CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761263Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761263
PDUFA Goal Date	December 29, 2022
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Reviewer Name(s)	Cristen Lambert, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD
Review Completion Date	December 7, 2022
Subject	Evaluation of Need for a REMS
Established Name	mosunetuzumab
Trade Name	Lunsumio
Name of Applicant	Genentech
Therapeutic Class	Bispecific CD20 directed CD3 T cell engager
Formulations	1 mg/mL solution in single dose vial 30 mg/30mL (1 mg/mL) solution in a single dose vial
Dosing Regimen	1 mg intravenously (IV) given on Cycle 1 Day 1, followed by 2 mg on Day 8, and 60 mg on Day 15. Then, 60 mg IV on Cycle 2 Day 1. Then, 30 mg IV on Day 1 for Cycles 3+.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Lunsumio (mosunetuzumab-axgb) is necessary to ensure the benefits outweigh its risks. Genentech submitted a Biologic Licensing Application (BLA) 761263 for Lunsumio with the proposed indication for the treatment of adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies. The serious risks associated with Lunsumio include cytokine release syndrome (CRS), neurologic toxicity (NT), infections, cytopenias, tumor flare, and embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed voluntary risk management activities consisting of communication materials, (b) (4)

DRM and the Division of Hematologic Malignancies 2 (DHM2) have determined that a REMS is not needed to ensure the benefits of Lunsumio outweigh its risks. The risks of CRS, NT, infections, cytopenias, tumor flare, and embryo-fetal toxicity will be described in the Warnings and Precautions section of the label. The risk of CRS will also be communicated in a Boxed Warning to alert healthcare providers of the serious and potentially life-threatening risk. The overall incidence of CRS at the recommended dose of Lunsumio is low, the incidence of Grade 3 and Grade 4 CRS is very low, and there were no deaths associated with CRS in the Lunsumio clinical trial. Expected prescribers and healthcare providers administering Lunsumio in a healthcare setting have experience in monitoring for, identifying and managing CRS, having gained experience with products such as Blincyto and chimeric antigen receptor (CAR) T-cell therapy.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lunsumio (mosunetuzumab-axgb) is necessary to ensure the benefits outweigh its risks. Genentech submitted a Biologic Licensing Application (BLA) 761263 for Lunsumio with the proposed indication of treatment of adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies. This application is under review in the Division of Hematologic Malignancies II (DHM2). The applicant did not submit a REMS with this application but proposed voluntary risk management activities to address the risk of CRS.

2. Background

2.1. Product Information

Lunsumio (mosunetuzumab-axgb), a new molecular entity[a], is a first in class bispecific CD20-directed CD3 T-cell engager, proposed for the treatment of adult patients with relapsed or refractory follicular

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

lymphoma who have received at least two prior lines of systemic therapy. The proposed mechanism of action of Lunsumio is to bind to the CD3 receptor expressed on the surface of T-cells and CD20 receptor expressed on the surface of lymphoma cells and some healthy B-lineage cells. In-vitro, mosunetuzumab-axgb activated T-cells lead to release of proinflammatory cytokines and induced lysis of B-cells. The likely settings for administration are in healthcare settings such as infusion centers, and inpatient community hospitals or academic centers.

Lunsumio is proposed as 1 mg/mL injection solution available in both 1 mg and 30 mg single-dose vials. The proposed dosage of Lunsumio is 1 mg intravenously on Cycle 1 Day 1; 2 mg on Cycle 1 Day 8; 60 mg on Cycle 1 Day 15; 60 mg on Cycle 2 Day 1; and 30 mg for Cycle 3+ Day 1. Each cycle is 21 days, and Lunsumio is proposed to be administered for 8 cycles[b], unless patients experience unacceptable toxicity or disease progression. The Applicant proposed that for patients who achieve a partial response or have stable disease in response to treatment after 8 cycles, an additional 9 cycles of treatment (17 cycles total) may be administered, unless patients experience progressive disease or unacceptable toxicity.

Lunsumio was granted conditional authorization in the European Union on June 3, 2022[1].

