Up Close with Mosunetuzumab

This resource provides an overview of mosunetuzumab-axgb (LUNSUMIO®, LUNSUMIO VELO™).

Indications

Dosing & Administration

Cytokine Release Syndrome (CRS)

Neurotoxicity (including ICANS)

Other Toxicities

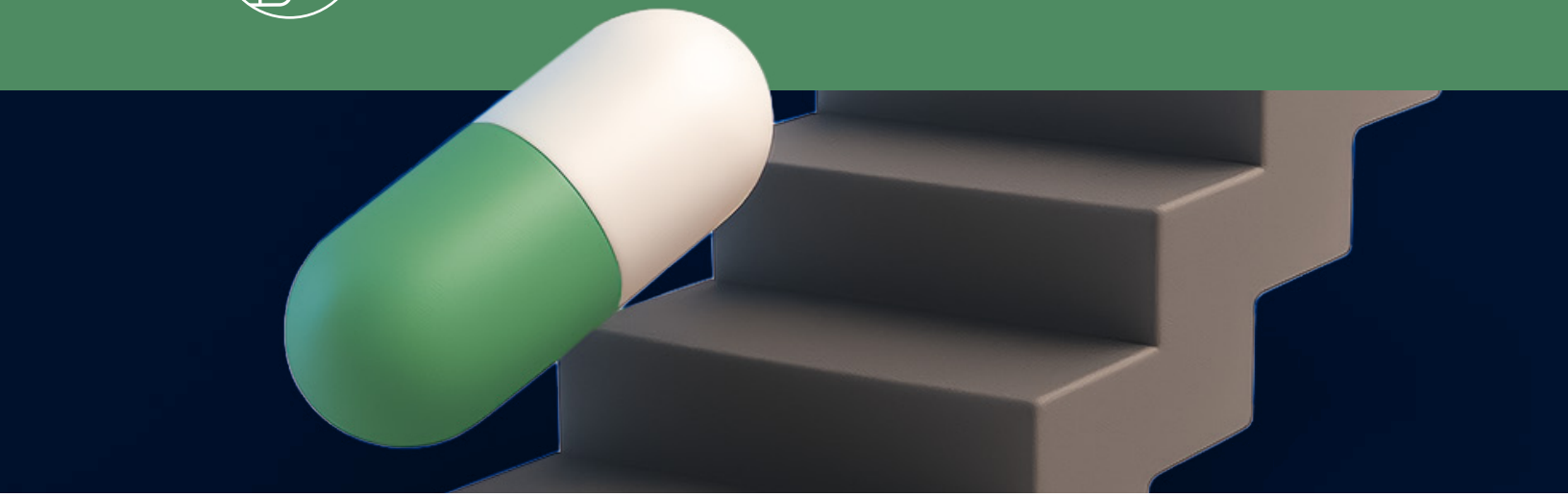
Indications

Mosunetuzumab is a **bispecific CD20-directed CD3 T-cell engager** indicated for the treatment of:

- Adult patients with **relapsed or refractory follicular lymphoma,** who have previously received **2 or more lines of systemic therapy.**

Note: This indication is approved under accelerated approval based on response rate. Continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Dosing & Administration



Mosunetuzumab is administered **intravenously (IV) or subcutaneously (SC)** in **21-day cycles**. Administer treatment for **8 cycles** unless disease progression or unacceptable toxicity occurs. Patients with a **partial response or stable disease** after Cycle 8 should receive **9 additional cycles**, for a total of 17 cycles.

Mosunetuzumab has a **unique step-up dosing** schedule as shown below to reduce the risk of cytokine release syndrome (CRS).

Mosunetuzumab IV Step-Up Dosing Schedule

Treatment Cycles		Dose of Mosunetuzumab / Route	Duration of Infusion
Cycle 1[a]	Day 1	1 mg IV	Administer over a minimum of 4 hours.
	Day 8	2 mg IV	
	Day 15	60 mg IV	
Cycle 2[a]	Day 1	60 mg IV	If infusions from Cycle 1 were well-tolerated, mosunetuzumab may be administered over 2 hours.
Cycles 3+[b]	Day 1	30 mg IV	

PO, orally

[a]Cycle 1 and 2 premedications (all patients)

- Premedicate with dexamethasone 20 mg IV (preferred) or methylprednisolone 80 mg IV and complete at least 1 hour prior to infusion of mosunetuzumab.
- Premedicate with diphenhydramine 50 mg to 100 mg IV/PO or equivalent antihistamine and complete at least 30 minutes prior to infusion of mosunetuzumab.
- Premedicate with acetaminophen 500 mg to 1000 mg PO and complete at least 30 minutes prior to infusion of mosunetuzumab.

