CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761289Orig1s000

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	761289
PDUFA Goal Date	October 23, 2022
OSE RCM #	2022-421
Reviewer Name(s)	Celeste Karpow, PharmD, MPH
Team Leader	Naomi Boston, PharmD
Division Director	Laura Zendel, PharmD, BCPS
Review Completion Date	September 26, 2022
Subject	Evaluation of Need for a REMS
Established Name	tremelimumab
Trade Name	Imjudo
Name of Applicant	AstraZeneca AB
Therapeutic Class	cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody
Formulation(s)	concentrate for dilution
Dosing Regimen	Patients with a body weight of 30 kg and more: 300 mg as a single dose in combination with durvalumab 1500 mg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks Patients with a body weight of less than 30 kg: 4 mg/kg as a single dose in combination with durvalumab 20 mg/kg followed by durvalumab as a single agent every 4 weeks

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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 Imjudo (tremelimumab) is necessary to ensure the benefits outweigh its risks. AstraZeneca AB submitted a Biologic Licensing Application (BLA) 761289 for tremelimumab with the proposed indication for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) in combination with durvalumab. The risks associated with tremelimumab include the following: severe and fatal immune-mediated adverse reactions, infusion related reactions, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Oncology 3 (DO3) determined a REMS is not needed to ensure the benefits of tremelimumab outweigh its risks. The efficacy of tremelimumab in patients with uHCC was supported in the HIMALAYA trial. HIMALAYA met its primary endpoint by demonstrating a statistically significant improvement in overall survival for patients randomized to tremelimumab 300 mg + durvalumab vs. sorafenib. As with other products for this indication, the serious risks associated with tremelimumab will be addressed in the warnings and precautions section of the label. The likely prescribers will be oncologists who are expected to be familiar managing the serious adverse events reported with tremelimumab as they are similar to other products approved to treat uHCC.

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) Imjudo (tremelimumab) is necessary to ensure the benefits outweigh its risks. AstraZeneca AB submitted a Biologic Licensing Application (BLA) 761289 for tremelimumab with the proposed indication of treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) in combination with durvalumab. This application is under review in the Division of Oncology 3 (DO3). The applicant did not submit a proposed REMS or risk management plan with this application. However, the applicant proposed a medication guide to be included as part of labeling.

2. Background

2.1. Product Information

Imjudo (tremelimumab), a new molecular entity[a], is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-blocking antibody, proposed for the treatment of adult patients with uHCC in combination with durvalumab. The mechanism of action of tremelimumab is to block the interaction between CTLA-4, a cell surface receptor on activated T cells, and the B7 ligands on antigen-presenting cells, resulting in tumor cell death through T cell activation and proliferation, and lymphocyte infiltration into tumors.

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

Potency is measured by a reporter gene bioassay. Tremelimumab is proposed as either a 300 mg single injection in combination with durvalumab 1500 mg at cycle 1/day 1, followed by durvalumab as a single agent every 4 weeks for patients with a body weight 30 kg or more or a 4 mg/kg injection in combination with durvalumab 20 mg/kg followed by durvalumab as a single agent every 4 weeks. Tremelimumab is proposed to be administered as an intravenous (IV) infusion after dilution. The expected duration of treatment is as long as clinical benefit is observed or until unacceptable toxicity.[b] Tremelimumab is not currently approved in any jurisdiction, nor has it been granted breakthrough therapy or fast track designation.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761289 relevant to this review:

- 01/15/2020: Orphan drug designation granted
- 02/23/2022: BLA 761289 submission for the treatment of adult patients with uHCC in combination with durvalumab
- 06/09/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tremelimumab

