Kyprolis® (carfilzomib)
(Intravenous)

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I. Length of Authorization [1,5,12,21,27]

Coverage will be provided for six months and may be renewed.

* *Combination therapy with lenalidomide and dexamethasone as treatment in multiple myeloma is limited to eighteen (18) 28-day treatment cycles.*
* *Treatment of Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma is limited to six (6) 21-day induction therapy treatment cycles and eight (8) 56-day maintenance therapy treatment cycles.*

II. Dosing Limits

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

- Kyprolis 10 mg powder for injection: 2 vials per 28 day supply
- Kyprolis 30 mg powder for injection: 1 vial per 28 day supply
- Kyprolis 60 mg powder for injection: 12 vials per 28 day supply

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

- **Multiple Myeloma**
  - 720 billable units every 28 days
- **Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma**
  - 320 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years old; AND

Multiple Myeloma † Φ [1,2,10,11,13-17,19,23,2e,4e,8e,10e,12e,35e,38e-40e]

- Used as primary therapy or for disease relapse after 6 months following primary induction therapy with the same regimen in patients with active (symptomatic) disease; AND

- Used in combination with lenalidomide and dexamethasone; **OR**
- Used in combination with dexamethasone and cyclophosphamide for non-transplant candidates; **OR**

- Used for previously treated myeloma for disease relapse or for progressive or refractory disease; **AND**
  - Used as a single agent †; **OR**
  - Used in combination with dexamethasone with or without lenalidomide †; **OR**
  - Used in combination with dexamethasone and daratumumab †; **OR**
  - Used in combination with dexamethasone and cyclophosphamide; **OR**
  - Used in combination with panobinostat; **AND**
    - Patient has received at least 2 prior regimens, including bortezomib and an immunomodulatory agent [i.e., lenalidomide, thalidomide, etc.]; **OR**
  - Used in combination with pomalidomide and dexamethasone; **AND**
    - Patient has received at least 2 prior therapies, including a proteasome inhibitor [i.e., bortezomib, etc.] and an immunomodulatory agent [i.e., lenalidomide, thalidomide, etc.]; **AND**
    - Disease has progressed on or within 60 days of completion of the last therapy

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma ‡ [2,18,28e-32e,34e]

- Used in combination with rituximab and dexamethasone (CaRD regimen); **AND**
  - Used as primary therapy

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 Approved Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,2,6]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet 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: cardiac toxicity, pulmonary toxicity, pulmonary hypertension, dyspnea, severe infusion related reactions, tumor lysis syndrome (TLS), thrombocytopenia, hepatic toxicity/failure, thrombotic microangiopathy (including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome [TTP/HUS]), acute renal failure, severe hypertension, posterior reversible encephalopathy syndrome (PRES), venous thromboembolic events, hemorrhage, progressive multifocal leukoencephalopathy (PML), etc.

V. Dosage/Administration [1,5,7-9,12,20-22,24-28]

Indication	Dose
Multiple Myeloma	20/27 regimen (*single agent*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 27 mg/m² on days 8, 9, 15, and 16 of a 28-day treatment cycle – Cycles 2 through 12: 27 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle – Cycle 13 and beyond: 27 mg/m² on days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity 20/56 regimen (*single agent*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 56 mg/m² on days 8, 9, 15, and 16 of a 28-day treatment cycle. – Cycles 2 through 12: 56 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle. – Cycle 13 and beyond: 56 mg/m² on days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity. 20/36 regimen for **NEWLY DIAGNOSED** disease (*combination with lenalidomide and dexamethasone*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 36 mg/m² days 8, 9, 15, and 16 of a 28-day treatment cycle – Cycles 2 through 8: 36 mg/m² days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle – Cycles 9 to 18: 36 mg/m² days 1, 2, 15, and 16 of a 28-day treatment cycle 20/27 regimen for **RELAPSED/REFRACTORY** disease (*combination with lenalidomide and dexamethasone*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 27 mg/m² on days 8, 9, 15, and 16 of a 28-day treatment cycle. – Cycles 2 through 12: 27 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle. – Cycles 13 to 18: 27 mg/m² on days 1, 2, 15, and 16 of a 28-day treatment cycle; beginning with cycle 19, lenalidomide and dexamethasone may be continued (until disease progression or unacceptable toxicity) without carfilzomib. 20/27 regimen (*combination with pomalidomide and dexamethasone*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 27 mg/m² on days 8, 9, 15, and 16 of a 28-day treatment cycle. – Cycles 2 through 6: 27 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle. – Cycle 7 and beyond: 27 mg/m² on days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity – **NOTE:** If disease progression occurs while on maintenance dosing, resume full dosing of 27 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle 20/36 regimen (*combination with pomalidomide and dexamethasone*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 36 mg/m² days 8, 9, 15, and 16 of a 28-day treatment cycle – Cycles 2 through 8: 36 mg/m² days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle – Cycle 9 and beyond: 36 mg/m² days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity

