# GENENTECH
# Request for an ICD-10-PCS Code for Administration of Mosunetuzumab

Centers for Medicare & Medicaid Services
ICD-10 Coordination and Maintenance Committee Meeting

March 8, 2022

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# Mosunetuzumab is a novel CD20xCD3 bispecific antibody for the treatment of third line or greater follicular lymphoma (3L+ FL)[1]

- **Mosunetuzumab** is the international, non-proprietary name* for the technology under consideration
- A **first-in-class**, full-length humanized IgG1 **bispecific antibody** that concomitantly binds **CD3** on **T-cells** and **CD20** on **malignant B-cells**
- Mosunetuzumab demonstrates **high response** rates and **anti-tumor** efficacy with a **manageable safety** profile in an area of high unmet **medical need**[2]
- **Off the shelf,** readily **available** treatment administered as an **intravenous infusion (IV)**
- Granted **Breakthrough Therapy Designation** (BTD) by the FDA in 2020 for patients with FL who have received 2 or more systemic therapies[3]
- **Under consideration by CMS for an NTAP for FY2023**

*** Subject to Food and Drug Administration (FDA) approval, the trade name for the product mosunetuzumab will be finalized**

CD20 – cluster of differentiation 20 receptor; CD3 – cluster of differentiation 3 receptor; IgG1 – Immunoglobulin G1 subclass; FDA – U.S. Food and Drug Administration; FL – follicular lymphoma; CMS – Centers for Medicaid and Medicare; NTAP – new technology add-on-payment.

1. Sun LL, et al. Anti-CD20/CD3 T cell-dependent bispecific antibody for the treatment of B cell malignancies. Sci Transl Med. 2015;7(287):287ra70. 2. Budde LE, et al. Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study. Oral Presentation at the 63rd ASH Annual Meeting and Exposition. 2021. 3. IND 120651. Grant – Breakthrough Therapy Designation. U.S. Food and Drug Administration. 2020

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# We are requesting an ICD-10-PCS ‘X’ code for mosunetuzumab for the treatment of 3L+ R/R FL indication

## Current ICD-10-PCS codes do not adequately describe the administration of mosunetuzumab for the 3L+ R/R FL indication

Genentech is requesting an ICD-10-PCS ‘X’ code for mosunetuzumab for the 3L+ R/R FL indication only

**Genentech submitted an NTAP application for mosunetuzumab to CMS for consideration for FY2023[1]**

3L+ – third and subsequent line; R/R – relapsed or refractory; FL – follicular lymphoma; NTAP – new technology add-on payment; CMS – Centers for Medicare and Medicaid.

1. Genentech Mosunetuzumab FY2023 NTAP Application.

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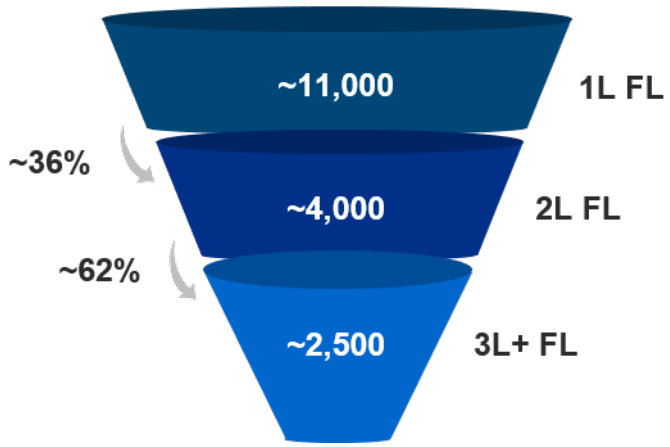
# FL is an incurable disease mainly affecting the elderly and is the leading cause of mortality among those affected

**FL is the second-most prevalent subtype of Non-Hodgkins Lymphoma (NHL)**

- Estimated to comprise 20-30% of NHL cases[1]
- Affects approximately **16,000 individuals annually in the US**[2]
- Median age of diagnosis is **63 years**[3]

