Velcade® (bortezomib)
(Intravenous/Subcutaneous)

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I. Length of Authorization [1,5,8,14,25,26,35-41]

Coverage will be provided for 6 months and may be renewed unless otherwise specified.

- Initial treatment for Multiple Myeloma: Coverage will be provided for a total of 9 cycles (42-days per cycle).
- Re-treatment of Multiple Myeloma, initial treatment of Mantle Cell Lymphoma, & Adult T-Cell Leukemia/Lymphoma: Coverage will be provided for a total of 8 cycles (21-days per cycle).
- Systemic Light Chain Amyloidosis as a single agent or in combination with cyclophosphamide and/or dexamethasone: Coverage will be provided for a total of 8 cycles (35-days per cycle as a single agent; 21- or 28-days per cycle in combination with cyclophosphamide and/or dexamethasone).
- Systemic Light Chain Amyloidosis in combination with melphalan and dexamethasone: Coverage will be provided for a total of 9 cycles (21-days per cycle)
- Systemic Light Chain Amyloidosis in combination with lenalidomide and dexamethasone: Coverage will be provided for a total of 8 cycles (28-days per cycle).
- Systemic Light Chain Amyloidosis in combination with daratumumab and hyaluronidase-fihj, cyclophosphamide, and dexamethasone: Coverage will be provided for a total of 2 years.
- Waldenström's Macroglobulinemia in combination with rituximab and/or dexamethasone: Coverage will be provided for a total of 6 cycles (28-days per cycle) or 8 cycles (21-days per cycle).
- Pediatric Hodgkin Lymphoma: Coverage will be provided for a total of 4 cycles (21-days per cycle).

II. Dosing Limits

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

- Velcade 3.5 mg powder for injection: 8 vials per 28 day supply

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

- **Multiple Myeloma (maintenance therapy for transplant ineligible patients) & Systemic Light Chain Amyloidosis:**
  - 280 billable units every 35 days

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- **Waldenström's Macroglobulinemia:**
  - 210 billable units every 28 days
- **Multiple Myeloma (initial treatment):**
  - 280 billable units every 42 days for cycles 1-4, then 140 billable units every 42 days cycles 5-9
- **Pediatric Hodgkin Lymphoma:**
  - 105 billable units every 21 days
- **All Other Indications:**
  - 140 billable units every 21 days

III. Initial Approval Criteria [1,2]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria [1]

- Will not be administered intrathecally; **AND**

Multiple Myeloma † Φ [1-5,13,15-20,24-26,27e,28e,58e]

- Used in combination with a corticosteroid containing regimen as primary therapy for symptomatic disease or for relapse (re-treatment) after 6 months following primary induction therapy with the same regimen; **OR**
- Used as maintenance therapy as a single agent; **OR**
- Used for relapsed or progressive disease in combination with a dexamethasone-containing regimen

Mantle Cell Lymphoma – B-Cell Lymphoma † Φ [1,2,12,21-23,27]

- Used as induction or additional therapy; **AND**
  - Used as a component of VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone); **OR**
- Used as subsequent therapy; **AND**
  - Used as a single agent; **OR**
  - Used in combination with rituximab

Systemic Light Chain Amyloidosis ‡ [2,10,46,30e-34e,56e,64e,65e]

- Patient has newly diagnosed disease OR used as repeat initial therapy if relapse-free for several years; **AND**
  - Used in combination with cyclophosphamide and dexamethasone; **OR**
  - Used in combination with dexamethasone with melphalan or lenalidomide; **OR**
  - Used in combination with daratumumab and hyaluronidase-fihj, cyclophosphamide, and dexamethasone; **OR**

- Patient has relapsed or refractory disease; **AND**
  - Used as a single agent; **OR**
  - Used in combination with dexamethasone with or without melphalan

Waldenström's macroglobulinemia/Lymphoplasmacytic Lymphoma ‡ [2,5,11,14,29,38,41e,43e-45e,52e,61e-62e]

- Used as primary therapy in combination with dexamethasone and rituximab; **OR**
- Used as a single agent; **OR**
- Used in combination with rituximab

Pediatric Acute Lymphoblastic Leukemia ‡ [2,8,28]