	20/45 regimen (*combination with panobinostat*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 45 mg/m² on days 8, 9, 15, and 16 of a 28-day treatment cycle. – Cycle 2 and beyond: 45 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity. 20/56 regimen (*combination with dexamethasone*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 56 mg/m² on days 8, 9, 15, and 16 of a 28-day treatment cycle. – Cycle 2 and beyond: 56 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity. 20/70 regimen (*combination with dexamethasone*) – Cycle 1: 20 mg/m² on day 1; if tolerated, increase to 70 mg/m² on day 8 and 15 of a 28-day treatment cycle. – Cycle 2 and beyond: 70 mg/m² on days 1, 8, and 15 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity 20/36 regimen for **NEWLY DIAGNOSED** disease (*combination with cyclophosphamide and dexamethasone*): – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 36 mg/m² days 8, 9, 15, and 16 of a 28-day treatment cycle – Cycles 2 through 9: 36 mg/m² days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle – Cycle 10 and beyond: 36 mg/m² on days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity. 20/36 regimen for **RELAPSED/REFRACTORY** disease (*combination with cyclophosphamide and dexamethasone*): • Induction – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 36 mg/m² days 8, 9, 15, and 16 of a 28-day treatment cycle – Cycles 2 through 6: 36 mg/m² days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle • Maintenance – Cycles 7 through 12: 36 mg/m² on days 1, 2, 15, and 16 of a 28-day treatment cycle – Cycles 13 and beyond: 36 mg/m² on days 1 and 2 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity 20/56 regimen (*combination with daratumumab and dexamethasone):* – Cycle 1: 20 mg/m² on days 1 and 2; if tolerated, increase to 56 mg/m² on days 8, 9, 15 and 16 of a 28-day treatment cycle – Cycle 2 and beyond: 56 mg/m² on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity 20/70 regimen (*combination with daratumumab and dexamethasone):* – Cycle 1: 20 mg/m² on day 1; if tolerated, increase to 70 mg/m² on day 8 and 15 of a 28-day treatment cycle – Cycle 2 and beyond: 70 mg/m² on days 1, 8, and 15 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity.
Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma	CaRD regimen (carfilzomib, rituximab, dexamethasone) • Induction – Cycle 1: 20 mg/m² on days 1, 2, 8 and 9 of a 21-day treatment cycle. – Cycles 2 through 6: 36 mg/m² on days 1, 2, 8 and 9 of a 21-day treatment; begin maintenance 8 weeks later. • Maintenance – 36 mg/m² on days 1 and 2 every 8 weeks for 8 cycles.

Note: Calculate the Kyprolis dose using the patient's actual body surface area at baseline. In patients with a body surface area greater than 2.2 m², calculate the dose based upon a body surface area of 2.2 m².

VI. Billing Code/Availability Information

HCPCS Code:

- J9047 – Injection, carfilzomib, 1 mg; 1mg = 1 billable unit

NDC:

- Kyprolis 10 mg powder in single-dose vial for injection: 76075-0103-xx
- Kyprolis 30 mg powder in single-dose vial for injection: 76075-0102-xx
- Kyprolis 60 mg powder in single-dose vial for injection: 76075-0101-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
C88.0	Waldenström macroglobulinemia
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
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; VGPR = very good partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; SCT = stem cell transplant

Multiple Myeloma

Primary therapy for transplant candidates							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + lenalidomide + dexamethasone (VRd)	1 preferred	Yes	Phase 3 (SWOG S0777), randomized, open-label	Lenalidomide + dexamethasone (Rd)	PFS	Newly diagnosed; with and without intent to transplant	• Addition of bortezomib to Rd resulted in significantly improved PFS and OS.
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.
Bortezomib + thalidomide + dexamethasone (VTd)	1 certain circumstances	Yes	Phase 3 (IFM2013-04), multicenter	Bortezomib + cyclophosphamide + dexamethasone (VCd)	VGPR	Newly diagnosed	• VTd resulted in a higher ORR compared to VCd.