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hepatocellular carcinoma (HCC) is a liver malignant tumor that develops in the setting of chronic liver disease.[1] It typically occurs in patients with liver cirrhosis or hepatitis B virus infection and rarely in a healthy liver.[2] Common risk factors for HCC include cirrhosis of any cause, hepatitis B virus, hepatitis C virus and Non-alcoholic fatty liver disease (NAFLD).[c,3] HCC affects males over two times as much as females and the incidence increases with age with a peak age of 65-70 years old.[3,4] The American Cancer Society estimates approximately 41,260 new cases of liver and intrahepatic bile duct cancer and approximately 30,520 deaths from liver and intrahepatic bile duct cancer in the United States in 2022.[d,5]

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

[c] 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.*

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

According to the National Cancer Institute's SEER database, between 2012-2018, the 5-year relative survival rate for patients diagnosed with liver and intrahepatic bile duct cancer was 20.8%.[e,5]

Although HCC in early stages may be curable with resection, liver transplantation, or ablation, most patients with unresectable HCC have a poor prognosis.[6] Forty percent of HCCs are diagnosed at an early state and are eligible for curative surgical treatments, such as liver transplantation or hepatic resection, or local ablations with radiofrequency.[2] However more than half of patients present with intermediate-stage HCC which requires either chemoembolization, radioembolization, or systemic treatment.[2] HCC is typically diagnosed late in the course of chronic liver disease.[7,8] The median survival of advanced HCC is 8 months based on the natural history of the disease.[2]

3.2. Description of Current Treatment Options

Treatment options are typically divided into surgical therapies or systemic therapies.[8] Surgical therapies include resection, cryoablation, and liver transplantation whereas systemic therapies include chemotherapy, molecularly targeted therapy, and immunotherapy with immune checkpoint inhibitors.[8] Although surgical therapies are available, liver-directed surgical therapies are not appropriate for patients with advanced or unresectable HCC. Systemic therapies are recommended in patients with advanced or unresectable HCC due to the pathophysiology of the disease.[2] The National Comprehensive Cancer Network (NCCN) Guidelines include the following FDA approved products as systemic therapy for HCC: atezolizumab + bevacizumab, sorafenib, lenvatinib, durvalumab, pembrolizumab, nivolumab, regorafenib, cabozantinib, ramucirumab, nivolumab + ipilimumab, and dostarlimab-gxly.[9] A communication plan REMS was required at the time of approval for Yervoy (ipilimumab) in 2011 to address the risk of immune mediated reactions. The Agency released the REMS in 2015 since the REMS was meeting the goals. The risks were communicated and are widely known in this prescribing population. None of these treatments currently carry a boxed warning or have a REMS for any risks.

Therapeutic options for patients with HCC have improved over the years, however the prognosis is often poor, especially in the setting of cirrhosis.[2] Products used to treat unresectable HCC are summarized in Table 1 in the Appendix.

4. Benefit Assessment

The pivotal trial, HIMALAYA (NCT03298451) supporting this application consisted of a randomized, open-label, multicenter Phase III study which evaluated tremelimumab 300 mg + durvalumab 1500 mg IV infusion on the same day followed by durvalumab every 4 weeks, durvalumab 1500 mg IV every 4 weeks as monotherapy, or sorafenib 400 mg as monotherapy given orally twice daily, until disease progression or unacceptable toxicity in 1,171 patients (tremelimumab 300 mg + durvalumab group = 393, durvalumab monotherapy group = 389, sorafenib group = 389) with unresectable HCC who were not eligible for locoregional therapy.[10] The primary endpoint of HIMALAYA was to assess the efficacy of

[e] 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.*

tremelimumab 300 mg + durvalumab with sorafenib by evaluating overall survival (OS).[11] HIMALAYA met its primary endpoint by demonstrating a statistically significant improvement in OS for patients randomized to tremelimumab 300 mg + durvalumab vs. sorafenib (median OS 16.4 months vs. 13.8 months, HR 0.78, p-value 0.0035).[11] The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on OS superiority.[f,11]