- Patient is at least 1 year of age*; **AND**
  - Patient has relapsed or refractory B-cell disease (B-ALL); **AND**
    - Used as a component of the COG AALL07P1 regimen (bortezomib, vincristine, doxorubicin, pegaspargase, prednisone); **AND**
      - Patient has Philadelphia (Ph) chromosome negative disease; **OR**
      - Patient has Philadelphia (Ph) chromosome positive disease; **OR**
  - Patient has relapsed or refractory T-cell disease (T-ALL); **AND**
    - Used in combination with a corticosteroid, vincristine, doxorubicin, and pegaspargase

** Pediatric patients may include certain adolescent and young adult (AYA) patients up to 30 years of age.*

Pediatric Hodgkin Lymphoma ‡ [3,45]

- Patient age is 18 years and under*; **AND**
- Used for relapsed or refractory disease in combination with ifosfamide and vinorelbine

** Pediatric Hodgkin Lymphoma patients may include certain adolescent and young adult (AYA) patients up to 39 years of age.*

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken in 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 [1,2,6]

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. Example of unacceptable toxicity include: peripheral neuropathy, hypotension, cardiac toxicity, pulmonary toxicity, posterior reversible encephalopathy syndrome, gastrointestinal toxicity, thrombocytopenia, neutropenia, tumor lysis syndrome, hepatic toxicity, thrombotic microangiopathy, etc.

V. Dosage/Administration [1,5,6,8,14,25,26,30,35-43]

Indication	Dose
Multiple Myeloma – initial treatment	1.3 mg/m^2 intravenously (IV)/subcutaneously (SC) in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles. In cycles 1-4, Velcade is given twice weekly (days 1, 4, 8, 11, 22, 25, 29, and 32). In cycles 5-9, Velcade is given once weekly (days 1, 8, 22, and 29).
Multiple Myeloma – maintenance therapy	<u>Following primary therapy with a bortezomib-containing regimen for transplant-ineligible patients:</u> 1.3 mg/m² IV/SC every two weeks or 1.6 mg/m^2 IV/SC once weekly (days 1, 8, 15, and 22) every 35 days until disease progression or unacceptable toxicity <u>Following autologous stem cell transplant:</u> 1.3 mg/m² IV/SC every two weeks until disease progression or unacceptable toxicity
Multiple Myeloma – re-treatment	1.3 mg/m² IV/SC twice weekly (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21) for up to 8 cycles
Mantle Cell Lymphoma – previously untreated	1.3 mg/m^2 IV/SC in combination with rituximab, cyclophosphamide, doxorubicin, and oral prednisone for six 3-week treatment cycles. Velcade is given twice weekly (Days 1, 4, 8, and 11) followed by a 10-day rest period on Days 12-21. For patients with a response first documented at cycle 6, two additional cycles are recommended.
Multiple myeloma & Mantle Cell Lymphoma-relapsed	1.3 mg/m² IV/SC twice weekly (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). • For extended therapy of more than 8 cycles, Velcade may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for 4 weeks (days 1, 8, 15, and 22), followed by a 13-day rest period (days 23 to 35)
Systemic Light Chain Amyloidosis	<u>Single agent:</u> 1.6 mg/m^2 IV/SC weekly (days 1, 8, 15, and 22) every 35 days or 1.3 mg/m² IV/SC twice weekly (days 1, 4, 8, and 11) every 21 days for up to 8 cycles <u>In combination with cyclophosphamide and/or dexamethasone:</u> 1.3 mg/m² IV/SC twice weekly (days 1, 4, 8, and 11) every 21 or 28 days for up to 8 cycles <u>In combination with melphalan and dexamethasone:</u> 1.3mg/m^2 IV/SC twice weekly (days 1, 4, 8, and 11) every 28 days for up to 9 cycles <u>In combination with lenalidomide and dexamethasone:</u> 1.3mg/m^2 IV/SC twice weekly (days 1, 8, and 15) every 28 days for up to 8 cycles

