Bendamustine:
Treanda®; Bendeka®; Belrapzo™ RTD
(Intravenous)

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I. Length of Authorization [1-3,5,8,13]

- Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL), Waldenström's Macroglobulinemia (WM)/Lymphoplasmacytic Lymphoma (LPL), Classic Hodgkin Lymphoma (cHL):
  - Coverage will be provided for six months and may NOT be renewed.
- Multiple Myeloma:
  - Coverage will be provided for eight months and may NOT be renewed.

II. Dosing Limits

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

- Treanda 100 mg lyophilized powder for injection: 6 vials every 21 days
- Treanda 25 mg lyophilized powder for injection: 3 vials every 21 days
- Bendeka 100 mg/4 mL multi-dose vial: 6 vials every 21 days
- Belrapzo 100 mg/4 mL RTD multi-dose vial: 6 vials every 21 days

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

NHL:
- 600 billable units every 21 days

WM/LPL:
- 450 billable units every 28 days

cHL:
- 600 billable units every 28 days

CLL/SLL & Multiple Myeloma:
- 500 billable units every 28 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

For Treanda® (J9033) requests: Patient must have had an inadequate response to an adequate trial of one of the following drugs: Bendeka® (J9034) OR Belrapzo® (J9036), unless contraindicated or not tolerated; **AND**

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

Universal Criteria [1]

- Patient must not have received bendamustine in a previous line of therapy; **AND**

Non-Hodgkin's Lymphoma (NHL) † Φ [1-4,15]

- Coverage is provided for B-Cell Lymphomas when:
  - Used as subsequent therapy †; **AND**
    - In combination with rituximab for:
      - Follicular Lymphoma
      - Gastric MALT Lymphoma
      - Mantle Cell Lymphoma
      - Nodal Marginal Zone Lymphoma
      - Non-Gastric MALT Lymphoma
      - Splenic Marginal Zone Lymphoma; **OR**
    - Used as a single agent for:
      - Follicular Lymphoma
      - High-grade B-cell Lymphomas; **OR**
    - In combination with obinutuzumab for:
      - Follicular Lymphoma
      - Gastric MALT Lymphoma
      - Nodal Marginal Zone Lymphoma
      - Non-Gastric MALT Lymphoma
      - Splenic Marginal Zone Lymphoma; **OR**
    - In combination with polatuzumab for:
      - DLBCL
      - High-grade B-cell Lymphomas with Translocations of MYC and BCL2 and/or BCL6 (Double/Triple Hit Lymphoma); **OR**
  - Used as first line therapy ‡; **AND**
    - In combination with rituximab for:
      - Follicular Lymphoma
      - Gastric MALT Lymphoma
      - Mantle Cell Lymphoma
      - Nodal Marginal Zone Lymphoma
      - Non-Gastric MALT Lymphoma

- Splenic Marginal Zone Lymphoma; **OR**
  - In combination with obinutuzumab for:
    - Follicular Lymphoma
    - Nodal Marginal Zone Lymphoma

- Coverage is provided for the following T-Cell Lymphomas ‡ [41e]
  - Peripheral T-Cell Lymphoma *(includes peripheral T-cell not otherwise specified and angioimmunoblastic T-cell)*
    - Used as second-line or subsequent therapy as a single agent for relapsed or refractory disease

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) † Φ [1-4,16,53e-56e,58e,61e-63e]

- Used as first-line therapy; **AND**
  - Used as a single agent †; **OR**
  - Used in combination with a CD20-directed agent (i.e., rituximab, ofatumumab, obinutuzumab, etc.) for disease without del(17p)/TP53 mutations *(excluding use in frail patients [i.e., not able to tolerate purine analogs])*; **OR**
- Used as subsequent therapy in combination with rituximab without del(17p)/TP53 mutations in patients <65 years without significant comorbidities

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL) ‡ [4,13,66e]

- Used in combination with rituximab

Adult Hodgkin Lymphoma (HL) ‡ [4,5,9-11,75e,84e,101e]

- Patient has classic Hodgkin Lymphoma; **AND**
  - Used as second-line or subsequent therapy for relapsed or refractory disease; **AND**
    - Used in combination with gemcitabine and vinorelbine; **OR**
    - Used in combination with brentuximab vedotin; **OR**
  - Used as third-line or subsequent therapy for relapsed or refractory disease; **AND**
    - Used as a single-agent; **AND**
      - Patient did not relapse within 3 months of autologous stem cell transplant (ASCT) or was ineligible for ASCT; **OR**
    - Used in combination with carboplatin and etoposide

Multiple Myeloma ‡ Φ [4]

- Used for relapsed or progressive disease; **AND**
- Used in combination with dexamethasone and either lenalidomide or bortezomib

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-labeled indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

IV. Renewal Criteria [1]

Authorizations cannot be renewed

V. Dosage/Administration [1-3,5,8,13]

Indication	Dose
Non-Hodgkin's Lymphoma	Up to 120 mg/m² on days 1 and 2 of a 21-day cycle, up to 8 cycles
CLL/SLL	Up to 100 mg/m² on days 1 and 2 of a 28-day cycle, up to 6 cycles
Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma	Up to 90 mg/m² on days 1 and 2 of a 28-day cycle, up to 6 cycles
cHL	Up to 120 mg/m² on days 1 and 2 of a 28-day cycle, up to 6 cycles
Multiple Myeloma	Up to 100 mg/m² on days 1 and 2 of a 28-day cycle, up to 8 cycles

VI. Billing Code/Availability Information

HCPCS Code:

- J9033 – Injection, bendamustine hcl (treanda), 1 mg; 1 billable unit = 1 mg
- J9034 – Injection, bendamustine hcl (bendeka), 1 mg; 1 billable unit = 1 mg
- J9036 – Injection, bendamustine hcl, (belrapzo/bendamustine), 1 mg; 1 billable unit = 1 mg

NDC(s):

- Treanda 100 mg lyophilized powder in a single-dose vial for reconstitution: 63459-0391-xx
- Treanda 25 mg lyophilized powder in a single-dose vial for reconstitution: 63459-0390-xx
- Treanda 45mg/0.5 mL solution in a single dose vial: 63459-0395-xx*§
- Treanda 45mg/0.5 mL solution in a single dose vial: 63459-0396-xx*§
- Bendeka 100 mg/4 mL multi-dose vial: 63459-0348-xx**§
- Belrapzo 100 mg/4 mL ready-to-dilute multi-dose vial: 42367-0521-xx