The supportive study, Study 22 (NCT02519348) consisted of a multicenter, open-label study which evaluated the safety and efficacy of tremelimumab 300 mg + durvalumab (n=75), durvalumab monotherapy (n=104), tremelimumab 75 mg + durvalumab (n=84), and tremelimumab 750 mg (n=69) with unresectable HCC who had progressed on, were intolerant to, or refused treatment with sorafenib and had not received prior immunotherapy.[10] Primary outcome measures in Study 22 were related to safety and overall survival was a secondary endpoint.[12,13] Study 22 had no prespecified efficacy hypotheses, so no formal statistical testing of efficacy endpoints was performed.[12] Time-to-event endpoints, including overall survival, progression-free survival, time to progression, duration of response, and time to onset of objective response, were analyzed using the Kaplan-Meier method.[12] The median of each time-to-event endpoint and its 95% CI was estimated based on the Kaplan-Meier curves.[12] Only patients with an objective response (best overall response of CR or PR) were included in the analysis of duration of response (DoR).[12] The median overall survival in months was 12.91 (95% CI 8.74, 16.79) for durvalumab monotherapy, 17.05 (10.55, 22.83) for tremelimumab 300 mg + durvalumab, and 17.05 (11.33, 20.24) for the tremelimumab group. The clinical team concluded that Study 22 provided a supportive role in demonstrating contribution of component of the proposed tremelimumab 300 mg + durvalumab regimen as patients showed improvement over patients in the durvalumab only arm.

5. Risk Assessment & Safe-Use Conditions

The safety of tremelimumab was evaluated in a total of 388 patients with uHCC in HIMALAYA (NCT03298451) who received at least one dose of durvalumab given at a dose of 1,500 mg IV every 4 weeks in combination with tremelimumab 300 mg IV for one dose for HCC and 374 patients who received sorafenib 400 mg orally twice daily.[14] Discontinuation due to an adverse event (AE) occurred in 14% patients in the treatment arm. The rate of dose delays or interruption due to a AE occurred in 35% of patients in the treatment arm.[13] The most common adverse reactions were diarrhea, pruritis, fatigue, musculoskeletal pain, abdominal pain and rash.

Deaths

Two fifty eight (66.5%) deaths were reported in patients who received durvalumab in combination with tremelimumab in the HIMALAYA trial.[14] Two hundred twenty-one (57%) deaths were due to disease progression, 11 (3%) were classified as 'other', and 30 (8%) were due to an adverse event. Fatal adverse reactions that occurred in at least 2 patients included death (1%), hemorrhage intracranial (0.5%),

[f] 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.*

cardiac arrest (0.5%), pneumonitis (0.5%), hepatic failure (0.5%), and immune-mediated hepatitis (0.5%). Twenty (5%) deaths occurred within 30 days after the last dose.[11] Similarly, there were two hundred seventy nine (72%) deaths reported in patients who received durvalumab monotherapy and two hundred eighty-three (76%) deaths reported in patients who received sorafenib monotherapy.[11] In patients who received durvalumab monotherapy, there were 245 (63%) deaths due to disease progression, 9 (2%) were classified as 'other', 26 (7%) were due to an adverse event, and twenty-two (6%) deaths occurred within 30 days after the last dose. In patients who received sorafenib, there were two hundred fifty-six (68%) deaths due to disease progression, 10 (3%) were classified as 'other', 27 (7%) were due to an adverse event, and fifty-six (15%) deaths occurred within 30 days after the last dose.

Serious Adverse Events (SAEs)

SAEs occurred in 41% of patients who received tremelimumab with durvalumab. These included hemorrhage (6%), diarrhea (4%), pneumonia (2.1%), sepsis (2.1), rash (1.5%), acute kidney injury (1.3%), vomiting (1.3%), and anemia (1.3)[13].

At the time of this writing, labeling negotiations were ongoing. DO3 determined the adverse events will be communicated in the warnings and precautions and adverse reactions sections of the USPI. A Medication Guide will also be included as part of labeling. The clinical team concludes that the safety profile of tremelimumab appears acceptable and the reported adverse events were consistent with the known safety profiles of individual components.