Bortezomib + cyclophosphamide + dexamethasone	2A preferred (for patients with renal insufficiency)	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 (KRd)	2A other	No	Phase 2	N/A	CR	Newly diagnosed, transplant-eligible and ineligible	• KRd with SCT results in high rates of CR.
Daratumumab + lenalidomide + bortezomib + dexamethasone (DRVd)	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 NDMM, with no new safety concerns.
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%.
Daratumumab + bortezomib + thalidomide + dexamethasone (DVTd)	2A certain circumstances	Yes	Phase 3 (CASSIOPEIA), open-label, randomized,	Bortezomib + thalidomide + dexamethasone (VTd)	sCR	Previously untreated disease	• DVTd improved response in transplant-eligible patients with newly diagnosed multiple myeloma.

			active-controlled				
Dexamethasone + thalidomide + cisplatin + doxorubicin + cyclophosphamide + etoposide + bortezomib (VTD-PACE)	2A certain circumstances	No	Phase 2 (Total therapy 3 – TT3)	N/A	----------	Newly diagnosed	• Multi-agent chemotherapy resulted in CR rate and 2-year survival rates of more than 80%.
Bortezomib + dexamethasone	None	Yes	Phase 3 (IFM 2005-01), randomized	Vincristine + doxorubicin + dexamethasone (VAD)	CR nCR	Previously untreated	• Bortezomib plus dexamethasone significantly improved postinduction and post-transplantation CR/nCR and at least VGPR rates compared with VAD and resulted in a trend for longer PFS.
Lenalidomide + dexamethasone	None	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.
Ixazomib + lenalidomide + dexamethasone	2B	No	No clinical literature evidence to support use.				
Carfilzomib + cyclophosphamide + dexamethasone	2A (for patients with renal insufficiency)	No	No clinical literature evidence to support use.				

Primary therapy for NON-transplant candidates							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + lenalidomide + dexamethasone (VRd)	1 preferred	Yes	Phase 3 (SWOG S0777), randomized, open-label	Lenalidomide + dexamethasone (Rd)	PFS	Newly diagnosed; with and without intent to transplant	• Addition of bortezomib to Rd resulted in significantly improved PFS and OS.
Daratumumab + bortezomib + melphalan + prednisone (DVMP)	1 preferred	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 + 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.
Daratumumab + lenalidomide + dexamethasone (DRd)	TBD	Yes	Phase 3 randomized, open-label, multi0center	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.
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	2A preferred	Yes	Phase 2 (Zepeta, et al.)	N/A	---	Untreated transplant ineligible	• CyBorD demonstrated an ORR of 95%.
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	2A preferred (for patients with renal insufficiency)	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 transplant-eligible and ineligible	• Extended treatment with CRd resulted in deep and durable responses with all patients achieving at least a partial response.
Carfilzomib + lenalidomide + dexamethasone (KRd)	2A other	No	Phase 3 (ENDURANCE), randomized, multi-center, open-label	Bortezomib + lenalidomide + dexamethasone (VRd)	OS PFS	Newly diagnosed non-transplant candidate	• The KRd regimen did not improve progression-free survival compared with the VRd regimen in patients with newly diagnosed multiple myeloma and had more toxicity.

Carfilzomib + cyclophosphamide + dexamethasone (CCyd)	2A other	No	Phase 2, multicenter, open-label	N/A	PR	Newly diagnosed, ineligible for SCT	• High response rates were demonstrated with CCyd.
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.
Cyclophosphamide + lenalidomide + dexamethasone	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%.
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.
Used for previously treated myeloma for disease relapse or for progressive or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Carfilzomib + lenalidomide + dexamethasone (CLd)	1 preferred	Yes in patients who have received 1-3 prior treatments	Phase 3 (ASPIRE), randomized, multicenter Final analysis of OS	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).
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 + 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.
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 preferred	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 monotherapy (Cohort 1: 20mg/m^2; Cohort 2 20mg/m^2 cycle 1, then 27mg/m^2)	None	Yes	Phase 2 (PX-171-004), multicenter, open-label	N/A	ORR	After 1-3 prior therapies	• Single-agent therapy with carfilzomib demonstrated to be clinically active in pretreated multiple myeloma.
Carfilzomib monotherapy	None	Yes	Phase 2 (PX-171-003), multicenter, open-label	N/A	ORR	After at least 2 prior lines of therapy, including bortezomib and IMiD therapy	• Durable responses in heavily pretreated disease were demonstrated with an ORR of 23.7% and DOR of 7.8 months.

