Immunomodulatory Drugs (IMiDs) in B-Cell Lymphomas: A Summary Resource

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Mechanism of Action and Molecular Targets

Lenalidomide is a thalidomide analogue immunomodulator that increases proliferation and activity of T-cells and natural killer cells, inhibits proinflammatory cytokines, causes delay in tumor growth, and inhibits angiogenesis.[1]

Indications and Recommendations

FDA-approved indications[2]:

- **Adults with MCL that has relapsed after 2 prior therapies including bortezomib**
- **Adults with pretreated FL**, in combination with a rituximab product
- **Adults with pretreated MZL**, in combination with a rituximab product
- Also approved for multiple myeloma and in patients with transfusion-dependent anemia due to myelodysplastic syndromes

The National Comprehensive Cancer Network (NCCN®) recommends lenalidomide for[3]:

- *First-line and later therapy for **FL**, in combination with either rituximab (preferred) or obinutuzumab (recommended, not preferred)*
- *Second-line and later therapy for **FL**, as monotherapy or in combination with obinutuzumab in patients who are not candidates for anti-CD20 monoclonal antibodies (recommended, not preferred)*
- *First-line therapy for **MZL**, in combination with rituximab (recommended, not preferred)*
- *Second-line or later therapy for **MZL**, in combination with rituximab (preferred) or obinutuzumab (recommended, not preferred)*
- *Second-line or later therapy for **MZL** in patients who are older or infirm, in combination with rituximab (preferred)*
- *Less-aggressive induction therapy for **MCL**, in combination with rituximab (preferred)*
- *Second-line or later therapy for **MCL**, in combination with rituximab (preferred if BTK inhibitor contraindicated) or rituximab and ibrutinib (recommended, not preferred) or rituximab and venetoclax (recommended, not preferred)*
- *First-line consolidation therapy for **DBLCL** in patients aged 60-80 years (optional)*
- *Second-line or later therapy for **DBLCL** patients who are not candidates for transplant, in combination with tafasitamab (preferred) or ± rituximab (in certain circumstances for nongerminal center B-cell DLBCL)*

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

Dosage and Administration Considerations[2]

Lenalidomide is administered orally in capsule form.

Dosing in B-Cell Lymphomas

- **MCL**: 25 mg daily orally on Days 1-21 of repeated 28-day cycles
- **FL** and **MZL**: 20 mg daily orally on Days 1-21 of repeated 28-day cycles for up to 12 cycles

Key Adverse Event Management

Key Considerations

Patients should be monitored for signs and symptoms of neutropenia and thrombocytopenia

MCL, MZL, and FL:

- Interrupt treatment if platelets <50,000/µL and/or neutrophils <500/µL, or neutrophils 1000/µL with associated temperature of ≥38.5°C, or neutrophils <1000/µL for ≥7 days; monitor CBC weekly and resume at a lower dose if platelets return to ≥50,000/µL and or neutrophils ≥1000/µL
  - For each subsequent drop in platelets <50,000/µL and/or neutrophils <1000/µL, interrupt treatment but do not dose below 5 mg daily in MCL or 2.5 mg daily in MZL or FL

Other warnings and precautions:

- Lenalidomide may cause birth defects and embryofetal death; pregnancy should be excluded before starting treatment and 2 types of contraception used to avoid pregnancy during treatment
- Due to embryofetal risk, lenalidomide is administered through a REMS program
- Lenalidomide has been associated with significantly increased risk of deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke in patients with multiple myeloma receiving concomitant dexamethasone; patients should be monitored and advised to seek immediate medical care for shortness of breath, chest pain, or limb swelling

CBC, complete blood count; REMS, Risk Evaluation and Mitigation Strategy.

Key Clinical Trials

Ongoing Clinical Trials

- Phase III study investigating mosunetuzumab with lenalidomide vs lenalidomide + rituximab in **R/R FL** (NCT04712097)
- Phase III InMIND study investigating tafasitamab with lenalidomide and rituximab vs placebo in **R/R FL** or **MZL** (NCT04680052)
- Phase III FIL_RENOIR12 study investigating rituximab and lenalidomide vs rituximab as maintenance after R-chemotherapy in **R/R FL** (NCT02390869)
- Phase III RELEVANCE study investigating rituximab and lenalidomide in untreated **FL** (NCT01476787)
- Phase III MAGNIFY study investigating lenalidomide + rituximab followed by lenalidomide vs rituximab as maintenance for **R/R FL**, **MZL**, or **MCL** (NCT01996865)
- Phase III study investigating recombinant humanized monoclonal antibody MIL62 + lenalidomide vs lenalidomide in rituximab-refractory **FL** (NCT04834024)
- Phase III study investigating tazemetostat with lenalidomide and rituximab vs lenalidomide + rituximab in **R/R FL** (NCT04224493)
- Phase III study investigating zanubrutinib + rituximab vs lenalidomide + rituximab in **R/R MZL** (NCT05100862)

References

1. Gribben. JCO. 2015;33:2803. 2. Lenalidomide PI. 3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: B-cell lymphomas. v.2.2022. nccn.org.