**Annually Treated FL Cases**




- FL is **incurable with currently available therapies,** and patients may experience **multiple relapses**[1]
- **Relapses** are characterized by **increasing refractoriness** and **decreasing duration of response (DOR)** to subsequent lines of therapy[4-6]
- The **most common cause of death for FL** is the **disease itself.** Another concern is **treatment-related mortality** given the toxicity of existing therapies[7]
- Treatment options for later lines of therapy **infrequently achieve a complete response (CR)** and/or are associated with **poor tolerability**[5]
- **Elderly patients** with FL have **increased toxicities** with each subsequent therapy and **decreased duration and quality of response**[1]

FL – follicular lymphoma; NHL – Non-Hodgkins lymphoma; 1L – first-line; 2L – second-line; 3L+ – third and subsequent line.

1. Castellino A, et al. Mediterr. J. Hematol. Infect. Dis. 2017;9(1):e2017009. 2. Shi Q, et al. J. Clin. Oncol. 2017;35(5):552-560. 3.Follicular Lymphoma. National Cancer Institute. SEER 2021. 4. Link BK, et al. Br. J. Haematol. 2019;184(4):660-663. 5. Rivas-Delgado A, et al. Br. J. Haematol. 2019;184(5):753-759. 6. Batlevi et al. Blood Cancer J. 2020;10(7):74. 7. Sarkozy C, et al. J. Clin. Oncol. 2019;37(2):144-152.

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# There is no established standard of care for FL in 3L+ settings, and current therapeutic options have several limitations

## Treatment landscape of FDA approved regimens in 3L+ FL

### PI3K Inhibitors

- Idelalisib[1]
- Duvelisib[2]
- Copanlisib[3]
- Umbralisib[4†]

**Clinical Data***

- ORR: 42-59%
  - CR: 1-17%
- mDOR: 10-12.2 mo.
- Disc. due to AEs: 15-35%

**Limitations**

- **Treat-to-progression** regimen
- **Suboptimal complete response** rate
- **Suboptimal duration of response**
- **Poor tolerability** with a variety of **toxicities**

### EZH2 Inhibitor

- Tazemetostat[5]

**Clinical Data***

- ORR: 69% Mut / 34% WT
  - CR: 12% Mut / 4% WT
- mDOR: 13 Mut / 10.9 WT mo.
- Disc. due to AEs: 8%

**Limitations**

- **Treat-to-progression** regimen
- **Limited utility** for 3L+ FL
  - Only ~20% patients have EZH2 Mut[6]
  - Lower activity in WT EZH2 tumors
- **Suboptimal complete response** rate
- **Suboptimal duration of response**

*** From US Prescribing Information**
**† Umbralisib is FDA approved in the 4L+ FL setting**

FL – follicular lymphoma; 3L+ – third and subsequent line; FDA – U.S. Food and Drug Administration; PI3K – phosphatidylinositol 3-kinase; ORR – overall response rate; CR – complete response; mDOR – median duration of response; Disc. – discontinuation; AE – adverse effects; EZH2 – enhancer of zeste homolog 2; Mut – mutant; WT – wild type; Mo. – month.

1. Zydelig (idelalisib) [prescribing information]. Foster City, CA: Gilead Sciences, Inc; 2020. 2. Copiktra (duvelisib) [prescribing information]. Las Vegas, NV: Secura Bio Inc; September 2021. 3. Aliqopa (copanlisib) [prescribing information]. Whippany, NJ: Bayer Healthcare Pharmaceuticals Inc; May 2021. 4. Ukoniq (umbralisib) [prescribing information]. Edison, NJ: TG Therapeutics Inc; February 2021. 5. Tazverik (tazemetostat) [prescribing information]. Cambridge, MA: Epizyme, Inc; July 2020. 6. Bödör C, et al. Blood. 2013;122:3165-3168.