**No longer commercially available; §Available generically from various manufacturers*

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
C82.00	Follicular lymphoma grade I, unspecified site
C82.01	Follicular lymphoma grade I, lymph nodes of head, face and neck
C82.02	Follicular lymphoma, grade I, intrathoracic lymph nodes
C82.03	Follicular lymphoma grade I, intra-abdominal lymph nodes
C82.04	Follicular lymphoma grade I, lymph nodes of axilla and upper limb
C82.05	Follicular lymphoma grade I, lymph nodes of inguinal regional and lower limb
C82.06	Follicular lymphoma grade I, intrapelvic lymph nodes
C82.07	Follicular lymphoma grade I, spleen
C82.08	Follicular lymphoma grade I, lymph nodes of multiple sites
C82.09	Follicular lymphoma grade I, extranodal and solid organ sites
C82.10	Follicular lymphoma grade II, unspecified site
C82.11	Follicular lymphoma grade II, lymph nodes of head, face and neck
C82.12	Follicular lymphoma, grade II, intrathoracic lymph nodes
C82.13	Follicular lymphoma grade II, intra-abdominal lymph nodes
C82.14	Follicular lymphoma grade II, lymph nodes of axilla and upper limb
C82.15	Follicular lymphoma grade II, lymph nodes of inguinal region and lower limb
C82.16	Follicular lymphoma grade II, intrapelvic lymph nodes
C82.17	Follicular lymphoma grade II, spleen
C82.18	Follicular lymphoma grade II, lymph nodes of multiple sites
C82.19	Follicular lymphoma grade II, extranodal and solid organ sites

ICD-10	ICD-10 Description
C82.20	Follicular lymphoma grade III, unspecified, unspecified site
C82.21	Follicular lymphoma grade III, unspecified, lymph nodes of head, face and neck
C82.22	Follicular lymphoma, grade III, unspecified, intrathoracic lymph nodes
C82.23	Follicular lymphoma grade III, unspecified, intra-abdominal lymph nodes
C82.24	Follicular lymphoma grade III, unspecified, lymph nodes of axilla and upper limb
C82.25	Follicular lymphoma grade III, unspecified, lymph nodes of inguinal region and lower limb
C82.26	Follicular lymphoma grade III, unspecified, intrapelvic lymph nodes
C82.27	Follicular lymphoma grade III, unspecified, spleen
C82.28	Follicular lymphoma grade III, unspecified, lymph nodes of multiple sites
C82.29	Follicular lymphoma grade III, unspecified, extranodal and solid organ sites
C82.30	Follicular lymphoma grade IIIa, unspecified site
C82.31	Follicular lymphoma grade IIIa, lymph nodes of head, face and neck
C82.32	Follicular lymphoma, grade IIIa, intrathoracic lymph nodes
C82.33	Follicular lymphoma grade IIIa, intra-abdominal lymph nodes
C82.34	Follicular lymphoma grade IIIa, lymph nodes of axilla and upper limb
C82.35	Follicular lymphoma grade IIIa, lymph nodes of inguinal region and lower limb
C82.36	Follicular lymphoma grade IIIa, intrapelvic lymph nodes
C82.37	Follicular lymphoma grade IIIa, spleen
C82.38	Follicular lymphoma grade IIIa, lymph nodes of multiple sites
C82.39	Follicular lymphoma grade IIIa, extranodal and solid organ sites
C82.40	Follicular lymphoma grade IIIb, unspecified site
C82.41	Follicular lymphoma grade IIIb, lymph nodes of head, face and neck
C82.42	Follicular lymphoma, grade IIIb, intrathoracic lymph nodes
C82.43	Follicular lymphoma grade IIIb, intra-abdominal lymph nodes
C82.44	Follicular lymphoma grade IIIb, lymph nodes of axilla and upper limb
C82.45	Follicular lymphoma grade IIIb, lymph nodes of inguinal region and lower limb
C82.46	Follicular lymphoma grade IIIb, intrapelvic lymph nodes
C82.47	Follicular lymphoma grade IIIb, spleen
C82.48	Follicular lymphoma grade IIIb, lymph nodes of multiple sites
C82.49	Follicular lymphoma grade IIIb, extranodal and solid organ sites
C82.50	Diffuse follicle center lymphoma unspecified site
C82.51	Diffuse follicle center lymphoma lymph nodes of head, face, and neck
C82.52	Diffuse follicle center lymphoma intrathoracic lymph nodes
C82.53	Diffuse follicle center lymphoma intra-abdominal lymph nodes
C82.54	Diffuse follicle center lymphoma lymph nodes of axilla and upper limb

ICD-10	ICD-10 Description
C82.55	Diffuse follicle center lymphoma lymph nodes of inguinal region and lower limb
C82.56	Diffuse follicle center lymphoma intrapelvic lymph nodes
C82.57	Diffuse follicle center lymphoma spleen
C82.58	Diffuse follicle center lymphoma lymph nodes of multiple sites
C82.59	Diffuse follicle center lymphoma extranodal and solid organ sites
C82.60	Cutaneous follicle center lymphoma, unspecified site
C82.61	Cutaneous follicle center lymphoma, lymph nodes of head, face and neck
C82.62	Cutaneous follicle center lymphoma, intrathoracic lymph nodes
C82.63	Cutaneous follicle center lymphoma, intra-abdominal lymph nodes
C82.64	Cutaneous follicle center lymphoma, lymph nodes of axilla and upper limb
C82.65	Cutaneous follicle center lymphoma, lymph nodes of inguinal region and lower limb
C82.66	Cutaneous follicle center lymphoma, intrapelvic lymph nodes
C82.67	Cutaneous follicle center lymphoma, spleen
C82.68	Cutaneous follicle center lymphoma, lymph nodes of multiple sites
C82.69	Cutaneous follicle center lymphoma, extranodal and solid organ sites
C82.80	Other types of follicular lymphoma unspecified site
C82.81	Other types of follicular lymphoma lymph nodes of head, face, and neck
C82.82	Other types of follicular lymphoma intrathoracic lymph nodes
C82.83	Other types of follicular lymphoma intra-abdominal lymph nodes
C82.84	Other types of follicular lymphoma lymph nodes of axilla and upper limb
C82.85	Other types of follicular lymphoma lymph nodes of inguinal region and lower limb
C82.86	Other types of follicular lymphoma intrapelvic lymph nodes
C82.87	Other types of follicular lymphoma spleen
C82.88	Other types of follicular lymphoma lymph nodes of multiple sites
C82.89	Other types of follicular lymphoma extranodal and solid organ sites
C82.90	Follicular lymphoma, unspecified, unspecified site
C82.91	Follicular lymphoma, unspecified, lymph nodes of head, face and neck
C82.92	Follicular lymphoma, unspecified, intrathoracic lymph nodes
C82.93	Follicular lymphoma, unspecified, intra-abdominal lymph nodes
C82.94	Follicular lymphoma, unspecified, lymph nodes of axilla and upper limb
C82.95	Follicular lymphoma, unspecified lymph nodes of inguinal region and lower limb
C82.96	Follicular lymphoma, unspecified, intrapelvic lymph nodes
C82.97	Follicular lymphoma, unspecified, spleen
C82.98	Follicular lymphoma, unspecified, lymph nodes of multiple sites
C82.99	Follicular lymphoma, unspecified, extranodal and solid organ sites