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761263 relevant to this review:

- 12/17/2018: Orphan Drug designation granted
- 6/2/2020: Breakthrough Therapy designation granted
- 4/29/2022: The Applicant submitted the final submission to complete the rolling submission for BLA 761263 for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies
- 6/28/2022: Priority Review designation granted
- 8/31/2022: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the discussions regarding a REMS program are still under review.[2] The Applicant proposed a voluntary risk management plan.
- 9/2/2022: The Applicant submitted a proposed risk management plan (b) (4)
- 10/4/2022: The Agency communicated to the Applicant via email[4] that a REMS for BLA 761263 would not be required

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma (NHL), and the most common of the indolent NHLs. Approximately 14,000[c] patients are diagnosed with FL each year and despite advances in diagnostic tools, approved therapies, and improved overall survival, FL remains incurable.[5]

Patients with FL have variable clinical courses and patients typically experience a series of remissions and relapses which become more refractory and less responsive to therapy. Some FL patients have an indolent course over decades while a subset undergo histologic transformation to more aggressive lymphoma with a short duration of response (DOR) after treatment and recurrence within 1-2 years after initial treatment.[6] Lymphoma, particularly histologic transformation, is the primary cause of death in FL patients with disease specific mortality of 10%[7] at 10 years. [d] Outcomes worsen significantly as patients progress through multiple lines of therapy with less than 10% of FL patients having refractory disease.[8] A recent meta-analysis[9] found that few relapsed/refractory (r/r) FL patients with two or more prior lines of therapy achieve complete response (CR), and approximately 1/3 of patients die within 24 months.

3.2. Description of Current Treatment Options

There is no standard therapy for r/r FL. Options for patients with symptomatic late relapse include immunotherapy with a single agent (e.g. rituximab), chemoimmunotherapy with an anti-CD20 antibody (e.g. obinutuzumab or rituximab) plus chemotherapy (e.g. bendamustine or lenalidomide), radioimmunotherapy ^{90}Y-ibritumomab tiuxetan, as well as novel agents (e.g. copanlisib, tazemetostat, chimeric antigen receptor (CAR) T-cell therapies).

Some third-line options include those approved for first- and/or second-line treatment, however patients who are refractory to anti-CD20 or alkylating agents will not likely gain benefit from re-use. Options in this setting are fewer and may have serious toxicities. FDA withdrew approval of the indications of FL for duvelisib, idelalisib, and umbralisib on 4/13/22, 5/26/22, and 5/31/22, respectively. The r/r FL indication for duvelisib and for idelalisib was withdrawn due to inability to complete a confirmatory trial for efficacy under accelerated approval regulations. Umbralisib was withdrawn due to safety concerns with a possible increased risk of death in patients receiving umbralisib in combination with a monoclonal antibody in a phase 3 trial. Copanlisib is the only phosphoinositide 3-kinase (PI3K) inhibitor remaining on the market under accelerated approval for FL. The approved CAR T-cell therapies

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

for r/r FL (Yescarta and Kymriah) are usually reserved for transformed FL due to toxicities including serious, potentially life-threatening CRS. There is a need for effective treatments for r/r FL that provide acceptable safety and tolerability.

Serious risks for approved bispecific T cell engagers include cytokine release syndrome (CRS), neurologic toxicity (NT), and administration/preparation errors. Risk management for serious risks associated with currently approved bispecific T cell engagers includes the use of a Boxed Warning (Kimmtrak), a Communication Plan (CP) REMS (Blincyto), and a REMS with Elements to Ensure Safe Use (ETASU) (Tecvayli). The approved CAR-T cell therapies (Yescarta and Kymriah) are also approved under a REMS with ETASU due to the risk of CRS. See Table 1: *Treatments for Relapsed and Refractory FL after Two or More Prior Therapies* in the Appendix for more details regarding the indications, safety, and risk management strategies for FDA-approved drugs to treat r/r FL.

4. Benefit Assessment

The pivotal trial (study GO29781, National Clinical Trial [NCT] 02500407) supporting this application consisted of a single ongoing multicenter, open-label, Phase I/II dose-escalation and dose-expansion study of mosunetuzumab administered as a single agent (and in combination with atezolizumab) in patients with relapsed and refractory hematologic malignancies expected to express CD20, including B-cell NHL and CLL. The initial patients enrolled (n = 33) were treated with escalating doses of single-agent mosunetuzumab administered as IV infusion on Day 1 of each 3-weekly (q3w) cycle (Group A fixed dosing schedule). Subsequently, an expansion group (Group B cycle 1 step-up dosing; n=414) was created to evaluate mosunetuzumab at a recommended expansion dose in specific B-cell NHL histologies. Expansion cohort B11 (n=218) was selected as the final recommended phase 2 dose (RP2D) administering 1 mg on D1, 2 mg on D8 and 60 mg on Day 15. Expansion cohort B11 also makes up the primary safety population and includes patients with relapsed and refractory hematologic malignancies including Grade 1 – 3a follicular lymphoma (FL), transformed FL, Richter's, diffuse large B cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). Among these patients, 90 patients with r/r FL who received 2 or more prior therapies make up the primary efficacy population.

