Antibody-Based Therapies for B-Cell Lymphomas: A Summary Resource

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Mechanism of Action and Molecular Targets

- Antibody-based therapies used in B-cell lymphomas target the CD19 or CD20 antigens expressed on the surface of B lymphocytes[1,2]
  - Tafasitamab-cxix is a humanized monoclonal anti-CD19 antibody recently approved by the FDA in combination with lenalidomide for the treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in patients who are not candidates for autologous stem cell transplant (ASCT)[3]
  - Obinutuzumab, ofatumumab, and rituximab are monoclonal antibodies that target CD20[2]

Indications and Recommendations for Use of Antibody-Based Therapy

- The antibody-based therapies currently approved or under investigation for B-cell lymphomas (as of December 2021)

FDA-Approved Antibody-Based Therapy for B-Cell Lymphomas	Indications and Recommendations
Obinutuzumab[4]	FDA-approved indications: • Patients with **follicular lymphoma R/R to rituximab-containing regimen**, in combination with bendamustine followed by obinutuzumab monotherapy • Adults with **previously untreated stage II bulky, III, or IV FL**, in combination with chemotherapy followed by obinutuzumab monotherapy in patients with at least partial remission • Patients with **previously untreated CLL**, in combination with chlorambucil *For B-cell lymphomas, National Comprehensive Cancer Network (NCCN®) guideline recommends obinutuzumab for[5]:* • *First-line therapy for **FL**, in combination with either bendamustine, CHOP, or CVP (all preferred), or with lenalidomide (recommended, not preferred)* • *First-line consolidation or extended dosing for **FL*** • *Second-line and subsequent therapy for **FL**, in combination with either bendamustine, CHOP, or CVP (all preferred), or as monotherapy or with lenalidomide (recommended, not preferred)* • *Second-line consolidation or extended dosing for **FL*** • *Second-line and subsequent therapy for **MZL**, in combination with either bendamustine (if bendamustine naive, preferred), or with CHOP, or CVP, or lenalidomide (recommended, not preferred)* • *Second-line consolidation or extended dosing for **MZL** if treated with bendamustine and obinutuzumab for recurrent disease*
Rituximab[6]	FDA-approved indications in hematologic malignancies: • Adults with **R/R low-grade or follicular CD20-positive B-cell NHL**, as monotherapy • Adults with **untreated follicular, CD20-positive B-cell NHL**, in combination with first-line chemotherapy, and as maintenance monotherapy in patients with complete or partial response on rituximab combined with chemotherapy • Adults with **nonprogressing low-grade CD20-positive B-cell NHL**, as monotherapy after CVP chemotherapy • Adults with **previously untreated DLBCL CD20-positive B-cell NHL**, in combination with CHOP or other anthracycline-based chemotherapy • Pediatric patients older than 6 months of age with **previously untreated, advanced-stage, CD20-positive, DLBCL, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia** in combination with chemotherapy • Adults with **previously untreated and previously treated CD20-positive CLL** in combination with fludarabine and cyclophosphamide