ICD-10	ICD-10 Description
C83.00	Small cell B-cell lymphoma, unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, 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
C83.30	Diffuse large B-cell lymphoma, unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face and neck
C83.32	Diffuse large B-cell lymphoma intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma, intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma, lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma, lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma, extranodal and solid organ sites
C83.80	Other non-follicular lymphoma, unspecified site
C83.81	Other non-follicular lymphoma, lymph nodes of head, face and neck
C83.82	Other non-follicular lymphoma, intrathoracic lymph nodes
C83.83	Other non-follicular lymphoma, intra-abdominal lymph nodes
C83.84	Other non-follicular lymphoma, lymph nodes of axilla and upper limb
C83.85	Other non-follicular lymphoma, lymph nodes of inguinal region and lower limb

ICD-10	ICD-10 Description
C83.86	Other non-follicular lymphoma, intrapelvic lymph nodes
C83.87	Other non-follicular lymphoma, spleen
C83.88	Other non-follicular lymphoma, lymph nodes of multiple sites
C83.89	Other non-follicular lymphoma, extranodal and solid organ sites
C83.90	Non-follicular (diffuse) lymphoma, unspecified site
C83.91	Non-follicular (diffuse) lymphoma, unspecified lymph nodes of head, face, and neck
C83.92	Non-follicular (diffuse) lymphoma, unspecified intrathoracic lymph nodes
C83.93	Non-follicular (diffuse) lymphoma, unspecified intra-abdominal lymph nodes
C83.94	Non-follicular (diffuse) lymphoma, unspecified lymph nodes of axilla and upper limb
C83.95	Non-follicular (diffuse) lymphoma, unspecified lymph nodes of inguinal region and lower limb
C83.96	Non-follicular (diffuse) lymphoma, unspecified intrapelvic lymph nodes
C83.97	Non-follicular (diffuse) lymphoma, unspecified spleen
C83.98	Non-follicular (diffuse) lymphoma, unspecified lymph nodes of multiple sites
C83.99	Non-follicular (diffuse) lymphoma, unspecified extranodal and solid organ sites
C84.40	Peripheral T-cell lymphoma, not classified, unspecified site
C84.41	Peripheral T-cell lymphoma, not classified, lymph nodes of head, face, and neck
C84.42	Peripheral T-cell lymphoma, not classified, intrathoracic lymph nodes
C84.43	Peripheral T-cell lymphoma, not classified, intra-abdominal lymph nodes
C84.44	Peripheral T-cell lymphoma, not classified, lymph nodes of axilla and upper limb
C84.45	Peripheral T-cell lymphoma, not classified, lymph nodes of inguinal region and lower limb
C84.46	Peripheral T-cell lymphoma, not classified, intrapelvic lymph nodes
C84.47	Peripheral T-cell lymphoma, not classified, spleen
C84.48	Peripheral T-cell lymphoma, not classified, lymph nodes of multiple sites
C84.49	Peripheral T-cell lymphoma, not classified, extranodal and solid organ sites
C84.60	Anaplastic large cell lymphoma, ALK-positive, unspecified site
C84.61	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of head, face, and neck
C84.62	Anaplastic large cell lymphoma, ALK-positive, intrathoracic lymph nodes
C84.63	Anaplastic large cell lymphoma, ALK-positive, intra-abdominal lymph nodes
C84.64	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of axilla and upper limb
C84.65	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of inguinal region and lower limb
C84.66	Anaplastic large cell lymphoma, ALK-positive, intrapelvic lymph nodes
C84.67	Anaplastic large cell lymphoma, ALK-positive, spleen
C84.68	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of multiple sites
C84.69	Anaplastic large cell lymphoma, ALK-positive, extranodal and solid organ sites
C84.70	Anaplastic large cell lymphoma, ALK-negative, unspecified site

ICD-10	ICD-10 Description
C84.71	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of head, face, and neck
C84.72	Anaplastic large cell lymphoma, ALK-negative, intrathoracic lymph nodes
C84.73	Anaplastic large cell lymphoma, ALK-negative, intra-abdominal lymph nodes
C84.74	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of axilla and upper limb
C84.75	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of inguinal region and lower limb
C84.76	Anaplastic large cell lymphoma, ALK-negative, intrapelvic lymph nodes
C84.77	Anaplastic large cell lymphoma, ALK-negative, spleen
C84.78	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of multiple sites
C84.79	Anaplastic large cell lymphoma, ALK-negative, extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site
C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites
C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma lymph nodes of head, face, and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma extranodal and solid organ sites
C86.2	Enteropathy-type (intestinal) T-cell lymphoma
C86.5	Angioimmunoblastic T-cell lymphoma
C88.0	Waldenström macroglobulinemia
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse

ICD-10	ICD-10 Description
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
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
Z85.72	Personal history of non-Hodgkin lymphomas
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; GCB = germinal center B-cell; HDT/ASCT = high dose therapy and autologous stem cell transplantation; alloSCT = allogeneic stem cell transplant; VGPR = very good partial response, MR = minimal response; SD = stable disease; PD = progressive disease

Non-Hodgkin's Lymphoma (NHL)

Follicular Lymphoma (FL) – First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab (BR)	2A preferred	No	Phase 3 (StiL), open-label, multi-center, randomized	R-CHOP	PFS	First line	• The primary endpoint of PFS was significantly longer with BR compared with R-CHOP.
Bendamustine + rituximab (BR)	2A preferred	No	Phase 3 (BRIGHT), randomized	R-CHOP or R-CVP	CR	First-line	• This trial also showed that bendamustine plus rituximab was non-inferior to RCHOP or RCVP with regard to CR rate and PFS
Obinutuzumab + bendamustine, CHOP, or CVP, followed by obinutuzumab maintenance	2A preferred	Yes	Phase 3 (GALLIUM), randomized, open-label, multi-center	Rituximab + bendamustine, CHOP, or CVP, followed by rituximab	PFS	First line	• Obinutuzumab-based immunochemotherapy and maintenance therapy resulted in longer progression-free survival than rituximab-based therapy. High-grade adverse events were more common with obinutuzumab-based chemotherapy.

