Darzalex® (daratumumab)
(Intravenous)

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I. Length of Authorization [1,6,16,17]

Coverage will be provided for six months and may be renewed (unless otherwise specified).

- Use for newly diagnosed multiple myeloma in combination with bortezomib, thalidomide, and dexamethasone may not be renewed.
- Use for newly diagnosed disease in combination with bortezomib, lenalidomide and dexamethasone may be renewed for up to a maximum of 2 years of maintenance therapy.
- Use for newly diagnosed or relapsed disease in combination with cyclophosphamide, bortezomib and dexamethasone may be renewed for up to a maximum of 80 weeks *(32 weeks of induction therapy and 48 weeks of maintenance therapy)*.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Darzalex 100 mg single-dose vial for injection: 3 vials per dose
  - *Weekly Weeks 1 to 6, then every three weeks Weeks 7-54, then every four weeks Week 55 onwards* ***OR***
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards* ***OR***
  - *Weekly Weeks 1 to 9, then every three weeks Weeks 10-24, then every four weeks Week 25 onwards)* ***OR***
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-16 for induction therapy, then every two weeks Weeks 1 to 8 for consolidation therapy* ***OR***
  - *Weekly Weeks 1 to 18, then every four weeks for up to 2 years for maintenance therapy;* ***OR***
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, and then every four weeks Weeks 25 to 32 for induction therapy, then every four weeks for up to 48 weeks for maintenance therapy*
- Darzalex 400mg single dose vial for injection: 4 vials per dose

- *Weekly Weeks 1 to 6, then every three weeks Weeks 7-54, then every four weeks Week 55 onwards* ***OR***
- *Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards* ***OR***
- *Weekly Weeks 1 to 9, then every three weeks Weeks 10-24, then every four weeks Week 25 onwards)* ***OR***
- *Weekly Weeks 1 to 8, then every two weeks Weeks 9-16 for induction therapy, then every two weeks Weeks 1 to 8 for consolidation therapy* ***OR***
- *Weekly Weeks 1 to 18, then every four weeks for up to 2 years for maintenance therapy;* ***OR***
- *Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, and then every four weeks Weeks 25 to 32 for induction therapy, then every four weeks for up to 48 weeks for maintenance therapy*

B. Max Units (per dose and over time) [HCPCS Unit]:

- Bortezomib/Melphalan/Prednisone Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 6, then every three weeks Weeks 7-54, then every four weeks Week 55 onwards)
- Lenalidomide or Pomalidomide or Carfilzomib or Selinexor Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards)
- Bortezomib/Dexamethasone Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 9, then every three weeks Weeks 10-24, then every four weeks Week 25 onwards)
- Monotherapy Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards)
- Bortezomib/Thalidomide Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 8, then every two weeks Weeks 9-16 for induction therapy, then every two weeks Weeks 1 to 8 for consolidation therapy)
- Bortezomib/Lenalidomide/Dexamethasone Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 18, then every four weeks for up to 2 years for maintenance therapy)
- Cyclophosphamide/Bortezomib/Dexamethasone Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, and then every four weeks Weeks 25 to 32 for induction therapy, then every four weeks for up to 48 weeks for maintenance therapy)

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria

- Therapy will not be used in combination with other anti-CD38 therapies (i.e., daratumumab, isatuximab, etc.); **AND**

Multiple Myeloma † Φ [1-11,13,14,16,17,18,15e-17e]

