Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-243-z Daratumumab

Stand: November 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Daratumumab **[in Kombination mit Bortezomib, Melphalan und Prednison zur Behandlung erwachsener Patienten mit neu diagnostiziertem multiplem Myelom, die für eine autologe Stammzelltransplantation nicht geeignet sind]** **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	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Daratumumab L01XC24 Darzalex®	<u>Zu bewertendes Anwendungsgebiet:</u> • Darzalex® ist indiziert in Kombination mit Bortezomib, Melphalan und Prednison für die Behandlung erwachsener Patienten mit neu diagnostiziertem Multiplen Myelom, die für eine autologe Stammzelltransplantation nicht geeignet sind. <u>Weitere zugelassene Anwendungsgebiete:</u> DARZALEX ist indiziert: • als Monotherapie für die Behandlung erwachsener Patienten mit rezidiviertem und refraktärem multiplen Myelom, die bereits mit einem Proteasom-Inhibitor und einem Immunmodulator behandelt wurden, und die während der letzten Therapie eine Krankheitsprogression zeigten. • in Kombination mit Lenalidomid und Dexamethason oder Bortezomib und Dexamethason für die Behandlung erwachsener Patienten mit multiplem Myelom, die bereits mindestens eine Therapie erhalten haben.
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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
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
Bendamustin L01AA09 Bendamustin Kabi	Primärtherapie bei multiplem Myelom (Durie-Salmon-Stadium II mit Progression oder Stadium III) in Kombination mit Prednison, bei Patienten im Alter über 65 Jahren, bei denen eine autologe Stammzelltransplantation nicht in Frage kommt und die zum Zeitpunkt der Diagnose eine klinische Neuropathie aufweisen, die die Anwendung von Thalidomid oder Bortezomib-haltigen Regimen ausschließt.
Weitere antineoplastische Arzneimittel	
Thalidomid L04AX02 Thalidomide Celgene	Thalidomide Celgene in Kombination mit Melphalan und Prednison ist indiziert für die Erstlinienbehandlung von Patienten mit unbehandeltem multiplen Myelom ab einem Alter von ≥ 65 Jahren bzw. Patienten, für die eine hochdosierte Chemotherapie nicht in Frage kommt.
Lenalidomid L04AX04 Revlimid®	<u>Multiples Myelom</u> Revlimid als Monotherapie ist indiziert für die Erhaltungstherapie von erwachsenen Patienten mit neu diagnostiziertem multiplem Myelom nach einer autologen Stammzelltransplantation. Revlimid als Kombinationstherapie (siehe Abschnitt 4.2) ist indiziert für die Behandlung von erwachsenen Patienten mit unbehandeltem multiplem Myelom, die nicht transplantierbar sind. […]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Bortezomib L01XX32 Velcade®	VELCADE ist in Kombination mit Melphalan und Prednison für die Behandlung erwachsener Patienten mit bisher unbehandeltem multiplen Myelom indiziert, die für eine Hochdosis-Chemotherapie mit hämatopoetischer Stammzelltransplantation nicht geeignet sind. VELCADE ist in Kombination mit Dexamethason oder mit Dexamethason und Thalidomid für die Induktionsbehandlung erwachsener Patienten mit bisher unbehandeltem multiplen Myelom indiziert, die für eine Hochdosis-Chemotherapie mit hämatopoetischer Stammzelltransplantation geeignet sind. […]
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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Immunstimulanzien	
Interferon alfa-2b L03A B05 IntronA®	Multiples Myelom Als Erhaltungstherapie bei Patienten, die nach einer initialen Induktions-Chemotherapie eine objektive Remission erreichten (mehr als 50%ige Reduktion des Myelomproteins). Gegenwärtige klinische Erfahrungen zeigen, dass eine Erhaltungstherapie mit Interferon alfa-2b die Plateauphase verlängert; jedoch wurden Effekte auf die Gesamtüberlebenszeit nicht endgültig bewiesen. […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-243-z (Daratumumab)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	24.08.2018

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

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Multiples Myelom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 26.03.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 575 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation für die Synopse:

zur Behandlung von Patienten mit neu diagnostiziertem multiplem Myelom, die für eine Stammzelltransplantation nicht geeignet sind.

Abkürzungen:

AE	Adverse events
ASCT	autologous stem cell transplantation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
CI	Confidence Interval
CON	Consolidation
CR	Complete Response
Cy-Dex	cyclophosphamide plus dexamethasone
DAHTA	DAHTA-Datenbank
EFS	Event free survival
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GvHD	graft-versus-host disease
HDT	High dose therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LEN	Lenalidomide
MM	Multiples Myelom
MRD	Minimal Residual Disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nCR	Near Complete Response
NDMM	Newly diagnosed multiple myeloma
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall Survival
PAD	bortezomib, adriamycin and dexamethasone
PFS	Progression Free Survival
RCT	Randomized controlled trial
RR	Relative Risk
SIGN	Scottish Intercollegiate Guidelines Network
SPM	secondary primary malignancy
TRIP	Turn Research into Practice Database
TTP	Time to progression
VBMCP-VBAD-B	doxorubicin, dexamethasone/bortezomib
VCD	Bortezomib, cyclophosphamide and dexamethasone
VDCR	bortezomib, dexamethasone and lenalidomide
VGPR	very good partial response
VTD	bortezomib/thalidomide/dexamethasone
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2017 [6]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden Krankenhausbehandlung: Stammzelltransplantation bei Multiplem Myelom. Vom 19. Januar 2017	Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 19. Januar 2017 beschlossen: I. Die Richtlinie des G-BA zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung) in der Fassung vom 21. März 2006 (BAnz.2006 S. 4466), zuletzt geändert am 15. September 2016 (BAnz AT 22.12.2016 B2), wird wie folgt geändert: In der Anlage II (Methoden, deren Bewertungsverfahren ausgesetzt sind) werden 1.im Abschnitt A (Aussetzung im Hinblick auf laufende oder geplante Studien) nach der Nummer 11.1 folgende Nummern 11.2 und 11.3 angefügt: „11.2 Autologe Mehrfachtransplantation (Tandemtransplantation) bei Multiplem Myelom Beschluss gültig bis 30. Juni 2022 11.3 Allogene Stammzelltransplantation bei Multiplem Myelom in der Erstlinientherapie Beschluss gültig bis 30. Juni 2022 (verbunden mit Beschluss zur Qualitätssicherung gemäß § 136 SGB V)“ (…)
IQWiG, 2015 [7]. Stammzelltransplantation bei Multiplem Myelom – Update (Rapid Report) Siehe auch: **IQWiG, 2011 [8]**	**Fragestellung:** Ziel der vorliegenden Untersuchung war die Beantwortung der Frage, ob und gegebenenfalls welche Änderungen des Fazits des Abschlussberichts N05-03C und des Arbeitspapiers GA11-01 sich aus zwischenzeitlich publizierter Literatur zum Thema des Auftrags N05-03C ergeben. **Methoden:** Für den vorliegenden Rapid Report fand im Grundsatz die gleiche Methodik Anwendung wie im Auftrag N05-03C. **Ergebnisse:** In den Bericht konnten für 9 mögliche verschiedene Vergleiche randomisierte kontrollierte Studien (RCT), kontrollierte klinische Studien (CCT) oder vergleichende Studien unterhalb des Evidenzniveaus eines CCT (sogenannte non-CCT) als relevante wissenschaftliche Literatur in die Bewertung einfließen. Dabei wurden Studien mit niedrigerem Evidenzgrad ausschließlich in die Bewertung einbezogen, wenn Studien mit höherem Evidenzgrad nicht in ausreichender Zahl und / oder Qualität für einen Vergleich vorlagen. Zu 3 von 9 Fragestellungen lagen weder zum Zeitpunkt des Abschlussberichts N05-03C noch bei Erstellung des Arbeitspapiers GA11-01 oder dieses Rapid Reports Daten vor. Dies betraf die folgenden Fragestellungen: • allogene Stammzelltransplantation mit nicht verwandtem Spender versus medikamentöse Therapie, • myeloablative allogene Stammzelltransplantation mit nicht verwandtem Spender versus autologe Stammzelltransplantation und • allogene Stammzelltransplantation mit dosisreduzierter Konditionierung versus medikamentöse Therapie. Zu 3 weiteren Fragestellungen konnten im Abschlussbericht N05-03C Studien identifiziert und für die Nutzenbewertung verwendet werden. Weitere Studien wurden hierzu im Rahmen der Update-Recherche nicht gefunden. Die Gesamtaussagen des Abschlussberichts N05-03C änderten sich daher nicht. → **Ergebnisse aus dem Abschlussbericht:** Alle Aussagen beziehen sich in erster Linie auf eine Stammzelltransplantation bei nicht vorbehandelten Patienten (bei 2 Vergleichen auch auf Mischpopulationen aus vor- und nicht vorbehandelten Patienten, in keinem Fall jedoch auf therapierefraktäre Patienten) mit Hinblick auf patientenrelevante Zielgrößen (Gesamt-überleben, ereignisfreies Überleben oder eine vergleichbare Zielgröße, unerwünschte Ereignisse sowie gesundheitsbezogene Lebensqualität). Für keinen Vergleich

	fanden sich Studien, die eine Aussage über die Lebensqualität der Betroffenen erlaubt hätten. Eine Bewertung des Stellenwerts der gemäß Leitlinien als Erstlinientherapie empfohlenen autologen Stammzelltransplantation (im Vergleich zu Nicht-Transplantationsstrategien) war nicht Gegenstand des Berichts. Folglich wurde die Bedeutung, die die autologe Stammzelltransplantation als Erstlinientherapie in Kombination mit und im Vergleich zu den *neueren* Substanzen (Thalidomid, Lenalidomid, Bortezomib u. a.) haben könnte, nicht untersucht. Zum Vergleich der zweifachen versus einfachen autologen Stammzelltransplantation wurden neben 2 in die Nutzenbewertung eingeschlossenen Studien 3 weitere, zwar seit Jahren abgeschlossene, aber bisher nicht im Volltext publizierte Studien identifiziert, die zusätzlich ca. dieselbe Anzahl von Patienten einschlossen. Trotz Autorenanfrage wurden keine Studienberichte oder bisher nicht öffentlich zugänglichen Manuskripte zur Verfügung gestellt. Da zudem die verfügbaren Informationen andeuten, dass die Ergebnisse dieser Studien nicht positiv sind, kann ein relevanter Publikationsbias nicht ausgeschlossen werden. Auch für die Kombination bestehend aus autologer und allogener Stammzelltransplantation mit *dosisreduzierter Konditionierung* wurden zusätzlich zu 4 in die Nutzenbewertung eingeschlossenen Studien 3 weitere Studien identifiziert, die in etwa dieselbe Anzahl von Patienten einschlossen, aber noch nicht im Volltext publiziert wurden. Von 2 dieser Studien wurde kürzlich eine finale Analyse vorgestellt, von der dritten Studie steht bisher nur eine Interimsanalyse zur Verfügung. Da damit für beide Fragestellungen die Bewertung nur auf Basis eines relevant unvollständigen Studienpools erfolgen konnte, kann in beiden Fällen kein Beleg oder Hinweis bzw. Anhaltspunkt für einen Zusatznutzen oder Schaden einer der beiden Therapieoptionen festgestellt werden. Für die allogene Stammzelltransplantation ließen sich mangels Studien keine Aussagen zur Verwendung *nicht verwandter* Spenderquellen treffen. Sofern *verwandte* Spender als Stammzellquelle eingesetzt wurden, ergaben sich für die allogene Stammzelltransplantation mit myeloablativer Konditionierung Anhaltspunkte für eine relevante Unterlegenheit hinsichtlich des Gesamtüberlebens und unerwünschter Ereignisse. Diese Unterlegenheit fand sich sowohl im Vergleich zur autologen Stammzell-transplantation als auch im Vergleich zur nicht myeloablativen Chemotherapie. Für die ausschließlich bei der allogenen Stammzelltransplantation auftretende GVHD (Grad III–IV) wurde ein Schaden als belegt angesehen. Dies muss vor dem Hintergrund einer fehlenden Überlegenheit der allogenen Stammzelltransplantation bei den anderen betrachteten Zielgrößen gesehen werden. Ein Einsatz der allogenen Stammzelltransplantation ist beim derzeitigen Kenntnisstand für die Indikation Multiples Myelom nur im Rahmen von klinischen Studien zu vertreten. Eine wesentliche Anforderung an künftige Studien sind die Erhebung von Lebensqualitätsdaten und die Verwendung randomisierter Studienkonzepte. Dies gilt umso mehr, als die Erkrankung auch heute noch für die meisten Patienten als unheilbar angesehen wird. **Ergebnisse aus dem Rapid Report →** Zu den drei übrigen Fragestellungen konnten durch die Update-Recherche weitere Studien identifiziert werden: *Allogene Stammzelltransplantation mit verwandtem Spender versus allogene Stammzelltransplantation mit nicht verwandtem Spender:* Es konnte in der Update-Recherche eine kleine retrospektive Studie (non-CCT) identifiziert werden (El-Cheikh 2012). In der Studie fand sich für keinen der berichteten Endpunkte wie Gesamtüberleben, therapie- beziehungsweise