5.1. Severe and Fatal Immune-Mediated Adverse Reactions

Tremelimumab is a monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response.[14] Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue.[14] Immune-mediated adverse reactions can occur at any time after starting tremelimumab in combination with durvalumab.[14] Section 5.1 of the draft labeling describes the risk of immune-mediated adverse reactions and provides recommendations for monitoring and management. Several types of immune-mediated adverse reactions are listed below:

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis occurred in 1.3% of patients receiving tremelimumab in combination with durvalumab, including Grade 3 (0.2%) and fatal (0.3%) adverse reactions.[14] Events resolved in 3 of the 5 patients and resulted in permanent discontinuation in one patient.[14] Systemic corticosteroids were required in all patients, of these four patients required high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).[14] One patient (1/5) required other immunosuppressants.[14]

Immune-Mediated Colitis

Immune-mediated colitis or diarrhea occurred in 6% of patients receiving tremelimumab in combination with durvalumab, including Grade 3 events in 3.6% of patients.[14] Events resolved in 22 of the 23 patients and resulted in permanent discontinuation in 5 patients.[14] All patients received systemic corticosteroids, and 20 of the 23 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or

equivalent per day).[14] Three patients also received other immunosuppressants.[14] Intestinal perforation has been observed in studies of tremelimumab in combination with durvalumab.[14]

Immune-Mediated Hepatitis

Immune mediated hepatitis occurred in 7.5% of patients receiving tremelimumab in combination with durvalumab, including Grade 3 events in 4.1% of patients, Grade 4 events in 0.3% and fatal adverse reactions in 0.8%.[14] Events resolved in 12 of the 29 patients and resulted in permanent discontinuation in 9 patients.[14] Systemic corticosteroids were required in all patients, all 29 patients required high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).[14] Eight patients (8/29) required other immunosuppressants.[14]

Immune-Mediated Endocrinopathies

- Adrenal Insufficiency: Immune-mediated adrenal insufficiency occurred in 1.5% of patients receiving tremelimumab in combination with durvalumab, including Grade 3 events in 0.3% of patients.[14] Events resolved in 2 of the 6 patients.[14] Systemic corticosteroids were required in all patients with adrenal insufficiency, of these one patient required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).[14]
- Hypophysitis: Immune-mediated hypophysitis/hypopituitarism occurred in 1.0% of patients receiving tremelimumab in combination with durvalumab.[14] Events resolved in 2 of the 4 patients.[14] Systemic corticosteroids were required in three patients (3/4) with hypophysitis, of these one of the three patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).[14] Two patients also required endocrine therapy.[14]
- Thyroiditis: Immune-mediated thyroiditis occurred in 1.5% of patients receiving tremelimumab in combination with durvalumab.[14] Events resolved in two of the six patients. Systemic corticosteroids were required in two patients (2/6) with immune-mediated thyroiditis, of these one patient required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).[14] All patients required other therapy including hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker.[14]
- Hyperthyroidism: Immune-mediated hyperthyroidism occurred in 4.6% of patients receiving tremelimumab in combination with durvalumab, including Grade 3 adverse reactions seen in 0.3% of patients.[14] Events resolved in 15 of the 18 patients. Two patients (2/18) required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day)[14]. Seventeen patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker).[14]
- Hypothyroidism: Immune-mediated hypothyroidism occurred in 10.8% of patients receiving tremelimumab in combination with durvalumab.[14] Events resolved in five of the 42 patients. One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).[14] All patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker).[14]
- Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis: Two patients (0.5%) had events of hyperglycemia requiring insulin therapy that had not resolved at last follow-up.[14]

Immune-Mediated Nephritis with Renal Dysfunction

Immune-mediated nephritis occurred in 1% of patients receiving tremelimumab in combination with durvalumab, including Grade 3 adverse reactions in 0.5% of patients.[14] Events resolved in three of the four patients and resulted in permanent discontinuation in twopatients.[14] Systemic corticosteroids were required in all patients with immune-mediated nephritis, of these three patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).[14]