	<u>In combination with daratumumab and hyaluronidase-fihj, cyclophosphamide, and dexamethasone:</u> 1.3mg/m^2 IV/SC weekly (days 1, 8, 15, and 22) every 28 days for up to 2 years
Waldenström's macroglobulinemia	<u>Single agent:</u> • 1.3 mg/m^2 IV twice weekly (days 1, 4, 8, and 11) every 21 days, until disease progression or unacceptable toxicity <u>In combination with rituximab and/or dexamethasone:</u> • 1.3 mg/m^2 IV/SC twice weekly (days 1, 4, 8, and 11) every 21 days for 4 continuous cycles, followed by a 12-week rest period, then up to 4 additional cycles given every 12 weeks • 1.6 mg/m^2 IV weekly (days 1, 8, and 15) every 28 days for up to 6 cycles
Pediatric Hodgkin Lymphoma	1.2 mg/m^2 IV/SC on days 1, 4, and 8 every 21 days for up to 4 cycles
All Other Indications	1.3 mg/m^2 IV/SC twice weekly (days 1, 4, 8, and 11) for 2 weeks of a 21 day cycle
Reconstituted concentration varies by route of administration: • *1 mg/mL intravenously* • *2.5 mg/mL subcutaneously*	

VI. Billing Code/Availability Information

<u>HCPCS Code</u>:

- J9041– Injection, bortezomib (velcade), 0.1 mg; 1 billable unit = 0.1 mg

<u>NDC</u>:

- Velcade 3.5 mg single-use vial powder for injection: 63020-0049-xx

VII. References (STANDARD)

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites

ICD-10	ICD-10 Description
C81.20	Mixed cellularity Hodgkin lymphoma, unspecified site
C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes
C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.30	Lymphocyte depleted Hodgkin lymphoma, unspecified site
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.70	Other Hodgkin lymphoma unspecified site
C81.71	Other Hodgkin lymphoma lymph nodes of head, face, and neck
C81.72	Other Hodgkin lymphoma intrathoracic lymph nodes
C81.73	Other Hodgkin lymphoma intra-abdominal lymph nodes
C81.74	Other Hodgkin lymphoma lymph nodes of axilla and upper limb

ICD-10	ICD-10 Description
C81.75	Other Hodgkin lymphoma lymph nodes of inguinal region and lower limb
C81.76	Other Hodgkin lymphoma intrapelvic lymph nodes
C81.77	Other Hodgkin lymphoma spleen
C81.78	Other Hodgkin lymphoma lymph nodes of multiple sites
C81.79	Other Hodgkin lymphoma extranodal and solid organ sites
C81.90	Hodgkin lymphoma, unspecified, unspecified site
C81.91	Hodgkin lymphoma, unspecified, lymph nodes of head, face, and neck
C81.92	Hodgkin lymphoma, unspecified, intrathoracic lymph nodes
C81.93	Hodgkin lymphoma, unspecified, intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified, lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified, intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified, spleen
C81.98	Hodgkin lymphoma, unspecified, lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C83.10	Mantle cell lymphoma, unspecified site
C83.11	Mantle cell lymphoma, lymph nodes of head, face and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C88.0	Waldenstrom macroglobulinemia
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma, in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.11	Plasma cell leukemia in remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.21	Extramedullary plasmacytoma in remission
C90.22	Extramedullary plasmacytoma in relapse

ICD-10	ICD-10 Description
C90.30	Solitary plasmacytoma not having achieved remission
C90.31	Solitary plasmacytoma in remission
C90.32	Solitary plasmacytoma in relapse
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.02	Acute lymphoblastic leukemia, in relapse
E85.81	Light chain (AL) amyloidosis
E85.89	Other amyloidosis
E85.9	Amyloidosis, unspecified
Z85.71	Personal history of Hodgkin Lymphoma
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), 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):

Jurisdiction(s): 6, K	**NCD/LCD/LCA Document (s):** A52371
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A52371&bc=gAAAAAAAAAAAAA==	

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; nCR = near 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; cHR = complete hematologic response; VGPR = very good partial response; SD = stable disease

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) , followed by lenalidomide	1 preferred	Yes	Phase 3 (SWOG S0777), randomized, open-label	Lenalidomide + dexamethasone (Rd) , followed by lenalidomide	PFS	Newly diagnosed	• Addition of bortezomib to Rd resulted in significantly improved PFS and OS
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	1 preferred	Yes	Phase 2	N/A	---------	Untreated transplant ineligible	• CyBorD demonstrated an ORR of 95%
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	1 preferred	Yes	Phase 2 (EVOLUTION), randomized, multicenter	Bortezomib + lenalidomide + dexamethasone (VRd) Bortezomib + lenalidomide + cyclophosphamide + dexamethasone (V DCR) CyBorD-modified	ORR	Untreated regardless of transplant eligibility	• No substantial difference was noted in VDCR over 3-drug combinations