Study GO29781 primary endpoint was Independent Review Facility (IRF)-assessed complete response (CR) rate. Secondary efficacy endpoints evaluated were CR rate by investigator (INV), overall response rate (ORR), duration of CR, duration of response (DOR), progression-free survival (all by IRF and INV), overall survival and patient reported outcome measures. Results for the B11 FL cohort show an IRF-assessed CR rate of 60%, an IRF-assessed ORR rate of 80% and a DOR of 22.8 months. [10] The clinical reviewer concluded that the Applicant provided evidence of effectiveness (based on overall response rate as assessed by an independent review committee) and provides a meaningful advantage over available therapies.[e] Some limitations include limited racial and ethnic representation and little data of treatment beyond 8 cycles.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5. Risk Assessment & Safe-Use Conditions

The primary safety population includes patients with hematologic malignancies exposed to Lunsumio as a single agent in study GO29781 (n=218). In this pooled safety population, the most common (≥20%) adverse reactions were cytokine release syndrome (39%), fatigue (36%), rash (34%), pyrexia (24%), and headache (21%).

In the relapsed or refractory follicular lymphoma R2PD cohort (n=90) of GO29781, serious adverse events occurred in 47% of patients who received Lunsumio.[11] Serious adverse reactions in ≥2% of patients included cytokine release syndrome, infection (including urinary tract infection, sepsis, pneumonia, EBV viremia, and COVID-19), renal insufficiency, pyrexia, and tumor flare. Permanent discontinuation of Lunsumio due to an adverse reaction occurred in 3% of patients.[11] Adverse reactions resulting in permanent discontinuation of Lunsumio include cytokine release syndrome and EBV viremia. Dosage interruptions or modifications of Lunsumio due to an adverse reaction occurred in 37% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included neutropenia, infection, and cytokine release syndrome.[11] Clinically relevant adverse reactions in <10% of patients who received Lunsumio included pneumonia, sepsis, COVID-19, EBV viremia, mental status changes, tumor lysis syndrome, renal insufficiency, anxiety, motor dysfunction, and tumor flare. Fatal adverse events in the R/R FL Cohort occurred in 2 patients (2%): 1 attributed to malignant neoplasm progression and 1 of unknown cause (Grade 2 ICANS, Grade 3 CRS (ASTCT), and Grade 4 AKI)[12]. The serious risks associated with Lunsumio are CRS, neurologic toxicity, infections, cytopenias, tumor flare, and embryo-fetal toxicity.

5.1. Cytokine Release Syndrome

In patients receiving Lunsumio at the recommended dose, as a single agent in Study GO29781(n=218) for hematologic malignancies (pooled safety population), cytokine release syndrome occurred in 39% of patients, with Grade 1 CRS occurring in 28% of patients, Grade 2 in 15%, Grade 3 in 2% and Grade 4 in 0.5% of patients[11] (CRS Grading per ASTCT criteria) [f]. No patients had a Grade 5 CRS event. Recurrent CRS occurred in 11% of patients. Most patients experienced CRS following doses of 1 mg on Cycle 1 Day 1 (15%), 2 mg on Cycle 1 Day 8 (5%), and 60 mg on Cycle 1 Day 15 (33%). Five percent of patients experienced CRS after receiving 60 mg on Cycle 2 Day 1 with 1% of patients experiencing CRS following subsequent dosages of Lunsumio. The median time to onset of CRS from the start of administration in Cycle 1 Day 1 was 5 hours (range: 1 hour to 3 days), Cycle 1 Day 8 was 28 hours (range: 5 hours to 3 days), Cycle 1 Day 15 was 25 hours (range: 0.1 hours to 16 days), and Cycle 2 Day 1 was 46 hours (range: 12 hours to 3 days).[11] CRS resolved in all patients, and the median duration of CRS was 3 days (range: 1 to 29 days). Clinical signs and symptoms of CRS included but were not limited to, fever, chills, hypotension, tachycardia, hypoxia, and headache.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The risk of CRS, which may be life threatening, will be communicated in *Warnings and Precautions* and a boxed warning to inform healthcare professionals of this serious risk. The label advises healthcare providers to administer Lunsumio to well-hydrated patients, premedicate before each dose in Cycle 1 and Cycle 2, and initiate treatment with the step-up dosing schedule to reduce the risk of CRS. The label states that Lunsumio should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome and neurologic toxicity. Providers are instructed to monitor patients following administration of Lunsumio and at the first sign of CRS, immediately evaluate patients for hospitalization and/or intensive care, manage per current practice guidelines, and administer supportive care. Healthcare providers should advise patients who experience CRS, or other adverse reactions that impair consciousness, not to drive and refrain from operating heavy machinery until resolution. The label advises providers to withhold or permanently discontinue Lunsumio based on CRS severity.