- Used in the treatment of newly diagnosed disease in patients who are ineligible for autologous stem cell transplant (ASCT) in combination with ONE of the following regimens:
  - Lenalidomide and dexamethasone; **OR**
  - Bortezomib, melphalan and prednisone; **OR**
  - Cyclophosphamide, bortezomib, and dexamethasone; **OR**
- Used in the treatment of newly diagnosed disease in patients who are eligible for autologous stem cell transplant (ASCT) in combination with ONE of the following regimens:
  - Bortezomib, lenalidomide, and dexamethasone; **OR**
  - Bortezomib, thalidomide, and dexamethasone (VTd); **OR**
  - Cyclophosphamide, bortezomib, and dexamethasone; **OR**
- Used for disease relapse after 6 months following primary induction therapy with the same regimen in combination with ONE of the following regimens:
  - Lenalidomide and dexamethasone for non-transplant candidates; **OR**
  - Cyclophosphamide, bortezomib, and dexamethasone; **OR**
- Used as subsequent therapy in combination with dexamethasone and ONE of the following:
  - Selinexor; **AND**
    - Used after at least three prior lines of therapy including a proteasome inhibitor (e.g., bortezomib, carfilzomib, etc.) and an immunomodulatory agent (e.g., lenalidomide, pomalidomide, etc.); **OR**
    - Patient is double-refractory to a proteasome inhibitor and an immunomodulatory agent; **OR**
  - Lenalidomide; **OR**
  - Bortezomib; **OR**
  - Carfilzomib; **OR**
  - Cyclophosphamide and bortezomib; **OR**
- Used in combination with pomalidomide and dexamethasone after at least two prior therapies including an immunomodulatory agent (e.g., lenalidomide, pomalidomide, etc.) and a proteasome inhibitor (bortezomib, carfilzomib, etc.); **OR**
- Used as single agent therapy; **AND**
  - Patient received at least three prior lines of therapy including a proteasome inhibitor (e.g., bortezomib, carfilzomib, etc.) and an immunomodulatory agent (e.g., lenalidomide, pomalidomide, etc.); **OR**
  - Patient is double-refractory to a proteasome inhibitor and an immunomodulatory agent

Systemic Light Chain Amyloidosis ‡ [2,12,15]

- Used as single agent therapy; **AND**
- Used for the treatment of relapsed/refractory disease

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,2,3,6,16,17]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion reactions including anaphylactic reactions, neutropenia, thrombocytopenia, etc.; **AND**
  - Use for newly diagnosed disease in combination with bortezomib, thalidomide, and dexamethasone after 24 weeks of induction/consolidation therapy may not be renewed.
  - Use for newly diagnosed disease in combination with bortezomib, lenalidomide and dexamethasone may be renewed for up to a maximum of 2 years of maintenance therapy.
  - Use for newly diagnosed or relapsed disease in combination with cyclophosphamide, bortezomib and dexamethasone may be renewed for up to a maximum of 80 weeks *(32 weeks of induction therapy and 48 weeks of maintenance therapy)*.

V. Dosage/Administration [1,3,5,12,18]

Indication	Dose
Multiple Myeloma	<u>Newly diagnosed disease in patients ineligible for ASCT in combination with bortezomib, melphalan and prednisone</u> ▪ 16 mg/kg body weight given as an intravenous infusion in a 6 week cycle: – Weekly Weeks 1 to 6 (six doses; cycle 1) – Every three weeks Weeks 7 to 54 (16 doses; cycles 2 to 9) – Every four weeks Week 55 onwards (cycle 10 and beyond) *Treat until disease progression or unacceptable toxicity*
	<u>Newly diagnosed disease in patients ineligible for ASCT in combination with bortezomib, thalidomide and dexamethasone</u> ▪ 16 mg/kg body weight given as an intravenous infusion in a 4 week cycle:

	▪ Induction – – Weekly Weeks 1 to 8 (eight doses; cycles 1 and 2) – Every two weeks Weeks 9 to 16 (four doses; cycles 3 and 4) *Stop for high dose chemotherapy and ASCT* ▪ Consolidation – – Every two weeks Weeks 1 to 8 (four doses; cycles 5 and 6)
	<u>Newly diagnosed disease in patients eligible for ASCT in combination with bortezomib, lenalidomide and dexamethasone</u> ▪ 16 mg/kg body weight given as an intravenous infusion as follows: ▪ Induction – **3 week cycle** – Weekly Weeks 1 to 12 (twelve doses; cycles 1 to 4) ▪ Consolidation – *(after ASCT)* – **3 week cycle** – Weekly Weeks 13 to 18 (six doses; cycles 5 and 6) ▪ Maintenance – **4 week cycle** – Every 4 or 8 weeks Weeks 1 to 102 for a maximum of 2 years of maintenance treatment
	<u>Newly diagnosed OR relapsed disease in combination with cyclophosphamide, bortezomib and dexamethasone</u> Induction ▪ 8 mg/kg body weight given as an intravenous infusion on days 1 and 2 (Week 1; total 2 doses) ▪ Followed by 16 mg/kg body weight given as an intravenous infusion in a 4 week cycle: – Weekly Weeks 2 to 8 (seven doses; cycles 1 and 2) – Every two weeks Weeks 9 to 24 (eight doses; cycles 3 to 6) – Every four weeks Week 25 to 32 (two doses; cycles 7 and 8) Maintenance *(after ASCT)* ▪ 16 mg/kg body weight given as an intravenous infusion every 4 weeks for up to 12 cycles (48 weeks)
	<u>Treatment as one of the following:</u> • Monotherapy for patients with relapsed/refractory multiple myeloma • Combination therapy with lenalidomide and low-dose dexamethasone for newly diagnosed patients ineligible for ASCT • Combination therapy with lenalidomide, pomalidomide, or selinexor and low-dose dexamethasone in patients with relapsed/refractory disease ▪ 16 mg/kg body weight given as an intravenous infusion in a 4 week cycle: – Weekly Weeks 1 to 8 (eight doses; cycles 1 and 2) – Every two weeks Weeks 9 to 24 (eight doses; cycles 3 to 6) – Every four weeks Week 25 onwards (cycle 7 and beyond) *Treat until disease progression or unacceptable toxicity*
	<u>Combination therapy with carfilzomib and dexamethasone for relapsed/refractory disease</u> ▪ 8 mg/kg body weight given as an intravenous infusion on days 1 and 2 (Week 1; total 2 doses) ▪ Followed by 16 mg/kg body weight given as an intravenous infusion in a 4 week cycle: – Weekly Weeks 2 to 8 (seven doses; cycles 1 and 2) – Every two weeks Weeks 9 to 24 (eight doses; cycles 3 to 6) – Every four weeks Week 25 onwards (cycle 7 and beyond)

	Treat until disease progression or unacceptable toxicity
	Combination therapy with bortezomib and dexamethasone for relapsed/refractory disease ▪ 16 mg/kg body weight given as an intravenous infusion: – Weekly Weeks 1 to 9 (nine doses) – Every three weeks Weeks 10 to 24 (five doses) – Every four weeks Week 25 onwards until disease progression *Treat until disease progression or unacceptable toxicity*
Systemic Light Chain Amyloidosis	▪ 16 mg/kg body weight given as an intravenous infusion: – Weekly Weeks 1 to 8 (eight doses) – Every two weeks Weeks 9 to 24 (eight doses) – Every four weeks Week 25 onwards until disease progression or unacceptable toxicity
**To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days (i.e., 8 mg/kg on Day 1 and Day 2 respectively).*	
Note: Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting Darzalex and continue for 3 months following treatment.	

VI. Billing Code/Availability Information

HCPCS Code:

- J9145 - Injection, daratumumab, 10 mg; 1 billable unit = 10 mg

NDC(s):

- Darzalex 100 mg/5 mL single-dose vial: 57894-0502-xx
- Darzalex 400 mg/20 mL single-dose vial: 57894-0502-xx

VII. References (STANDARD)

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VIII. References (ENHANCED)

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma, in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse
E85.81	Light chain (AL) amyloidosis

ICD-10	ICD-10 Description
E85.89	Other amyloidosis
E85.9	Amyloidosis, unspecified
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; ASCT = autologous stem-cell transplant; TEE = thromboembolic events; AE = adverse event; IMiD = immunomodulatory agent; PI = proteasome inhibitor; MRD = minimal residual disease; sCR = stringent complete response (having a normal serum FLC [Free Light Chain] ratio and absence of clonal cells in bone marrow)

Multiple Myeloma

Newly diagnosed disease who are ineligible for autologous stem cell transplant							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab + bortezomib + melphalan + prednisone (DVMP)	1 (other recommended regimen)	Yes	Phase 3 (ALCYONE), randomized	Bortezomib + melphalan + prednisone (VMP)	PFS	Newly diagnosed, ineligible for transplant	• DVMP resulted in a lower risk of disease progression or death compared to VMP.
Daratumumab + lenalidomide + dexamethasone (DRd)	1 preferred	Yes	Phase 3 randomized, open-label, multi-center	Lenalidomide + dexamethasone (Rd)	PFS	Newly diagnosed MM ineligible for ASCT	• Among patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation, the risk of disease progression or death was significantly lower among those who received daratumumab plus lenalidomide and dexamethasone than among those who received lenalidomide and dexamethasone alone.