Rituximab + cyclophosphamide + vincristine + prednisone (R-CVP)	2A preferred	Yes	Phase 3 (MARCUS), multi-center, open-label	Cyclophosphamide + vincristine + prednisone (CVP)	TTF	First line	• The addition of rituximab to the CVP regimen significantly improves the clinical outcome including TTF, ORR, and 4-year OS rate in patients with previously untreated advanced follicular lymphoma
Rituximab + cyclophosphamide + vincristine + prednisone (R-CVP)	2A preferred	Yes	Phase 3 (FOLL05), randomized, open-label, multi-center	R-CHOP vs. rituximab + fludarabine + mitoxantrone (R-FM)	TTF	First line	• In this study, R-CHOP and R-FM were superior to R-CVP in terms of 3-year TTF and PFS. In addition, R-CHOP had a better risk-benefit ratio compared with R-FM.
Lenalidomide + rituximab	2A preferred	Yes	Phase 3 (RELEVANCE), multi-center, randomized, open-label	Chemotherapy + rituximab (RCHOP, RCVP, BR)	CR PFS	First line	• Among patients with previously untreated follicular lymphoma, efficacy results were similar with rituximab plus lenalidomide and rituximab plus chemotherapy (with both regimens followed by rituximab maintenance therapy).
Follicular Lymphoma – Second-line therapy and subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab	2A preferred	Yes after prior rituximab	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.
Obinutuzumab + CHOP or FC (fludarabine + cyclophosphamide)	2A preferred (in patients refractory to rituximab)	Yes	Phase 1b (GAUDI), randomized, open-label	N/A	Safety	Relapsed or refractory FL	Obinutuzumab plus chemotherapy resulted in 93% to 96% response rates

Bendamustine + obinutuzumab (BO), followed by maintenance obinutuzumab in non-progressing patients	2A preferred (in patients refractory to rituximab)	Yes	Phase 3 (GADOLIN), randomized, controlled, open-label, multi-center	Bendamustine (B)	PFS	Refractory to rituximab	• Obinutuzumab plus bendamustine followed by obinutuzumab maintenance has improved PFS over bendamustine monotherapy in rituximab-refractory patients with indolent non-Hodgkin lymphoma, with manageable toxicity
Bendamustine	2A preferred	Yes after prior rituximab	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.
Rituximab (weekly x4)	2A preferred	Yes	Single-arm, multi-center	N/A	-----	Relapsed disease	• The response rate of 48% with rituximab is comparable to results with single-agent cytotoxic chemotherapy. Toxicity was mild.
Lenalidomide	2A other	No	Phase 2	N/A	ORR	Relapsed or refractory disease	• Lenalidomide produced durable responses with an ORR of 23% and duration of response longer than 16 months in patients with relapsed or refractory NHL.
Lenalidomide + rituximab	2A preferred	No	Phase 3 (AUGMENT), multi-center, randomized, double-blind	Rituximab + placebo	PFS	Relapsed or refractory disease	• Lenalidomide plus rituximab more than doubled the media PFS however, a subgroup analysis did not reveal a PFS benefit for patients with marginal zone lymphoma.
Ibritumomab tiuxetan	2A other	Yes	Phase 3, randomized	Rituximab	ORR	Relapsed or refractory disease	• Ibritumomab tiuxetan produced a statistically significant higher ORR and CR compared with rituximab alone.

Obinutuzumab	2A other	No	No clinical literature evidence to support use.				
Marginal Zone Lymphoma (MZL) – First line							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab (BR)	2A preferred	No	Phase 3 (StiL), open-label, multi-center, randomized	R-CHOP	PFS	First line	• Among the patients with marginal zone lymphoma, median PFS with BR was not significantly different from that with R-CHOP.
Bendamustine + rituximab (BR)	2A preferred	No	Phase 3 (BRIGHT), randomized	R-CHOP or R-CVP	CR	First-line	• Among the patients with marginal zone lymphoma, BR resulted in similar CR (20 versus 24%) and overall response rates (92 versus 71%).
Bendamustine + rituximab (BR)	2A preferred	No	Phase 2 (MALT-2008-01)	N/A	-----	First-line	• The combination of bendamustine and rituximab in first line treatment of MALT lymphoma achieved an ORR of 100% after only 3 cycles. CR rate after completing treatment plan was 98%.
Obinutuzumab + bendamustine, CHOP, or CVP, followed by obinutuzumab maintenance	2A preferred	Yes	Phase 3 (GALLIUM), randomized, open-label, multi-center	Rituximab + bendamustine, CHOP, or CVP, followed by rituximab	PFS	First line	• Obinutuzumab-based immunochemotherapy and maintenance therapy resulted in longer progression-free survival than rituximab-based therapy. High-grade adverse events were more common with obinutuzumab-based chemotherapy.
Marginal Zone Lymphoma (MZL) – Second-line and subsequent therapy							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bendamustine + rituximab	2A preferred	Yes after prior rituximab	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 + obinutuzumab (BO), followed by maintenance obinutuzumab in non-progressing patients	2A preferred	Yes	Phase 3 (GADOLIN), randomized, controlled, open-label, multi-center	Bendamustine (B)	PFS	Refractory to rituximab	• Obinutuzumab plus bendamustine followed by obinutuzumab maintenance has improved PFS over bendamustine monotherapy in rituximab-refractory patients with indolent non-Hodgkin lymphoma, with manageable toxicity
Ibrutinib	2A preferred	Yes	Phase 2, single-arm, open-label	N/A	ORR	Relapsed after ≥ 1 prior therapy with CD20 monoclonal antibody regimen	• Single-agent ibrutinib induced durable responses with an ORR of 48% and median PFS of 14 months.
Lenalidomide + rituximab	2A preferred	No	Phase 3 (AUGMENT), multi-center, randomized	Rituximab + placebo	PFS	Relapsed or refractory disease	• Lenalidomide plus rituximab more than doubled the media PFS however, a subgroup analysis did not reveal a PFS benefit for patients with marginal zone lymphoma.
Mantle Cell Lymphoma (MCL) – Less aggressive induction therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Bendamustine + rituximab (BR)	2A preferred (less aggressive therapy)	No	Phase 3 (StiL), open-label, multi-center, randomized	R-CHOP	PFS	First line	• The primary endpoint of PFS was significantly longer with BR compared with R-CHOP however OS outcomes were not significantly different between treatment arms.
Rituximab + bendamustine + cytarabine (RBAC)	2A other	No	Phase 2	N/A	ORR	First line, not eligible for HDT/ASCR	• RBAC demonstrated an ORR of 100% and CR rate of 95% in patient with previously untreated mantle cell lymphoma.
Bortezomib + rituximab _ cyclophosphamide + doxorubicin + prednisone (VR-CAP)	2A preferred (less aggressive therapy)	Yes	Phase 3, randomized Final OS results	R-CHOP	PFS	First line (not candidates for HDT/ASCR)	• VR-CAP significantly prolonged PFS and OS versus R-CHOP in newly diagnosed, BMT-ineligible MCL pts, with additional but manageable toxicity.
Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)	2A preferred (less aggressive therapy)	No	Phase 3, randomized	Rituximab, fludarabine, and cyclophosphamide (R-FC)	CR	First-line	• The addition of rituximab to CHOP chemotherapy was associated with a significantly longer median OS and 4-year OS rates than R-FC, although response rates and median duration of response were similar for both regimens.
Modified hyper-fractionated cyclophosphamide, vincristine doxorubicin, dexamethasone (Hyper CVAD) + rituximab	2A other	No	Phase 2	N/A	-----	First-line	• Modified R-hyper CVAD was effective induction therapy for untreated MCL with an ORR of 77%.