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# There is no established standard of care for FL in 3L+ settings, and current therapeutic options have several limitations (cont'd)

## Treatment landscape of FDA approved regimens in 3L+ FL (cont'd)

**CAR-T Cell Therapy**

Axicabtagene ciloleucel[1]

### Clinical Data*

- ORR: 91%
  - CR: 60%
- mDOR: 76% at 12 mo.
- CRS: 84% any Gr, 8% Gr≥3
- NEs: 49% any Gr, 16% Gr ≥3

### Limitations

- **Poor tolerability**
  - High rate of **CRS**
  - Severe **neurotoxicity**
- **Limited accessibility**
  - Long waiting periods
  - Travel to authorized sites
  - Co-location near treatment site for 4 weeks post-infusion
- Requires **chemotherapy lymphodepletion**
- Patients **restricted from driving** for at least 8 weeks
- More **narrow eligible patient population**

**A pivotal Phase II study of mosunetuzumab demonstrated clinically meaningful outcomes in patients with 3L+ FL**

*** From US Prescribing Information**

FL – follicular lymphoma; 3L+ – third and subsequent line; FDA – U.S. Food and Drug Administration; CAR – chimeric antigen receptor; ORR – overall response rate; CR – complete response; mDOR – median duration of response; Mo. – months; CRS – cytokine release syndrome; Gr. – grade; NE – neurological event.

1. Yescarta (axicabtagene ciloleucel) [prescribing information]. Santa Monica, CA: Kite Pharma Inc; April 2021.

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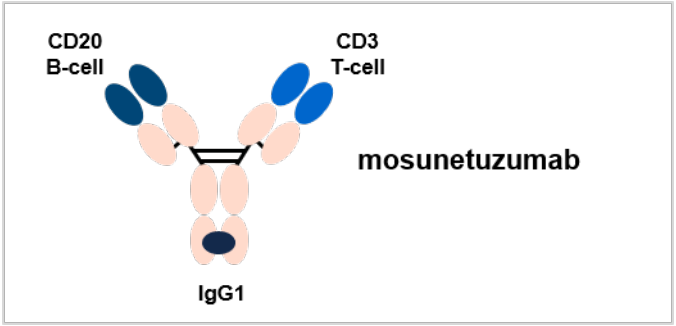
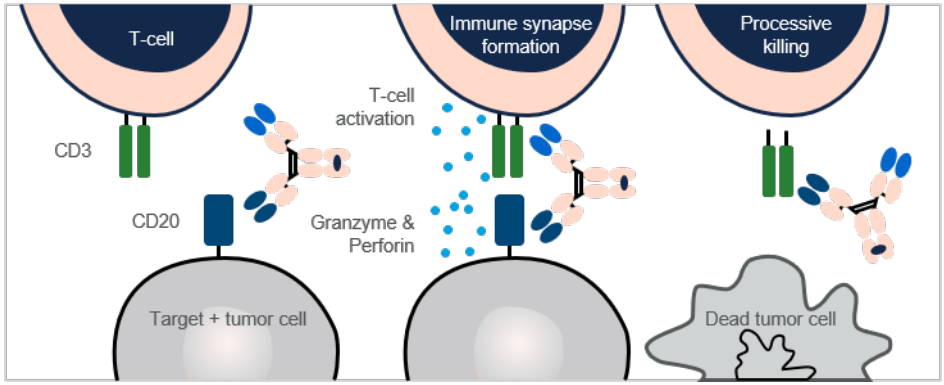
# Upon FDA approval, mosunetuzumab is anticipated to be a novel first-in-class therapy for the treatment of 3L+ FL[1]

**Full-length humanized IgG1 bispecific antibody that concomitantly binds CD3 on T-cells and CD20 on malignant B-cells**

98-100% of FL cases are positive for CD20[2,3]




- Crosslinking leads to **T-cell activation**, which redirects T-cells to engage and **eliminate malignant B-cells**
- **Off the shelf,** readily **available** treatment which **does not require ex-vivo T-cell manipulation**
- **FDA approval** is anticipated by **June 30, 2022**




Granted **Breakthrough Therapy Designation** (BTD) by the FDA in 2020 in patients with FL who have received 2 or more systemic therapies

FDA – U.S. Food and Drug Administration; 3L+ – third and subsequent line; FL – follicular lymphoma; IgG1 – Immunoglobulin G1 subclass; CD3 – cluster of differentiation 3 receptor; CD20 – cluster of differentiation 20 receptor; FDA – U.S. Food and Drug Administration.