[b]Cycle 3+ premedications (any patient that experienced CRS of any grade with a previous dose)

- Premedicate with dexamethasone 20 mg IV (preferred) or methylprednisolone 80 mg IV and complete at least 1 hour prior to infusion of mosunetuzumab.
- Premedicate with diphenhydramine 50 mg to 100 mg IV/PO or equivalent antihistamine and complete at least 30 minutes prior to infusion of mosunetuzumab.
- Premedicate with acetaminophen 500 mg to 1000 mg PO and complete at least 30 minutes prior to infusion of mosunetuzumab.

Mosunetuzumab SC Step-Up Dosing Schedule		
Treatment Cycles		**Dose of Mosunetuzumab / Route**
Cycle 1[a]	Day 1	5 mg SC
	Day 8	45 mg SC
	Day 15	45 mg SC
Cycles 2+[b]	Day 1	45 mg SC

PO, orally

[a]Cycle 1 premedications (all patients)

- Premedicate with dexamethasone 20 mg PO (preferred) or IV or methylprednisolone 80 mg PO or IV.
- Optional: Premedicate with diphenhydramine 50 mg to 100 mg IV/PO or equivalent antihistamine.
- Optional: Premedicate with acetaminophen 500 mg to 1000 mg PO.

[b]Cycles 2+ premedications (any patient that experienced CRS of any grade with a previous dose)

- Premedicate with dexamethasone 20 mg PO (preferred) or IV or methylprednisolone 80 mg PO or IV.
- Optional: Premedicate with diphenhydramine 50 mg to 100 mg IV/PO or equivalent antihistamine.
- Optional: Premedicate with acetaminophen 500 mg to 1000 mg PO.

The recommended **number of treatment cycles** depends on the **response** to mosunetuzumab.

- For patients **who achieve a complete response upon completion of cycle 8**:
  - No further subsequent treatment is required.
- For patients **who receive a partial response or have stable disease in response to mosunetuzumab after 8 cycles**:
  - Patients should receive an additional 9 cycles of mosunetuzumab (17 total).

Recommendations for Restarting Therapy with Mosunetuzumab IV Infusion After Dose Delay			
Patient's Treatment History		**Time Since Last Dose Administered**	**Action for Next IV Dose**
Cycle 1			
Day 1	1 mg	1 week to 2 weeks	Administer 2 mg (Cycle 1 Day 8), then resume the planned treatment schedule.
		> 2 weeks	Repeat 1 mg (Cycle 1 Day 1), then administer 2 mg (Cycle 1 Day 8) and resume the planned treatment schedule.
Day 8	2 mg	1 week to 2 weeks	Administer 60 mg (Cycle 1 Day 15), then resume the planned treatment schedule.
		> 2 weeks to < 6 weeks	Repeat 2 mg (Cycle 1 Day 8), then administer 60 mg (Cycle 1 Day 15) and resume the planned treatment schedule.
		≥ 6 weeks	Repeat 1 mg (Cycle 1 Day 1) and 2 mg (Cycle 1 Day 8), then administer 60 mg (Cycle 1 Day 15) and resume the planned treatment schedule.
Day 15	60 mg	1 week to < 6 weeks	Administer 60 mg (Cycle 2 Day 1), then resume the planned treatment schedule.
		≥ 6 weeks	Repeat 1 mg (Cycle 2 Day 1) and 2 mg (Cycle 2 Day 8), then administer 60 mg (Cycle 2 Day 15), followed by 30 mg (Cycle 3 Day 1) and then resume the planned treatment schedule.

Recommendations for Restarting Therapy with Mosunetuzumab IV Infusion After Dose Delay - continued

Patient's Treatment History		Time Since Last Dose Administered	Action for Next IV Dose
Cycle 2			
Day 1	60 mg	3 weeks to < 6 weeks	Administer 30 mg (Cycle 3 Day 1), then resume the planned treatment schedule.
		≥ 6 weeks	Repeat 1 mg (Cycle 3 Day 1) and 2 mg (Cycle 3 Day 8), then administer 30 mg (Cycle 3 Day 15)*, followed by 30 mg (Cycle 4 Day 1) and then resume the planned treatment schedule.
Cycles 3+			
Day 1	30 mg	3 weeks to < 6 weeks	Administer 30 mg, then resume the planned treatment schedule.
		≥ 6 weeks	Repeat 1 mg on Day 1 and 2 mg on Day 8 during the next cycle, then administer 30 mg on Day 15*, followed by 30 mg on Day 1 of subsequent cycles.

*For the Day 1, Day 8, and Day 15 doses in the next cycle, administer premedication as described above for all patients.