Mantle Cell Lymphoma (MCL) – Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab	2A certain circumstances	Yes for indolent NHL after prior rituximab	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.
Rituximab + bendamustine + cytarabine (RBAC)	2A certain circumstances	No	Phase 2	N/A	ORR	Relapsed or refractory disease	• RBAC demonstrated an ORR of 80% and CR rate of 70% in patient with relapsed or refractory mantle cell lymphoma.
Bortezomib	2A certain circumstances	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 certain circumstances	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%.
Acalabrutinib	2A preferred	Yes (after at least one prior therapy)	Phase 2, open-label	N/A	ORR	Relapsed or refractory MCL	• Acalabrutinib treatment provided a high rate of durable responses and a favorable safety profile in patients with relapsed or refractory mantle cell lymphoma.

Ibrutinib	2A preferred	Yes (after at least one prior therapy)	Phase 3 (RAY), randomized, open-label	Temsirolimus	PFS	Relapsed or refractory MCL	• Ibrutinib demonstrated significant improvement in ORR and PFS over temsirolimus in patients with relapsed or refractory MCL.
Ibrutinib ± rituximab	2A preferred	Yes (after at least one prior therapy)	Phase 2, single-center, single-arm, open-label	N/A	ORR	Relapsed or refractory MCL	• Ibrutinib combined with rituximab demonstrated an ORR of 88%.
Lenalidomide + rituximab	2A preferred	Yes (after two prior therapies, one of which included bortezomib)	Phase 1/2	N/A	ORR	Relapsed or refractory MCL	• Lenalidomide plus rituximab is effective for patients with relapsed or refractory MCL with an ORR of 57%.
Gemcitabine + oxaliplatin + rituximab	2A certain circumstances	No	Prospective clinical trial	N/A	-----	Relapsed or refractory MCL	• GemOx plus rituximab demonstrated an ORR of 78% and CR rate of 50% in patients with relapsed or refractory MCL.
Venetoclax + rituximab	2A certain circumstances	No	No clinical literature to support use.				
Bendamustine	Not recommended	Yes for indolent NHL after prior rituximab	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.

Bendamustine	Not recommended	Yes for indolent NHL after prior rituximab	Phase 2, multi-center	N/A	-----	Relapsed or refractory disease	• Bendamustine monotherapy is higher effective in patients with relapsed or refractory indolent B-cell NHL and MCL.
Diffuse Large B-cell Lymphoma – Second-line or subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine	2B	No	Phase 2	N/A	-----	Relapsed or refractory high-grade NHL	• Bendamustine as a single agent is effective against aggressive lymphoma, even in cases of refractory disease with an ORR of 44%.
Bendamustine + rituximab (BR)	2B	No	Phase 2, multi-center	N/A	ORR	Relapsed or refractory DLBCL	• Bendamustine plus rituximab demonstrating an ORR of 63% and CR of 37% in patients with relapsed or refractory DLBCL, including in patients previously treated with rituximab-containing chemotherapy.
Bendamustine + rituximab + polatuzumab vedotin-piiq	2A preferred (non-candidates for transplant	Yes (after ≥ 2 prior therapies)	Phase 2 (Study GO29365), randomized, multi-center, open-label	Bendamustine + rituximab	CR	Relapsed or refractory DLBCL after at least one prior regimen	• In a randomized setting, BR+P showed longer survival compared to BR, with median OS surpassing 12 months.
Gemcitabine + oxaliplatin (GemOx) + rituximab	2A preferred (non-candidates for transplant)	No	Phase 2, multi-center	N/A	ORR	Relapsed or refractory DLBCL	• GemOx-R as salvage treatment for DLBCL demonstrated an ORR of 61%

Brentuximab vedotin	2A certain circumstances (CD30+ disease; non-candidates for transplant)	No	Phase 2, open-label	N/A	ORR	Relapsed or refractory DLBCL	• Activity with brentuximab vedotin was observed in relapsed/refractory DLBCL (ORR 44%), and responses occurred across a range of CD30 expression.
Lenalidomide	2A certain circumstances (non-GCB DLBCL; non-candidates for transplant)	No	Phase 2/3, multi-center, randomized, open-label	Investigator's Choice (gemcitabine, rituximab, etoposide, or oxaliplatin)	ORR	Relapsed or refractory DLBCL after ≥ 2 prior therapies	• Lenalidomide monotherapy demonstrated a clinical benefit with an ORR of 27.5% with a more evident benefit in patients with non-GCB DLBCL.
High-Grade B-cell Lymphomas							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab + polatuzumab vedotin-piiq	2A preferred (non-candidates for transplant	Yes (after ≥ 2 prior therapies)	Phase 2 (Study GO29365), randomized, multi-center, open-label	Bendamustine + rituximab	CR	Relapsed or refractory DLBCL after at least one prior regimen	• In a randomized setting, BR+P showed longer survival compared to BR, with median OS surpassing 12 months.
Bendamustine	2A	No	Phase 2	N/A	-----	Relapsed or refractory high-grade NHL	• Bendamustine as a single agent is effective against aggressive lymphoma, even in cases of refractory disease with an ORR of 44%.
Monomorphic Post-Transplant Lymphoproliferative Disorder							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Bendamustine ± rituximab	2A	No	No clinical literature to support use.				
Rituximab	2A	No	Retrospective analysis, multi-center	N/A	-----	PTLD after solid organ transplant and initial reduced immunosuppression	• This retrospective analysis suggests significantly improved PFS and OS associated with early rituximab-based treatment in PTLD.
Rituximab, followed by cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP	2A	No	Phase 2, prospective, multi-center	N/A	ORR	Failure to initial reduced immunosuppression	• Use of sequential immunochemotherapy with rituximab and CHOP demonstrated an ORR of 90%.
AIDS-related B-cell Lymphomas							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine ± rituximab	2A	No	None				
Various regimens (ICE, dose adjusted EPOCH, ESHAP)	2A	No	Retrospective analysis	N/A	-----	Relapsed or refractory HIV-associated lymphomas	• Salvage chemotherapy with ICE, dose adjusted EPOCH, or ESHAP demonstrated an ORR of 31%.

T-Cell Lymphomas

Adult T-Cell Leukemia/Lymphoma - Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine	2A	No	None				
Lenalidomide	2A preferred	No	Phase 2 (ATLL-002), multicenter, single-arm, open-label	N/A	ORR	After at least one prior therapy	• Lenalidomide demonstrated clinically meaningful antitumor activity with an ORR of 42% and an acceptable toxicity profile in patients with relapsed or recurrent aggressive ATL
Mogamulizumab	2A preferred	No	Phase 2, multicenter Follow-up analysis	N/A	ORR	After at least one prior therapy	• Mogamulizumab monotherapy may improve PFS and OS in some patients with relapsed aggressive ATL, especially those who develop a skin rash as a moderate immune-related adverse event
Peripheral T-Cell Lymphoma (PTCL) – Second-line or subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine	2A other	No	Phase 2 (BENTLEY), multi-center	N/A	ORR	After at least 1 prior therapy	• Bendamustine showed an encouraging high response rate across the two major PTCL subtypes with an ORR of 50%.
Brentuximab vedotin	1 (ALCL) 2A preferred for CD30+ PTCL	Yes (ALCL only)	Phase 2 (NCT00866047), multicenter, open-label, single-arm	N/A	ORR	After at least one prior therapy	• Brentuximab vedotin induced an ORR of 86% and CRs in more than half of patients with recurrent systemic ALCL