5.2. Neurologic Toxicity

Neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) was observed in the Lunsumio clinical program. Neurologic toxicity occurred in 39% of patients who received Lunsumio at the recommended dose, with Grade 3 neurologic toxicity occurring in 3% of patients.[11] The most frequent neurologic toxicities were headache (21%), peripheral neuropathy (13%), dizziness (11%), and mental status changes (6%) which include confusional state, disturbance in attention, cognitive disorder, delirium, encephalopathy, and somnolence. ICANS was reported in 1% of patients who received Lunsumio at the recommended dose in the clinical trial.

The risk of neurologic toxicity will be included in *Warnings and Precautions*. The label advises healthcare providers to monitor for signs and symptoms during treatment with Lunsumio and upon first sign of neurologic toxicity, evaluate and provide supportive care based on severity. The label advises providers to withhold or permanently discontinue Lunsumio based on severity and to follow management recommendations. The label also advises patients who experience neurologic toxicity such as tremors, dizziness, insomnia, severe neurotoxicity, or any other adverse reactions that impair consciousness should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

5.3. Infections

Serious infections, including opportunistic infections, occurred in 17% of patients who received the recommended dose in the clinical trial. Grade 3 or 4 infections occurred in 14%, and fatal infections occurred in 0.9% of patients. The most common Grade 3 or greater infections were pneumonia, sepsis, upper respiratory tract infection, and urinary tract infection.

The risk of serious or fatal infections will be included in *Warnings and Precautions*. The label advises healthcare providers to monitor for signs and symptoms of infection prior to and during treatment and to not administer Lunsumio in the presence of active infection. The label also advises to administer

prophylactic antimicrobials according to guidelines and to withhold Lunsumio or consider permanent discontinuation based on severity of infection.

5.4. Cytopenias

Serious or severe cytopenias, including neutropenia, anemia, and thrombocytopenia were observed in the Lunsumio clinical program. Grade 3 or 4 decreased neutrophils occurred in 38%, decreased hemoglobin in 19%, and decreased platelets in 12% of patients who received the recommended dosage in the clinical trial. Grade 4 decreased neutrophils occurred in 19% and febrile neutropenia occurred in 2%

The risk of cytopenias will be included in *Warnings and Precautions*. The label advises healthcare providers to monitor complete blood counts throughout treatment and based on the severity of the cytopenia, temporarily withhold, or permanently discontinue Lunsumio. The label also advises to consider prophylactic granulocyte colony-stimulating factor administration.

5.5. Tumor Flare

Tumor flare occurred in 4% of patients who received Lunsumio at the recommended dosage in the clinical trial. Manifestations included new or worsening pleural effusions, localized pain and swelling at the sites of lymphoma lesions, and tumor inflammation.

The risk of tumor flare will be included in *Warnings and Precautions*. The label advises healthcare providers to closely monitor patients with bulky tumors or disease located in close proximity to airways or a vital organ and institute standard treatment of complications like compression or obstruction that may develop.

5.6. Embryo-Fetal Toxicity

No pregnancies were reported during the study and women of childbearing potential were required to use contraception while receiving Lunsumio and for at least 3 months after the last infusion. The Applicant submitted an assessment for reproductive and developmental risk using a weight-of-evidence approach[10]. Based on its mechanism of action, Lunsumio may cause fetal harm when administered to a pregnant woman.

The risk of embryo-fetal toxicity will be included in *Warnings and Precautions*. The label advises healthcare providers to counsel females of reproductive potential to use effective contraception during treatment with Lunsumio and for 3 months after the last dose.