	transplantationsbezogene Mortalität oder Spender-gegen-Wirt-Erkrankung (GvHD) ein statistisch signifikanter Unterschied. Es konnte für keinen Endpunkt ein Anhaltspunkt für einen Nutzen oder Schaden ermittelt werden. *Allogene Stammzelltransplantation mit dosisreduzierter Konditionierung versus allogene Stammzelltransplantation mit myeloablativer Konditionierung:* Es konnte zusätzlich zu den 3 bereits im Abschlussbericht N05-03C eingeschlossenen Studien (Badros 2002, Crawley 2007, Shaw 2003) eine weitere Publikation identifiziert werden (Bensinger 2012). Bei der Studie handelte es sich ebenso wie bei den 3 anderen um einen non-CCT. Bezüglich der Endpunkte Gesamtüberleben, therapiebezogene Mortalität und GvHD wies sie in dieselbe Richtung wie die 3 zuvor eingeschlossenen Studien. Zudem berichtete die neu eingeschlossene Bensinger-2012-Studie als einzige Studie innerhalb dieser Fragestellung Daten zu schwerwiegenden unerwünschten Ereignissen. Alle schwerwiegenden unerwünschten Ereignisse wie tödlich verlaufende Infektionen (26 % vs. 4 %), multiples Organversagen (11 % vs. 0 %), idiopathisches Pneumoniesyndrom (6 % vs. 0 %) und tödlich verlaufende akute GvHD (13 % vs. 0 %) traten in der Gruppe mit allogener Stammzell-transplantation und myeloablativer Konditionierung statistisch signifikant häufiger auf als in der Gruppe mit allogener Stammzelltransplantation und dosisreduzierter Konditionierung. Einzig die tödlich verlaufende chronische GvHD (1 % vs. 9 %) kam in letztgenannter Gruppe statistisch signifikant häufiger vor als in der Gruppe mit allogener Stammzelltransplantation und myeloablativer Konditionierung. Aufgrund der insgesamt geringen qualitativen Ergebnissicherheit hat sich die Gesamtbewertung des Abschlussberichts N05-03C nicht geändert: Es konnte bei dieser Fragestellung zu keinem der Endpunkte ein Anhaltspunkt für einen Nutzen oder Schaden abgeleitet werden. Zur gesundheitsbezogenen Lebensqualität oder zu psychosozialen Aspekten fanden sich in den eingeschlossenen Studien keine Angaben *Allogene Stammzelltransplantation mit dosisreduzierter Konditionierung versus autologe Stammzelltransplantation:* In insgesamt 6 Studien wurde die allogene Stammzelltransplantation mit dosisreduzierter Konditionierung mit einer autologen Stammzelltransplantation verglichen. 4 dieser Studien waren bereits Bestandteil des Abschlussberichts N05-03C (Björkstrand 2011, Bruno 2007, Garban 2006, Rosinol 2008). Eine weitere wurde im Arbeitspapier GA11-01 evaluiert (BMT CTN 0102). In der Update-Recherche zu diesem Rapid Report wurde neben einem Studien-Update zur Björkstrand-2011-Studie eine sechste Studie identifiziert (HOVON 50/54). Bei allen Studien handelte es sich um kontrollierte klinische Studien, wobei 2 die Kriterien einer sogenannten genetischen randomisierten Studie erfüllten. Bezüglich des Gesamtüberlebens ergab sich insgesamt ein uneinheitliches Bild mit einem statistisch signifikanten Ergebnis (Bruno 2007: Hazard Ratio = 0,5, 95 %-Konfidenzintervall [0,3; 0,8], p-Wert < 0,001) zugunsten einer Behandlungsstrategie mit Hybridtransplantation (auto-allo-RIC) im Vergleich zu einer zweifachen autologen Stammzelltransplantation (auto-auto). In der Studie Björkstrand 2011, in der die Patienten im Kontrollarm fakultativ eine einfache oder zweifache autologe Stammzelltransplantation erhalten hatten, war bis zu einer Nachbeobachtungszeit von ca. 33 Monaten ein numerischer Vorteil der (auto-)auto-Gruppe zu beobachten (vgl. Abschlussbericht N05-03C). Nach diesem Zeitpunkt zeichnete sich ein numerischer Vorteil der auto-allo-RIC-Gruppe ab, der zum Zeitpunkt von 8 Jahren nach der ersten Transplantation statistisch signifikant war (p-Wert = 0,03). In den 4 anderen Studien (BMT CTN 0102, Garban 2006, HOVON 50/54, Rosinol 2008) ergaben sich keine statistisch signifikanten Unterschiede zwischen den Behandlungsgruppen. Die in diesem Rapid Report neu hinzugewonnenen Informationen aus der HOVON-50/54-Studie und dem Studien-Update zur Björkstrand-2011-Studie änderten gegenüber dem Arbeitspapier GA11-01 die Ableitung der Beleglage nicht: Die Studien ergaben einen Hinweis darauf, dass die Behandlungsstrategie mit dosisreduzierter Konditionierung und allogener Stammzelltransplantation im

	Vergleich zu einer (zweifachen) autologen Stammzelltransplantation einen Zusatznutzen im Gesamtüberleben bietet. Der Anteil aller therapiebezogenen Todesfälle war in allen Studien, die die Ergebnisse zu diesem patientenrelevanten Endpunkt berichteten, in der auto-allo-RIC-Gruppe tendenziell höher als in der (auto-)auto-Gruppe. In 3 Studien (BMT CTN 0102, Björkstrand 2011, HOVON 50/54) wurden statistisch signifikante Nachteile für die auto-allo-RIC-Gruppe berichtet ($p < 0,001$), wobei sich dieser Nachteil in der BMT-CTN-0102-Studie nur auf einen Teil der Patienten bezog. Bei Björkstrand 2011 wurden statistische Analysen nur für die 2-, 3- und 5-Jahres-Raten, aber nicht für die 8-Jahres-Raten berichtet. Die in diesem Rapid Report neu hinzugewonnenen Informationen aus der HOVON-50/54-Studie und dem Studien-Update zur Björkstrand-2011-Studie änderten die Ableitung der Beleglage des Arbeitspapiers GA11-01 nicht: Unverändert lässt die vorhandene Evidenz den Hinweis darauf zu, dass die allogene Stammzelltransplantation und dosisreduzierte Konditionierung (nach vorausgehender autologer Stammzelltransplantation) im Vergleich zu einer (zweifachen) autologen Stammzelltransplantation eine erhöhte therapiebezogene Mortalität und damit einen Schaden nach sich zieht. Sekundäre Neoplasien wurden in keiner Studie berichtet. Zu schwerwiegenden Infektionen und weiteren Grad-3- bis Grad-5-Toxizitäten kamen in diesem Rapid Report keine neuen Informationen hinzu, weshalb die Bewertung des Arbeitspapiers GA11-01 bestehen blieb: Die Datenlage war unzureichend und es fand sich somit kein Anhaltspunkt für einen Nutzen oder Schaden. Der Anteil der akuten GvHD (Grad II–IV) und der chronischen GvHD (extensiv) in der auto-allo-RIC-Gruppe hatte eine Spannbreite von 11 bis 48 % und 23 bis 66 %. Die in diesem Rapid Report neu hinzugewonnenen Informationen aus der HOVON-50/54-Studie und dem Studien-Update zur Björkstrand-2011-Studie änderten die Ableitung der Beleglage des Arbeitspapiers GA11-01 nicht: Dieser für die allogene Stammzelltransplantation spezifische Nebenwirkungsaspekt tritt unter der Vergleichsbehandlung nicht auf und wurde somit als Beleg für einen Schaden der allogenen Stammzelltransplantation und dosisreduzierter Konditionierung nach vorausgehender autologer Stammzelltransplantation gewertet. Zur gesundheitsbezogenen Lebensqualität oder zu psychosozialen Aspekten fanden sich in den eingeschlossenen Studien keine Angaben. **Gesamtfazit:** Unter Berücksichtigung der zwischenzeitlich publizierten und in diesem Rapid Report neu eingeschlossenen Studien änderte sich gegenüber den früheren Berichten für keine der 9 Fragestellungen die Ableitung der Beleglage oder das Fazit.

Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

Systematische Reviews

Al-Ani et al., 2017 [1]. Post-transplant consolidation plus lenalidomide maintenance vs lenalidomide maintenance alone in multiple myeloma: A systematic review	1. Fragestellung to compare the efficacy of post-ASCT consolidation plus lenalidomide maintenance (CON+LEN) vs lenalidomide maintenance alone (LEN alone) in NDMM.
	2. Methodik Population: adult patients with NDMM treated with ASCT Intervention / Komparator: LEN maintenance following transplant with or without post-transplant consolidation or LEN maintenance alone Endpunkte: PFS, OS, CR, MRD, adverse events Recherche: a systematic literature search to identify potential studies in MEDLINE (1946 to 2015), EMBASE (1946 to 2015), CENTRAL (1946 to 2015) using an OVID interface (1946 to 2015). → The search was conducted in April 2016 and updated in May 2017. Anzahl eingeschlossene Studien/Patienten (Gesamt): Fourteen studies were included with 2275 participants with NDMM treated with ASCT and lenalidomide maintenance Qualitätsbewertung der Studien: The methodological quality of the selected single arm phase II studies was assessed according to Newcastle-Ottawa Quality Assessment Scale.
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: Overall, the risk of bias for the included RCT was low. However, it is noteworthy to state that the adequate sequence generation, allocation concealment and blinding of participants were unclear in most RCTs. The methodological quality of single arm phase II studies was good in regards to representativeness of exposed cohort and adequacy of follow-up. Nevertheless, overall, the missing information in the 7 included abstracts hampers proper assessment of studies' quality. • Two groups were identified: CON+LEN group (n = 1102) and LEN alone group (n = 1173). • No statistically significant difference in the complete response rate between the two groups. • Interestingly, we found that very good partial response or better rate is around 1.5-fold significantly higher in the CON+LEN group compared to

	LEN alone group [RR: 1.46; 95% CI: 1.25-1.70; P < .0001]. • No significant difference between the two groups regarding PFS and OS at 3-4 years follow-up. • The risk of secondary primary malignancy (SPM) was also similar between the two groups. Data on adverse events were limited.
	4. Fazit der Autoren: We acknowledge that the data we are presenting in this systematic review are still immature, as the included studies report on 3 to 4 years of follow-up only. It is still too soon for anyone to draw any firm conclusion about the usefulness of consolidation therapy post-transplant. Overall, our analysis demonstrated deepening of the responses with consolidation, but this did not translate into improved PFS and OS; however, the benefit of depth of response was not confirmed by MRD negativity due insufficient data. The risk of toxicities associated with additional consolidation therapy should also be considered. Future studies on post-transplant consolidation should highlight the MRD and survival endpoints, as well as the risk stratification for potential individualized decisions on consolidation treatment.
Zeng et al., 2017 [17]. Induction regimens for transplant-eligible patients with newly diagnosed multiple myeloma: a network meta-analysis of randomized controlled trials	1. Fragestellung to compare the early efficacy and survivals of induction regimens for transplant-eligible patients with untreated multiple myeloma
	2. Methodik Population: the participants were transplant-eligible patients with newly diagnosed MM Intervention/ Komparator: different pre-ASCT induction therapies Endpunkte: ORR, PFS, OS Recherche: PubMed, Embase, and Cochrane Library until 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 RCTs that included 4,763 patients were analyzed Qualitätsbewertung der Studien: Cochrane Collaboration's tool for assessing the risk of bias was used to evaluate the quality of the included trials
	3. Ergebnisdarstellung Qualität der Studien: The included RCTs had low risks of selection bias about random sequence generation, attrition bias, reporting bias, and other biases, in which the rates of low risk were 100%, 92.3%, 92.3%, and 76.9%, respectively. Studies without clear information on allocation concealment, performance bias and detection bias accounted for 53.8%, 92.3%, and 92.3%, respectively. Netzwerkmetaanalyse:

	• *13 included trials were able to be used to evaluate ORR:* For the pairwise comparison of regimens, VTD had significantly higher ORR than other regimes, except for VDCR and VDR to which the superiority was non-significant. VDR, VDCR, VDC, VD, VBMCP-VBAD-B, TD, RD, and PAD had significantly higher ORR than VAD, Dex, and Cy-Dex. TAD showed significantly higher ORR than Cy-Dex and VAD, but had significantly poorer ORR than PAD, VBMCP-VBAD-B, VDC, VDCR, VDR, and VTD. Meanwhile, VDCR had significantly higher ORR than VDR. VBMCP-VBAD-B resulted in significantly better ORR than VD and TD. No statistically significant difference was found for other comparisons. VTD was ranked the best regimen in terms of ORR. • *Eight studies involving 10 regimens were included in NMA for OS:* Results showed that VTD was significantly better than TAD and VAD, and PAD was also significantly superior to VAD. Meanwhile, Cy-Dex had a shorter OS than the other nine regimens. On the other hand, there was no statistically significant difference among VTDC, Cy-Dex, Dex, VD, VBMCP-VBAD-B, PAD, VTD, and TD. VTDC was ranked the best regimen for OS with relatively higher probability. • *Eight out of 14 trials reported data on PFS*: PAD, VD, VTD, VBMCP-VBAD-B, TAD, and VTDC had significant superiority when compared with TD (Table S3). PAD, VD, VTD, VBMCP-VBAD-B, TAD, and VTDC had significantly better PFS than TD. Furthermore, TAD and PAD resulted in significantly better PFS than VAD. VBMCP-VBAD-B had significantly better PFS than VTD. No statistically significant difference was found for other comparisons. TAD was ranked the best regimen for PFS with relatively higher probability.
	4. Fazit der Autoren: The NMA demonstrated that the VTD, VTDC, and TAD regimens are most beneficial in terms of ORR, OS, and PFS for transplant-eligible patients with NDMM, respectively. 5. Kommentare zum Review • Many comparisons in the NMA were based on single study • the survival of NDMM could be influenced by transplantation schemes, consolidation therapy, and maintenance therapy
Liu et al., 2017 [11]. Comparing efficacy and survivals of initial treatments for elderly patients with newly diagnosed multiple myeloma: a network meta-analysis of	1. Fragestellung to evaluate the efficacy and clinical outcome of initial therapies for elderly patients with multiple myeloma (MM)
	2. Methodik Population: elderly patients with newly diagnosed MM who were unsuitable for HDT Intervention/Komparator: initial therapy for MM patients Endpunkte: CR/nCR, ORR, PFS and OS Recherche: PubMed, Embase, and the Cochrane Library and the Science

randomized controlled trials.	Citation Index as well as relevant websites until 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 19 RCTs containing 7,235 participants and 17 treatments Qualitätsbewertung der Studien: Jadad scale
	3. Ergebnisdarstellung Qualität der Studien: Jadad Scale: maximal score for an included study was 5 and studies were classified on the basis of quality as high (score: 3–5) versus low (score: 0–2). As compared to the classic melphalan plus prednisone (MP) regimen, the majority of other initial regimens showed higher rates of complete response/near complete response, overall response rate (ORR) and better PFS as well as OS • These four outcomes favored the two lenalidomide plus dexamethasone regimens (continuous lenalidomide and 18 cycles of lenalidomide plus dexamethasone), especially continuous lenalidomide plus dexamethasone regimen, over the majority of other regimens including the two established standard treatments (MP plus thalidomide or bortezomib) for elderly patients with newly diagnosed MM.
	4. Fazit der Autoren: Our NMA demonstrated that the two lenalidomide plus dexamethasone initial treatments (18 cycles of lenalidomide plus dexamethasone and continuous lenalidomide plus dexamethasone), especially the continuous lenalidomide plus dexamethasone, resulted in better efficacy and prognosis for the elderly patients with MM.
Liu et al., 2015 [12]. Bortezomib-based vs non-bortezomib-based post-transplantation treatment in multiple myeloma patients: a systematic review and meta-analysis of Phase III randomized controlled trials	1. Fragestellung to evaluate the efficacy and safety of bortezomib-based vs non-bortezomib-based post-transplantation therapy in patients with multiple myeloma.
	2. Methodik Population: the participants were patients with newly diagnosed MM of any stage and who had been treated with induction chemotherapies followed by ASCT Intervention: bortezomib-containing regimens Komparator: placebo or other non-bortezomib-containing regimens Endpunkte: PFS/EFS (event-free survival), OS as well as response rate of CR/nCR, VGPR (very good partial response), and PR (partial response), adverse events Recherche: PubMed, Embase, the Cochrane Library and the Science Citation Index, and other relevant websites until 2014