Immune-Mediated Dermatology Reactions

Immune-mediated rash or dermatitis occurred in 4.9% of patients receiving tremelimumab in combination with durvalumab, including Grade 4 adverse reactions in 0.3% of patients and Grade 3 adverse reactions in 1.5% of patients.[14] Events resolved in 13 of the 19 patients and resulted in permanent discontinuation in 2 patients.[14] Systemic corticosteroids were required in all patients with immune-mediated rash or dermatitis, of these 12 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants.[14]

Immune-Mediated Pancreatitis

Immune-mediated pancreatitis occurred in 2.3% of patients receiving tremelimumab in combination with durvalumab, including Grade 4 adverse reactions in 0.3% of patients and Grade 3 adverse reactions in 1.5% of patients.[14] Events resolved in six of the nine patients.[14] Systemic corticosteroids were required in all patients with immune-mediated pancreatitis, of these seven patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).[14]

Other Immune-Mediated Adverse Reactions

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in patients who received tremelimumab in combination with durvalumab or were reported with the use of other immune-checkpoint inhibitors.[14]

- Cardiac/vascular: Myocarditis, pericarditis, vasculitis.[14]
- Nervous system: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.[14]
- Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment.[14] Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.[14]
- Gastrointestinal: Gastritis, duodenitis.[14]
- Musculoskeletal and connective tissue disorders: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.[14]
- Endocrine: Hypoparathyroidism.[14]
- Other (hematologic/immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, and immune thrombocytopenia.[14]

Recommendations for management of immune-mediated adverse reactions in the prescribing information include:

- Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of tremelimumab in combination with durvalumab.
- Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions.
- Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose.
- Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue tremelimumab and durvalumab depending on severity
- In general, if combination of tremelimumab and durvalumab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month.
- Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

5.2. Infusion-Related Reactions

Infusion-related reactions occurred in 2.6% of patients receiving tremelimumab in combination with durvalumab.[14] Recommendations for management of infusion-related reactions are to interrupt, slow the rate of, or permanently discontinue tremelimumab and durvalumab based on the severity. For Grade 1 or 2 infusion-related reactions, prescribers may consider using pre-medications with subsequent doses.

5.3. Embryo-Fetal Toxicity

In animal studies, CTL4 blockade is associated with higher incidence of pregnancy loss.[14] There is a potential risk to a fetus if tremelimumab is used in pregnant women and females of reproductive potential[14]. The recommendation for the management of embryo-fetal toxicity is for females of reproductive potential to use effective contraception during treatment with tremelimumab and for at least three months after the last dose of tremelimumab.[14]

6. Expected Postmarket Use

If approved, tremelimumab will primarily be used in inpatient hospital or outpatient infusion settings and administered under the care and supervision of healthcare providers. We expect this product will be dispensed from pharmacy settings familiar with compounding high risk and hazardous products. The likely prescribers will be oncologists.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tremelimumab beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of tremelimumab based on the efficacy and safety information currently available.

Unresectable HCC is a liver malignant tumor that develops in the setting of chronic liver disease due to cirrhosis, hepatitis, and NAFLD, among other conditions, that develops in the setting of chronic liver disease.[1] The estimated number of new cases of liver and intrahepatic bile duct cancer in the United States in 2022 is 41,260. Although HCC may be curable with resection, liver transplantation, or ablation in the early stages of disease, most patients with unresectable HCC have a poor prognosis.[6]

Tremelimumab is a human IgG2 monoclonal antibody directed against CTLA-4 and provides a treatment option for patients with unresectable HCC. The efficacy of tremelimumab was supported by the HIMALAYA trial in patients who were not eligible for locoregional therapy. Specifically, HIMALAYA met its primary endpoint of overall survival superiority of tremelimumab 300 mg + durvalumab vs. sorafenib.[11]