6. Expected Post-market Use

Lunsumio will be administered in both inpatient and outpatient settings (e.g., infusion centers) and the likely prescribers are hematologists and/or oncologists, who are expected to be able to monitor, diagnose, and manage the aforementioned risks. The expected prescribers of Lunsumio and healthcare

providers likely have experience with therapies that have a risk of CRS, such as Blincyto (blinatumomab), Kimmtrak (tebentafusp-tebn), and Yescarta (axicabtagene ciloleucel).

The CRS incidence and severity in the post-market setting may vary from that in the controlled clinical program of Lunsumio. The overall incidence of CRS seen in the Lunsumio clinical program was low with mostly Grade 1 and 2 severities; however, it is unknown how this may change in the post-market setting with a more diverse patient population and non-protocolized CRS management strategies, among other variables.

There are differences in how the risk was managed in the clinical trial compared to how the risk may be addressed in the post-market setting. Tocilizumab was protocolized and utilized in the Lunsumio clinical program to manage grade 1-4 CRS, but tocilizumab is only approved for CRS related to CAR-T cell therapies. Providers in the post-market setting will be expected to utilize other CRS management strategies, such as supportive care, hospitalization, and adherence to premedication protocols for CRS management and mitigation. Furthermore, since CRS onset occurred over a wide range of time (0.1 hours to 16 days) in the clinical trial, prescribers in the post market setting will be expected to educate patients on signs and symptoms of CRS and to contact their healthcare provider immediately if they experience these symptoms. CRS associated with mosunetuzumab presents with a fever in 98% of patients and we expect patients who are eligible to receive Lunsumio therapy would be familiar with identifying and monitoring for fevers at home.

7. Risk Management Activities Proposed by the Applicant

Genentech states that:

> "A positive benefit-risk profile has been established for mosunetuzumab in the treatment of patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies. Therefore, we believe that the safety profile of mosunetuzumab can be appropriately described in the full prescribing information. Based on this assessment, a REMS is not included."

During the course of the review, Genentech proposed a voluntary non-REMS risk management plan comprised of communication materials, (b) (4) . The goals of these materials are to educate healthcare providers (HCPs) on early recognition and management of CRS, and patients on early recognition and presentation to healthcare facilities.

Reviewer's Comments: *We note that these activities proposed by the applicant are outside of the scope of a REMS program and will not be reviewed by DRM.*

8. Discussion of Need for a REMS

The Clinical Reviewer recommends accelerated approval of Lunsumio for relapsed and refractory follicular lymphoma after two prior therapies based on the efficacy and safety information currently available.

The serious risks associated with Lunsumio are CRS, neurologic toxicities, infections, neutropenia, tumor flare, and embryo-fetal toxicity. The serious risks of infections, neutropenia, tumor flare, and embryo-fetal toxicity are similar to other products used to treat r/r FL such as rituximab, obinutuzumab bendamustine, and copanlisib. None of these products are currently approved with a REMS and the risks are described and communicated through the *Warnings and Precautions* in labeling. Lenalidomide is associated with tumor flare and embryo-fetal toxicity and has a REMS with goals to prevent the risk of embryo-fetal exposure to lenalidomide and to inform prescribers, patients, and pharmacists of the serious risks and safe-use conditions for lenalidomide[13].

The main safety concern of Lunsumio is the risk of CRS. CRS is an acute systemic inflammatory response triggered by infections and certain drugs such as antibody-based therapies (e.g. rituximab), non-protein-based cancer drugs (e.g. oxaliplatin), and T-cell engaging immunotherapies (e.g. bispecific antibodies; CAR-T). As T-cells are engaged, subsequent activation of immune cells results in release of cytokines. CRS is characterized by a variety of symptoms ranging from mild (headache, fever, fatigue, myalgia), to more severe (hypotension, high fever, organ failure). CRS has a wide range of incidence (2 to 100%) and severity (0 to 46% incidence of CRS > Grade 2) among approved therapies.[14] Prior to development of consensus grading for CRS by the American Society for Transplantation and Cellular Therapy (ASTCT) in 2019, CRS grading varied widely among institutions which adds complexity to comparisons between products and clinical trials started at various points in time.[15]

In the context of approved therapies for r/r FL, the safety profile of Lunsumio is more favorable regarding CRS compared to CAR-T therapies such as Yescarta. The overall CRS incidence is 39% in the primary safety cohort for Lunsumio compared to 84% for Yescarta indicated for indolent NHL[16]. Furthermore, incidence of ≥Grade 3 CRS in FL patients is lower in Lunsumio (2.5%)[12] clinical trials compared to Yescarta (8%)[16]. Yescarta, like all approved CAR-T therapies, was approved with a REMS with ETASU to ensure healthcare settings are certified and have on-site, immediate access to tocilizumab for CRS treatment and to ensure healthcare providers who prescribe, dispense, or administer Yescarta are educated on CRS risk and management. A REMS was required to mitigate the risk of CRS in CAR-T cell therapies because both the CRS incidence and severity are high and to ensure that tocilizumab is on site for CRS treatment.