Bortezomib + doxorubicin + dexamethasone (PAD) followed by bortezomib maintenance	1	Yes	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 + dexamethasone	1 (use in certain circumstances)	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.
Bortezomib + thalidomide + dexamethasone (VTD)	1 (useful in certain circumstances)	Yes	. multicenter	Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	VGPR	Newly diagnosed	• VTD resulted in a higher ORR compared to CyBorD.
Carfilzomib + lenalidomide + dexamethasone (KRd)	2A	No	Phase 2	N/A	CR	Newly diagnosed, transplant-eligible	• KRd with SCT results in high rates of CR
Ixazomib + lenalidomide + dexamethasone	2B	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
Lenalidomide + dexamethasone	1	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 thrombosis occurred with Rd despite aspirin prophylaxis

Cyclophosphamide + lenalidomide + dexamethasone	2A						
Primary therapy for non-transplant candidates							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + lenalidomide + dexamethasone	1 preferred	Yes	Phase 3 (SWOG S0777), randomized, open-label	See clinical trial information under 'Primary therapy for transplant candidates' above.			
Bortezomib + daratumumab + melphalan + prednisone (DVMP)	1 preferred	Yes	Phase 3 (ALCYONE), randomized	Bortezomib + melphalan + prednisone (VMP)	PFS	Newly diagnosed	• DVMP resulted in a lower risk of disease progression or death compared to VMP
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	2A preferred	Yes	Phase 2	N/A	ORR	Primary therapy for non-transplant eligible candidates	• CyBorD demonstrated an ORR of 95% for the treatment of non-transplant eligible patients with MM.
Bortezomib + dexamethasone (VD), followed by bortezomib maintenance	2A (useful under certain circumstances)	Yes	Phase 3b (UPFRONT), randomized, open-label, multi-center	Bortezomib + thalidomide + dexamethasone (VTD), followed by bortezomib maintenance vs. Melphalan + prednisone + bortezomib (VMP), followed by bortezomib maintenance	PFS	Previously untreated	• Although all bortezomib-containing regimens produced good outcomes, VTD and VMP did not appear to offer an advantage over VD in transplantation-ineligible patients with myeloma.

Lenalidomide + dexamethasone	1 preferred	Yes	Phase 3 (SWOG S0232), randomized, double-blind, placebo-controlled	See clinical trial information under 'Primary therapy for transplant candidates' above.			
Maintenance							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib	2A	Yes	Phase 3 (HOVON-65/GMMG-HD4), open-label, randomized	See clinical trial information under 'Primary therapy for transplant candidates' above.			
Bortezomib	2A	Yes	Phase 3b (UPFRONT), randomized, open-label, multi-center	See clinical trial information under 'Primary therapy for non-transplant candidates' above.			
Lenalidomide	1 preferred	Yes (after ASCT)	Phase 3 (IFM 2005-02), randomized, double-blind Updated Analysis	Placebo	PFS	Consolidation after ASCT	• Lenalidomide maintenance after transplantation significantly prolonged progression-free and event-free survival among patients with multiple myeloma. • Despite an increase in hematological adverse events and second primary malignancies, lenalidomide maintenance therapy after ASCT significantly improved time to progression.
Lenalidomide (after melphalan + prednisone + lenalidomide [MPR])	1 preferred	Yes (after ASCT)	Phase 3 MM-015, randomized, double-blind	Placebo (after melphalan + prednisone + lenalidomide [MPR] or	PFS	After non-transplant primary treatment (melphalan,	• MPR-R significantly prolonged progression-free survival in patients with newly diagnosed multiple myeloma who were ineligible for transplantation, with the greatest benefit observed in patients 65 to 75 years of age.