1. Sun et.al. [abstract]. Sci. Transl. Med. 2015;7:287ra70. 2. Ray S, et al. Am. J. Clin. Pathol. 2005;124(4):576-583. 3. Yuan C, et al. PLMI. May 2013:21.

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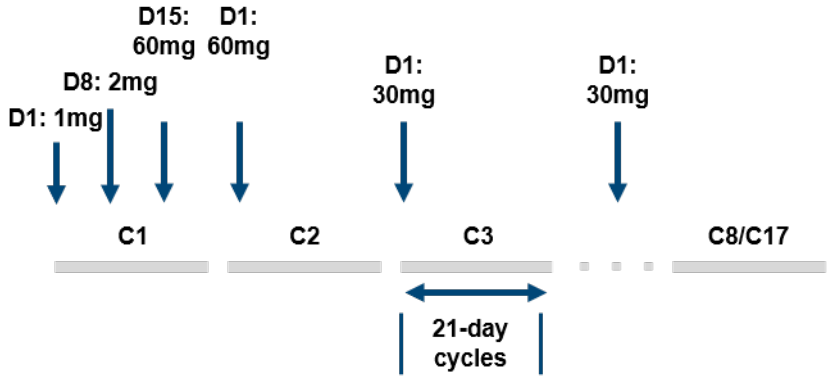
# GO29781*: A single-arm, pivotal Phase II expansion trial of mosunetuzumab IV in R/R patients with 3L+ FL[1]

## Mosunetuzumab Administration

- Q3W intravenous administration
- C1 step-up dosing (CRS mitigation)
- **Fixed-duration treatment**
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**
- **CRS must be resolved for 3 days** prior to next dose of mosunetuzumab if hospitalization occurs due to CRS




## Key Inclusion Criteria (FL cohort)

- FL (Grade 1-3a)
- ECOG PS 0-1
- ≥2 prior regiments, including:
  - ≥1 anti-CD20 AB
  - ≥1 alkylating agent

## Baseline Characteristics (N=90)

- Median age: 60 years (range: 29-90)
- Stage III–IV disease: 76.7%
- FLIPI 3–5: 44.4%
- Median no. prior lines: 3 (range: 2–10)
- Refractory to last therapy: 68.9%
- Double refractory†: 53.3%
- POD24: 52.2%

## Primary Objective

- CR (best response) rate by PET/CT assessed by an independent review facility (IRF)[2]

*** NCT02500407**
**† Refractory to an anti-CD20 monoclonal antibody and alkylator**

IV – intravenous; R/R – relapsed or refractory; 3L+ – third and subsequent line; FL – follicular lymphoma; Q3W – every three weeks; C – cycle; CRS – cytokine release syndrome; CR – complete response; PR – partial response; SD – stable disease; D – day; ECOG PS – Eastern Clinical Oncology Group Performance Status; CD20 – cluster of differentiation 20 receptor; AB – antibody; N – number; FLIPI – Follicular Lymphoma Interntional Prognostic Index; No. – number; POD24 – progression of disease within 24 months from initial therapy; PET/CT – positron emission tomography/computed tomography.