Several other approved bispecific T-cell engagers have a risk of CRS. Blincyto (blinatumomab) is indicated for R/R acute lymphoblastic leukemia and had a CRS incidence of 7 to 15% in clinical trials.[17] Blincyto was approved in 2014 with a Communication Plan (CP) REMS. The goals of the Blincyto CP REMS were to mitigate the risks of CRS, neurotoxicity, and administration and preparation errors. The release of the Blincyto REMS was approved on December 5, 2022, citing the communication plan requirements have been fulfilled and knowledge surveys of healthcare professionals demonstrate acceptable understanding of the risks of CRS and neurologic toxicities[18]. Additional supporting evidence from a postmarketing medication error review is reassuring that there were no adverse events associated with the medication errors that occurred and no regulatory action is warranted to mitigate errors.[19] Kimmtrak (tabentafusp-tebn), indicated for metastatic uveal melanoma, had an overall incidence of CRS of 89% in clinical trials with only 0.8% of patients having Grade 3 CRS, and no reports of Grade 4 CRS or death[20]. Kimmtrak was approved in January 2022 without a REMS due to the incidence

and severity of CRS with Kimmtrak appearing less than other products approved with a REMS to mitigate the risk of CRS as well as oncologists and healthcare settings becoming familiar with and knowledgeable of monitoring, diagnosing and managing CRS over the years. Further supporting the recommendation that a REMS was not needed to mitigate the risks associated with Kimmtrak was the indication in uveal melanoma, a very rare disease, with specialized prescribers likely associated with research and academic healthcare settings that administer biologics with similar risk and management. Metastatic uveal melanoma has a poor prognosis with no other treatment options therefore it is important that patients have no delays or barriers to receiving therapy. Lunsumio has an overall CRS incidence (39%) which falls between overall CRS incidence for Blincyto and Kimmtrak and is similar to Kimmtrak as it has mostly Grade 1 and 2 CRS with no deaths from CRS.

Tecvayli (teclistamab), indicated for multiple myeloma, is a bispecific T-cell engager recently approved in October 2022 with an overall CRS incidence of 72% in clinical trials.[21] Tecvayli differs from other bispecific T-cell engagers since it is subcutaneous and can be administered in the outpatient setting. Healthcare providers in outpatient oncology clinics may not be as familiar with the risk of CRS and appropriate monitoring and management. CRS occurred beyond step-up dosing in the clinical program, and with outpatient SQ administration, it is important for patients to identify CRS and contact their prescriber for CRS management. The review team was also concerned about the incidence and severity of neurologic toxicity associated with Tecvayli, including immune effector cell-associated neurotoxicity syndrome (ICANS). Tecvayli was approved with a REMS with ETASU with a goal to mitigate CRS and neurologic toxicity including ICANS by educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS. Of note, ICANS incidence in the Tecvayli clinical trials was 6% with 1.8% of patients having recurrent ICANS.[21] The incidence of ICANS in Lunsumio patients at the recommended dose was 1%.

The European Medicine Agency granted conditional approval to mosunetuzumab in June 2022 with an obligation to provide long term safety data by completing the confirmatory phase III study (Study GO42909 – A Randomized Phase III trial of mosunetuzumab plus lenalidomide versus rituximab plus lenalidomide in patients with r/r FL after at least one prior systemic therapy regimen).[22] The EMA conditional approval includes additional risk minimization measures for CRS associated with mosunetuzumab consisting of a patient card describing key symptoms of CRS and when to seek urgent attention from a healthcare provider. The patient card also contains a warning message for healthcare professionals treating patients that the patient is receiving Lunsumio.