The serious risks associated with tremelimumab include severe and fatal immune-mediated adverse reactions, immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatology reactions, immune-mediated pancreatitis, other immune-mediated adverse reactions, infusion-related reactions, and embryo-fetal toxicity. These risks will be addressed in the warnings and precautions section of the label. Serious adverse events occurred in 41% of patients in the tremelimumab plus durvalumab group compared to 30% in the control group of patients who received sorafenib and Grade 3-4 immune-mediated adverse events occurred in 13% of patients in the tremelimumab plus durvalumab group compared to 2% in the control group of patients who received sorafenib in the HIMALAYA trial. However, the incidence of adverse events leading to death was similar across all arms. In addition, discontinuing or delaying a dose due to an adverse event was higher in the control arm on sorafenib while the frequency of a serious AE was greater in the tremelimumab plus durvalumab arm. Overall, the results from the HIMALAYA trial suggest that the tremelimumab arm is not more toxic compared to the control arm.

The risks observed with tremelimumab are similar to the risks with other approved therapies for uHCC, such as nivolumab and ipilimumab. Specifically, nivolumab and ipilimumab, along with durvalumab and tremelimumab are associated with immune-mediated adverse reactions, infusion-related reactions, and embryo-fetal toxicity. Additionally, the likely prescribers are oncologists who are expected to have experience managing the adverse events reported with tremelimumab. Based on the efficacy and risks associated with tremelimumab for the treatment of adult patients with uHCC in combination with durvalumab, this reviewer's recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for tremelimumab to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. Table 1

Product Trade Name (Generic) Year of Approval	Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Risk Management Approaches/ Boxed Warning, Medication Guide
FDA Approved Treatments				
Nexavar (sorafenib) 12/01/2005	for the treatment of patients with uHCC.	400 mg orally twice daily without food (at least 1 hour before or 2 hours after a meal) until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity.	palmar–plantar erythrodysesthesia, asthenia, hypertension, and diarrhea	Warnings and Precautions
Lenvima (lenvatinib) 02/13/2015	for the first-line treatment of patients with uHCC	12 mg for patients greater than or equal to 60 kg or 8 mg for patients less than 60 kg orally once daily until disease progression or until unacceptable toxicity	Grade 3 or 4 adverse events include hypertension, decreased weight, and palmar–plantar erythrodysesthesia. Other side effects include proteinuria and asthenia.	Warnings and Precautions
Stivarga (regorafenib) 09/27/2012	for the treatment of patients with HCC who have been previously treated with sorafenib	160 mg (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle. Continue treatment until disease progression or unacceptable toxicity	palmar–plantar erythrodysesthesia	Warnings and Precautions

Cometriq (cabozantinib) 04/25/2016	for the treatment of patients with HCC who have been previously treated with sorafenib;	60 mg once daily until disease progression or unacceptable toxicity administered as a single agent	Grade 3 or 4 adverse events include arterial hypertension, palmar–plantar erythrodysesthesia, diarrhea, asthenia, and increased aspartate aminotransferase level	Medication Guide; Warnings and Precautions
Cyramaza (ramucirumab) 04/21/2014	as a single agent, is indicated for the treatment of patients with HCC who have an alpha fetoprotein (AFP) of ≥400 ng/mL and have been treated with sorafenib	8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be administered over 30 minutes. Continue until disease progression or unacceptable toxicity.	hyponatremia, increased aspartate aminotransferase, bleeding and arterial hypertension	Warnings and Precautions
Avastin (bevacizumab) approved for HCC 05/29/2020; originally approved 02/26/2004	in combination with atezolizumab, is indicated for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy	15 mg/kg intravenously after administration of 1,200 mg of atezolizumab intravenously on the same day, every 3 weeks until disease progression or unacceptable toxicity	hypertension, proteinuria, and low-grade diarrhea, bleeding	Warnings and Precautions
Tecentriq (atezolizumab) 05/18/2016	in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.	840 mg every 2 weeks or 1200 mg every 3 weeks or 1680 mg every 4 weeks Administer prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg every 3 weeks.	hypertension, some cases of esophageal varices hemorrhage, gastrointestinal disorders, and interstitial pneumonia	Medication Guide; Warnings and Precautions

