	Median OS, Months
All Patients	39.1 (30.8-47.4)	7.5	16.6
Bortezomib-Refractory Status			
0% (Relapsed only)[b]	57.2 (45.1-69.4)	8.5	19.7
<50% Refractory	28.3 (11.7-44.8)	–	–
≥50% to <100% Refractory	18.9 (12.8-25.0)	5.9	20.4
100% (Refractory only)	22.6 (10.7-34.4)	–	11.2
Unknown	49.3 (40.2-58.4)	6.0	–
Previous Therapies			
≤4	43.4 (31.4-55.5)	8.2	13.3
>4	29.2 (12.7-45.7)	7.1	20.0
Unknown	45.1 (31.8-58.4)	5.6	–
Patients With Previous ASCT			
<50%	55.8 (40.5-71.0)	8.8	19.7
≥50%	19.5 (12.9-26.0)	6.4	15.9
Unknown	45.3 (33.7-56.9)	5.8	13.0
Time Since Last Bortezomib			
<9 Months	49.3 (33.4-65.1)	9.5	19.7
≥9 Months	43.5 (31.2-55.8)	7.3	–
Unknown	29.7 (20.3-39.1)	5.9	15.4
Therapy Received			
Bortezomib with or without dex	50.7 (38.4-63.0)	7.9	19.2
Combination	35.6 (27.0-44.3)	7.1	16.1

Abbreviations: ASCT = autologous stem cell transplantation; dex = dexamethasone; ORR = overall response rate; OS = overall survival; TTP = time to progression.
[a]Pooled, weighted average data are shown from studies in which data were available; not all studies reported data for each of the end points.
[b]Analyses were not conducted according to specific response to previous bortezomib because of limited data availability.

⇒ Compared with studies including relapsed patients only, studies including patients refractory to bortezomib were associated with lower ORR by 28 to 41 percentage points (< 50% refractory: -33.20; P = .044; ≥50% to <100% refractory: -41.34%; P= .035).

Table 4 Pooled Weighted Analysis of the Subset of Studies of Bortezomib With Dexamethasone Retreatment in an Elderly Population (Median Age > 65 Years) With a Low Percentage of Previous Autologous Stem Cell Transplantation

	Hrusovsky et al[12]	Petrucci et al[34]	Pooled Estimate
Study Characteristics			
Sample size, n	60	126	
Regimen	Bortezomib with dex	Bortezomib with dex	
Study design	Chart review and survey	Phase 2 trial	
Median age at retreatment, years	66.2	67	
Bortezomib-refractory patients, %	0	0	
Median time since last bortezomib, months	8.6	13.9	
Median number of previous therapies, n	4.7	2	
Patients with previous ASCT, %	27	30	
Response and Outcomes			
ORR, %	63.3	39.7	51.1
Median TTP, months	9.3	7.9	8.4
Median OS, months	19.2	–	19.2

Abbreviations: ASCT = autologous stem cell transplantation; dex = dexamethasone; ORR = overall response rate; OS = overall survival; TTP = time to progression.

⇒ In studies of bortezomib with or without dexamethasone in patients with a median age > 65 years and with a lower percentage of patients receiving previous ASCT (-30%), retreatment remained active. The pooled average ORR was 51%. Median TTP and OS were 8.4 and 19.2 months, respectively.

⇒ The findings of our analyses indicate that bortezomib retreatment is efficacious in the subset of patients whose disease had relapsed after, but who were not refractory to, their previous bortezomib therapy. The pooled, weighted average ORR in these patients was 57.2%, and the pooled weighted average median TTP and OS were 8.5 and 19.7 months, respectively.

	4. Anmerkungen/Fazit der Autoren ⇒ The findings of this systematic literature review and meta-analysis demonstrate that bortezomib-based retreatment is effective and generally well tolerated in relapsed and/or refractory MM patients with previous exposure to bortezomib ⇒ The pooled, weighted average ORR of 39% is notable in this setting, in the context of the ORRs of 43% and 52% reported with I.V. bortezomib with or without dexamethasone in bortezomib-naive patients with 1 to 3 previous therapies in the APEX and MMY-3021 phase III studies, respectively.35,36 ⇒ However, it should be highlighted that at least 5 of the studies of bortezomib retreatment in this meta-analysis only included patients who had previously responded to bortezomib (i.e., patients who might have been inherently more sensitive to bortezomib). ⇒ Retreatment with bortezomib alone or in combination appeared to be effective and well tolerated, especially in relapsed MM patients, with an ORR of 57.2% and median TTP and OS of 8.5 and 19.7 months, respectively. In an era of new and emerging treatment options for relapsed and/or refractory MM, these data indicate that bortezomib retreatment might be an effective therapeutic option in previously treated MM patients.
	5. Hinweis FBMed ⇒ Keine Angaben zur Qualität Studien ⇒ Keine Klinische Phase 3 Studien

Leitlinien

NCCN, 2015: [8] 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 2A)**

	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)
Bird et al., 2014: [1] Guidelines for the	1. Fragestellung k.A.