DRM, Division of Hematologic Malignancies 2 (DHM2), and the Office of Oncologic Diseases (OOD) safety team discussed the risk of CRS with Lunsumio and determined that a REMS is not necessary to ensure the benefits outweigh the risks of CRS for Lunsumio. The overall incidence of CRS at the recommended dose of Lunsumio is low and the incidence of Grade 3 and Grade 4 CRS is very low. There were no deaths associated with CRS in the Lunsumio clinical trial. Also, patients were not required to be hospitalized for administration of the IV infusion in the clinical trial, which is consistent with the expected post market setting for administration. The expected prescribers (hematologists and oncologists) and other healthcare providers, are familiar with monitoring for, identifying, and treating the risk of CRS associated with other products with a similar risk.

The Review Team recommends strengthening labeling for the risk management of CRS associated with Lunsumio. The Lunsumio USPI will contain a Boxed Warning for CRS. Labeling will include recommendations to administer pre-medications, to administer Lunsumio in a healthcare setting, and to utilize practice guidelines for CRS management. The Lunsumio USPI will also include recommendations to healthcare providers for management of CRS with actions to take based on presenting symptoms. Actions include withholding Lunsumio, infusing at a lowered rate, increasing frequency of monitoring, considering hospitalization, supportive therapy and/or intensive care, and permanently discontinuing Lunsumio.

There remains uncertainty regarding CRS in the post-market setting. It was concluded that data for tocilizumab use for CRS management in patients who received Lunsumio in the clinical trial do not support inclusion of tocilizumab in the Lunsumio USPI.[10] The Agency has issued a PMR to conduct a randomized clinical trial in patients with r/r FL to verify clinical benefit of Lunsumio and routine pharmacovigilance may provide more data to further assess this uncertainty. [10]

Due to the varying nature of the CRS risk associated with approved products, the range of CRS risk management strategies, and anticipated applications with CRS risk to be reviewed in the near future, the REMS Oversight Committee (ROC)[g] requested an overview of Lunsumio risk management strategies in the context of the CRS risk management landscape. The risk management strategy for CRS in Lunsumio, associated rationale, and the CRS risk landscape were presented to the ROC on December 6, 2022.[23] The ROC acknowledged the challenges in CRS risk management and the considerations of the review team due to the variety of risk characterization in current and future applications. The ROC did not make recommendations regarding Lunsumio risk management due to the informative basis of this ROC meeting.

9. Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of Lunsumio outweigh the risks. In general, healthcare providers who treat r/r follicular lymphoma are familiar with the risk of CRS, neurologic toxicities, infections, cytopenias, tumor flare, and embryo-fetal toxicity and the importance of patient monitoring and education.

At the time of this review, evaluation of labeling was ongoing. Should the Division of Hematologic Malignancies II have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

Table 1: Treatments for Relapsed and Refractory FL after Two or More Prior Therapies

[g] As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

Product Trade Name (Generic) **Year of Approval**	**Relevant Indication**	**Dosing/Administration**	**Important Safety and Tolerability Issues**	**Additional Risk Management Approaches**
FDA Approved Treatments				
Rituxan[24] (rituximab) 1997	Single Agent: Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL	375 mg/m^2 IV	**Boxed warning:** fatal infusion-related reactions, mucocutaneous reactions, HBV reactivation, PML **Other:** TLS, infections, cardiac arrhythmias and angina, renal toxicity, bowel obstruction and perforation, embryo-fetal toxicity, immunization	Medication Guide
Gazyva[25] (obinatuzumab) 2016	In combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen	1000 mg IV infusion of Days 1, 8, 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	**Boxed warning:** HBV reactivation, PML **Other:** infusion reactions, hypersensitivity reactions including serum sickness, TLS, infections, neutropenia, thrombocytopenia, DIC, immunization, embryo-fetal toxicity	
Zevalin[26] (^{90}Y-ibritumomab tiuxetan) 2002	Relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL)	0.3-0.4 millicurie (mCi) per kg actual body weight (max dose 32 mCi) Given IV as part of combined treatment regimen with rituximab	**Boxed warning:** infusion reactions, cytopenias, cutaneous and mucocutaneous reactions, do not exceed 32mCi of Y-90 Zevalin **Other:** leukemia and MDS, embryo-fetal toxicity, extravasation, immunization	
Treanda[27] (bendamustine) 2008	Indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.	120 mg/m^2 IV on days 1 and 2 of a 21-day treatment cycle	Myelosuppression, infections, infusion reactions and anaphylaxis, TLS, skin reactions, other malignancies, use in pregnancy	