			Long-term follow-up				
Belinostat	2A preferred (*2A only for ALCL)	Yes	Phase 2 (BELIEF), non-randomized, open-label	N/A	ORR	After at least one prior therapy	• Belinostat induced responses across all types of PTCL • Response rates were significantly higher for AITL than other subtypes • A response was not seen in patients with Anaplastic large cell lymphoma ALK-positive disease (2 patients) and Enteropathy-associated TCL (2 patients).
Gemcitabine	2A	No	Small series study	N/A	-----	Relapsed or refractory disease	• Gemcitabine proved to be effective in pretreated MF and PTCL patients with an ORR of 51%.
Ifosfamide + carboplatin + etoposide (ICE)	2A	No	Retrospective study	N/A	-----	Relapsed or refractory disease	• Second-line therapy with ICE followed by HDT/ASCT demonstrated an ORR of 70% however within 1 year, 70% of patients had relapsed.
Gemcitabine + dexamethasone + cisplatin (GDP)	2A	No	Retrospective analysis	N/A	-----	Relapsed or refractory disease	• Results suggest that GDP is an effective secondary therapy for relapsed PTCL and can lead to long-term survival.
Mycosis Fungoides (MF)/Sezary Syndrome (SS)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Bendamustine	2A preferred	No	No clinical literature evidence to support use.				
Brentuximab vedotin	2A preferred (primary therapy and for relapsed or refractory disease)	Yes (CD30+ MF relapsed or refractory disease only)	Phase 3 (ALCANZA), international, open-label, randomized, multicenter	Physician's Choice (methotrexate or bexarotene)	ORR ≥ 4 months	After at least one prior therapy	• Significant improvement in objective response lasting at least 4 months was seen with brentuximab vedotin versus physician's choice of methotrexate or bexarotene
Mogamulizumab	2A preferred (primary or subsequent treatment of stage IA-III MF and stage IV Sezary syndrome)	Yes (relapsed or refractory MF/SS only)	Phase 3 (MAVORIC), randomized, open-label, multicenter	Vorinostat	PFS	After at least one prior therapy	• Mogamulizumab significantly prolonged progression-free survival compared with vorinostat
Liposomal doxorubicin	2A preferred (stage IV non-Sezary or visceral disease, or LCT – both primary therapy and relapsed or refractory disease)	No	Phase 2	N/A	----------	After at least one prior therapy	• Liposomal doxorubicin resulted an ORR 84% with minimal toxicity.
Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders – Relapsed or refractory disease for cutaneous anaplastic large cell lymphoma (ALCL)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine	2A	No	No clinical evidence				

Brentuximab vedotin	2A preferred (primary treatment) 2A (relapsed or refractory disease)	Yes (for Anaplastic Large Cell Lymphoma)	Phase 3 (ALCANZA), international, open-label, randomized, multicenter	Physician's Choice (methotrexate or bexarotene)	ORR ≥ 4 months	After at least one prior therapy	• Significant improvement in objective response lasting at least 4 months was seen with brentuximab vedotin versus physician's choice of methotrexate or bexarotene
Methotrexate (low-dose)	2A	No	Retrospective study	N/A	-----	--------	• Low-dose methotrexate demonstrated to be effective (ORR 87%) in patients with primary cutaneous CD30+ lymphoproliferative disease
Hepatosplenic Gamma-Delta T-Cell Lymphoma – Subsequent therapy after 2 primary treatment regimens							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine	2A	No	Retrospective multi-center study	N/A	-----	Relapsed or refractory disease	• Bendamustine as a single agent is effective in patients with relapsed or refractory PTCL however this study included only 1 patient with hepatosplenic TCL.

Chronic lymphocytic leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ibrutinib	1 preferred	Yes	Phase 3 (RESONATE-2), randomized, open-label	Chlorambucil	PFS	First line	• Ibrutinib was superior to chlorambucil in previously untreated patients with CLL or small lymphocytic lymphoma, as assessed by progression-free survival, overall

							survival, response rate, and improvement in hematologic variables.
Ibrutinib	1 preferred	Yes	Phase 3 (A041202)	Ibrutinib + rituximab vs. Bendamustine + rituximab (BR)	PFS	First line	• Among older patients with untreated CLL, treatment with ibrutinib was superior to treatment with bendamustine plus rituximab with regard to progression-free survival. There was no significant difference between ibrutinib and ibrutinib plus rituximab with regard to progression-free survival.
Bendamustine	None	Yes	Phase 3 (02CLLIII), randomized	Chlorambucil (oral)	ORR PFS	First line	• Bendamustine was significantly more effective than chlorambucil in achieving remissions in treatment-naïve pts with B-CLL Binet stage B/C; median PFS and duration of remission were also significantly longer
Bendamustine + rituximab (BR)	2A	No	Phase 3 (MABLE), randomized	Chlorambucil + rituximab	CR	First line	• Bendamustine plus rituximab demonstrated a complete response rate of 24% and was superior to chlorambucil plus rituximab in first-line therapy for CLL. Improvement in PFS was significant however there was no difference in ORR or OS.
Ibrutinib	1 preferred	Yes	Phase 3 (Alliance A041202)	Ibrutinib + rituximab vs. Bendamustine + rituximab (BR)	PFS	First line	• Among older patients with untreated CLL, treatment with ibrutinib was superior to treatment with bendamustine plus rituximab with regard to progression-free survival. There was no significant difference between ibrutinib and ibrutinib plus rituximab with regard to progression-free survival.
Bendamustine + ofatumumab	2A	No	Phase 2, open-label, single-arm, multi-center	N/A	ORR	First line and relapsed disease	• The combination of ofatumumab and bendamustine was effective in these previously untreated or relapsed populations. ORR for previously untreated patients was 85% and 74% for patients with relapsed disease