Recommendations for Restarting Therapy with Mosunetuzumab SC After Dosage Delay

Patient's Treatment History		Time Elapsed Since Last Dose	Recommended Next Actions
Cycle 1			
Day 1	5 mg	1 to 2 weeks	Administer 45 mg (Cycle 1 Day 8)[a], then continue treatment plan as scheduled.
		> 2 weeks	Repeat 5 mg (Cycle 1 Day 1)[a], then administer 45 mg (Cycle 1 Day 8)[a] and resume treatment plan as scheduled.
Day 8	45 mg	1 to < 6 weeks	Administer 45 mg (Cycle 1 Day 15)[a], then resume treatment plan as scheduled.
		≥ 6 weeks	Repeat 5 mg[a], then administer 45 mg (Cycle 1 Day 15)[a] 7 days later and resume treatment plan as scheduled.
Day 15	45 mg	1 to < 6 weeks	Administer 45 mg (Cycle 2 Day 1), then resume treatment plan as scheduled.
		≥ 6 weeks	Repeat 5 mg (Cycle 2 Day 1)[a], then administer 45 mg (Cycle 2 Day 8)[a] followed by 45 mg on Day 1 of subsequent cycles.
Cycles 2+			
Day 1	45 mg	3 to < 6 weeks	Administer 45 mg, then resume treatment plan as scheduled.
		≥ 6 weeks	Repeat 5 mg[a] on Day 1 during the next cycle, then administer 45 mg[a] on Day 8, followed by 45 mg on Day 1 of subsequent cycles.

[a]Administer premedications as described above for Days 1, Day 8, and Day 15 of doses in the next cycle.

Cytokine Release Syndrome

What is it? Cytokine release syndrome (CRS) is a systemic inflammatory response that can occur when the immune system is activated and releases large amounts of cytokines—proteins that help regulate immune responses.

Signs and symptoms:

- Chills
- Fever
- Low blood pressure
- Low tissue oxygen level
- Rapid heartbeat
- Trouble breathing

CRS is frequently graded using the [American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.]

Why it matters:

CRS occurred in **39%** (IV) and **30%** (SC) of patients in the study GO29781.

- With the **IV formulation, most CRS events** occurred **during Cycle 1**, with the highest incidence occurring after the **Cycle 1 Day 15** dose, the first 60-mg dose.
  - The **median time to onset** of CRS was:
    - Cycle 1 Day 1: 5 hours (range: 1 hour to 3 days)
    - Cycle 1 Day 8: 28 hours (range: 5 hours to 3 days)
    - Cycle 1 Day 15: 25 hours (range: 0.1 hours to 16 days)
    - Cycle 2 Day 1: 46 hours (range: 12 hours to 3 days)
  - The **median duration** of CRS was **3 days** (range: 1 to 29 days).
  - **Concurrent neurologic adverse reactions** associated with CRS **occurred in 6% of patients**, including, but not limited to anxiety, confusion, and headache.
- With the **SC formulation**, **most CRS events** occurred **after the first two doses**, with the **highest frequency after Cycle 1 Day 1**.
  - The **median time to onset** of CRS was:
    - Cycle 1 Day 1: 17 hours (range: 7 to 33 hours)
    - Cycle 1 Day 8: 62 hours (range: 30 to 113 hours)
  - CRS resolved in all patients after a **median duration of 2 days** (range: 1 to 15 days).
  - **Concurrent neurologic adverse reactions** associated with CRS **occurred in 5% of patients**, including, but not limited to headache, dizziness, lethargy, memory impairment, and peripheral neuropathy.

THE BOTTOM LINE: CRS is primarily low-grade, predictable, and manageable.

Neurotoxicity (including ICANS)

What is it? Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is characterized by various neurologic symptoms resulting from the activation of the immune system and the resultant inflammatory processes.

Signs and symptoms:

- Confusion
- Dizziness
- Headache
- Memory issues
- Motor Deficits
- Shaking
- Trouble finding or words speaking

ICANS is frequently graded using the ASTCT consensus criteria.

Why it matters:

ICANS was reported in **1%** (IV) and **3.1%** (SC) **of patients** in the clinical trial, however across a broader clinical trial population, ICANS **occurred or was suspected in 2.1%** (IV) and **2.2%** (SC) of trial participants.

- **IV** and **SC** formulations: The **time to onset** of ICANS or suspected ICANS was **17 days** (range: 1 to 48 days).
- ICANS resolved in most cases and lasted a few days.

THE BOTTOM LINE:

ICANS is uncommon, primarily low-grade, and resolves in the majority of cases over a few days.