	Anzahl eingeschlossene Studien/Patienten (Gesamt): Three randomized controlled trials comprising 1,518 participants Qualitätsbewertung der Studien: Jadad scale
	3. Ergebnisdarstellung Qualität der Studien: Jadad scale: the maximal score for an included study was 5 and studies were classified on the basis of quality as high (score: 3–5) vs low (score: 0–2). ORR: The adjusted pooled OR for overall response rate (CR/nCR+VGPR+PR) was 1.85 (95% CI: 1.29–2.64), and the pooled ORs for consolidation and maintenance therapy studies were 1.63 (95% CI: 0.81–3.82) and 1.93 (95% CI: 1.28–2.92), respectively. Moreover, from the cumulative forest plot, OR has an increasing trend as consolidation studies are added. Pooled OR from cumulative analysis of consolidation therapy was 1.63 (95% CI: 0.81–3.82), and no significant difference was found. After adding the maintenance treatment study conducted by Pieter Sonneveld, the OR was larger than 1 (OR =1.85, 95% CI: 1.29–2.64). On the other hand, our integrate analysis demonstrated that the rate of CR/nCR in bortezomib-based groups was significantly higher than that in non-bortezomib-based groups (53.0% vs 39.8%, *P*,0.001), and the pooled OR for the rates of CR/nCR was 1.75 (95% CI: 1.42–2.15), and the pooled ORs for consolidation and maintenance therapy studies were 1.62 (95% CI: 1.18–2.22) and 1.86 (95% CI: 1.40–2.46), respectively. Meanwhile, the cumulative meta-analysis indicated that the beneficial effect of bortezomib-based post-transplantation treatment was more obvious when it was administrated as maintenance treatment with more narrow confidence interval (OR =1.75, 95% CI: 1.42–2.15 vs OR =1.62, 95% CI: 1.18–2.22). PFS: All the included three trials reported PFS, and the pooled HR for PFS shown in Figure 3A was 0.73 (95% CI: 0.67–0.81), indicating that there was a 27% reduction in the risk of disease progression or death with bortezomib-based therapy after ASCT. Moreover, the pooled ORs for consolidation and maintenance therapy studies were 0.73 (95% CI: 0.65–0.81) and 0.75 (95% CI: 0.63–0.90), respectively. Meanwhile, pooled HR from the cumulative meta-analysis for PFS confirmed the beneficial effect of bortezomib-based over non-bortezomib-based post-transplantation therapy. OS: All the three trials reported 3-year OS, and all the trials claimed that there was no statistical difference between experimental and control groups, which is consistent with our traditional and cumulative meta-analysis (HR for 3-year OS

	was 0.78, 95% CI: 0.57–1.06, *P*=0.90) The pooled HRs for consolidation and maintenance therapy studies were 0.81 (95% CI: 0.53–1.25) and 0.75 (95% CI: 0.48–1.16), respectively. <u>Adverse events:</u> Incidence rates of overall adverse events and grade 3 and 4 peripheral neuropathy were similar in the bortezomib-based groups and the non-bortezomib-based groups (P=0.12 and P=0.41, respectively).
	4. Fazit der Autoren: In conclusion, post-transplantation therapy (especially maintenance therapy) with bortezomib-based regimen contributes to improved response rate and PFS with a favorable safety profile. However, prolonged follow-up period is required to confirm the beneficial effect of bortezomib-based post-transplantation therapy conferred on OS.
Kouroukis et al., 2014 [9]. Bortezomib in multiple myeloma: systematic review and clinical considerations	1. Fragestellung to determine the appropriate use of bortezomib alone or in combination with other agents in patients with multiple myeloma (MM).
	2. Methodik Population: patients with MM Intervention: bortezomib as a single agent Komparator: bortezomib in combination with other regimens Endpunkte: survival, QoL, disease control (for example, TTP), response duration, response rate, and adverse effects Recherche: MEDLINE [Ovid (October 2004 through August 2012)], EMBASE [Ovid (2004 week 42 through August 27, 2012], and Cochrane Library (August 2012) databases. In addition, conference proceedings of the American Society of Clinical Oncology (2005–2012) and the American Society of Hematology (2005–2011) and reference lists from the selected sources were searched for relevant trials Anzahl eingeschlossene Studien/Patienten (Gesamt): The literature search identified twenty-six unique studies: three guidelines based on systematic reviews, six systematic reviews, seventeen RCTs and forty-seven related publications. Seven abstract publications of interim analyses of ongoing trials were also identified. 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 / AMSTAR Tool for systematic reviews

	3. Ergebnisdarstellung Qualität der Studien: Two trials reported in abstract form were randomized noncomparative phase II trials. Because the authors of those trials did not compare the treatment. Nine studies were available as fully published reports. Eight of the nine fully published RCTs reported the a priori sample size required to find a statistically significant difference in the primary endpoints: TTP, progression-free survival (PFS), complete response (CR), pharmacokinetics and pharmacodynamics, and response rate. Eight of the nine studies presented a final analysis, and seven of the eight conducted an intention-to-treat analysis. Three studies were terminated early because the intervention significantly improved TTP. One study conducted a blinded outcomes assessment16, and three studies reported concealment of allocation. None of the studies reported a loss to follow up exceeding 8%. The included studies were funded by pharmaceutical companies, government or philanthropic organizations, or by a foundation. Among the studies reported in abstract form, one study stated that the analysis was final. The other five were identified as interim. *Hinweis: Ergebnisdarstellung fokussiert auf unbehandelte/de novo MM Patienten die für eine Transplantation geeignet sind.* **Previously Untreated MM:** *Indirect Comparison*: The network meta-analysis by Kumar et al. indirectly compared bortezomib and thalidomide (both in combination with melphalan and prednisone) in newly diagnosed mm patients. No differences were detected for most outcomes, but benefits in CR [relative risk (RR): 2.34; 95% confidence interval (CI): 1.12 to 4.90] and in grade 3 or 4 adverse events (RR: 0.53; 95% ci: 0.38 to 0.73) were observed in favour of the bortezomib combination. *Direct Comparison*: Eleven RCTs—nine full-text publications and two abstracts examined the use of bortezomib in patients with de novo MM. • (…)Transplantation Therapy: Six RCTs enrolled younger untreated mm patients who were candidates for ASCT **Studienergebnisse:** ***TTP:*** None of the studies involving patients who were candidates for ASCT reported on this endpoint. ***Overall Survival:*** (…) In the studies of transplant patients, Sonneveld *et al.*31 demonstrated a statistically significant difference in OS (HR: 0.77; 95% ci: 0.60 to 1.00; p = 0.049); in the other studies, median OS was not significantly different for the control groups or was not estimable. *Quelle:* *31. Sonneveld P, Schmidt–Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol 2012;30:2946–55* ***PFS:*** (…) Among the studies of patients who were candidates for ASCT, Sonneveld *et al.*31 found a significantly longer PFS in patients allocated to

	bortezomib, doxorubicin, and dexamethasone than in patients allocated to vincristine, doxorubicin, and dexamethasone (HR: 0.74; 95% CI: 0.62 to 0.89; *p* < 0.001). Cavo *et al.*15 suggested a significantly better PFS, projected to be 36 months, for bortezomib, dexamethasone, and thalidomide compared with dexamethasone and thalidomide (HR: 0.63; 95% CI: 0.45 to 0.88; *p* < 0.006). Harousseau *et al.*16 compared a bortezomib–dexamethasone combination with a vincristine–doxorubicin–dexamethasone combination, but PFS did not reach statistical significance in favour of the bortezomib arm (*p* = 0.057). In an abstract publication, Rosinol *et al.*84 found that PFS was statistically significantly longer in the bortezomib–thalidomide arm than in the thalidomide-alone or interferon arms (PFS at 2 years: 78% vs. 63% vs. 49%; *p* = 0.01). *Quellen:* *15. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010;376:2075–85.* *16. Harousseau JL, Attal M, Avet–Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol 2010;28:4621–9.* *31. Sonneveld P, Schmidt–Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized* *84. Rosinol L, Cibeira MT, Mateos MV, et al. A phase III PETH-EMA/GEM randomised trial of posttransplant maintenance in multiple myeloma: superiority of bortezomib. Bone Marrow Transplant 2012;47:S2.* ***QOL:*** Health-related QOL was measured using various domains of the European Organisation for Research on Treatment of Cancer Quality of Life Questionnaire–Core (QLQ-C30)88 in two studies 47,76. In a sub-analysis of the vista trial24, Dhawan *et al.*47 showed that newly diagnosed mm patients treated with bortezomib, melphalan, and prednisone had a higher sustained rate of improvement in health-related QoL than did patients treated with melphalan and prednisone (14 of 15 domains). They also reported a statistically significant improvement in 3 domains: Nausea/Vomiting (*p* = 0.0095), Appetite Loss (*p* = 0.0170), and Diarrhea (*p* = 0.0082)47. Niesvitsky *et al.*76 found no statistically significant differences between arms. *Quellen:* *24. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906–17.* *47. Dhawan R, Robinson D Jr, Meunier J, et al. Sustained health-related quality of life (HRQoL) improvement in newly diagnosed multiple myeloma patients treated with bortezomib/melpha- lan/prednisone versus melphalan/prednisone: results from the VISTA trial [abstract 1881]. Blood 2009;114:.* *76. Niesvizky R, Flinn IW, Rifkin R, et al. Patient-reported quality of life (QOL) in elderly, newly diagnosed multiple myeloma (MM) patients receiving bortezomib-based combinations: results from all randomized patients in the community-based,phase 3b UPFRONT study [abstract 1864]. Blood 2011;118:.*

	88. Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. Int J Gynecol Cancer 2003;13:741–8 ***Response Rate:*** (…) Among patients who were candidates for transplantation, Harousseau *et al.*16 found a statistically significant difference in CR in favour of a bortezomib–dexamethasone combination both after induction and after a first transplant (induction: 14.8% vs. 6.4%, p = 0.004; first transplant: 16.1% vs. 8.7%, p = 0.016). Sonneveld *et al.*31 found a statistically significant difference in CR in favour of bortezomib at induction and at maintenance (7% vs. 2% and 21% vs. 9% respectively, $p < 0.001$). For or after first transplant, no statistically significant difference was detected16. Cavo *et al.*15 reported a significant difference in CR in favour of bortezomib–dexamethasone–thalidomide compared with thalidomide–dexamethasone at induction, after first transplantation, at second transplantation after consolidation, and overall. Moreau *et al.*28 found no statistically significant difference in CR and objective response rate between study arms. *Quellen:* *15. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010;376:2075–85.* *16. Harousseau JL, Attal M, Avet–Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol 2010;28:4621–9.* *28. Moreau P, Avet–Loiseau H, Facon T, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood 2011;118:5752–8,5982.* *31. Sonneveld P, Schmidt–Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol 2012;30:2946–55.*
	4. Fazit der Autoren: (…) In patients who are eligible for ASCT, bortezomib-based induction before transplantation is a recommended option.
Qiao et al., 2015 [15]. Efficacy and Safety of Lenalidomide in the Treatment of Multiple Myeloma: A Systematic Review and Meta‐analysis of Randomized	1. Fragestellung to evaluate efficacy and safety of lenalidomide for MM using a meta‐analysis.
	2. Methodik Population: Patients with newly diagnosed or previously treated MM Intervention/Komparator: Lenalidomide‐containing regimens versus non-lenalidomide‐containing regimens for newly diagnosed or relapsed/refractory MM treated with standard chemotherapy (other drugs of