Daratumumab + cyclophosphamide + bortezomib + dexamethasone (D-VDd)	2A certain circumstances	No	Phase 2 (LYRA), multi-center, single-arm	N/A	ORR	Newly diagnosed (transplant eligible and ineligible) and relapsed disease	• In newly diagnosed patients, very good partial response or better (≥VGPR) and overall response rates after 4 induction cycles were 44% (primary endpoint) and 79%, respectively, and 56% and 81% at end of induction. Similar response rates were observed in the small number of patients with relapsed multiple myeloma.
Bortezomib + lenalidomide + dexamethasone (VRd)	1 preferred	Yes	Phase 3 (SWOG S0777), randomized, open-label	Lenalidomide + dexamethasone (Rd)	PFS	Newly diagnosed, not planned for immediate ASCT	• Addition of bortezomib to Rd resulted in significantly improved PFS and OS.
Lenalidomide + high-dose dexamethasone (Rd)	None for high-dose dexamethasone	Yes	Phase 3 (SWOG S0232), randomized, double-blind, placebo-controlled	High-dose dexamethasone (Dex)	PFS	Newly diagnosed	• Lenalidomide plus dexamethasone is superior to dexamethasone alone as first-line therapy in terms of response rates and PFS. • Higher incidence of TEE occurred with Rd despite aspirin prophylaxis.
Lenalidomide + low-dose dexamethasone	1 preferred	Yes	Phase 3 (E4A03), randomized, open-label	Lenalidomide + high-dose dexamethasone	ORR	Newly diagnosed prior to ASCT	• Lenalidomide plus low-dose dexamethasone is associated with better short-term OS and lower toxicity compared to lenalidomide plus high-dose dexamethasone.
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	2A preferred	Yes	Phase 2	N/A	---------	Untreated transplant ineligible	• CyBorD demonstrated an ORR of 95%.

Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	2A preferred	Yes	Phase 2 (EVOLUTION), randomized, multicenter	Bortezomib + lenalidomide + dexamethasone (VRd) Bortezomib + lenalidomide + cyclophosphamide + dexamethasone (VDCR) CyBorD-modified	ORR	Untreated regardless of transplant eligibility	• No substantial difference was noted in VDCR over 3-drug combinations.
Carfilzomib + lenalidomide + dexamethasone	2A other	No	Phase 1/2 Follow-up analysis	N/A	CR	Newly diagnosed	• Extended treatment with CRd resulted in deep and durable responses with all patients achieving at least a partial response.
Ixazomib + lenalidomide + dexamethasone	2A other	No	Phase 1/2	N/A	VGPR	Newly diagnosed	• All-oral combination with ixazomib demonstrated some activity (58% VGPR or better) in newly diagnosed multiple myeloma.
Newly diagnosed disease in patients eligible for autologous stem cell transplant							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab + lenalidomide + bortezomib +	2A other	No	Phase 2 (GRIFFIN), randomized	Bortezomib + lenalidomide + dexamethasone (RVd)	sCR	Newly diagnosed transplant=eligible	• Daratumumab with RVd induction and consolidation improved depth of response (sCR) compared to RVd alone in patients with transplant-eligible

dexamethasone (DRVd)							NDMM, with no new safety concerns.
Daratumumab + bortezomib + thalidomide + dexamethasone (DVTd)	2A certain circumstances	Yes	Phase 3 (CASSIOPEIA), open-label, randomized, active-controlled	Bortezomib + thalidomide + dexamethasone (VTd)	sCR	Previously untreated disease	• DVTd improved response in transplant-eligible patients with newly diagnosed multiple myeloma.
Daratumumab + cyclophosphamide + bortezomib + dexamethasone (D-VCd)	2A certain circumstances	No	Phase 2 (LYRA), multi-center, single-arm	N/A	ORR	Newly diagnosed (transplant eligible and ineligible) and relapsed disease	• In newly diagnosed patients, very good partial response or better (≥VGPR) and overall response rates after 4 induction cycles were 44% (primary endpoint) and 79%, respectively, and 56% and 81% at end of induction. Similar response rates were observed in the small number of patients with relapsed multiple myeloma.
Bortezomib + lenalidomide + dexamethasone (VRd)	1 preferred	Yes	Phase 3 (SWOG S0777), randomized, open-label	Lenalidomide + dexamethasone (Rd)	PFS	Newly diagnosed	• Addition of bortezomib to Rd resulted in significantly improved PFS and OS.
Cyclophosphamide + lenalidomide + dexamethasone (CRd)	2A certain circumstances	Yes	Phase 2	N/A	ORR	Untreated disease	• CRd is an effective upfront therapy of multiple myeloma with an ORR of 85% and 2-year OS rate of 87%.
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	2A preferred	Yes	Phase 2	N/A	---------	Untreated transplant ineligible	• CyBorD demonstrated an ORR of 95%.