	For B-cell lymphomas, National Comprehensive Cancer Network (NCCN®) guideline recommends obinutuzumab for[5]: • *First-line, second-line, and subsequent therapy for **FL**, in combination with either bendamustine, CHOP, CVP, or lenalidomide (all preferred) or as monotherapy (recommended, not preferred)* • *First-line, second-line, and subsequent therapy for older or infirm patients with **FL** unable to tolerate other recommended treatments, either as monotherapy (preferred) or in combination with chlorambucil or cyclophosphamide (recommended, not preferred)* • *First-line and second-line consolidation or extended dosing for **FL*** • *First-line therapy for **MZL**, in combination with either bendamustine, CHOP, CVP, or alone for SMZL (all preferred) or as monotherapy for extranodal (MALT) and nodal MZL or in combination with lenalidomide (recommended, not preferred)* • *First-line therapy for older or infirm patients with **MZL** unable to tolerate other recommended treatments, either as monotherapy (preferred) or in combination with chlorambucil or cyclophosphamide (recommended, not preferred)* • *First-line extended therapy for **MZL*** • *Second-line and subsequent therapy for **MZL**, in combination with bendamustine (if bendamustine naive) or in combination with CHOP, CVP, or lenalidomide (all preferred) or alone (recommended, not preferred)* • *Second-line therapy for older or infirm patients with **MZL** unable to tolerate other recommended treatments, either as monotherapy or in combination with lenalidomide (preferred) or in combination with chlorambucil or cyclophosphamide (recommended, not preferred)* • *Aggressive induction therapy for **MCL**, either as RDHA plus platinum, alternative R-CHOP/ R-DHAP, or in combination NORDIC regimen, hyperCVAD, or bendamustine/high-dose cytarabine (all preferred) or in combination with bendamustine (recommended, not preferred)* • *Less aggressive induction therapy for **MCL**, in combination with either bendamustine, VR-CAP, lenalidomide or as R-CHOP (all preferred) or as R-BAC500 or in combination with modified hyperCVAD (recommended, not preferred)* • *Maintenance therapy for **MCL** after HDT/ASCT, or after less aggressive therapy* • *Second-line and subsequent therapy for **mantle cell lymphoma**, in combination with ibrutinib or lenalidomide (all preferred) or in combination with either bendamustine, bendamustine/high-dose cytarabine (R-BAC500), bortezomib, DHAP, DHAX, GemOx, ibrutinib and lenalidomide, or venetoclax (all in certain circumstances)* • *First-line therapy for **DLBCL**, either as R-CHOP (preferred) or in combination with DA-EPOCH (recommended, not preferred)* • *First-line therapy for patients with **DLBCL** and poor left ventricular function, either in combination with DA-EPOCH or as RCDOP, RCEPP, RCEOP, or RGCVP* • *First-line therapy for patients with **DLBCL** who are very frail or aged older than 80 years with comorbidities, either as RCDOP, RCEPP, R-mini-CHOP, or RGCVP* • *Second-line and subsequent therapy for DLBCL with intention to proceed to transplant, in combination with DHAP, DHAX, GDP, or ICE (all preferred) or in combination with ESHAP, GemOx, or MINE (recommended, not preferred)* • *Second-line and subsequent therapy for patients with **DLBCL** who are not candidates for transplant, in combination with GemOx or with polatuzumab vedotin ± bendamustine (all preferred), or in combination with CEPP, CEOP, DA-EPOCH, GDP, or gemcitabine and vinorelbine or as a single agent (recommended, not preferred), or in combination with either bendamustine or lenalidomide (in certain circumstances)*
Tafasitamab-cxix[3]	FDA-approved indications: • Adults with **R/R DLBCL who are not eligible for ASCT**, in combination with lenalidomide (accelerated approval) *For B-cell lymphomas, National Comprehensive Cancer Network (NCCN®) guideline recommends tafasitamab-cxix for[5]:* • *Second-line and subsequent therapy for **DLBCL** in patients who are not candidates for transplant, in combination with lenalidomide*

Antibody-Based Therapy Under Investigation in B-Cell Lymphoma	Settings Under Late-Stage Investigation
Ofatumumab	• Phase II MIRO study in investigating ofatumumab in patients with stage I/II **FL** (NCT02710643) • Phase II trial is investigating ofatumumab and bendamustine ± bortezomib in patients with untreated **FL** (NCT01286272) • *Currently, FDA approved for the treatment of **previously untreated patients with CLL** in combination with chlorambucil when fludarabine-based therapy is considered inappropriate, for the treatment of **relapsed CLL** in combination with fludarabine and cyclophosphamide, for extended therapy for patients **with CR or PR after ≥2 previous lines of therapy for recurrent/progressive CLL**, and for the treatment of patients with **CLL refractory to fludarabine and alemtuzumab***

CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; HDT, high-dose therapy; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; SMZL, splenic marginal zone lymphoma.

Dosage and Administration Considerations[3,4,6]

- FDA-approved antibody-based therapies should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reaction
- Patients should be premedicated to reduce risk of infusion-related reaction

FDA-Approved Antibody-Based Therapy	Dosing in Lymphomas
Obinutuzumab[4]	• **FL:** 1000 mg on Days 1, 8, and 15 of cycle 1, 1000 mg on Day 1 of cycles 2-6 or cycles 2-8, and then 1000 mg every 2 months for up to 2 years • Provide prophylaxis for TLS to patients with high tumor burden • Administer only as IV infusion, not as IV push or bolus
Rituximab[6]	• **NHL:** 375 mg/m^2 by infusion (or 250 mg/m^2 in combination with ibritumomab tiuxetan) • Provide aggressive IV hydration and antihyperuricemic therapy in patients at high risk of TLS • Administer only as IV infusion, not as IV push or bolus
Tafasitamab-cxix[3]	• **DLBCL:** 12 mg/kg as an IV infusion in 28-day cycles on Days 1, 4, 8, 15 and 22 of cycle 1, Days 1, 8, 15 and 22 of cycle 2 and 3, and Days 1 and 15 of cycle 4 and beyond
Investigational Antibody-Based Therapy	
Ofatumumab	In phase III HOMER trial[7]: • Ofatumumab administered as 1000 mg every week for 4 weeks (induction phase) followed by 1000 mg once every 2 months for 4 additional doses (extended phase)

TLS, tumor lysis syndrome.