1. Budde E, et al. ASH Abstract 2021. https://ash.confex.com/ash/2021/webprogram/Paper145872.html 2. Cheson et al. J Clin Oncol 2007;25:579–8

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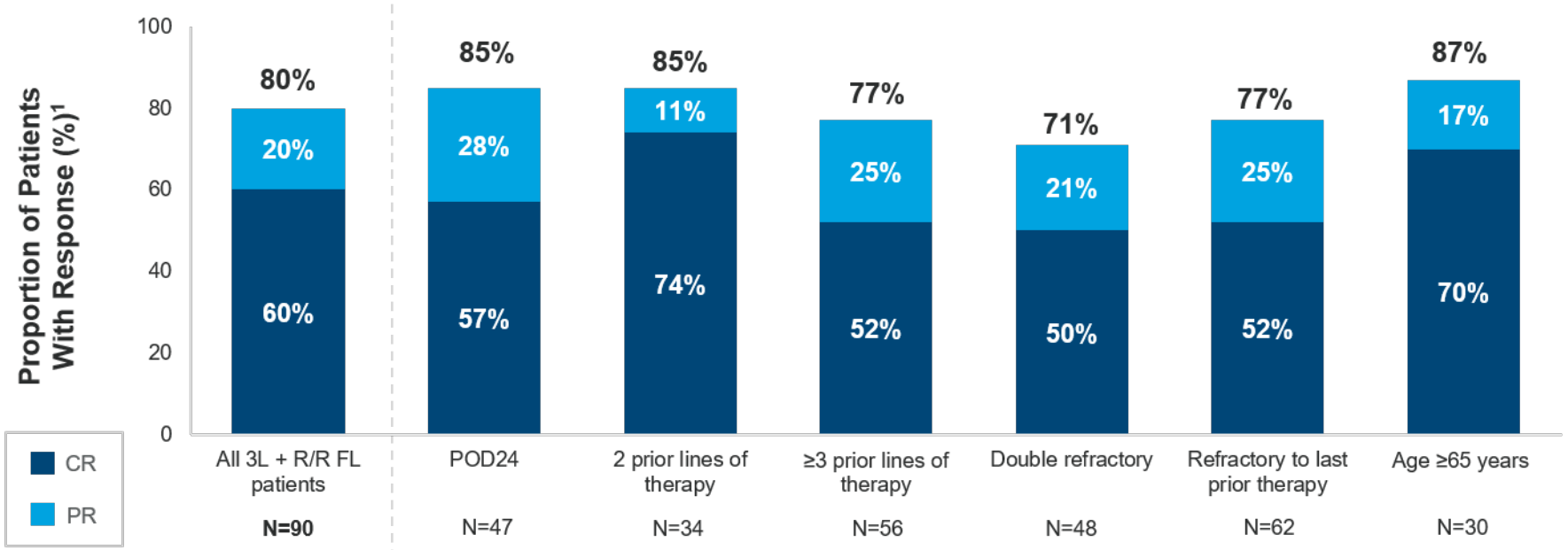
# Mosunetuzumab demonstrated high response rates in patients with 3L+ R/R FL as assessed by an independent review facility[1]




**Median DOR**
22.8 months
(95% CI: 9.7-NE)

**Median Time on Study**
18.3 months (2.0-27.5)

**Median Age**
60 years old (29-90)

**High and consistent response rates were observed in high-risk populations**, including those with double refractory disease, POD24, refractory to prior Anti-CD20 mAbs, those who received ≥3 prior therapies, and patients ≥ 65 years old

3L+ – third and subsequent line; R/R – relapsed or refractory; FL – follicular lymphoma; CR – complete response; PR – partial response, N – number; POD24 – progression of disease within 24 months from the start of initial therapy; DOR – duration of response; mAb – monoclonal antibody; CD20 – cluster of differentiation 20 receptor; mAb – monoclonal antibody.

1. Budde LE, et al. Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study. Oral Presentation at the 63rd ASH Annual Meeting and Exposition. 2021.