Controlled Trials Siehe auch: **Gao et al. 2014 [5] & Yang et al. 2013 [16]**	these regimens must be the same), or lenalidomide maintenance therapy versus placebo for MM after ASCT Endpunkte: overall response (OR), complete response (CR), PFS, OS, and Grade 3 or 4 toxicities Recherche: PubMed, EMBASE and the Cochrane Center Register of Controlled Trials updated to May 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): Seven randomized clinical trials were identified, which included a total of 2357 patients with MM who received lenalidomide‐ containing, noncontaining lenalidomide regimens or placebo as induction therapy or maintenance therapy. Qualitätsbewertung der Studien: Jadad quality scores
	3. Ergebnisdarstellung Qualität der Studien: **Table 1: Characteristics of included studies in the meta-analysis** **Previous untreated multiple myeloma** • Three RCTs, with a total of 544 patients, suggested that lenalidomide‐ containing regimens achieved a statistically significant higher OR rates (pooled RR: 1.49; 95% CI: 1.30–1.71; P < 0.00001, incidence, 75.5% vs. 50.6%) and CR rates (pooled RR: 4.08; 95% CI: 2.02–8.23; P < 0.0001, incidence, 13.4% vs. 3.4%) compared with the no lenalidomide‐ containing regimens. There was no significant heterogeneity among the reported OR and CR. • Considering the differences in consolidation/maintenance therapy after initial induction therapy and follow‐ up time, we did not perform meta‐ analyses for PFS and OS for previous untreated MM. **Maintenance therapy for multiple myeloma post autologous stem cell transplantation** • Two RCTs reported the data of a total of 1074 patients with MM after ASCT, who received lenalidomide or placebo as maintenance therapy. We did not perform meta‐ analyses for OR and CR in MM patients post‐ ASCT because the relevant data could not be obtained from the study by

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

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

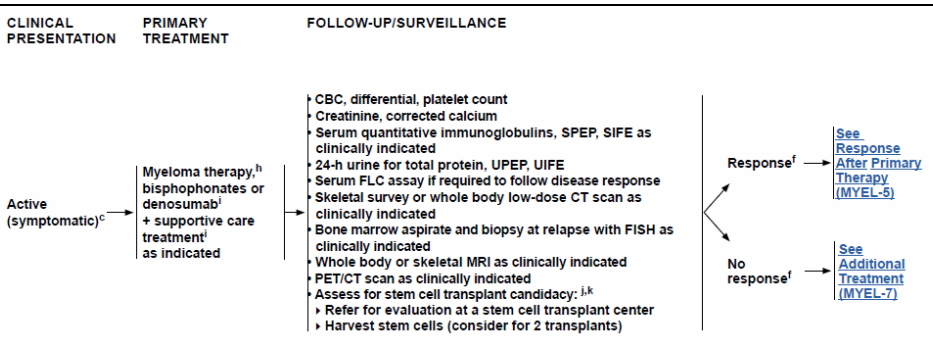
	McCarthy et al. • Lenalidomide maintenance therapy significantly improved 3‐year PFS (pooled RR: 1.43; 95% CI: 1.28–1.60; P < 0.00001; P heterogeneity = 0.43; I2 = 0%) among patients post‐ASCT, but not significantly improved OS. There was a significant heterogeneity (I2 = 84%) with respect to the reported OS rate, so the random‐effects model was used. **Toxizität:** • The data of major AEs were extracted from the seven RCTs and analyzed by a meta‐analysis. • As for hematological AEs, patients treated with lenalidomide had a significantly higher rate of Grade 3–4 neutropenia, febrile neutropenia, anemia, and thrombocytopenia. Of those, neutropenia was the most common (48.9% vs. 14.7%; *P* < 0.00001), followed by thrombocytopenia (17.4% vs. 7.4%; *P* < 0.00001). • With regard to nonhematological AEs: lenalidomide treatment was associated with a significantly higher rate of grade 3/4 infection, DVT and diarrhea. Of those, infection is the most common (14.3% vs. 7.7%; *P* < 0.0001), followed by DVT (6.2% vs. 2.3%; *P* = 0.0001). • Non-hematological AEs: Also, three trials and a second analysis of two trials by Dimopoulos *et al*. reported data on SPMs. There were 75 and 25 SPMs, respectively, observed in a sample of 1042 patients with lenalidomide therapy and 1035 patients with placebo. Lenalidomide therapy had a significantly higher risk of SPMs (pooled RR: 2.92; 95% CI: 1.87–4.56; P < 0.00001; incidence, 7.2% vs. 2.4%). • Heterogeneity was found for some AEs, which was possibly because of the use of different agents at various dosages in these studies.
	4. Fazit der Autoren: This meta‐analysis demonstrates that lenalidomide‐containing regimens were associated with better response rates and survival rates with acceptable toxicity rates for the induction treatment of MM. However, lenalidomide maintenance therapy does not improve OS at the price of the increased AEs. Continued studies are needed to ascertain whether lenalidomide maintenance therapy is beneficial to MM patients after ASCT.
Leiba et al., 2014 [10]. Bortezomib-Cyclophosphamide-Dexamethasone (VCD) versus Bortezomib-Thalidomide-Dexamethasone (VTD) –based regimens as induction therapies	1. Fragestellung to undertake a meta-analysis of the currently available literature, in order to compare the response rates and toxicity profiles of both the VCD and VTD regimens as induction therapies in transplant-eligible, newly diagnosed MM patients.
	2. Methodik Population: patients with newly diagnosed transplant-eligible MM Intervention/Komparator: VTD vs. VCD Endpunkte: complete response (CR)/near complete response (nCR), very good partial response (VGPR), partial response (PR) and the overall response rate (ORR), overall grade 3–4

in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis	adverse events and grade 3–4 neuropathy Recherche: PubMed, Medline, EMBASE and the Cochrane central register of trials, and the American Society of Hematology, the American Society of Clinical Oncology and the European Haematology Association web sites. The last search was performed on January 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): Eight clinical trials were eligible for analysis. Overall 672 patients were treated with either VCD (n = 157) or VTD (n = 515) as induction therapy. Qualitätsbewertung der Studien: The quality of the study methods was assessed based on the method of randomization, allocation concealment, blinding, number of dropouts, other risks of bias, and whether intention-to-treat analysis
	3. Ergebnisdarstellung Qualität der Studien: k.A. • Patients treated with VTD presented with a significantly higher complete/near complete response (34% vs. 6%, P = 0,002) as well as a higher very good partial response rate or better, following induction therapy (62% vs. 27%, P < 0,0001). • Although grade 3–4 neurotoxicity was more frequent during VTD therapy (11% vs. 6%, P = 0,057), a higher incidence of overall grade 3–4 adverse events was found in the VCD-treated patients (74% vs. 51%,P < 0,001).
	4. Fazit der Autoren: In summary, in this meta-analysis comparing VTD versus VCD induction therapy in newly diagnosed, transplant-eligible MM patients, VTD induction therapy showed higher CR/nCR and VGPR rates. Borderline significant differences in grade 3–4 neurotoxicity were found between the two regimens. Larger studies will be needed to re-examine this issue. Overall, the rates of severe adverse events were significantly higher in the VCD regimen compared to the VTD regimen. Our findings provide support for the superiority of VTD as an induction regimen in newly diagnosed MM patients without an extra burden of toxicity. In light of the limited number of trials and their heterogeneity, randomized controlled trials are needed to confirm these results.

Leitlinien

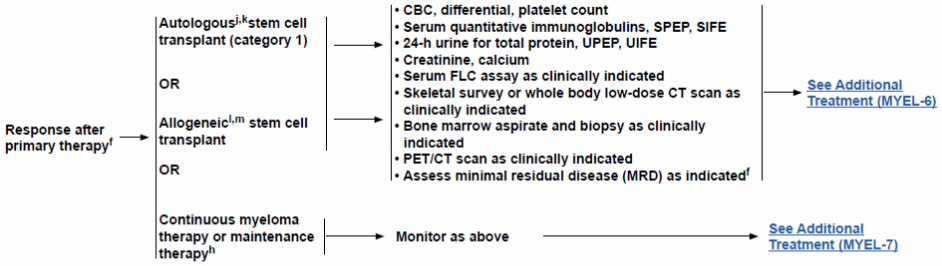
NICE, 2018 [14]. Myeloma: diagnosis and management	Fragestellung/Zielsetzung: This guideline covers the diagnosing and managing of myeloma (including smouldering myeloma and primary plasma cell leukaemia) in people aged 16 and over. It aims to improve care for people with myeloma by promoting the most effective tests and treatments for myeloma and its complications.
	Methodik Grundlage der Leitlinie Methodenreport beschreibt systematische Evidenzaufbereitung und Konsensusprozesse (je nach Bedarf formal oder informal) - eigene Checklisten Anwendung von GRADE GoR schlagen sich in den Formulierungen wider ""To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations."
	Managing newly diagnosed myeloma **First-line treatment** 1.5.1 Bortezomib is recommended as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. [This recommendation is from Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (NICE technology appraisal guidance 311).] 1.5.2 Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma inpeople for whom high-dose chemotherapy with stem cell transplantation isconsidered inappropriate. [This recommendation is from Bortezomib and thalidomide for the first-line treatment of multiple myeloma (NICE technology appraisal guidance 228).] 1.5.3 Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if: • high-dose chemotherapy with stem cell transplantation is considered inappropriate and • the person is unable to tolerate or has contraindications to thalidomide. [This recommendation is from Bortezomib and thalidomide for the first-line treatment of multiple myeloma (NICE technology appraisal guidance 228).]

	First autologous stem cell transplantation 1.5.4 Consider using frailty and performance status measures that include comorbidities to assess the suitability of people with myeloma for first autologous stem cell transplant. 1.5.5 Do not use age or the level of renal impairment alone to assess the suitability of people with myeloma for first autologous stem cell transplant. **Allogeneic stem cell transplantation** 1.5.6 Take into account that only a small number of people with myeloma are suitable for allogeneic stem cell transplantation. 1.5.7 When assessing whether people with myeloma are suitable for an allogeneic stem cell transplant, take into account: • whether the person has chemosensitive disease • how many previous lines of treatment they have had • whether a fully human leukocyte antigen (HLA) matched donor is available • how graft-versus-host disease (GvHD) and other complications may get worse with age • the risk of higher transplant-related mortality and morbidity, versus the potential for long-term disease-free survival • improving outcomes with other newer treatments • the person's understanding of the procedure and its risks and benefits. 1.5.8 Consider allogeneic stem cell transplantation as part of a clinical trial if one is available.
NCCN, 2018 [13]. Multiple Myeloma: NCCN Evidence Blocks Version 4.2018	Fragestellung/Zielsetzung: Treatment recommendations for MM patients.
	Methodik Grundlage der Leitlinie Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar - eigenes Graduierungssystem (siehe Tabellenblatt "NCCN Kategorien") - industriefinanziert - Angaben zu CoI in zugehörigen Publikationen des JNCCN zu finden Systematische Literaturrecherche: between April 1, 2016 - May 3, 2017 LoE/GoR: All recommendations are category 2A unless otherwise indicated.



[c]See Definition of Multiple Myeloma (Smoldering and Active) (MYEL-A).
[f]See Response Criteria for Multiple Myeloma (MYEL-C).
[h]See Myeloma Therapy (MYEL-D).
[i]See Supportive Care Treatment for MM (MYEL-E).
[j]Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival, although progression-free survival can be prolonged by an early transplant. (See Discussion section).
[k]Renal dysfunction and advanced age are not contraindications to transplant.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[f]See Response Criteria for Multiple Myeloma (MYEL-C).
[h]See Myeloma Therapy (MYEL-D).
[j]Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival, although progression-free survival can be prolonged by an early transplant. (See Discussion section).
[k]Renal dysfunction and advanced age are not contraindications to transplant.
[l]Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative, preferably in a clinical trial. Current data do not support miniallografting alone.
[m]A majority of phase 3 trials do not show a survival advantage for allogeneic SCT compared with autologous SCT. (See Discussion section).

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ACTIVE (SYMPTOMATIC) MYELOMA | **ADDITIONAL TREATMENT**

Post-allogeneic stem cell transplant:

Progressive disease[f] → Therapy for previously treated myeloma[h] or Clinical trial or Donor lymphocyte infusion

Response or stable disease[f] → Maintenance therapy on clinical trial or Observe → Progressive disease[f] → Therapy for previously treated myeloma[h] or Clinical trial or Donor lymphocyte infusion

Post-autologous stem cell transplant (single or tandem):

Progressive disease[f] → Therapy for previously treated myeloma[h] or Clinical trial or Allogeneic stem cell transplant[l]

Response or stable disease[f] → Maintenance therapy (category 1)[h] or Clinical trial → Progressive disease[f] → Therapy for previously treated myeloma[h] or Clinical trial ± additional autologous stem cell transplant[n] or Allogeneic stem cell transplant[l]

[f]See Response Criteria of Multiple Myeloma (MYEL-C).
[h]See Myeloma Therapy (MYEL-D).
[l]Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative preferably on a clinical trial. Current data do not support miniallografting alone.
[n]Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression. Retrospective studies suggest a 2- to 3-y minimum length of remission for consideration of a second autologous stem cell transplant.

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MYELOMA THERAPY[a-d]

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.