Product Trade Name (Generic) **Year of Approval**	**Relevant Indication**	**Dosing/Administration**	**Important Safety and Tolerability Issues**	**Additional Risk Management Approaches**
Revlimid[28] (lenalidomide) 2019	Previously treated FL, in combination with a rituximab product	20 mg PO QDay on Days 1-21 of 28-day cycles	**Boxed warning:** embryo-fetal toxicity, hematologic toxicity, venous and arterial thromboembolism **Other:** increased mortality/cardiac, second primary malignancies, increased mortality in MM when pembrolizumab added to dexamethasone and a thalidomide analogue, hepatotoxicity, cutaneous reactions, TLS, tumor flare, impaired stem cell mobilization, early mortality in MCL, hypersensitivity	Medication Guide **REMS** (embryo-fetal toxicity)
Zydelig[29] (idelalisib) 2014 **FL indication withdrawn on May 26, 2022**	~~Relapsed follicular B-cell NHL (FL) in patients who have received at least two prior systemic therapies.~~	150 mg PO BID	**Boxed warning**: hepatotoxicity, severe diarrhea, colitis, pneumonitis, infections, intestinal perforation **Other:** severe cutaneous reactions, anaphylaxis, neutropenia, embryo-fetal toxicity	Medication Guide **Communication Plan REMS previously released**
Aliqopa[30] (copanlisib) 2017	Adult patients with relapsed FL who have received at least 2 prior systemic therapies	60 mg IV on Days 1, 8, and 15 of a 28 day cycle on an intermittent schedule (3 weeks on and 1 week off)	Infections, hyperglycemia, hypertension, non-infectious pneumonitis, neutropenia, cutaneous reactions, embryo-fetal toxicity	
Copiktra[31] (duvelisib) 2018 **FL indication withdrawn on April 13, 2022**	~~Adult patients with relapsed or refractory FL after at least 2 prior systemic therapies~~	25 mg PO BID	**Boxed warning:** infections, diarrhea or colitis, cutaneous reactions, pneumonitis **Other:** hepatotoxicity, neutropenia, embryo-fetal toxicity **FDA issued warning on June 30, 2022 about possible increased risk of death and serious side effects[32]**	Medication Guide **Communication Plan REMS**

Product Trade Name (Generic) **Year of Approval**	**Relevant Indication**	**Dosing/Administration**	**Important Safety and Tolerability Issues**	**Additional Risk Management Approaches**
Ukoniq[33] (umbralisib) 2021 **Withdrawn from market May 31, 2022 due to safety concerns**	~~Relapsed or refractory FL who have received at least three prior lines of systemic therapy~~	800 mg PO daily	Infections, neutropenia, diarrhea or non-infectious colitis, hepatotoxicity, cutaneous reactions, allergic reactions, embryo-fetal toxicity	Medication Guide
Tazverik[34] (tazemetostat) 2020	Adult patients with relapsed or refractory FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test Adult patients with relapsed or refractory FL who have no satisfactory alternative treatment options	800 mg PO BID	Secondary malignancies, embryo-fetal toxicity	Medication Guide
Yescarta[16] (axicabtagene ciloleucel) 2021	Adult patients with relapsed or refractory FL after two or more lines of systemic therapy	2 x 10^6 chimeric antigen receptor (CAR)-positive viable T-cells per kg of body weight, with a maximum of 2 x 10^8 CAR-positive viable T-cells	**Boxed warning:** cytokine release syndrome, neurologic toxicities **Other:** hypersensitivity reactions, infections, cytopenias, hypogammaglobulinemia, secondary malignancies, effects on ability to drive and use machines	Medication Guide **REMS** (cytokine release syndrome and neurologic toxicities)
Kymriah[35] (tisagenlecleucel) 2022	Adult patients with relapsed or refractory FL after two or more lines of systemic therapy	0.6 to 6.0 x 108 CAR-positive viable T cells	**Boxed warning:** cytokine release syndrome, neurologic toxicities **Other:** hypersensitivity reactions, infections, cytopenias, hypogammaglobulinemia, secondary malignancies, effects on ability to drive and use machines	Medication Guide **REMS** (cytokine release syndrome and neurologic toxicities)

NHL, non-Hodgkin's lymphoma; IV, intravenous; HBV, Hepatitis B virus; PML, Progressive Multifocal Leukoencephalopathy; TLS, tumor lysis syndrome; DIC, disseminated intravascular coagulation; MM, multiple myeloma; MCL, mantle cell lymphoma

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