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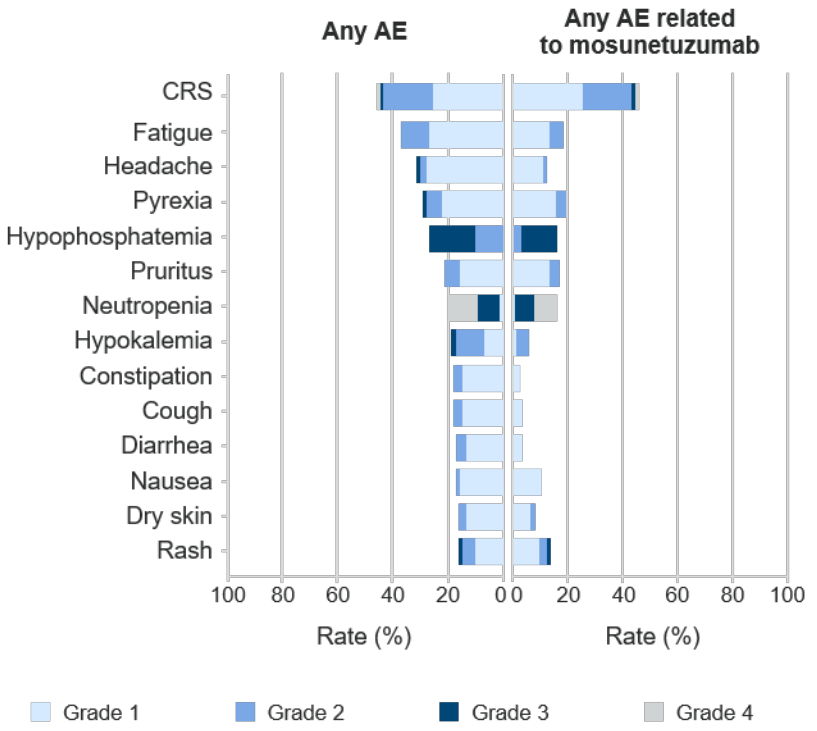
# Adverse events associated with mosunetuzumab[1]

## Adverse events leading to discontinuation are not common (4.4%)

| N (%) | N=90 |
|---|---|
| **AE** | 90 (100%) |
| Mosunetuzumab related* | 83 (92.2%) |
| **Grade 3–4 AE** | 63 (70.0%) |
| Mosunetuzumab related* | 46 (51.1%) |
| **Serious AE** | 42 (46.7%) |
| Mosunetuzumab related* | 30 (33.3%) |
| **Grade 5 (fatal) AE** | 2 (2.2%)† |
| Mosunetuzumab related* | 0 |
| **AE leading to discontinuation of treatment** | 4 (4.4%)‡ |
| Mosunetuzumab related* | 2 (2.2%)‡ |

**AEs (≥15%) by Grade and Relationship with Mosunetuzumab**




*** AE considered related to treatment by the investigator**
**† mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (1 patient each)**
**‡ mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each)**

N – number; AE – adverse event.

1. Budde LE, et al. Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study. Oral Presentation at the 63rd ASH Annual Meeting and Exposition. 2021.

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# CRS events are predominantly low grade and manageable

## Cytokine Release Syndrome (CRS)[1]

CRS is caused by the activation of lymphocytes and myeloid cells, with subsequent release of inflammatory cytokines

Manifestations are highly variable, ranging from mild symptoms to life-threatening multiorgan dysfunction

## CRS Events[2]

- CRS was the most common AE (44.4%; 40/90)
  - 7 patients received tocilizumab
  - 10 patients received corticosteroids
- **Mostly confined to Cycle 1**
- **CRS events were generally low grade[3]; high grade CRS was uncommon**
  - Gr 1: 25.6%
  - Gr 2: 16.7%
  - Gr 3: 1.1%
  - Gr 4: 1.1% (1 patient with FL in leukemic phase)
- **All events resolved after a median duration of 3 days**

**The successful management of CRS enabled almost all patients to continue therapy and benefit from treatment**

CRS – cytokine release syndrome; AE – adverse event; Gr. – grade.