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES (assess for response after each cycle)
Preferred Regimens • Bortezomib/lenalidomide[e]/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone[f]
Other Recommended Regimens • Bortezomib/doxorubicin/dexamethasone (category 1) • Carfilzomib[g,h]/lenalidomide[e]/dexamethasone • Ixazomib/lenalidomide[e]/dexamethasone (category 2B)
Useful In Certain Circumstances • Bortezomib/dexamethasone (category 1)[i] • Bortezomib/thalidomide/dexamethasone (category 1) • Lenalidomide[e]/dexamethasone (category 1)[i] • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)

[a]Selected, but not inclusive of all regimens.
[b]Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[c]Subcutaneous bortezomib is the preferred method of administration.
[d]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[e]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[f]Preferred initial treatment in patients with acute renal insufficiency. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[g]Optimal dosing in this regimen has not been defined.
[h]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[i]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES (assess for response after each cycle)
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[j,j] • Bortezomib/cyclophosphamide/dexamethasone[f]
Other Recommended Regimens • Carfilzomib[g]/lenalidomide/dexamethasone • Carfilzomib[g]/cyclophosphamide/dexamethasone • Ixazomib/lenalidomide/dexamethasone
Useful In Certain Circumstances • Bortezomib/dexamethasone[i]
MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[k] (category 1)
Other Recommended Regimens • Bortezomib

See Evidence Blocks on MYEL-D (EB-1)

[a]Selected, but not inclusive of all regimens.
[b]Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[c]Subcutaneous bortezomib is the preferred method of administration.
[d]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[f]Preferred initial treatment in patients with acute renal insufficiency. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[h]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[i]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.
[j]Continuously until progression. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917.
[k]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.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Engelhardt et al., 2014 [4]. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma	Fragestellung/Zielsetzung: Recommendations for the management of newly diagnosed MM
	Methodik Grundlage der Leitlinie These recommendations were developed by an interdisciplinary panel of clinical experts on MM based on evidence of published data including randomized clinical studies, meta-analyses, systematic reviews and other available published clinical studies through August 2013. Expert consensus was used to suggest recommendations where there were no sufficient data. Grades of recommendations were assigned using the GRADE criteria. The recommendations were circulated among each panel member who made their comments, while the recommendations were also discussed in the EMN Trialist meeting (Baveno, Italy, 15-16 September 2013). The manuscript subsequently underwent two rounds of revision until the EMN experts reached a consensus. LoE/GoR Table 1. Grade recommendations for grading levels of evidence. Grade 1 — Evidence strongly suggests that the benefit of the procedure outweighs potential risks or risks of the procedure outweighs potential benefits 2 — Evidence suggests the benefit and risk of a procedure is finely balanced or uncertain A — Consistent evidence from systemic reviews of high-quality randomized studies or from high-quality randomized studies or from high-quality observational studies B — Evidence from randomized and observational studies with important methodological flaws C — Evidence from randomized and observational studies with major methodological flaws or other sources of evidence (e.g. case series)
	Recommended approach to initial therapy The current paradigm for treatment of newly diagnosed MM is divided into three phases: induction, consolidation, and maintenance. The approach to each phase of therapy is individualized based on the features of the disease, age, comorbidities and personal preferences. Patients with renal failure (RF) from myeloma should start induction as soon as possible with bortezomib and dexamethasone-based regimens. In addition, MM patients with RF should avoid nephrotoxic drugs and maintain euvolemia. The role of mechanical removal of free light chains by plasmapheresis or high cut-off dialysis in the management of myeloma-related RF remains unclear, and is currently assessed in clinical trials in conjunction with chemotherapy. Several studies revealed significant activity of rapidly acting bortezomib-based regimens, such as bortezomib-doxorubicin-dexamethasone (PAD), bortezomib-melphalan-prednisone (VMP) or bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide (VMPT-VT)). Both latter combinations were tested in untreated patients with RI: RI reversed in 16 of 63 (25%) patients receiving VMPT-VT versus 31 of 77 (40%) with VMP, suggesting that the multi-drug combination VMPT-VT had no advantage in RI reversal over VMP, although it was superior with normal RF and

moderate RI.30 Moreover, analgesia and bisphosphonates for painful bone lesions should be started. Consultation with an orthopedic oncologist for bone lesions at HR of fracture may be needed along with local radiotherapy to promptly ameliorate localized bone pain. Hypercalcemia should be managed with intravenous fluids and bisphosphonates.

Quelle:

30. Morabito F, Gentile M, Mazzone C, Rossi D, Di Raimondo F, Bringhen S, et al. Safety and efficacy of bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in untreated multiple myeloma patients with renal impairment. Blood. 2011;118(22):5759-66.

Recommendations for patients who are eligible for HDT and ASCT

- novel-agent-based induction and upfront ASCT in medically fit patients lead to sustained remission and continues to be the standard of care in this patient cohort **(1A)**. Current trials are investigating the role of novel agent combinations without up-front ASCT versus single- or tandem-ASCT. Induction therapy needs to include a triple combination of bortezomib with either adriamycin or thalidomide and dexamethasone **(PAD or VTD; 1A)**, or with cyclophosphamide and dexamethasone **(VCD; 2B)**.

Allogeneic transplantation

- currently, allo-SCT may be considered for young patients with HR disease who are willing to accept the TRM and investigational nature of this therapy for a chance of a better long-term survival **(2B)**. Carefully designed studies with long-term follow up are important to prove that allo-SCT should not be abandoned in MM.49

  Quelle:

  49. Gahrton G, Iacobelli S, Bjorkstrand B, Hegenbart U, Gruber A, Greinix H, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. Blood. 2013;121(25):5055-63.

Table 3. Induction regimens.

	Regimen	CR rate (%)	Common toxicities (>10%)
Transplant eligible	PAD	11	PNP, infection
	VTD	33	PNP, infection, gastrointestinal events
	VCD	22 (47)*	Thombocytopenia, neutropenia, anemia
	RVD	29	Lymphopenia
	Rd	24	Neutropenia, venous thrombosis
Transplant ineligible	VMP	24	Neutropenia, thrombocytopenia, anemia, PNP
	MPT	13	Neutropenia, venous thrombosis, PNP, infection
	MPR	16	Neutropenia, anemia, thrombocytopenia, infection

*PAD: bortezomib, doxorubicin, dexamethasone; VTD: bortezomib, thalidomide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone; RVD: lenalidomide, bortezomib, dexamethasone; Rd: lenalidomide, lou-dose dexamethasone; VMP: bortezomib, melphalan, prednisone; MPT: melphalan, prednisone, thalidomide, MPR: melphalan, prednisone, lenalidomide; CR: complete response; PNP: peripheral neuropathy; *VCD-mod.[31]*

Consolidation and maintenance therapy following induction therapy or transplant

- Thalidomide **(1B)** or lenalidomide **(1A)** maintenance post ASCT increases PFS and possibly OS **(2A)**. Bortezomib-based regimens are a valuable treatment option, especially for patients who failed VGPR or CR/nCR after ASCT **(2A)**.

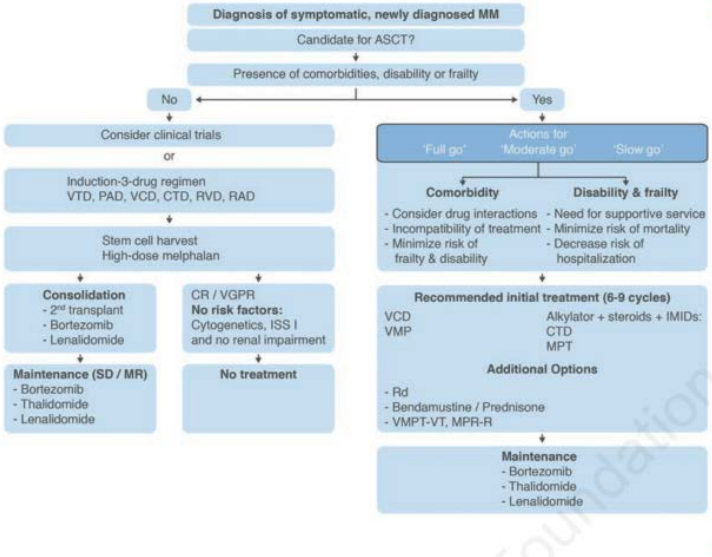


Figure 2. The initiation of most suitable and well-tolerable treatment in symptomatic, newly diagnosed MM patients involves the consideration of various factors, including whether this patient is a candidate for ASCT and presents with comorbidities, disability and frailty. In relation to these issues, either a 3-drug induction regimen, stem cell collection and ASCT may be considered, or with frailty, initial treatment according to 'full-go', 'moderate-go' or 'slow-go' protocols. 'Full go' patients are defined as those without risk factors of advanced age >75 years, moderate or severe frailty (patients needing help for household tasks and personal care) and comorbidities (FCI = 0), 'moderate-go' with at least one of these risks and 'slow-go' with at least two or more of these risk factors. Intermediate assessment of response (if in e.g. non-transplant eligible patients 6-9 cycles of CTD or VCD are performed) is important.

Options for initial treatment in patients not eligible for Transplant

VMP or MPT are the standards of care for transplant-ineligible patients **(1A).** Due to its excellent tolerability, lesser induction of polyneuropathy (PNP) and longer therapy endurance, weekly bortezomib schedules are preferred, especially in elderly, unfit or frail patients **(2B).** MPR+R increases PFS, but OS data are needed. Rd is also an effective option for these patients **(2B).**

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Alberta Provincial Hematology Tumour Team, 2015 [2]. Multiple Myeloma	Fragestellung/Zielsetzung: (…) • What are the most suitable management strategies of multiple myeloma and related disorders?
	Methodik **DEVELOPMENT PANEL:** This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of the Alberta Provincial Hematology Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. **SEARCH STRATEGY:** The MEDLINE (1966 through July 2012), PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews databases were searched. In addition, the ASCO and ASH Abstracts and Proceedings databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. **TARGET POPULATION:** The following guidelines apply to adults over the age of 18 years. Different principles may apply to pediatric patients.

	LoE/GoR: kein Graduierungssystem (Formulierungen im Text) **Sonstige methodische Hinweise:** Leitlinie entspricht nicht einer S3-Leitlinie (fehlende Informationen zur Bewertung, Klassifizierung und der konkreten Verknüpfung von Empfehlungen mit der zugrundeliegenden Evidenz) und wird daher als ergänzende Quelle aufgeführt.
	Treatment Guidelines for Newly Diagnosed Multiple Myeloma Patients ≤ 65 Years Old and Transplant-Eligible: Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, patients who are 65 years old or younger and are transplant-eligible should receive a course of therapy consisting of: • Pre-transplant induction with a 3-drug regimen that includes a novel agent • High dose melphalan +/- bortezomib followed by autologous stem cell transplantation • Post transplant consolidation • Maintenance lenalidomide and/or bortezomib until disease progression. Induction Regimens: Induction regimens should contain at least one novel agent (e.g. bortezomib, lenalidomide, thalidomide). There is consensus amongst the myeloma physicians that a triple drug based induction regimen results in superior outcomes with improved rate and depth of responses (higher CR and sCR rates). Four randomized trials comparing doublet versus triplet-based regimen are in favor of triplet-based regimen since the latter results in improved responses as well as progression free survival.20-25 *Quellen:* *20. Gertz MA, Lacy MQ, Dispenzieri A, Greipp PR, Litzow MR, Henderson KJ, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and −17p13 in myeloma patients treated with high-dose therapy. Blood 2005 Oct;106(8):2837-40.* *21. Paiva B, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation BLOOD, 15 NOVEMBER 2008 □ VOLUME 112, NUMBER 10. 4017-2023* *22. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376:2075-2085.* *23. Cavo M et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012 Jul 5;120(1):9-19.* *24. Rosinol L et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM studyBlood. 2012;120(8): 1589-1596* *25. Garderet L et al. Superiority of the Triple Combination of Bortezomib-Thalidomide-Dexamethasone Over the Dual Combination of Thalidomide-Dexamethasone in Patients With Multiple Myeloma Progressing or Relapsing After Autologous Transplantation: The MMVAR/IFM 2005-04 Randomized Phase III Trial From the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation J Clin Oncol. 2012 Jul 10;30(20):2475-2482*

Bortezomib-based induction regimens:
Numerous studies have shown that the depth of response achieved following ASCT is predictive of outcome. Patients achieving CR, nCR, and/or VGPR after transplantation have longer remissions and survival times than those with lesser responses. It has been suggested that if induction regimens with higher initial response rates were used prior to transplant, this should produce deeper responses post transplant, resulting in better PFS and OS. Until recently, this potential benefit of more effective induction had not been shown. A large meta-analysis failed to demonstrate any survival advantage for combination chemotherapy (i.e. VAD, VBMCP) compared to melphalan + prednisone.33
Quelle:
33. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. J Clin Oncol 1998 Dec;16(12):3832-42.

A randomized trial comparing induction with TD versus VAD showed higher response rates to TD induction, but similar response rates (VGPR 42% vs 44%) after transplant. However, recent studies of bortezomib based regimens suggest the choice of induction regimen may indeed affect outcome post transplant33-36. They showed an improvement in response with higher CR/near CR post-transplant, and superior progression free survival for those receiving bortezomib based regimens, with an improvement in overall survival seen in one study. 33-36
Quellen:
33. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. J Clin Oncol 1998 Dec;16(12):3832-42.
34. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple my- eloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010;28:4621-4629.
35. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/ GMMG-HD4 Trial. J Clin Oncol 2012 Aug 20;30(24):2946-2955.
36. Rosiñol L, Oriol A, Teruel AI, et al: .Superiority of bortezomib, thalidomide and dexamethasone (VTD) as induction pre-transplantation therapy in multiple myeloma: a randomized phase III PETHEMA/GEM study. Blood. 2012 Jul 12.