Imfinzi (durvalumab) 05/01/2017	for the treatment of adult patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy; for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) in combination with etoposide and either carboplatin or cisplatin; for the treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC) in combination with gemcitabine and cisplatin.	10 mg/kg every 2 weeks or 1,500 mg every 3 or 4 weeks or 20 mg/kg every 3 or 4 weeks or 1,500 mg every 3 weeks	Immune-Mediated Adverse Reactions, Infusion-Related Reactions, Complications of Allogeneic HSCT, Embryo-Fetal Toxicity	Medication Guide; Warnings and Precautions
Opdivo (nivolumab) 12/22/2014	in combination with ipilimumab, is indicated for the treatment of adult patients with HCC who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response	1 mg/kg every 3 weeks with ipilimumab 3 mg/kg intravenously for 4 doses; or 240 mg every 2 weeks to 480 mg every 4 weeks after completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity	palmar–plantar erythrodysesthesia and aspartate amino acid transferase increase	Medication Guide; Warnings and Precautions
Yervoy (ipilimumab) 03/25/2011	In combination with nivolumab, is indicated for the treatment of patients with HCC who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall	3 mg/kg every 3 weeks with nivolumab 1 mg/kg for 4 doses. After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity.	Severe and fatal immune-mediated adverse reactions, Infusion-related reactions; Complications of Allogeneic Hematopoietic Stem	Medication Guide; Warnings and Precautions

	response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.		Cell Transplant; Embryo-Fetal Toxicity;	
Keytruda (pembrolizumab) 09/04/2014	for the treatment of patients with HCC who have been previously treated with sorafenib	200 mg every 3 weeks or 400 mg every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months.	metabolic lab changes	Medication Guide; Warnings and Precautions

10.2. References

1. Schwartz J, Carithers R. Epidemiology and risk factors for hepatocellular carcinoma. 2022. https://www.uptodate.com/contents/epidemiology-and-risk-factors-for-hepatocellular-carcinoma?search=hepatocellular%20carcinoma&topicRef=2489&source=see_link. Accessed Feb 01, 2022.
2. Falette Puisieux M, Pellat A, Assaf A, et al. Therapeutic Management of Advanced Hepatocellular Carcinoma: An Updated Review. *Cancers (Basel).* 2022;14(10).
3. Llovet JM. Tumors of the Liver and Biliary Tree. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson JL, eds. *Harrison's Principles of Internal Medicine 21e.* New York, NY: McGraw-Hill Education; 2022.
4. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72(1):7-33.
5. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. https://seer.cancer.gov/statfacts/html/livibd.html. Accessed July 27, 2022.
6. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *The New England journal of medicine.* 2020;382(20):1894-1905.
7. Schwartz J, Carithers R, Sirlin C. Clinical features and diagnosis of hepatocellular carcinoma. 2022. https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hepatocellular-carcinoma?search=hepatocellular%20carcinoma&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2. Accessed July 27, 2022.
8. Stuart K. Systemic treatment for advanced hepatocellular carcinoma. 2022. https://www.uptodate.com/contents/systemic-treatment-for-advanced-hepatocellular-carcinoma?search=hepatocellular%20carcinoma&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3. Accessed July 27, 2022.
9. Network NCC. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hepatobiliary Cancers. 2022.
10. AstraZeneca, AB. BLA 761289 Application Orientation Meeting In:2022.
11. FDA Midcycle Meeting. In: Division of Oncology 3 (DO3).
12. AstraZeneca, AB. Clinical Overview Durvalumab in Combination with Tremelimumab for the Treatment of Patients with Unresectable Hepatocellular Carcinoma. In:2022.

13. AstraZeneca, AB. Summary of Clinical Safety. In:2022.
14. Proposed prescribing information for tremelimumab as currently edited by FDA. In:2022.

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