Bortezomib + doxorubicin + dexamethasone (PAD) followed by bortezomib maintenance	2A certain circumstances	No	Phase 3 (HOVON-65/GMMG-HD4), open-label, randomized	Vincristine + doxorubicin + dexamethasone (VAD) followed by thalidomide maintenance	PFS	Newly diagnosed stage II or III, eligible for transplant	• Bortezomib containing regimen during induction and maintenance treatment resulted in a better response, PFS, and OS.
Carfilzomib + lenalidomide + dexamethasone (KRd)	2A other	No	Phase 2	N/A	CR	Newly diagnosed, transplant-eligible and ineligible	• KRd with SCT results in high rates of CR.
Bortezomib + thalidomide + dexamethasone (VTd)	1 certain circumstances	No	Phase 3 (IFM2013-04), multicenter	Bortezomib + cyclophosphamide + dexamethasone (VCd)	VGPR	Newly diagnosed	• VTd resulted in a higher ORR compared to VCd.
Ixazomib + cyclophosphamide + dexamethasone, followed by ixazomib maintenance	2A certain circumstances	No	Phase 2	N/A	CR	Elderly transplant-ineligible newly diagnosed patients	• Ixazomib plus cyclophosphamide and dexamethasone demonstrated an ORR 73% in elderly transplant-ineligible newly diagnosed multiple myeloma patients.
Bortezomib + thalidomide + dexamethasone + cisplatin + doxorubicin + cyclophosphamide + etoposide (VTD-PACE)	2A certain circumstances	No	Phase 2	N/A	-----	Newly diagnosed MM	• Bortezomib combined with multi-agent chemotherapy demonstrated a near-complete remission rate of 83% and a 2-year survival rate of 86%.

Carfilzomib + cyclophosphamide + dexamethasone	2A (for patients with renal insufficiency)	No	No clinical literature evidence to support use.

Previously Treated Multiple Myeloma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab + bortezomib + dexamethasone (DVd)	1 preferred	Yes after at least one prior therapy	Phase 3 (CASTOR), randomized	Bortezomib + dexamethasone (Vd)	PFS	Second-line and later	• Addition of daratumumab to Vd significantly improved PFS and ORR compared to Vd alone.
Daratumumab + lenalidomide + dexamethasone (DRd)	1 preferred	Yes after at least one prior therapy	Phase 3 (POLLUX), randomized	Lenalidomide + dexamethasone (Rd)	PFS	After 1 or more prior therapies	• Addition of daratumumab to Rd significantly lengthened PFS.
Daratumumab + carfilzomib + dexamethasone (KdD)	1 preferred	Yes after 1-3 prior lines of therapy	Phase 3 (CANDOR), randomized, open-label	Carfilzomib + dexamethasone (Kd)	PFS	1-3 prior therapies	• KdD significantly prolonged progression-free survival versus Kd in patients with relapsed or refractory multiple myeloma and was associated with a favorable benefit-risk profile.
Daratumumab + cyclophosphamide + bortezomib + dexamethasone (D-VCd)	2A certain circumstances	No	Phase 2 (LYRA), multi-center, single-arm	N/A	ORR	Newly diagnosed (transplant eligible and ineligible) and relapsed disease	• In patients with relapsed multiple myeloma, ORR was 12.3% and VGPR or better was seen in 57.1% of patients.