Carfilzomib + cyclophosphamide + dexamethasone (KCD)	2A	No	Phase 2 (MUK five), randomized	Bortezomib + cyclophosphamide + dexamethasone (VCD)	VGPR	First relapse or refractor to no more than 1 prior line of therapy	• VGPR with KCD therapy is non-inferior to VCD. • However, ORR is superior to VCD.
Carfilzomib + cyclophosphamide + thalidomide + dexamethasone	2A certain circumstances	No	No clinical literature evidence to support use.				
Carfilzomib + panobinostat	2A	No	Phase 1/2, single-arm, open-label, multicenter	N/A	ORR	After at least 1 prior therapy	• Combination of carfilzomib and panobinostat is an effective treatment option for patients with relapsed/refractory multiple myeloma.
Carfilzomib + pomalidomide + dexamethasone	2A	No	Phase 1/2	N/A	----------	After at least 1 prior therapy (if enrolled as second-line therapy, must be lenalidomide-refractory)	• KRd is highly active (PR 84%) in less-pretreated lenalidomide-refractory disease.
Panobinostat (PAN) + bortezomib (BTZ) + dexamethasone (Dex)	1	Yes after at least 2 prior therapies with regimens including bortezomib and an IMiD agent	Phase 3 (PANORAMA-1), randomized, placebo-controlled, double-blind Subgroup analysis	Bortezomib + dexamethasone + placebo	PFS	After 1-3 prior therapies	• Benefit from PAN-BTZ-Dex was greatest (7.8 month improvement) in patients who received ≥2 prior regimens including bortezomib and an IMiD agent.

Lenalidomide + bortezomib + dexamethasone (RVD)	2A preferred	Yes	Phase 2, prospective, multicenter	N/A	PFS	After 1-3 prior therapies	• RVD combination therapy is active with durable responses in heavily pretreated patients .

Waldenström's Macroglobulinemia (WM)/Lymphoplasmacytic Lymphoma

Primary therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Carfilzomib + rituximab + dexamethasone	2A other	No	Phase 2 (CaRD), prospective, open-label, single stage	N/A	ORR	No prior PI or rituximab; no more than 1 prior therapy; symptomatic patients	• CaRD offers a neuropathy-sparing approach for proteasome inhibitor-based therapy in WM.
Ibrutinib + rituximab	1 preferred	Yes	Phase 3 (iNNOVATE), randomized	Placebo + rituximab	PFS	Both treated and untreated disease	• Use of ibrutinib–rituximab resulted in significantly higher rates of PFS than the use of placebo–rituximab, both among those who had received no previous treatment and among those with disease recurrence.
Bendamustine + rituximab (BR)	2A preferred	No	Phase 3, randomized, multicenter	Cyclophosphamide + doxorubicin + vincristine + prednisone + rituximab (R-CHOP)	PFS	Untreated disease	• In patients with previously untreated WM, BR can be considered as a preferred first-line treatment approach to R-CHOP because of increased PFS and fewer toxic effects.

Bortezomib + rituximab + dexamethasone (BDR)	2A preferred	No	Phase 2 WMCTG Clinical Trial 05-180	N/A	ORR PFS	Untreated disease	• Results demonstrate that BDR produces rapid and durable responses, along with high rates of response and complete remissions in WM.
Bortezomib + rituximab + dexamethasone (BDR)	2A preferred	No	Phase 2, multicenter	N/A	ORR	Untreated disease	• BDR is an active regimen and induces long-lasting responses in patients with newly diagnosed WM.
Rituximab + cyclophosphamide + dexamethasone (DRC)	2A preferred	No	Phase 2 Final analysis	N/A	----------	Untreated disease; symptomatic patients	• DCR is an active, well-tolerated treatment for symptomatic patients with WM.
Rituximab + cyclophosphamide + dexamethasone (DRC)	2A preferred	No	Retrospective analysis	N/A	----------	Untreated disease	• DRC is an effective and well-tolerated frontline treatment.