Other Toxicities

Mosunetuzumab may cause other adverse reactions, such as **opportunistic infections, cytopenias, tumor flares, hemophagocytic lymphohistiocytosis, and embryo-fetal toxicity.**

Why it matters:
In addition to the risks of CRS and neurotoxicity (including ICANS), care teams need to be on the lookout for other **mosunetuzumab**-associated toxicities.

Infections. Mosunetuzumab may cause serious and fatal infections.

- **Serious infections**, including opportunistic infections, occurred in **17% of patients**, with **Grade 3 or 4 infections in 14%** (IV) and **16%** (SC), and **fatal infections in 0.9%** (IV) and **3.2%** (SC).
  - The most common serious infections reported were pneumonia, sepsis, upper respiratory tract infections (IV), and COVID-19 (SC).

THE BOTTOM LINE:

Care teams should **monitor patients for signs of infection before and during treatment**; treat appropriately.

- Avoid administration in patients with active infections; withhold or discontinue mosunetuzumab based on severity.

Cytopenias. Mosunetuzumab may cause serious or severe cytopenias, including anemia, neutropenia, and thrombocytopenia.

- In GO29781, **Grade 3 or 4 cytopenias** occurred in **up to 92%** (IV) and **69%** (SC) **of patients** enrolled in the trial.
  - IV Mosunetuzumab: decreased lymphocytes, 92%; decreased neutrophils, 38%; decreased hemoglobin, 19%; and decreased platelets, 12%.
  - SC Mosunetuzumab: decreased lymphocytes, 69%; decreased neutrophils, 26%; decreased hemoglobin, 10%; and decreased platelets, 6%.

THE BOTTOM LINE:

Care teams should **monitor complete blood counts throughout treatment.**

- **Withhold or discontinue mosunetuzumab based on neutropenia severity**; consider prophylactic granulocyte colony-stimulating factor.

Tumor Flare. Mosunetuzumab may cause serious or severe tumor flare.

- Among the patients enrolled in GO29781, **4%** (IV) and **1.1%** (SC) **of patients experienced tumor flare**.
  - Manifestations included, but were not limited to localized pain, swelling and pain at lymphoma lesions, tumor inflammation, and new or worsening pleural effusions.

THE BOTTOM LINE:

Care teams should **monitor patients with bulky tumors or disease located near an airway or vital organ**.

- Additionally, care teams should carefully **monitor patients for signs and symptoms of compression or obstruction caused by mass effect** secondary to tumor flare.
- If compression or obstruction develops, institute standard treatment for these complications.

Hemophagocytic Lymphohistiocytosis. Mosunetuzumab may cause a serious or fatal condition of hemophagocytic lymphohistiocytosis (HLH). HLH is a potentially life-threatening, hyperinflammatory syndrome that is independent of CRS. Most cases occurred within the first 28 days of treatment. Three cases were preceded by diagnosed or suspected CRS, and four occurred with concurrent EBV and/or CMV infection.

- HLH occurred in 0.5% (7/1,536) of patients included in the broader clinical trial population. Of those 7 cases, 6 patients had fatal outcomes.
  - Manifestations of HLH include fever, hemophagocytosis, coagulopathy, splenomegaly, hepatitis, elevated ferritin, and cytopenias.

THE BOTTOM LINE:

Care teams should **monitor for signs and symptoms of HLH**, and consider HLH when CRS is atypical or prolonged or when features of macrophage activation are present.

- For suspected HLH, interrupt mosunetuzumab and promptly evaluate and treat the patient according to current practice guidelines.

Risk of Medication Errors with Incorrect Product Use. Mosunetuzumab is available in two formulations: as an injection for SC use (LUNSUMIO VELO™) and an injection for IV use (LUNSUMIO®). Check the product labels to ensure that the correct formulation is being prescribed, dispensed, and administered to the patient. Do not substitute LUNSUMIO VELO™ for or with LUNSUMIO®.

Embryo-Fetal Toxicity. Mosunetuzumab may cause fetal harm when administered to a pregnant woman.

- Advise **females of reproductive potential** to use effective contraception **during treatment and for 3 months after** the last dose.
- Verify pregnancy status before initiating mosunetuzumab.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed during treatment and for 3 months after the last dose.
- **Geriatric Use**
  - **IV Mosunetuzumab:** Among 90 patients, 33% were ≥65 years old and 8% were ≥75 years old.
  - **SC Mosunetuzumab:** Among 94 patients, 51% were ≥65 years old.
  - For both datasets, there were insufficient patients to determine differences in safety or effectiveness by age group.
- **Pediatric Use:** The safety and efficacy of mosunetuzumab have not been established in pediatric patients.

References:

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4. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol.* 2022;23(8):1055-1065. doi:10.1016/S1470-2045(22)00335-7