Daratumumab + selinexor + dexamethasone	2A certain circumstances after at least 4 prior therapies, including a proteasome inhibitor and an immunomodula-tory agent or who are double refractory	No	Phase 1b/2 (STOMP), multi-center, open-label	N/A	Maximum tolerated dose	Fourth-line or subsequent therapy, after a proteasome inhibitor and an immunomodula-tory agent, or who are double refractory	• Daratumumab in combination with selinexor and dexamethasone demonstrated an ORR of 73% and a median PFS of 12.5 months in patients with proteasome and immunomodulatory drug refractory multiple myeloma.
Ixazomib + lenalidomide + dexamethasone	1 preferred	Yes after at least one prior therapy	Phase 3 (TOURMALINE MM1), double-blind, randomized, placebo-controlled	Lenalidomide + dexamethasone (Rd)	PFS	After 1-3 prior therapies	• Addition of ixazomib to Rd significantly increased PFS.
Elotuzumab + lenalidomide + dexamethasone (ELd)	1 other	Yes in adults who have received 1-3 prior treatments	Phase 3 (ELOQUENT-2), randomized 3-year follow-up	Lenalidomide + dexamethasone (Ld)	PFS ORR	After 1-3 prior therapies	• Patients with relapsed or refractory multiple myeloma who received a combination of elotuzumab, lenalidomide, and dexamethasone had a significant relative reduction of 30% in the risk of disease progression or death.
Carfilzomib + lenalidomide + dexamethasone (CLd)	1 preferred	Yes in patients who have received 1-3 prior treatments	Phase 3 (ASPIRE), randomized, multicenter	Lenalidomide + dexamethasone (Ld)	PFS	After 1-3 prior therapies	• CLd combination resulted in a significantly improved PFS and OS (improved survival by 7.9 months).

			Final analysis of OS				
Carfilzomib (twice weekly) + dexamethasone (Cd)	1 other	Yes in patients who have received 1-3 prior treatments	Phase 3 (ENDEAVOR), randomized, open-label, multicenter Interim overall survival analysis	Bortezomib + dexamethasone (Bd)	PFS	After 1-3 prior therapies	• Carfilzomib with dexamethasone demonstrated a 2-fold improvement in PFS and a significant increase in OS compared to bortezomib with dexamethasone.
Daratumumab	2A certain circumstances	Yes after at least 3 prior therapies including lenalidomide and a proteasome inhibitor or who are double-refractory to a PI and IMiD	Phase 2	N/A	ORR	After 3 lines of therapy including an IMiD and PI or double refractory to PI and IMiD	• Daratumumab monotherapy demonstrated to be effective in heavily pretreated and refractory patients based on an ORR of 29.2%.
Daratumumab + pomalidomide + dexamethasone (DPd)	2A other	Yes after at least 2 prior therapies including lenalidomide and a	Phase 1b (MMY1001), open-label, multicenter	N/A	Safety	After at least 2 prior lines of therapy, including lenalidomide and bortezomib (excluding	• DPd demonstrated an ORR of 60%. • Increased neutropenia was observed with DPd regimen compared to that seen in individual therapies.

		proteasome inhibitor				daratumumab or pomalidomide)	

Systemic Light Chain Amyloidosis

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab	2A	No	Retrospective analysis	N/A	-----	Relapsed or refractory disease	• Daratumumab is effective with a hematologic response rate of 76% in heavily pretreated systemic light chain amyloidosis patients.
Daratumumab	2A	No	Phase 2	N/A	Safety	Relapsed or refractory disease	• In a single-center phase 2 trial that enrolled 22 patients with a median of two prior therapies, hematologic very good partial response (VGPR) or better was seen in 86% of patients with a median time to first response of four weeks.
Daratumumab	2A	No	Phase 2, single-arm, multi-center	N/A	ORR	Relapsed or refractory disease	• In aa multicenter phase 2 trial that enrolled 40 patients with a median of three prior therapies, hematologic VGPR or better was seen in 48 percent with a median time to first response of one week.
Bortezomib + melphalan + dexamethasone	2A	No	Phase 2	N/A	cHR	All lines of therapy	• Adding bortezomib to melphalan and dexamethasone is clinically active with a hematologic response of 94%.

Bortezomib ± dexamethasone	2A	No	Phase 1/2	N/A	Safety Maximum tolerated dose	Previously treated	• Bortezomib in previously treated light chain amyloidosis resulted a hematologic response rate of 68.8%.
Ixazomib ± dexamethasone	2A	No	Phase 2	N/A	Safety Maximum tolerated dose	After ≥1 prior lines of therapy	• Weekly oral ixazomib demonstrated a hematologic ORR of 52% in patients with relapsed ore refractory light chain amyloidosis.
Pomalidomide + dexamethasone	2A	No	Phase 2	N/A	HR	After ≥1 prior lines of therapy	• A hematologic response rate of 48% was seen with pomalidomide and dexamethasone in patients with previously treated light chain amyloidosis.