diagnosis and management of multiple myeloma 2014	2. Methodik In 2006 guidelines for the diagnosis and management of multiple myeloma were published (Smith et al, 2006). These current guidelines represent a major revision. The guideline has been split into 2 documents, focussing on the 'Diagnosis and management of multiple myeloma' and 'Supportive care in multiple myeloma 2011' (Snowden et al 2011). They are designed to be used together and to complement each other. This current guideline has undergone addendums. The first addendum in 2013 was a change to section 2.4 (pages 7-8) and changing levels of evidence to the GRADE system. The second addendum in 2014 was a change to section 7.1.2 (page 22) and section 9.4 (pages 35-36). **GoR** **Strong (grade 1):** Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'. **Weak (grade 2):** Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'. **LoE** **(A) High** Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations. **(B) Moderate** Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis),or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient). **(C) Low** Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.
	3. Ergebnisse Because of disease heterogeneity and variability in patient-specific factors including co-morbidities and the persistence of toxicities related to previous therapy, there can be no standard approach recommended for the treatment at relapse (GRADE: k.A.) ⇒ The most appropriate management should be determined on an individual basis depending on the timing of relapse, age, prior therapy, BM function and co-morbidities, and patient preference **(Grade A1)** ⇒ Extensive trial data support the use of thalidomide, bortezomib and lenalidomide-based regimens as treatment modalities at first and subsequent relapse **(Grade A1)** ⇒ Clinical effectiveness of thalidomide, bortezomib and lenalidomide is not dependent on the number of previous lines of therapy, or type of therapy previously received. **(Grade C2)** ⇒ Unless contraindicated, treatment with thalidomide, bortezomib or

	lenalidomide treatment should be delivered with dexamethasone +/- chemotherapy to increase the response rate. **(Grade A1)** ⇒ A second ASCT may be considered in patients who had a good response to the initial transplant procedure (≥18 months to disease progression)**(Grade B1)** ⇒ Where possible, patients should be treated in the context of a clinical trial. Phase I/II trials are appropriate for patients with relapsed/refractory myeloma **(Grade A1)** ⇒ Good supportive therapy is essential **(Grade A1)**
	4. Anmerkung FbMed
Kouroukis et al., 2013: [7] Bortezomib in Multiple Myeloma and Lymphoma (siehe auch: Kouroukis et al., 2014: [6] Bortezomib in multiple myeloma: a practice guideline)	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
Chen et al., 2012: [2] Lenalidomide in Multiple Myeloma: Guideline Recommendations Report Date: May 30, 2012 (siehe auch: Chen et	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-

al., 2013: [3] Lenalidomide in multiple myeloma: a practice guideline)	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.

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**

Suchschritt	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

Suchschritt	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

Suchschritt	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

Literatur

1. **Bird J, Owen RG, D'Sa S, Snowden JA, Ashcroft J, Yong K, Cook G, Feyler S, Davies F, Morgan G, Cavenagh J, Low E, Behrens J, Jenner M, Pratt G, on behalf of the Haematooncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum**. Guidelines for the diagnosis and management of multiple myeloma 2014. London (GBR): BCSH 2014; http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf, Zugriff am 08.05.2015.

2. **Chen C, Baldassarre F, Kanjeekal S, Herst J, Hicks L, Cheung M, and the Hematology Disease Site Group**. Lenalidomide in multiple myeloma (Evidence-Based Series 6-5). Toronto (CAN): Cancer Care Ontario 2012; https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=137819, Zugriff am 08.05.2015.

3. **Chen C, Baldassarre F, Kanjeekal S, Herst J, Hicks L, Cheung M**. Lenalidomide in multiple myeloma-a practice guideline. Curr Oncol 2013; 20 (2): e136-e149.

4. **Gemeinsamer Bundesausschuss (G-BA)**. 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 - Pomalidomid vom 20. Februar 2014. Berlin (GER): G-BA 2014; http://www.g-ba.de/downloads/39-261-1931/2014-02-20_AM-RL-XII_Pomalidomid_2013-09-01-D-075.pdf, Zugriff am 06.05.2015.

5. **Knopf KB, Duh MS, Lafeuille MH, Gravel J, Lefebvre P, Niculescu L, Ba-Mancini A, Ma E, Shi H, Comenzo RL**. Meta-analysis of the efficacy and safety of bortezomib re-treatment in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk 2014; 14 (5): 380-8.

6. **Kouroukis CT, Baldassarre FG, Haynes AE, Imrie K, Reece DE, Cheung MC**. Bortezomib in multiple myeloma: a practice guideline. Clin Oncol (R Coll Radiol) 2014; 26 (2): 110-9.

7. **Kouroukis CT, Cheung M, Reece D, Baldassarre FG, Hayes AE, Imrie K, Cheung M, and the members of the Hematology Disease Site Group**. Bortezomib in multiple myeloma and lymphoma (Evidence-Based Series 6-18, Version 2). Toronto (CAN): Cancer Care Ontario 2013; https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34323, Zugriff am 08.05.2015.

8. **National Comprehensive Cancer Network (NCCN)**. Multiple Myeloma (Version 4.2015). NCCN Clinical Practice Guidelines in Oncology. Toronto (CAN): NCCN 2015; http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf, Zugriff am 08.05.2015.

Anhang

Abb.1 Therapy for previously treated MM *(NCCN 2015)* [8]

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
Therapy for Previously Treated Multiple Myeloma	• Repeat primary induction therapy (if relapse at >6 mo) • Bortezomib (category 1) • Bortezomib/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1) • Bortezomib/thalidomide/dexamethasone • Carfilzomib • Carfilzomib/lenalidomide/dexamethasone (category 1) • Cyclophosphamide/bortezomib/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide • Lenalidomide/dexamethasone[9] (category 1) • Panobinostat/bortezomib/dexamethasone[10] (category 1) • Pomalidomide[11]/dexamethasone • Thalidomide/dexamethasone[9]	• Bendamustine • Bortezomib/vorinostat • Lenalidomide/bendamustine/dexamethasone

[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.
[8]Consideration for appropriate regimen is based on the context of clinical relapse.
[9]Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.
[10]Indicated in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.
[11]Indicated for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

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.

MYEL-D
(2 OF 2)

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2015
Multiple Myeloma

NCCN Guidelines Index
Multiple Myeloma Table of Contents
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.

MYEL-D
(1 OF 2)