Bortezomib and dexamethasone based regimens for 3-4 cycles are well tolerated and shown to be more effective than older regimens, improving response rate, PFS, and OS post transplant. Bortezomib and dexamethasone should be included as part of multi-drug regimens as standard induction therapy prior to stem cell transplantation, along with a third agent such as cyclophosphamide (CyBorD31) and lenalidomide* (VRD37). (…)
Quellen:
31. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia 2009;23(7):1337-1341
37. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple

	myeloma. Blood 2010;116(5):679-686. CYBORD: Patients should receive 4-6 cycles prior to stem cell collection. Cycles are repeated every 28 days. Each cycle consists of: • Cyclophosphamide 300mg/m2 orally weekly for 4 weeks • Bortezomib 1.5mg/m2 intravenously or subcutaneously weekly for 4 weeks • Dexamethasone 40mg orally weekly for 4 weeks. A twice-weekly schedule can be used for sicker patients requiring a more rapid initial response to therapy. VRD*: Patients should receive no more than 4 cycles prior to attempted stem cell mobilization. Cycles are repeated every 28 days. Each cycle consists of: • Lenalidomide 25mg orally daily for 21 days • Bortezomib 1.5mg/m2 subcutaneously weekly for 4 weeks • Dexamethasone 40mg orally weekly for 4 weeks. A 21-day schedule can be used for sicker patients requiring a more rapid initial response to therapy: • Lenalidomide 25mg orally daily for 14 days • Bortezomib 1.3mg/m2 subcutaneously twice weekly for 2 weeks • Dexamethasone 40mg orally twice weekly for 2 weeks. ***Thalidomide-based regimens:*** Several large randomized trials have compared induction therapy with thalidomide to dexamethasone.38-46. In patients eligible for SCT, a thalidomide-based induction regimen resulted in a significantly higher response rate (CR and VGPR) and PFS/TTP/EFS. The impact on OS of induction therapy with thalidomide followed by autologous stem cell transplant remains a matter of debate. Only one study did demonstrate an overall survival advantage with thalidomide –VADoxil38. Randomized controlled trials of thalidomide have demonstrated higher incidence of adverse events with thalidomide as compared to standard therapy. In particular, VTE, peripheral neuropathy, & constipation are increased. Risk of VTE (between 4 and 20%) is greater when thalidomide is combined with steroid &/or chemo but less when thalidomide used as maintenance. *Quellen:* *38. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR, Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006 Jan;24(3):431-6.* *39. Rajkumar SV, Rosinol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol 2008 May;26(13):2171-7.* *40. Ludwig H, Hajek R, Tothova E, Drach J, Adam Z, Labar B, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood 2009 Apr;113(15):3435-42.* *41. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple*

	myeloma. Blood 2005 Jul;106(1):35-9. *42. Macro M, Divine M, Uzunhan Y, Jaccard A, Bouscary D, Leblond V, et al. Dexamethasone + thalidomide (Dex/Thal) compared to VAD as a pre-transplant treatment in newly diagnosed multiple myeloma (MM): a randomized trial [abstract]. Blood 2006;108(11 Part 1):22.* *43. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, van der Holt B, Martin H, Barge R, et al.Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. Haematologica 2008 Jan;93(1):124- 7.* *44. Zamagni E, Valdre L, Cini M, Legnani C, Tosi P, Tacchetti P, et al. Baseline Thrombophilic alterations and risk of venous thromboembolism in 266 multiple myeloma patients primarily treated with thalidomide and high-dose dexamethasone [abstract]. Blood 2007;110(11).* *45. Zervas K, Dimopoulos MA, Hatzicharissi E, Anagnostopoulos A, Papaioannou M, Mitsouli C, et al. Primary treatment of multiple myeloma with thalidomide, vincristine, liposomal doxorubicin and dexamethasone (T-VAD doxil): a phase II multicenter study. Ann Oncol 2004 Jan;15(1):134-8.* *46. Barlogie B, Jagannath S, Desikan KR, Mattox S, Vesole D, Siegel D, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 1999 Jan;93(1):55-65.* ***Lenalidomide-based induction regimen:*** The combination of lenalidomide and dexamethasone is a well tolerated and convenient oral regimen resulting in high response rates when followed by ASCT, with 3 year PFS and OS of 64% and 94% respectively47. Two large randomized trials comparing an induction therapy with a lenalidomide-based regimen have reported high rates of CR/VGPR and high 2-year PFS and OS rates.48,49. Lenalidomide with low-dose dexamethasone (40 mg PO weekly) (Ld) is superior to lenalidomide with standard-dose dexamethasone (LD) (40 mg PO days 1-4, 9-12, 17-20). The impact of a lenalidomide-based induction regimen on survival post-ASCT is unclear since transplant is often deferred until relapse in these studies. Patients treated with 4 cycles of lenalidomide followed by ASCT had a 2 year OS of 93%, similar to those treated with Ld until disease progression. Because prolonged therapy with lenalidomide can impair stem cell mobilization, consider stem cell collection within 4 cycles of induction lenalidomide. *<u>Quellen</u>:* *47. Siegel DS, Jacobus S, Rajkumar VS, et al. Outcome with lenalidomide plus dexamethasone followed by early autologous stem cell transplantation in the ECOG E4A03 randomized clinical trial [Abstract]. Blood. 2010;116:38.* *48. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010 Jan;11(1):29-37* *49. Zonder JA, Crowley J, Hussein-Bolejack V, Moore DF, Whittenberger BF, Abidi MH, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): results of the randomized, double-blinded, placebo-controlled SWOG trial S0232 [abstract]. Blood 2007;110(11):32a.* ***Other Regimens:*** Single agent dexamethasone is associated with suboptimal response and should not be used as the only therapy for myeloma. The VAD regimen should not be used

due to the toxicity of this regimen (neurotoxicity, cardiac toxicity, myelosuppression) and its inferior outcomes compared to bortezomib containing regimens.

2. Stem Cell Transplantation:

Autologous Stem Cell Transplant (ASCT):

Four large randomized trials have demonstrated the superiority of autologous stem cell transplantation to standard dose chemotherapy with significant prolongation of TTP and OS.50-53 Other trials, with several caveats have failed to demonstrate the same benefit from ASCT.54-57 Patients are considered transplant eligible if they are under the age of 65, meet minimal requirements for underlying organ function and all other transplant eligibility requirements of the Calgary or Edmonton transplant programs. There is no proven benefit to transplant over standard therapy for patients over the age of 65. These patients can be considered for ASCT if they are meet all transplant eligibility criteria, are physiologically very fit, and have no significant comorbid illnesses.

Transplant eligible patients should receive 3-4 cycles of induction therapy before proceeding to ASCT. The achievement of CR is not required to proceed to transplant. Patients who fail to achieve CR after 3-4 cycles of induction, including those with primary refractory disease, can still benefit from high dose therapy and ASCT and should still be referred for transplant evaluation. Patients with renal failure on dialysis are candidates for autologous stem cell transplant and should be referred without significant delays for transplant evaluation. Twenty to twenty-five percent of patients do recover their renal function and become dialysis-independent up to 6 months post-transplant.

Quellen:

50. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiplemyeloma. Intergroupe Francais du Myelome.NEnglJ Med 1996;335(2):91-7.

51. Morgan GJ, Davies FE, Hawkins K, Brown J, Bell SE, Drayson MT, et al. The MRC Myeloma VII Trial of standard versus intensive treatment in patients <65 years of age with multiple myeloma [abstract]. Blood 2002;100: 178a. Abstract 668.

52. Palumbo A, Bringhen S, Petrucci MT, Musto P, Rossini F, et al. Intermediate dose melphalan improves survival of myeloma patients aged 50 to 70 : results of a randomized phase 3 study. Blood 2004 Nov;104(10):3052-7.

53. Palumbo A, Cavallo F, Gay F, etal. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. N Engl J Med 2014; 371:895-905September 4, 2014DOI: 10.1056/NEJMoa1402888

54. Fermand JP, Katsahian S, Devine M, Leblond V, Dreyfus F, Macro M, et al. High dose therapy and autologous blood stem cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005 Dec;23(36):9227-33.

55. Bladé J, Sureda A, Ribera JM, Diaz-Mediavilla J, Palomera L, Fernandez-Calvo J, et al. High-dose therapy autotransplantation/intensification vs. continued conventional chemotherapy in multiple myeloma patients responding to initial treatment chemotherapy. Results of a prospective randomized trial from the Spanish Cooperative Group PETHEMA [abstract]. Blood 2001;98:815a. Abstract 3386.

56. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol 2006

	Feb;24(6):929-36. *57. Segeren CM, Sonneveld P, van der Holt B, Vellenga E, Croockewit AJ, Verhoef GE, et al. Overall and event-free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study. Blood 2003 Mar;101(6):2144-51.* Four studies have been conducted to date comparing tandem autologous to tandem autologous- allogeneic stem cell transplant. In a French study trial (IFM99-03) of high risk patients (del13 and high β2), no difference in outcome was seen between the two approaches. However it should be noted that only patients with high risk disease were enrolled into this study and high dose ATG was used in the conditioning regimen.65 In a study by Bruno and colleagues, allogeneic transplant was by far superior however in this study the results of the tandem autologous arm were lower than expected and the study had several reporting caveats.66 Early results from the PETHEMA group suggest superior results with allogeneic transplant; however they only report a trend for better PFS, not OS.68The largest study comparing autologous to transplantation was performed by the US Blood and Marrow Clinical Trials Network. 625 patients were biologically assigned to receive either a tandem ASCT with melphalan 200 mg/m2 (n = 436) or ASCT with melphalan 200 mg/m2 followed by an allogeneic SCT conditioned with fludarabine and 200 cGy of total body irradiation (n = 189). The 3-year PFS was 46% for the tandem autologous arm versus 43% for the autologous-allogeneic arm (*P* = .67). OS at 3 years was also not significantly different between the groups: 80% for the tandem autografts versus 77% for the autologous-allogeneic arm. Assignment to the autologous-allogeneic arm was associated with worsened survival in patients with stage I and II disease, but not in those with stage III disease68. At this point, allogeneic transplant is not considered a standard part of therapy for newly diagnosed or relapsed myeloma and should be performed only in the setting of a clinical trial. *Quellen:* *65. Garban F, Attal M, Michallet M, Hulin C, Bourhis JH, YakoubAgha I, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006 May;107(9):3474-80.* *66. Bruno B, Rotta M, Patriarca F, Mordini N, Allione B, Carnevale-Schianca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007 Mar;356(11):1110-20.* *68. Krishnan A, Pasquini MC, Logan B, et al: Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol. 2011 Dec;12(13):1195-203.* **3. Post-Transplant Therapy:** ***Consolidation:*** All patients should receive 2 cycles of consolidation therapy in addition to maintenance therapy. Both bortezomib23 and lenalidomide69 based regimens have been used. Compared to thalidomide and dexamethasone, the combination of bortezomib, thalidomide, and dexamethasone as consolidation after ASCT significantly improved CR (46% vs 60%) and CR/nCR rates (61% vs 73%). With a median follow-up of 30.4 months from start of consolidation, 3-year progression-

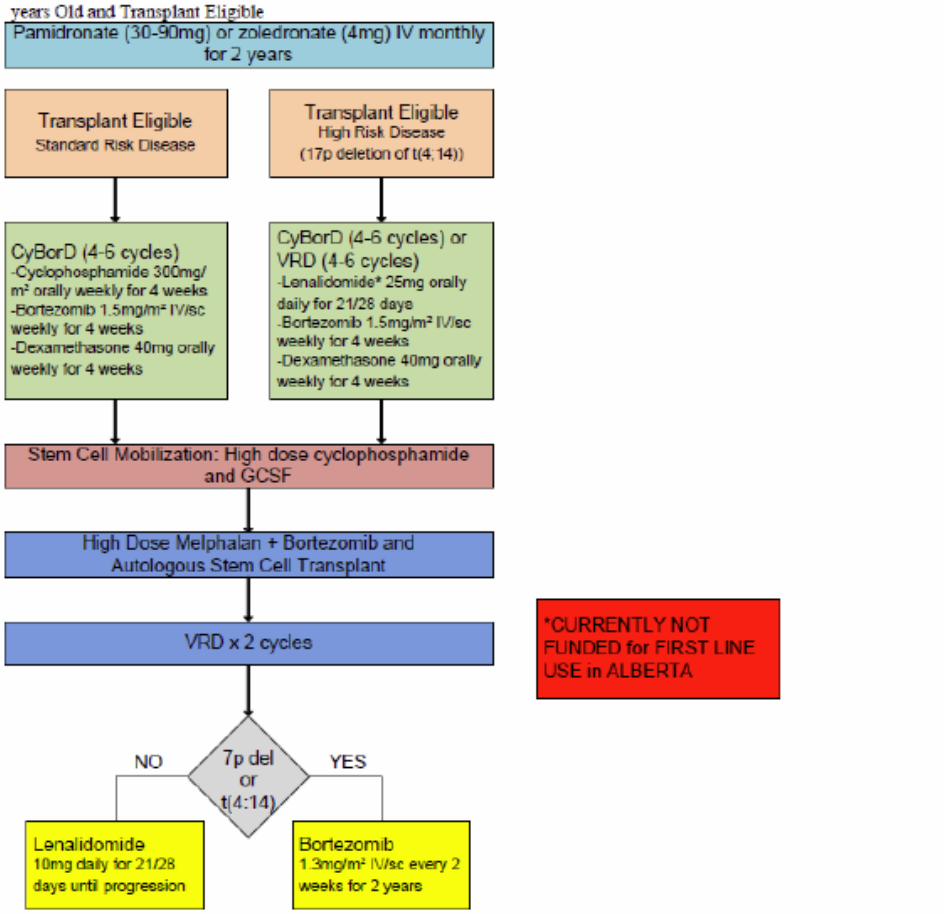
	free survival was significantly longer for the VTD group (60% vs 48% for TD). Grade 2 or 3 peripheral neuropathy (8.1% vs 2.4%) was more frequent with VTD (grade 3, 0.6%) versus TD consolidation. Our recommendation is for 2 cycles of consolidation with VRD* in all patients post ASCT. Lenolidomide in place of thalidomide should be used to minimize risk of neuropathy. • Bortezomib 1.3 mg/m2 on days 1, 8, 15, and 22 • Lenaldomide 10mg/d, days 1-21/28 (or Thalidomide 100 mg daily) • Dexamethasone 40 mg on days 1, 8, 15, 22 *Quellen:* *23. Cavo M et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012 Jul 5;120(1):9-19.* *69. McCarthy PL, Owzar K, Hofmeister CC, et al: Lenalidomide after stem-cell transplantation for multiple myeloma.N Engl J Med. 2012;366:1770-1781.* ***Maintenance Therapy:*** *Lenalidomide:* Two phase III trials have examined the role of lenalidomide maintenance following ASCT. The CALGB 100104 (n=460) trial compared a strategy of maintenance with lenalidomide (10mg daily) to placebo following ASCT69.At a median follow up of 34 months, maintenance resulted in an improved TTP of 46 months versus 27 months for placebos (p<0.001). Overall survival was also improved, with HR for death 0.62 (p<0.03). Lenalidomide maintenance was associated with an increase in second primary malignancies (SPM) (7.8% vs 2.6%). However event free survival analysis including SPM as study related events continued to show improved survival outcomes in favor of the maintenance arm. The IFM 2005-02 trial70 randomized 614 patients to maintenance with lenalidomide 10-15mg daily following ASCT. All patients received two cycles of consolidation with lenalidomide 25mg daily for 21 of 28 days prior to starting maintenance. With a median follow up of 45 months, the 4 year PFS was 43% for lenalidomide compared to 22% for placebo (p<0.001). There was no difference in OS (73% vs 75%). There were 23 second primary malignancies in the lenalidomide group and 9 in the placebo group. A retrospective analysis of 11 clinical trials of lenalidomide-based therapy for relapsed/refractory multiple myeloma including 3846 patients reported an incidence rate of second primary malignancies (SPMs) of 3.6271. Incidence rate of invasive (hematologic and solid tumor) SPMs was 2.08, consistent with the background incidence of developing cancer. In a separate analysis of pooled data from pivotal phase 3 trials of relapsed or refractory MM (n = 703), the overall IR of SPMs was 3.98 (2.51-6.31) with lenalidomide/dexamethasone and 1.38 (0.44-4.27) with placebo/dexamethasone. IRs of non-melanoma skin cancers were 2.40 (1.33-4.33) and 0.91 (0.23-3.66), respectively. IRs of invasive SPMs were 1.71 (0.86-3.43) and 0.91 (0.23-3.66), respectively. *Quellen:* *69. McCarthy PL, Owzar K, Hofmeister CC, et al: Lenalidomide after stem-cell transplantation for multiple myeloma.N Engl J Med. 2012;366:1770-1781.* *71. Dimopoulos MA, Richardson PG, Brandenburg N, et al: A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood. 2012 Mar 22;119(12):2764-7*