1. Neelapu SS, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62. 2. Budde LE, et al. Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study. Oral Presentation at the 63rd ASH Annual Meeting and Exposition. 2021. 3. Lee DW, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-638

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# Mosunetuzumab demonstrates high clinical efficacy and tolerable safety in 3L+ FL, a patient population with high unmet needs

**There are unmet needs with current FDA-approved therapies for 3L+ FL**

- PI3K inhibitors have low response rates, suboptimal duration of response, and well-characterized toxicities
- The EZH2 inhibitor has limited utility since only ~20% of patients have EZH2 mutations, and the drug shows lower activity in WT EZH2 patients
- CAR-T cell therapy has high rates of severe CRS and neurotoxicity, requires lymphodepleting chemotherapy, and requires hospitalization at an authorized treatment center, which leads to limited accessibility

**Mosunetuzumab is a breakthrough in the treatment of 3L+ FL**

- Granted Breakthrough Therapy Designation by the FDA in 2020
- Therapeutic potential in late-line, high-risk patient populations

**Mosunetuzumab has high efficacy and a manageable safety profile**

- High overall and complete response rates
- Deep, durable responses in heavily pre-treated population
- Well tolerated, few discontinuations due to adverse events
- Gr 3 neurologic AEs were uncommon, and no Gr 4 or 5 events occurred
- CRS events generally low grade; all resolved

**Mosunetuzumab allows for easier access to treatment**

- No mandatory hospitalization
- Patients can be treated in local community setting
- Readily available, off-the-shelf therapy
- Fixed treatment duration

3L+ – third and subsequent line; FL – follicular lymphoma; FDA – U.S. Food and Drug Administration; PI3K – phosphoinositide 3-kinase; EZH2 – enhancer of zeste homolog 2; WT – wild type; CAR-T – chimeric antigen receptor T-cell; CRS – cytokine release syndrome; Gr. – grade; AE – adverse event.

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# Adverse events, such as CRS, will require some patients to be admitted inpatient[1]

- Mosunetuzumab will be administered through **intravenous infusion (IV)**
- **Mosunetuzumab can be administered in the inpatient and outpatient settings**
- In the **inpatient setting,** mosunetuzumab will be documented in the **"medication administration" section of the medical record**

| Estimated Patients on Mosunetuzumab | | |
|---|---|---|
| | **FY 2022** | **FY 2023** |
| **Estimated patients with 2 or more systemic therapies on mosunetuzumab[2]** | 190 | 570 |
| **% of patients on Medicare FFS*** | 35 | 35 |
| **Estimated number of Medicare FFS patients** | 67 | 201 |
| **% of patients hospitalized due to serious CRS in pivotal trial** | 20 | 20 |
| **Estimated number of inpatient Medicare FFS patients** | 13 | 40 |

*** Gazyva used to as an analog to estimate % of Medicare patients. This is only Medicare FFS and does not include Medicare Advantage, which is an additional ~20%.**

CRS – cytokine release syndrome; FY – fiscal year; FFS – fee-for-service.

1. Budde LE, et al. Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study. Oral Presentation at the 63rd ASH Annual Meeting and Exposition. 2021. 2. SEER data used for incidence, followed by patient estimation based on expected mosunetuzumab share in 3L+ FL.

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# We request a new ICD-10-PCS ‘X’ code for mosunetuzumab in the treatment of 3L+ FL patients

**Mosunetuzumab is being considered by CMS for NTAP in FY2023 for the treatment of 3L+ FL**

**Current ICD-10-PCS codes do not adequately describe the administration of mosunetuzumab for the 3L+ FL indication**

**Therefore, please create a new ICD-10-PCS ‘X’ code for mosunetuzumab for the 3L+ FL indication**

3L+ – third and subsequent line; FL – follicular lymphoma; CMS – Centers for Medicare and Medicaid. NTAP – new technology add-on payment; FY – fiscal year.

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