Bendamustine + obinutuzumab	2A	No	Phase 2, multi-center	N/A	CR	First line	• Bendamustine plus obinutuzumab is an effective regimen with an ORR of 89% for first-line treatment of CLL patients inducing a complete response rate of 49% after 6 cycles of therapy.
Fludarabine + cyclophosphamide + rituximab (FCR)	2A	Yes	Phase 3 (CLL10), randomized, open-label, international	Bendamustine + rituximab (BR)	PFS	First line	• The combination of fludarabine, cyclophosphamide, and rituximab demonstrated superiority over bendamustine plus rituximab in terms of PFS and MRD negativity in fit patients with CLL. However, bendamustine and rituximab is associated with less toxic effects.
Fludarabine + rituximab (concurrent or sequential)	2A (in patients < 65y without significant comorbidities)	No	Phase 2, randomized	N/A	-----	First-line	• Rituximab administered concurrently with fludarabine in previously untreated CLL patients demonstrates marked clinical efficacy (ORR 90%) and acceptable toxicity.
Chlorambucil + obinutuzumab	2A	Yes	Phase 3 (CLL11), randomized, open-label	Chlorambucil + rituximab vs. Chlorambucil	PFS	First line	• Combining an anti-CD20 antibody with chemotherapy improved outcomes in patients with CLL and coexisting conditions. In this patient population, a significant improvement in PFS and OS was shown with obinutuzumab compared to rituximab when each was combined with chlorambucil.
Acalabrutinib + obinutuzumab (O) or acalabrutinib monotherapy	2A preferred	Yes	Phase 3 (ELEVATE TN), randomized	Obinutuzumab (O) + chlorambucil (Clb)	PFS	Treatment-naïve CLL	• Acalabrutinib + O and acalabrutinib monotherapy significantly improved PFS vs O + Clb, with tolerable safety in patients with treatment-naive CLL.
Venetoclax + obinutuzumab (O)	2A preferred	No	Phase 3, randomized, open-label, multi-center	Chlorambucil (Clb) + obinutuzumab (O)	PFS	Previously untreated	• Among patients with untreated CLL and coexisting conditions, venetoclax-obinutuzumab was associated with longer progression-free survival than chlorambucil-obinutuzumab.

Relapsed/Refractory therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab (BR)	2A	No	Phase 2	N/A	Bendamustine + rituximab + placebo	Relapsed or refractory disease	• Chemoimmunotherapy with BR is effective and safe in patients with relapsed CLL and has notable activity in fludarabine-refractory disease.
Venetoclax + rituximab (VenR)	1 preferred	Yes (after at least one prior therapy)	Phase 3 (MURANO), randomized	Bendamustine + rituximab (BR)	PFS	Relapsed or refractory disease	• Among patients with relapsed or refractory chronic lymphocytic leukemia, venetoclax plus rituximab resulted in significantly higher rates of progression-free survival than bendamustine plus rituximab.
Idelalisib + rituximab	2A preferred	Yes	Phase 3, randomized, multi-center, double-blind, placebo-controlled	Placebo + rituximab	PFS	Relapsed disease	• The combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival, response rate, and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy.
Fludarabine + cyclophosphamide + rituximab (FCR) – reduced dose	2A	No (first-line only)	Phase 3 (REACH), randomized	Fludarabine + cyclophosphamide (FC)	PFS	First relapse	• FCR significantly improved PFS in patients with previously treated CLL however, the difference is OS was not significantly different.
Fludarabine + cyclophosphamide + ofatumumab	2A	Yes	Phase 3 (COMPLEMENT 2), randomized, multi-center, open-label	Fludarabine + cyclophosphamide (FC)	PFS	Relapsed CLL	• OFA + FC improved PFS with manageable safety for patients with relapsed CLL compared with FC alone, thus providing an alternative treatment option for patients with relapsed CLL.
Obinutuzumab	2A	No	Phase 1/2 (GAUGUIN)	N/A	ORR	Relapsed or refractory disease	• Obinutuzumab monotherapy is active in patients with heavily pretreated relapsed/ refractory CLL with an ORR of 30%.

Ofatumumab	2A	Yes	Phase 2	N/A	ORR	Fludarabine- and alemtuzumab-refractory disease OR fludarabine-refractory with bulky lymphadenopathy (>5 cm)	• Ofatumumab is an active, well-tolerated treatment with an ORR of 43-49% in fludarabine-refractory patients with very poor-prognosis CLL.

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma

Primary Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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.
Bortezomib (IV) + dexamethasone + rituximab (BDR)	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%.
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%.

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine ± rituximab	2A	No	Phase 2	N/A	-----	Relapsed or refractory disease	• Bendamustine demonstrated clinical activity with an overall ORR of 83.3% in previously treated WM both as monotherapy (4 patients) and with CD20-directed monoclonal antibodies.
Bendamustine ± ofatumumab or rituximab	2A preferred for BR 2A for BO (for rituximab-intolerant individuals) 2A for bendamustine	No	Prospective study	N/A	-----	Relapsed or refractory WM	• Bendamustine based therapy including regimens with ofatumumab demonstrated clinical activity with an overall ORR of 83.3%
Rituximab + dexamethasone + cyclophosphamide (RDC)	2A preferred	No	Comparative study	Bendamustine + rituximab	-----	Previously untreated and relapsed or refractory disease	• Bendamustine plus rituximab did not demonstrate to be superior to combination therapy with rituximab, dexamethasone, and cyclophosphamide in treatment naïve and previously treated patients with WM.
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 + rituximab	2A	No	Phase 2	N/A	-----	Recurrent or refractory disease	• Bortezomib plus rituximab demonstrated an ORR of 90% in

							patients with recurrent or refractory WM.
Everolimus	2A	No	Phase 2 (RAD001)	N/A	-----	Relapsed or refractory WM	• Everolimus demonstrated high single-agent activity with an ORR of 73% however grade 3 or higher toxicities were observed in 67% of patients.
Ibrutinib	2A preferred	Yes	Phase 2	N/A	ORR	After at least one prior therapy	• Ibrutinib was highly active, associated with durable responses pretreated patients with Waldenström's Macroglobulinemia with an ORR of 90.5%. Patients with MYD88 and CXCR4 wild-type disease resulted a higher ORR compared to MYD88 and CXCR4 mutation positive disease.
Ofatumumab	2A (for rituximab-intolerant individuals)	No	Phase 2	N/A	ORR	Untreated and previously treated	• Ofatumumab shows clinical activity with an ORR of 43% in patients with WM, including those who relapse after rituximab therapy.

Adult Hodgkin Lymphoma (HL)

Classic Hodgkin Lymphoma – Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine	2A (subsequent)	No	Phase 2	N/A	ORR	Relapsed or refractory disease (including failure to HDT/ASCR)	• This study confirms the efficacy of bendamustine in heavily pretreated patients with HL (ORR 53%).