Management of Key Acute Adverse Events

- Key adverse events with antibody-based therapy vary among agents but include infusion or injection-related reaction, TLS (associated with obinutuzumab and rituximab), and hepatitis B virus (HBV) reactivation (associated with obinutuzumab and rituximab)[3,4,6,8]

Key Adverse Events in Approved Agents[3,4,6]	Agents	Considerations
Infusion-related reaction	Obinutuzumab Tafasitamab-cxix	• Management varies according to severity; premedication with corticosteroids, antihistamines, or acetaminophen may be required
Hypersensitivity reactions	Obinutuzumab	• Discontinue permanently if hypersensitivity reaction, including serum sickness, occurs
TLS	Obinutuzumab Rituximab	• Occurs when malignant cells disintegrate and release cell content into the peripheral blood; may occur soon after initiation of treatment; treat with vigorous hydration, management of hyperuricemia, and frequent monitoring of electrolytes with aggressive correction according to prescribing information and NCCN guideline[5]

Infection	Obinutuzumab Rituximab Tafasitamab-cxix	• Treat any active infections prior to starting therapy • Monitor for signs and symptoms of infection • Manage any infection according to prescribing information and NCCN guideline[5] • HBV reactivation: screen all patients for HBV before initiating agents associated with risk of HBV reactivation, consult a specialist and monitor patients with current or past infection; stop treatment immediately if HBV reactivation occurs
Neutropenia and thrombocytopenia or myelosuppression	Obinutuzumab Tafasitamab-cxix	• Monitor for neutropenia and thrombocytopenia regularly with laboratory tests, especially during the first cycle of therapy (obinutuzumab) • Monitor complete blood counts before administration of each treatment cycle and throughout treatment (tafasitamab-cxix) • Monitor patients with neutropenia for signs of infection • Manage cytopenia events according to prescribing information and NCCN guideline[5]
Cardiac and renal toxicity	Rituximab	• Monitor cardiac function during and after all infusions for patients who develop clinically significant arrythmias or who have a history of arrhythmia or angina – Discontinue in cases of serious or life-threatening cardiac events • Monitor closely for signs of renal failure – Discontinue in cases of rising serum creatinine or oliguria

- Avoid immunization with live virus vaccines during treatment with obinutuzumab or rituximab and until B-cell recovery

Hold, dose reduce, or discontinue depending on severity and persistence of these and any other AEs experienced while receiving these agents[3,4,6]

Key Clinical Trials

Antibody-Based Therapy	Ongoing Clinical Trials
Obinutuzumab	• Phase III CITADEL-302 study investigating parsaclisib with obinutuzumab or rituximab in R/R **FL** and **MCL** (NCT04796922) • Phase III FORTplus study investigating radiotherapy and obinutuzumab or rituximab in early-stage **FL** (NCT05045664)
Rituximab	• Phase III COASTAL study investigating zandelisib and rituximab in R/R **FL** and **MZL** (NCT04745832) • Phase III study investigating mosunetuzumab with lenalidomide and rituximab in R/R **FL** (NCT04712097)
Tafasitamab	• Phase III InMIND study investigating tafasitamab with lenalidomide and rituximab in R/R **FL** or **MZL** (NCT04680052)
Ofatumumab	• Phase II MIRO study in investigating ofatumumab in patients with stage I/II **FL** (NCT02710643) • Phase II trial is investigating ofatumumab and bendamustine ± bortezomib in patients with untreated **FL** (NCT01286272)

References

1. Makita. Ann Oncol. 2018;29:1086. 2. Luo. Sci Rep. 2021;11:3255. 3. Tafasitamab-cxix PI. 4. Obinutuzumab PI. 5. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: B-cell lymphomas. v.5.2021. nccn.org. 6. Rituximab PI. 7. Maloney. Blood Adv. 2020;4:3886. 8. Ofatumumab PI.