				melphalan + prednisone [MP])		prednisone, lenalidomide)	
Bortezomib + lenalidomide	2A	No	No clinical literature to support use.				
Relapsed or progressive disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + lenalidomide + dexamethasone	2A preferred	Yes	Phase 2, multi-center	N/A	6-mon PFS	Relapsed or refractory MM (prior bortezomib, thalidomide, or lenalidomide were allowed)	• Bortezomib plus lenalidomide and dexamethasone demonstrated to be clinically active with a 6-month PFS rate of 75% in heavily pretreated patients with relapsed and/or refractory MM, including patients who have had prior lenalidomide, bortezomib, thalidomide, and SCT.
Daratumumab + bortezomib + dexamethasone	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
Bendamustine + bortezomib + dexamethasone	2A	No	Phase 2, prospective, single-arm, open-label	N/A	ORR	After 1-3 prior therapies	• BVd regimen demonstrated a high response rate of 71.5%
Bortezomib + liposomal doxorubicin + dexamethasone	1	No	Phase 3, randomized	Bortezomib	TTP	Relapsed or refractory MM	• Bortezomib plus liposomal doxorubicin and dexamethasone superior to bortezomib monotherapy for the treatment of patients with relapsed or refractory multiple myeloma.
Bortezomib + cyclophosphamide + dexamethasone	2A	Yes	Phase 2	N/A	-----	Relapsed disease	• Bortezomib combined with dexamethasone and cyclophosphamide demonstrated an ORR of 90% in patients with relapsed MM.

Bortezomib + dexamethasone	1	Yes	Phase 3b, multi-center, open-label	N/A	ORR	Relapsed or refractory MM	• Bortezomib, alone and combined with dexamethasone was associated with an ORR of 67% in heavily pretreated patients with relapsed or refractory MM.
Elotuzumab + bortezomib + dexamethasone	2A	No	Phase 2, open-label, randomized, proof-of-concept	Bortezomib + dexamethasone (Bd)	PFS	After 1-3 prior therapies	• EBd combination demonstrated a 28% reduction in risk of disease progression or death however did not reach statistical significance
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
Pomalidomide + bortezomib + dexamethasone	2A	No	Phase 3 (OPTIMISMM), randomized, open-label	Bortezomib + dexamethasone	PFS	Relapsed or refractory disease after lenalidomide	• Patients with relapsed or refractory multiple myeloma who previously received lenalidomide had significantly improved progression-free survival when treated with pomalidomide, bortezomib, and dexamethasone compared with bortezomib and dexamethasone.
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 preferred	Yes (in patients who have received 1-3 prior treatment)	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 + 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
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
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

Bendamustine + lenalidomide + dexamethasone	2A	No	Phase 1/2, open-label	N/A	ORR	After at least 1 prior lie of therapy	• This first phase 1/2 trial testing bendamustine, lenalidomide, and dexamethasone as treatment of relapsed refractory MM was active with an ORR of
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
POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + cyclophosphamide + dexamethasone	2A	No	Case study	N/A	-----	Relapsed disease	• In a case study of one patient with relapsed POEMS syndrome, bortezomib was effective in improving peripheral neuropathy and resulting in a complete response.

Mantle Cell Lymphoma

Initial therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + rituximab + cyclophosphamide + doxorubicin + prednisone (VR-CAP)	2A preferred (less aggressive therapy)	No	Phase 3 (LYM-3002), randomized, open-label	Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP)	OS	Newly diagnosed MCL who are not candidates for HDT/ASCR	• Compared with R-CHOP, VR-CAP was associated with significantly longer survival, and had a manageable and expected safety profile.
Bendamustine + rituximab (BR)	2A preferred (less	No	Phase 3 (StiL), open-label,	R-CHOP	PFS	First line	• The primary endpoint of PFS was significantly longer with BR compared with R-CHOP however OS

	aggressive therapy)		multi-center, randomized				outcomes were not significantly different between treatment arms.
Lenalidomide + rituximab, followed by maintenance	2A preferred (less aggressive therapy)	No	Phase 2, multi-center	N/A	ORR	Untreated MCL	• Lenalidomide plus rituximab demonstrated durable responses with a 3-year OS rate of 90%.
Modified rituximab-HyperCVAD, followed by rituximab maintenance	2A preferred (less aggressive therapy)	No	Phase 2 pilot study, multi-center	N/A	-----	Induction and maintenance therapy	• In a multicenter trial, modified R-hyperCVAD was effective induction therapy for untreated MCL with an ORR of 77%.
Second-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib	2A preferred (extended response duration to prior treatment)	Yes	Phase 2 (PINNACLE)	N/A	-----	Relapsed or refractory MCL after at least one prior therapy	• Single agent bortezomib induced an ORR of 33% in patients with relapsed or refractory MCL.
Bortezomib + rituximab	2A preferred (extended response duration to prior treatment)	Yes	Phase 2	N/A	-----	Relapsed or refractory MCL	• R-bortezomib had significant activity in patients with relapsed or refractory MCL with an ORR of 29%.