	Bortezomib: The phase III HOVON-65/ GMMG-HD4 trial randomized 827 patients to receive VAD induction followed by ASCT and maintenance therapy with thalidomide (arm A) or bortezomib, doxorubicin, and dexamethasone (PAD) followed by ASCT and maintenance with bortezomib every 2 weeks for 2 years (arm B)22. The strategy of bortezomib-based induction with bortezomib maintenance resulted in superior response rates (≥ VGPR 76% vs 56%, p<0.001) and PFS (35 vs 28 months, p=0.02). The study was not designed to evaluate the benefit of bortezomib maintenance on its own. However, the number of patients achieving a response upgrade after starting maintenance was similar between the thalidomide and bortezomib maintenance arms suggesting similar effects of these two strategies. An analysis of PFS calculated from the time of last HDM showed a significant difference in favor of the bortezomib arm (31 versus 26 months). This indicates that although post-transplantation bortezomib and thalidomide both achieved similar response upgrades, bortezomib contributed more to improvement of PFS. Importantly in this study, for patients with del17p, PAD followed by bortezomib maintenance significantly improved PFS (mPFS in arm B vs arm A: 26.2 vs 12.0 months; *P*=.024) and overall survival (3-year OS rate in arm B vs arm A: 69% vs 17% *P*=.028) *Quelle:* *22. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376:2075-2085.* *Thalidomide:* Thalidomide maintenance has consistently been associated with an improvement in PFS with a variable effect on OS. However it does lead to reduction in quality of life, and is frequently discontinued due to side effects and toxicity. Four large randomized trials have reported an improvement in TTP and OS with the use of thalidomide maintenance.72-75 The four trials used different doses (100-400 mg) of thalidomide as well as different durations of therapy (6-48 months). The median duration of therapy in the IFM99-02 study was approximately 18 months, with a median thalidomide dose of 200 mg. The IFM99-02 trial compared no maintenance (arm A), maintenance pamidronate (arm C) or maintenance thalidomide (<400 mg) + pamidronate (arm B), 2 months post-tandem autologous transplant in myeloma patients with only one risk factor (β2 microglobulin >3 mg/L or del13).72 • Maintenance thalidomide improved response rate (higher CR and VGPR rate with thalidomide: 55% arm A, 57% arm B, 67% arm C) • Thalidomide improved 3-year EFS: 36% arm A, 37% arm B and 52% arm C • Thalidomide improved 4-year OS: 77% arm A, 74% arm B, 87% arm C • Pamidronate did not decrease the incidence of bone events • Patients with del13 or those who achieved a VGPR or better did not benefit from thalidomide *Quellen:* *72. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 2006 Nov;108(10):3289-94.* *73. Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell*

	transplantation procedure. J Clin Oncol 2009 Apr;27(11):1788-93. *74. Zangari M, van Rhee F, Anaissie E, Pineda-Roman M, Haessler J, Crowley J, Barlogie B. Eight-year median survival in multiple myeloma after total therapy 2: roles of thalidomide and consolidation chemotherapy in the context of total therapy 1. Br J Haematol 2008;141:433-44.* *75. Cavo M, Di Raimondo F, Zamagni E, Patriarca F, Tacchetti P, Casulli AF, et al. Short-term thalidomide incorporated into double autologous stem-cell transplantation improves outcomes in comparison with double autotransplantation for multiple myeloma. J Clin Oncol 2009 Oct;27(30):5001-7.* *α-Interferon (IFN):* Clinical trials of IFN maintenance produce conflicting results. However it has considerable toxicity and very poor tolerance. With the availability of better tolerated, more effective therapies, the use of IFN is not recommended.39, 56, 76, 77 *Quellen:* *39. Rajkumar SV, Rosinol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol 2008 May;26(13):2171-7.* *56. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol 2006 Feb;24(6):929-36.* *76. Cunningham D, Powles R, Malpas J, Raje N, Milan S, Viner C, et al. A randomized trial of maintenance interferon following high-dose chemotherapy in multiple myeloma: long-term follow-up results. Br J Haematol 1998 Jul;102(2):495-502.* *77. Bjorkstrand B, Svensson H, Goldschmidt H, Ljungman P, Apperley J, Mandelli F, et al. Alpha-interferon maintenance treatment is associated with improved survival after high-dose treatment and autologous stem cell transplantation in patients with multiple myeloma: a retrospective registry study from the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transpl 2001;27(5):511-5.* *Prednisone:* In non-transplant patients, one randomized study by Berenson and the SWOG group showed better EFS (14 vs. 5 months; p=0.03) and OS (37 vs. 26 months; p=0.05) with prednisone 50 mg compared to prednisone 10 mg.78 Prednisone is not recommended for maintenance following ASCT. Members of the Alberta Provincial Hematology Tumour Board recommend maintenance therapy with lenalidomide or bortezomib for patients without progressive disease following ASCT. The risk of SPMs must be taken into account before initiating lenalidomide treatment. In the context of the observed progression free survival benefit after ASCT, the benefit/risk profile of lenalidomide/dexamethasone remains positive. Maintenance with bortezomib (with or without lenalidomide) should be considered in patients with del17p. *Quelle:* *78. Berenson JR, Crowley JJ, Grogan TM, Zangmeister J, Briggs AD, Mills GM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. Blood 2002;99(9):3163-8.*

	Summary: Regimens containing bortezomib and dexamethasone as well as a third agent (cyclophosphamide, lenalidomide) are the standard induction regimen prior to stem cell transplantation for transplant eligible patients with standard risk or high risk myeloma requiring treatment. VAD or single agent dexamethasone should not be used. • CYBORD is the recommended regimen for initial therapy of newly diagnosed transplant eligible patients. Patients should receive 4-6 cycles prior to stem cell collection. Cycles are repeated every 28 days. A twice weekly schedule can be used for sicker patients requiring a more rapid initial response to therapy. • High risk patients (17p deletion, t(4;14)) should receive a bortezomib based regimen and should be considered for initial therapy with a combination of bortezomib, lenalidomide and dexamethasone (VRD)*. **Lenalidomide is not currently funded for up front treatment of myeloma.** • Patients refractory to VCD (fail to achieve at least PR) should be switched to second line therapy with lenalidomide and dexamethasone or VRD (bortezomib days 1,4,8,11, Lenalidomide days 1-14, weekly dexamethasone) for several cycles prior to stem cell mobilization • Cyclophosphamide 2.5g/m2 followed by growth factor administration is used for stem cell collection • The standard stem cell transplant regimen consists of a single transplant conditioned with high dose (200mg/m2) Melphalan with bortezomib (1.3mg/m2 day -5, -2, +1, and +4) • Following transplant: o All patients should receive 2 cycles of VRD* o Following consolidation, patients with 17p deletion or t(4:14) should receive bortezomib (1.3mg/m2) every 2 weeks for 2 years. All others should receive lenalidomide 10mg daily for 21-28/28 days every 4 weeks until disease progression

Figure 1. Summary of Treatment Recommendations in Multiple Myeloma Patients ≤65 years Old and Transplant Eligible



*This is an evidence based recommendation. Lenalidomide is currently NOT funded for front line use in ALBERTA. Bortezomib based consolidation is currently funded only for those not achieving VGPR post-ASCT

Patients > 65 Years Old or Transplant Ineligible:

Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, combinations of melphalan and prednisone with novel agents (thalidomide, lenalidomide, or bortezomib) have been shown to be superior to melphalan and prednisone alone as initial therapy for transplant ineligible patients. The standard therapy for these patients should therefore include a novel agent, alkylator, and steroids. However, in frail patients, and those with significant com-morbidities or advanced age (>75 years), there is an increased risk of toxicities. For these patients, consideration should be given to dose reductions of the initial regimen, and/or the use of two-drug combinations such as RD or VD79.

Quelle:

79. Palumbo A and Anderson K. Multiple Myeloma nejm 2011;364:1046

Bortezomib-Based Regimens:

The VISTA trial randomized patients to bortezomib + melphalan + prednisone (VMP) versus MP for 9 cycles80. Regimens:

- MP (melphalan + prednisone) cycles 1-9 (6 week cycles)
  - melphalan 9mg/m2 days 1-4
  - prednisone 60mg/m2 days 1-4

- VMP (bortezomib + melphalan + prednisone)

	o cycles 1-4 (6 week cycles): MP plus bortezomib 1.3mg/m2 IV days 1,4,8,11,22,25,29,32 o cycles 5-9 (6 week cycles): MP plus bortezomib 1.3mg/m2 IV days 1,8,22,29 The mean response duration was 19.9 months in the bortezomib group versus 13.1 months in the control group. Median TTP was 24.0 months in the bortezomib group versus 16.6 months in the control group (HR= 0.48). OS after a median follow-up of 16.3 months was not reached in either group: 45 patients (13%) in the bortezomib group and 76 patients (22%) in the control group died. The hazard ratio for overall survival was 0.61 for the bortezomib group (p=0.008) A modified VISTA regimen has also been used, with 6 cycles of VMP followed by VP maintenance81: • Cycle 1 (6 week cycle): o bortezomib 1·3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32 o melphalan 9 mg/m² on days 1-4 o prednisone 60 mg/m² on days 1-4 • Cycle 2-5 (5 week cycles): o bortezomib 1·3 mg/m² on days 1, 8, 15, and 22) o melphalan 9 mg/m² on days 1-4 o prednisone 60 mg/m² on days 1-4 • Maintenance (up to 3 years): o bortezomib 1·3 mg/m² on days 1, 4, 8, and 11 every 3 months o plus either prednisone (50 mg every other day) or thalidomide (50 mg per day) *Quelle:* *81. Mateos MV et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly Multiple Myeloma patients included in the GEM2005MAS65 trial Blood. 2012 Aug 13.* The VMP regimen was compared to VMP plus thalidomide followed by maintenance with bortezomib plus thalidomide (VMPT-VT)82. VMPT followed by VT as maintenance was superior to VMP alone in patients with multiple myeloma who are ineligible for autologous stem-cell transplantation. The 3-year PFS was 56% in patients receiving VMPT-VT and 41% in those receiving VMP (P = .008). Complete response were 38% in the VMPT-VT group and 24% in the VMP group (P < .001). The 3-year overall survival was 89% with VMPT-VT and 87% with VMP (HR, 0.92; 95% CI, 0.53 to 1.60; P = .77). Grade 3 to 4 neutropenia (38% v 28%; P = .02), cardiologic events (10% v 5%; P = .04), and thromboembolic events (5% v 2%; P = .08) were more frequent among patients assigned to the VMPT-VT group than among those assigned to the VMP group; treatment-related deaths were 4% with VMPT-VT and 3% with VMP. *Quelle:* *82. Palumbo et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial.J Clin Oncol. 2010 Dec 1;28(34):5101-9.* VMP-VT regimen: Cycles 1-4 (42 day cycles): • Melphalan 9 mg/m2 on days 1 to 4 • Prednisone 60 mg/m2 on days 1 to 4 • Bortezomib 1.3 mg/m2 iv on days 1, 4, 8, 11, 22, 25, 29, and 32 • Thalidomide 50 mg per day continuously. Cycles 5-9 • Melphalan 9 mg/m2 on days 1 to 4 • Prednisone 60 mg/m2 on days 1 to 4

- Bortezomib 1.3 mg/m2 iv on days 1, 8, 22, and 29
- Thalidomide 50 mg per day continuously.

Maintenance:
- After the last VMPT course, patients received maintenance therapy with bortezomib 1.3 mg/m2 every 14 days and thalidomide 50 mg per day for 2 years or until progression or relapse

The combination of cyclophosphamide, bortezomib and dexamethasone has been shown in a number of phase II trials to be well tolerated, and produces superior response rates83. It is currently the regimen of choice for first line therapy for non-transplant eligible myeloma patients.
- Cyclophosphamide 300mg/m2 orally weekly for 4 weeks
- Bortezomib 1.5mg/m2 intravenously or subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

Patients should receive 9-12 cycles followed by maintenance bortezomib (1.3mg/m2 every 2 weeks for 2 years).
Quelle:
83. Khan ML, Reeder CB, Kumar SK, et al. A comparison of lenalidomide/dexamethasone versus cyclophosphamide/lenalidomide/dexamethasone versus cyclophosphamide/bortezomib/dexamethasone in newly diagnosed multiple myeloma.Br J Haematol. 2012 Feb;156(3):326-33. doi: 10.1111/j.1365-2141.2011.08949.x. Epub 2011 Nov 23.