Nivolumab	2A (subsequent therapy)	Yes (after ASCT and brentuximab vedotin or 3 or more lines of systemic therapy that includes ASCT)	Phase 2	N/A	ORR	Relapsed or refractory disease after HDT/ASCR and brentuximab vedotin	• Nivolumab demonstrated a response rate of 66.3% and an acceptable safety profile in patients with cHL who progressed following autologous stem-cell transplantation and brentuximab vedotin.
Pembrolizumab	2A (subsequent therapy)	Yes (after 3 or more prior lines of therapy)	Phase 1b (KEYNOTE-013)	N/A	ORR AEs	Relapsed or refractory disease after brentuximab vedotin	• Pembrolizumab was associated with a favorable safety profile and induced favorable responses (ORR 65%) in a heavily pretreated patient cohort.
Pembrolizumab	2A (subsequent therapy)	Yes (after 3 or more prior lines of therapy)	Phase 2 (KEYNOTE-087)	N/A	ORR	Relapsed or refractory disease after ASCT and/or brentuximab vedotin	• Pembrolizumab was associated with high response rates with an ORR of 69%.
Gemcitabine + carboplatin + dexamethasone (GCD) (+ rituximab)	2A (subsequent therapy)	No	Phase 2, multi-center	N/A	ORR	Relapsed or refractory disease	• GCD(R) is a safe and effective regimen for relapsed lymphoma with an overall ORR of 67%.
Etoposide + ifosfamide + mesna + mitoxantrone (MINE)	2A (subsequent therapy)	No	Phase 2	N/A	-----	Refractory disease after prior cytarabine/ platinum treatment	• The MINE regimen induced responses in a moderate fraction of patients after their prior exposure to cytarabine/ platinum salvage therapy

Carmustine + cytarabine + etoposide + melphalan (Mini-BEAM)	2A (subsequent therapy)	No	Clinical trial	N/A	-----	Relapsed or refractory HL	• Mini-BEAM is a safe and effective regimen for treatment of refractory or relapsed Hodgkin's disease with an ORR of 84%
Carmustine + cytarabine + etoposide + melphalan (Mini-BEAM)	2A (subsequent therapy)	No	Long-term study	N/A	-----	Relapsed or refractory HL	• Results showed an ORR of 84% with Mini-BEAM before ASCT for refractory or relapsed HD patients.
Brentuximab vedotin	2A (second-line)	Yes (after failure of HDT/ASCR or at least 2 prior chemo regimens in patients not candidates for HDT/ASCR)	Phase 2 3-year follow-up	N/A	ORR	Relapsed or refractory CD30-positivedisease after HDT/ASCR	• Brentuximab vedotin induced an ORR of 75% in patients with relapsed or refractory HL after auto-SCT.
Brentuximab vedotin	2A (second-line)	Yes (after failure of HDT/ASCR or at least 2 prior chemo regimens in patients not candidates for HDT/ASCR)	Phase 2	N/A	ORR	Relapsed or refractory disease (prior to HDT/ASCR), first-line salvage therapy	• Brentuximab vedotin as first-line salvage therapy is effective (ORR 69%). 90% of patients were effectively bridged to ASCR and 52% did not require multiagent chemotherapy.

Bendamustine + brentuximab vedotin	2A (second-line or subsequent therapy)	No	Phase 1-2	N/A	CR	Relapsed or refractory disease after one previous line of chemo	• Bendamustine plus brentuximab vedotin achieved an ORR of 92.5% with a complete remission rate of 73.6%.
Bendamustine + brentuximab vedotin	2A (second-line or subsequent therapy)	No	Phase 1-2, multi-center	N/A	ORR	Relapsed or refractory disease after one previous line of chemo	• This study shows that brentuximab vedotin plus bendamustine, with a favorable safety profile, is an active salvage regimen for heavily pretreated patients with relapsed or refractory Hodgkin's lymphoma
Bendamustine + gemcitabine + vinorelbine (BeGEV)	2A (second-line or subsequent therapy)	No	Phase 2, multi-center, open-label	N/A	CR	Relapsed or refractory disease after one previous line of chemo	• This phase II study demonstrates that BeGEV is an effective salvage regimen able to induce CR in a high proportion of patients with relapsed or refractory HL before ASCT
Dexamethasone + cytarabine + cisplatin (DHAP)	2A (second-line or subsequent therapy)	No	Prospective study	N/A	-----	Relapsed or refractory disease	• Treatment with DHAP demonstrated and ORR of 89%.
Ifosfamide + carboplatin + etoposide (ICE)	2A (second-line or subsequent therapy)	No	Comprehensive protocol study	N/A	-----	Relapsed or refractory disease	• ICE demonstrated the efficacy of giving ICE in patients with relapsed or refractory Hodgkin's Lymphoma with an ORR of 88%.
Ifosfamide + carboplatin + etoposide (ICE)	2A (second-line or subsequent therapy)	No	Retrospective analysis	Dexamethasone + cytarabine + cisplatin (DHAP)	-----	Relapsed or refractory disease	• In patients with relapsed or refractory Hodgkin's Lymphoma, ICE demonstrated to have higher response rates than DHAP.
Ifosfamide + carboplatin + etoposide (ICE)	2A (second-line or	No	Prospective study	N/A	-----	Relapsed or refractory disease	• The high response rate, in particular the complete remission rate, the low toxicity profile, and the very high mobilizing potential of the IGEV

	subsequent therapy)						regimen strongly suggest that patients with relapsed/refractory Hodgkin's lymphoma may benefit from the use of this salvage induction regimen.
Bendamustine + carboplatin + etoposide ± rituximab	2A (subsequent therapy)	No	Phase 1/2, multi-center	N/A	Max dose Safety Efficacy (secondary endpoint)	Relapsed or refractory NHL or HL	• The combination of bendamustine, rituximab (in CD20+ disease), etoposide and carboplatin led to ORR and CR rates of 85% and 70% in the HL cohort.
Brentuximab vedotin + nivolumab (up to 4 cycles)	2A	No	Phase 1/2	N/A	CR	Initial salvage therapy	• The combination of brentuximab vedotin and nivolumab demonstrated an ORR of 82% as initial salvage therapy.
Brentuximab + nivolumab (up to 4 cycles) *Ongoing*	2A	No	Phase 2 (CheckMate 744)	N/A	CMR rate	Relapsed or refractory disease	• Brentuximab plus nivolumab demonstrated high complete metabolic response rates with no new safety signals for younger patients with relapsed or refractory cHL.
Nodular Lymphocyte-Predominant Hodgkin Lymphoma – Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab	2A	No	Retrospective registry study	N/A	-----	All lines of therapy	• Treatment outcomes with bendamustine plus rituximab was 100% in both ORR and CR in patients with nodular lymphocyte-predominant Hodgkin lymphoma.

Pediatric Hodgkin Lymphoma

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Brentuximab vedotin + bendamustine	2A	No	Phase 1-2, multi-center	N/A	ORR	Relapsed or refractory disease after at least one previous line of chemo	• This study shows that brentuximab vedotin plus bendamustine, with a favorable safety profile, is an active salvage regimen for heavily pretreated adult patients with relapsed or refractory Hodgkin's lymphoma.

Multiple Myeloma

Relapsed or progressive disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + bortezomib + dexamethasone (BVd)	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%
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
Bendamustine	2A	No	Dose escalation study	N/A	-----	Recurrent MM after high-dose chemo	• This study of single agent bendamustine demonstrated an

							ORR of 51% in patients with relapsed MM.
Bendamustine	2A	No	Retrospective analysis	N/A	-----	Relapsed or refractory MM	• In patients with advanced multiple myeloma bendamustine is effective with an ORR of 36%.
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
Bortezomib + liposomal doxorubicin + dexamethasone	2A	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.
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-	Phase 3 (ENDEAVOR), randomized,	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

		3 prior treatments	open-label, multicenter Interim overall survival analysis				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
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