Bendamustine + rituximab	2A preferred (extended response duration to prior treatment)	No	Phase 3, randomized, multi-center, open-label, non-inferiority	Fludarabine + rituximab	PFS	Relapsed or refractory disease	• In combination with rituximab, bendamustine was more effective than fludarabine with higher response rate and superior PFS.
Bendamustine	2A preferred (extended response duration to prior treatment)	No	Phase 2 (RABBIT-14), randomized	Standard treatment	-----	Relapsed or refractory disease	• Monotherapy with bendamustine induced favorable responses with an ORR of 83% compared to standard therapy.

Systemic Light Chain Amyloidosis

Newly diagnosed disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + cyclophosphamide + dexamethasone (CyBORD)	2A preferred	No	Retrospective analysis	N/A	-----	All lines of therapy	• The combination of CyBORD reported an ORR of 94%
Bortezomib + cyclophosphamide + dexamethasone (CyBORD)	2A preferred	No	Retrospective analysis	N/A	-----	All lines of therapy	• CyBORD is an effective regimen for systemic light chain amyloidosis with a hematologic response rate of 81.4%.
Bortezomib + cyclophosphamide + dexamethasone (CyBORD)	2A preferred	No	Prospective observational study	N/A	-----	Newly diagnosed	• Upfront bortezomib resulted in an ORR 65% and an OS of 72 months.

Bortezomib ± dexamethasone	2A	No	Retrospective analysis	N/A	-----	All lines of therapy	• Bortezomib with or without dexamethasone is active in AL amyloidosis and induces rapid responses and high rates of hematologic (71%) and organ responses.
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 + lenalidomide + dexamethasone	2A	No	Prospective study	N/A	-----	Previously untreated	• Bortezomib with lenalidomide and dexamethasone was successful in inducing a hematologic response in 71% of patients with newly diagnosed AL amyloidosis.
Daratumumab hyaluronidase-fihj + CyBorD (bortezomib + cyclophosphamide + dexamethasone)	1 preferred	Yes	Phase 3 (ANDROMEDA), open-label, randomized, active-controlled	CyBorD	CHR	Newly diagnosed disease	• The addition of daratumumab to CyBorD was superior to CyBorD alone, resulting in deeper and more rapid hematologic responses and improved clinical outcomes with an acceptable safety profile.
Oral melphalan + dexamethasone	2A preferred (transplant ineligible) 2A	No	Prospective study	N/A	-----	Ineligible for ASCT	• In patients with primary amyloidosis who are ineligible for ASCT, melphalan and dexamethasone demonstrated a hematologic response of 67%.
Oral melphalan + dexamethasone	2A preferred (transplant ineligible) 2A	No	Phase 3, randomized	High-dose melphalan followed by ASCT	OS	Newly diagnosed disease	• The outcome of treatment of AL amyloidosis with high-dose melphalan plus autologous stem-cell rescue was not superior to the outcome with standard-dose melphalan plus dexamethasone.
Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Bortezomib (once- and twice-weekly)	2A	No	Phase 1/2, multi-center	N/A	-----	Relapsed disease	• In relapsed systemic light chain amyloidosis, bortezomib demonstrated a hematologic response of 50%.
Bortezomib + dexamethasone	2A	No	Prospective study	N/A	-----	Relapsed or refractory disease	• Efficacy of bortezomib in association with dexamethasone was demonstrated by a hematologic response rate of 94% in patients with relapsed or refractory disease.
Bortezomib + melphalan + dexamethasone	2A	No	See 'Newly diagnosed' Bortezomib + melphalan + dexamethasone data above				
Oral melphalan + dexamethasone	2A	No	See 'Newly diagnosed' Oral melphalan + dexamethasone data above				

Waldenström's macroglobulinemia/Lymphoplasmacytic Lymphoma

Primary therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + dexamethasone + rituximab	2A preferred	No	Phase 2	N/A	-----	First line	• BDR induced durable responses in previously untreated WM with an ORR of 85% and 3-year OS rate of 81%.