Lenalidomide-Based Regimens:
Lenalidomide is currently not funded for first-line use in multiple myeloma.
In the MM015 trial, 459 patients were randomly assigned to receive melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R) therapy until a relapse or disease progression or to receive MPR or MP without maintenance therapy84. The median progression-free survival was significantly longer with MPR-R (31 months) than with MPR (14 months; hazard ratio, 0.49; P<0.001) or MP (13 months; hazard ratio, 0.40; P<0.001). Response rates were superior with MPR-R and MPR (77% and 68%, respectively, vs. 50% with MP; P<0.001 and P=0.002, respectively, for the comparison with MP). The progression-free survival benefit associated with MPR-R was noted in patients 65 to 75 years of age but not in those older than 75 years of age (P=0.001 for treatment-by-age interaction). The 3-year rate of second primary tumors was 7% with MPR-R, 7% with MPR, and 3% with MP.
MPR-R regimen: Nine 28-day cycles of
- Melphalan 0.18 mg/kg days 1 through 4
- Prednisone 2 mg per kilogram days 1 through 4
- Lenalidomide 10 mg on days 1 through 21
- Followed by lenalidomide maintenance (10 mg on days 1 through 21 of each 28-day cycle) until disease progression or the development of unacceptable adverse effects

Quelle:
84. Palumbo A et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma.N Engl J Med. 2012 May 10;366(19):1759-69.

The FIRST study compared MPT for 12 cycles (18months) to lenalidomide and dexamethasone for 18 cycles (18months) and len/dex until disease progression in newly diagnosed myeloma patients not eligible for stem cell transplant85. The continuous Rd strategy was superior to MPT with improved response rate, PFS and duration of response. Overall survival at 4 years was improved with continuous Rd, but this did not reach statistical significance (4-year OS 59% vs 51%, p=0.0168).
Quelle:

85. Facon T, et al. Initial Phase 3 Results Of The First (Frontline Investigation Of Lenalidomide + Dexamethasone Versus Standard Thalidomide) Trial (MM-020/IFM 07 01) In Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible For Stem Cell Transplantation (SCT). Blood: November 15, 2013; 122 (21)

Thalidomide-Based Regimens*:*

- The IFM99-06 and IFM 01-01 trials also reported higher OS rates.86, 87
- MPT was also shown in one trial (IFM99-06) to be superior to tandem transplant with reduced intensity melphalan conditioning (100 mg/m2 x 2).86
- Increased toxicity (DVT/pulmonary embolism 12% versus 4% with MP) and higher rates of neutropenia have been reported with MPT therapy.

Table 5. Melphalan + Prednisone + Thalidomide (MPT) Regimens

Regimen	Dosing
IFM99-06 Regimen[86]	Melphalan 0.25 mg/kg on days 1–4 q 6 weeks x 12 cycles Prednisone 2 mg/kg on days 1–4 q 6 weeks x 12 cycles Thalidomide at the maximum tolerated dose, but < 400 mg/day, x 12 cycles.
IFM01-01 Regimen[87] (patients >75 years)	Melphalan 0.20 mg/kg on days 1–4 q 6 weeks x 12 cycles Prednisone 2 mg/kg on days 1–4 q 6 weeks x 12 cycles Thalidomide 100 mg PO daily, x 12 cycles.
Palumbo Regimen[88]	Melphalan 4 mg/m^2 on days 1–7 q 4 weeks x 6 cycles Prednisone 40 mg/m^2 on days 1–7 q 4 weeks x 6 cycles Thalidomide 100 mg /day continuously until relapse or progressive disease

- Thrombosis prophylaxis is required with the use of thalidomide or lenalidomide. There is no consensus at the present time regarding the optimal DVT/pulmonary embolism prophylaxis. Acceptable options include: o Daily ASA (81 or 325 mg)
  - o Prophylactic dose of low molecular weight heparin (LMWH)
  - o Coumadin with therapeutic INR (2-3)

Summary:

- CYBOR-D, VMP, and lenalidomide* plus dexamethasone (given until disease progression) are suitable options for newly diagnosed, transplant ineligible myeloma patients. However, lenalidomide is currently not approved for initial therapy
- Therefore, CYBORD for 9-12 cycles is the recommended therapy for newly diagnosed, transplant ineligible patients. Alternatively, patients may be treated with VMP for 9 cycles. Following initial therapy, all patients should receive maintenance with bortezomib 1·3 mg/m² every 2 weeks for 2 years
- Bortezomib based therapy is preferred over lenalidomide based therapy for patients with 17p deleted myeloma.

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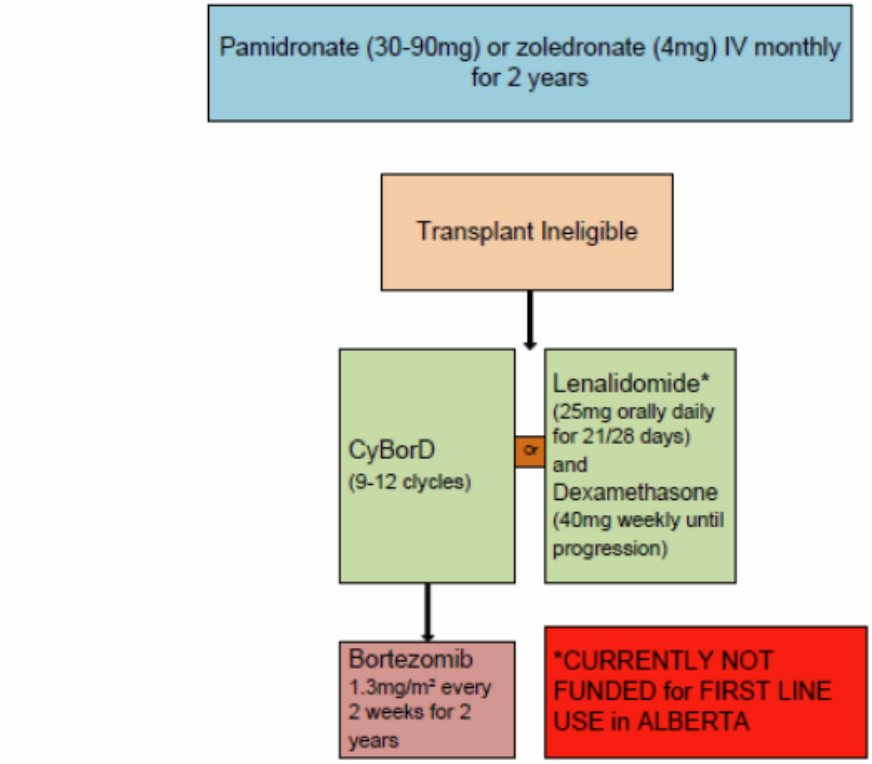
<tr><td></td><td> 

*This is an evidence based recommendation. Lenalidomide is currently NOT funded for front line use in ALBERTA</td></tr>
<tr><td rowspan="2">Chen et al., 2013 [3]

Lenalidomide inmultiple myeloma - a practice guideline</td><td>Fragestellung/Zielsetzung:
• Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with previously untreated multiple myeloma (including smoldering and symptomatic patients, and candidates or non-candidates for transplant) compared with non-lenalidomide-containing treatments?
• Which multiple myeloma patients, both previously untreated and relapsed or refractory, are more or less likely to benefit from treatment with lenalidomide?
• Are outcomes in myeloma patients improved with the use of lenalidomide as maintenance or consolidation treatment (after transplant and non-transplant treatments) compared with either non-lenalidomide-containing treatment or no maintenance or consolidation treatment?</td></tr>
<tr><td>Methodik

The literature was systematically searched using electronic databases (MEDLINE, EMBASE, and the Cochrane Library; meeting proceedings of the American Society of Hematology, the American Society of Clinical Oncology, and the International Myeloma Workshops), relevant Web sites such as CancerGuidelines.ca, the U.S. National Guideline Clearinghouse, the Canadian Medical Association Infobase, the Physician Data Query database, and the American College of Physicians Journal Club; and reference lists of included articles (January 2000 to February 2012)

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

Internal and External Review: Before submission of the draft report for external review, the systematic review and practice guideline were reviewed by the PEBC</td></tr>
</table>

	Report Approval Panel. LoE/GoR: k.A. Sonstige methodische Hinweise: Leitlinie entspricht nicht einer S3-Leitlinie (fehlende Informationen zur Bewertung, Klassifizierung und der konkreten Verknüpfung von Empfehlungen mit der zugrundeliegenden Evidenz) und wird daher als ergänzende Quelle aufgeführt.
	Question 1—Previously Untreated Patients **Previously Untreated Symptomatic Multiple Myeloma:** • Single-Agent Lenalidomide: Lenalidomide alone cannot be recommended for standard use in this setting. • Lenalidomide and Dexamethasone: The combination of lenalidomide and dexamethasone is an acceptable first-line treatment option for myeloma. (…) • Other Lenalidomide Combinations: No other combinations can be recommended. ***Key Evidence → Previously Untreated Symptomatic Multiple Myeloma:*** No RCTs comparing lenalidomide alone with a non-lenalidomide regimen for first-line therapy both in candidates and in non-candidates for transplant were located. The study by Zonder *et al.*9 showed an improved median 1-year PFS (78% vs. 52%, p = 0.002) and improved OS (77% vs. 48%, $p < 0.0001$) in patients receiving lenalidomide plus dexamethasone compared with placebo plus dexamethasone. Rajkumar *et al.*10 demonstrated a longer median PFS for lenalidomide plus low-dose dexamethasone than for lenalidomide plus high-dose dexamethasone (25.3 months vs. 19.1 months, p = 0.026), with an improved safety profile (grade 3 or greater adverse events: p = 0.02 for neutropenia, p = 0.0003 for DVT, and p = 0.04 for infections) in favour of the low-dose dexamethasone arm. No RCTs of lenalidomide in combination with other agents in this setting were identified. *Quellen:* *9. Zonder JA, Crowley J, Hussein MA, et al. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). Blood 2010;116:5838–41.* *10. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus lowdose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29–37.* *Qualifying Statements:* The Zonder and Rajkumar studies have limitations: Both studies were stopped early because of observed benefit, and the Rajkumar study used overall response rate as a primary outcome. In the Rajkumar study, the improved safety profile and lower rate of early deaths with low-dose dexamethasone has led to widespread adoption of that approach. From a safety perspective, the Hematology DSG endorses it. It should be noted, however, that compared with low-dose dexamethasone, high-dose dexamethasone, although more toxic, was associated with higher response rates. Therefore, in select patient populations with acute myeloma-related complications, benefit might still be obtained from the robust efficacy of high-dose dexamethasone. **Question 3—Subgroups Most Likely to Benefit** Which multiple myeloma patients, both previously untreated and relapsed or refractory, are more or less likely to benefit from treatment with lenalidomide?

	• For patients with untreated myeloma, the evidence isinsufficient to recommend lenalidomide in specific patient subgroups. When lenalidomide is combined with dexamethasone, the use of low-dose rather than high-dose dexamethasone may be preferable from a safety perspective, regardless of age. **Question 4—Maintenance or Consolidation Treatment** Are outcomes in myeloma patients improved with the use of lenalidomide as maintenance or consolidation treatment (after transplant and non-transplant treatments) compared with either non-lenalidomide-containing treatment or no maintenance or consolidation treatment? • Candidates for Transplant: In the absence of a final full publication of supporting trials in the post-transplant setting (currently published as conference abstracts), the Hematology DSG recommends that lenalidomide maintenance at 10–15 mg daily continuously until progression is a reasonable option. *Key Evidence*: In three companion abstract publications, a significant improvement in PFS ($p < 0.0001$) was reported with maintenance compared with no maintenance after transplant. In addition, an ongoing randomized study, presented in preliminary form, strongly supported the benefit of post-transplant maintenance, with an OS advantage. The median TTP was 43.6 months compared with 21.5 months, and PFS was also favourable for the lenalidomide group (HR: 0.43; one-sided unadjusted $p < 0.0001$). These combined data provide emerging support for the use of lenalidomide maintenance post transplant, which the Hematology dsg considers a reasonable post-transplant option. ***Qualifying Statements:*** The Palumbo, Attal, and McCarthy maintenance trials were recently published in full, but were not captured within our search cut-off dates. Therefore all recommendations in the present guidelines are based on ongoing trial data available at the time of the literature search. Data from the study by Attal *et al.* is based on a final analysis of the completed data, but presented in abstract form. That study was stopped early for benefit. Data from the study by McCarthy *et al.* is based on an interim analysis that had already shown OS benefit. Although the abstract data are adequately compelling for the Hematology DSG to recommend maintenance in post-transplant patients, evaluation of the full publications with further maturation is required before full recommendations can be made.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 26.03.2018

#	Suchfrage
#1	MeSH descriptor: [Multiple Myeloma] explode all trees
#2	(multiple or "plasma cell"):ti,ab,kw and (myeloma or myelomas):ti,ab,kw (Word variations have been searched)
#3	(kahler* next disease):ti,ab,kw or (Myelomatosis or Myelomatoses):ti,ab,kw (Word variations have been searched)
#4	#1 or #2 or #3
#5	#4 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 26.03.2018

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[Title/Abstract]) OR “Plasma Cell”[Title/Abstract])
3	(myeloma[Title/Abstract]) OR myelomas[Title/Abstract]
4	#2 AND #3
5	((kahler*[Title/Abstract] AND disease[Title/Abstract])) OR (Myelomatosis[Title/Abstract] OR Myelomatoses[Title/Abstract])
6	#1 OR #4 OR #5
7	(#6) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
8	(#6) AND (((((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]))))
9	(#7 OR #8)
10	(#9) AND ("2013/03/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT ("The Cochrane database of systematic reviews"[Journal])

Leitlinien in Medline (PubMed) am 26.03.2018

#	Suchfrage

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[Title/Abstract]) OR “Plasma Cell”[Title/Abstract])
3	(myeloma[Title/Abstract]) OR myelomas[Title/Abstract]
4	#2 AND #3
5	((kahler*[Title/Abstract] AND disease[Title/Abstract])) OR (Myelomatosis[Title/Abstract] OR Myelomatoses[Title/Abstract])
6	#1 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
8	(#7) AND ("2013/03/01"[PDAT] : "3000"[PDAT])

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