Bortezomib	2A	No	Phase 2	N/A	-----	Untreated and previously treated	• Bortezomib is an active agent in relapsed or refractory WM with an ORR of 85%.
Bortezomib	2A	No	Phase 2	N/A	ORR	Untreated and previously treated	• Bortezomib has an ORR of 78% in WM, but neurotoxicity can be dose limiting.
Bortezomib + rituximab	2A preferred	No	Phase 2	N/A	ORR	Newly diagnosed	• The combination of weekly bortezomib and rituximab exhibited significant activity with an ORR of 88% and minimal neurological toxicity in patients with untreated WM.
Bortezomib + dexamethasone	2A	No	No clinical literature to support use.				
Rituximab + bendamustine	2A preferred	No	Phase 3 (StiL), randomized, multi-center	R-CHOP	PFS	First-line	• Bendamustine plus rituximab demonstrated a significantly longer PFS than R-CHOP and may be a preferable option to R-CHOP as primary therapy.
Rituximab + cyclophosphamide + dexamethasone (R-CD)	2A preferred	No	Phase 2	N/A	-----	First line	• R-DC demonstrated an ORR of 83% and 2-year PFS of 67%.
Cladribine	2A	No	Phase 2	N/A	-----	Newly diagnosed or previously treated	• Cladribine as a single-agent demonstrated to be effective in patients with WM with an ORR of 59%.
Cladribine + rituximab	2A	No	Phase 2	N/A	-----	Newly diagnosed or previously treated	• The combination of rituximab and cladribine demonstrated an ORR of 90% in newly diagnosed or previously treated WM.
Rituximab + cyclophosphamide	2A	No	Phase 3, randomized,	CHOP	-----	Untreated	• The addition of rituximab to front-line chemotherapy improved treatment outcome in patients with LPL or WM.

+ doxorubicin + vincristine + prednisone (R-CHOP			open-label, multi-center				
Fludarabine	2A	No	Phase 3 (WM1), randomized, open-label, multi-center	Chlorambucil	ORR	Untreated	• Fludarabine significantly improved PFS and OS compared to chlorambucil in patients with WM.
Fludarabine + rituximab	2A	No	Phase 2, multi-center	N/A	ORR	Untreated and previously treated	• Fludarabine and rituximab demonstrated to be active in WM with an ORR of 95%.
Fludarabine + cyclophosphamide + rituximab	2A	No	Prospective study, multi-center	N/A	-----	Untreated and previously treated	• The FCR regimen proved to be active in patients with WM with an ORR of 79%.
Ibrutinib	1 preferred	Yes	Phase 2	N/A	-----	Untreated	• Ibrutinib is highly active in patients with WM with an ORR of 100%. CXCR mutation status affects responses to ibrutinib.
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.
Rituximab	2A	No	Phase 2 (E3A98), multi-center	N/A	-----	Untreated and previously treated	• Rituximab produced an ORR of 52.5% in the treatment of WM.
Rituximab + cyclophosphamide + prednisone	2A	No	Retrospective study	R-CHOP vs. R-CVP	-----	Untreated and	• Cyclophosphamide and prednisone plus rituximab demonstrated comparable responses among patients with

						previously treated	WM receiving R-CHOP, R-CVP, and R-CP. R-CP demonstrated and ORR of 95%.
Previously treated WM/LPL							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib	2A	No	See 'Bortezomib' under primary therapy above				
Bortezomib + rituximab	2A	No	Phase 2	N/A	ORR	Relapsed or refractory WM	• The combination of weekly bortezomib and rituximab showed significant activity with an ORR of 81% and minimal neurologic toxicity in patients with relapsed WM.
Bortezomib + dexamethasone	2A	No	No clinical literature to support use.				
Ibrutinib	2A preferred	Yes	Phase 2	N/A	ORR	Previously treated	• Ibrutinib was highly active in pretreated patients with WM with an ORR of 90.1%. MYD88 mutation positive and CXCR4 wild-type had the highest ORR.
Bendamustine ± rituximab	2A	No	Phase 2	N/A	-----	Relapsed or refractory WM	• Bendamustine is active and produced durable responses with an ORR of 83.3% and PFS of 13.2 months in previously treated WM, both as monotherapy and with CD20-directed monoclonal antibodies.
Cladribine ± rituximab	2A	No	See 'Cladribine' and 'Cladribine + rituximab' under primary therapy above				
Rituximab	2A	No	Phase 2	N/A	-----	Untreated and previously treated	• Rituximab demonstrated an ORR of 50% in pretreated patients with WM.
Fludarabine + rituximab	2A	No	See 'Fludarabine + rituximab' under primary therapy above				

Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + dexamethasone	2A (single-agent bortezomib)	No	Case report	N/A	-----	----------	• One patient with multicentric Castleman's disease accompanying myeloma was successfully treated with bortezomib-based therapy.
Bortezomib ± rituximab	2A	No	No clinical literature to support use.				

Adult T-Cell Leukemia/Lymphoma

Second-line or subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib	2A	No	Phase 2, multi-center	N/A	ORR	Relapsed or refractory disease	• Bortezomib demonstrated an ORR of 6.7% in patients with relapsed or refractory adult T-cell leukemia/ lymphoma.

Pediatric Acute Lymphoblastic Leukemia

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

COG AALL07P1 regimen (bortezomib + vincristine + doxorubicin + pegaspargase + prednisone)	2A	No	Phase 2	N/A	CR	First relapse	• The COG AALL07P1 regimen demonstrated that adding bortezomib to chemotherapy is clinically active with a CR rate of 68% in young patients with relapsed B-cell and T-cell ALL.
Bortezomib + vincristine + doxorubicin + pegaspargase + dexamethasone	2A	No	Phase 2 (TACL)	N/A	-----	Relapsed disease after 2-3 previous regimens	• Combination therapy with bortezomib and chemotherapy is active in B-precursor ALL with an ORR of 73%.
UKALL R3 backbone chemotherapy (mitoxantrone)	2A	No	Open-label, randomized trial	Idarubicin	PFS	First relapse	• As compared with idarubicin, mitoxantrone conferred a significant benefit in progression-free and overall survival in children with relapsed acute lymphoblastic leukemia.
COG AALL01P2 (Block 1: vincristine + prednisone + pegasparaginase + doxorubicin + cytarabine + methotrexate; Block 2: etoposide + cyclophosphamide + methotrexate; Block 3: cytarabine + L-asparaginase; plus imatinib for Ph+)	2A	No	Phase 2	N/A	-----	First relapse	• The AALL01P2 regimen is a tolerable and active reinduction platform for the treatment of B-precursor ALL with a CR rate of 68% in patients with early relapse and 96% in patients with late relapse. Alternative strategies are needed for T-ALL.

Blinatumomab	1 for relapsed/ refractory Philadelphia-chromosome negative B-ALL	Yes (Not restrictive of Ph-status)	Phase 3 (TOWER), randomized	Standard of care: • FLAG ± anthracycline-based regimen • HiDAC-based regimen • High-dose methotrexate-based regimen • Clofarabine-based regimen	OS	Relapsed or refractory disease	• Treatment with blinatumomab resulted in significantly longer OS than chemotherapy

AIDS-Related Kaposi Sarcoma

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib	2A other	No	Pilot Trial AMC-063	N/A	-----	Subsequent therapy	• Bortezomib is well-tolerated and active in AIDS-Kaposi sarcoma with a partial response rate of 60% in patients with relapsed or refractory AIDS-related Kaposi Sarcoma.

Pediatric Hodgkin Lymphoma

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bortezomib + ifosfamide + vinorelbine	2A	No	Phase 2, multi-center, open-label	N/A	CR	Relapsed or refractory disease	• Bortezomib added to ifosfamide and vinorelbine resulted in an ORR of 83% in pediatric patients with relapsed or refractory Hodgkin lymphoma.

Gemcitabine + dexamethasone + cisplatin	2A	No	Phase 2	N/A	-----	Relapsed or refractory disease	• Gemcitabine with dexamethasone and cisplatin demonstrated an ORR of 69.5% in patients with relapsed or refractory Hodgkin's disease.
Ifosfamide + carboplatin + etoposide (ICE)	2A	No	Analysis by intent to treat and development of a prognostic model	N/A	-----	Relapsed or refractory disease	• Ifosfamide with carboplatin and etoposide resulted an ORR of 88% as salvage treatment for patients with relapsed or refractory Hodgkin disease.
Etoposide + prednisolone + ifosfamide + cisplatin (EPIC)	2A	No	Retrospective study	N/A	-----	Relapsed or refractory disease	• The EPIC regimen demonstrated a 5-year OS of 75.8% and a 5-year PFS of 59.9% in children with relapsed or refractory Hodgkin lymphoma.