CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761310Orig1s000

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	761310
PDUFA Goal Date	November 14, 2022
OSE RCM #	2022-639
Reviewer Name	Bob Pratt, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	November 10, 2022
Subject	Evaluation of the need for a REMS
Established Name	Mirvetuximab soravtansine
Trade Name	Elahere
Name of Applicant	ImmunoGen Inc.
Therapeutic Class	Antibody-drug conjugate: Folate receptor alpha-directed antibody and DM4 (maytansine-derivative) microtubule inhibitor conjugate
Formulation(s)	100 mg/20 mL (5 mg/mL) in single dose vials
Dosing Regimen	6 mg/kg adjusted ideal body weight (AIBW) administered once every 3 weeks by intravenous infusion

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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 (NME) Elahere (mirvetuximab soravtansine) is necessary to ensure the benefits outweigh the risks. ImmunoGen Inc. submitted a Biologics License Application (BLA) 761310 for Elahere for the proposed indication of the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. This indication will be approved under accelerated approval based on tumor response rate and durability of response. Regular approval for Elahere will be contingent upon verification and description of clinical benefit in a confirmatory trial. The serious risks associated with Elahere are ocular toxicity, pneumonitis, peripheral neuropathy, and embryo-fetal toxicity. The Applicant did not propose a REMS or a risk management program and asserted that the label, along with standard post-approval safety surveillance and reporting activities, will provide adequate assurance of the safe and effective use of Elahere.

DRM and the Division of Oncology 1 (DO1) agree that a REMS is not needed to ensure the benefits of Elahere outweigh its risks for the proposed indication. The efficacy of Elahere was demonstrated in 106 patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, in which patients treated with Elahere had an overall response rate of 32% with a median duration of response of 7 months in a disease that is not curable. The efficacy results represent a meaningful advantage compared to available therapies, and these results are reasonably likely to predict clinical benefit. The serious risks associated with Elahere include ocular toxicity, pneumonitis, peripheral neuropathy, and embryo-fetal toxicity, which will be communicated in the Warnings and Precautions section of the label. In addition, the serious risk of ocular toxicity will be described in a Boxed Warning. In the safety population, 61% of patients (N=283/464) experienced an ocular treatment-emergent adverse event, of which 49% of these patients had complete resolution of the event and 39% had partial improvement. Recommendations in the Boxed Warning will instruct healthcare providers to conduct an ophthalmic exam, including visual acuity and slit lamp exam prior to initiation of treatment, every other cycle for the first 8 cycles, and as clinically indicated, as well as use of lubricating and ophthalmic topical steroid eye drops during treatment. The ophthalmic monitoring schedule is more stringent than what was required in the clinical protocol of the pivotal study. Safety and tolerability of Elahere were acceptable for a patient population with a serious and life-threatening illness and limited treatment options. In addition, the likely prescribers of Elahere will be gynecologic oncologists who are expected to be familiar with the management of the associated serious risks. Overall, the review team concluded that the benefit-risk assessment for Elahere is favorable.

1 Introduction

This review evaluates whether a REMS for the new molecular entity (NME)[a] Elahere (mirvetuximab soravtansine) is needed to ensure its benefits outweigh the risks. ImmunoGen Inc. submitted a Biologics License Application (BLA) 761310 for Elahere for the proposed indication of the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. This indication will be approved under accelerated approval based on tumor response rate and durability of response. Regular approval for Elahere will be contingent upon verification and description of clinical benefit in a confirmatory trial. The serious risks associated with Elahere are ocular toxicity, pneumonitis, peripheral neuropathy, and embryo-fetal toxicity. The Applicant did not propose a REMS or a risk management program for this NME.

2 Background

2.1 PRODUCT INFORMATION

Elahere, an NME, is a chimeric folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate.[1] FRα is a receptor isoform that is highly expressed in >90% of ovarian cancer cells. FRα transports folate into the cells and allows them to grow where there is a lack of folate, providing a growth advantage to tumor cells.[2] The anticancer activity of Elahere results from the binding of the antibody-drug conjugate to FRα, followed by internalization and intracellular release of the maytansinoid, DM4. Maytansinoids are anti-mitotic agents that disrupt the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death.[1]

Elahere will be supplied as a single-dose vial containing 100 mg of mirvetuximab soravtansine in 20 mL (5 mg/mL) of sterile solution. The proposed dose is 6 mg/kg adjusted ideal body weight administered once every 3 weeks (21-day cycle) as an intravenous infusion until disease progression or unacceptable toxicity.[b] Elahere is not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761310 relevant to this review:

- 7/14/2014: Orphan product designation granted for the treatment of ovarian cancer.
- 6/15/2018: Fast Track designation granted.
- 1/20/2022: IND 111915 Pre-BLA Meeting. There was no discussion related to REMS.
- 3/28/2022: Submission of BLA 761310 for the treatment of adult patients with folate receptor alpha positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens

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

- 6/30/2022: Mid-cycle Communication meeting held with the Applicant. There was no discussion related to REMS.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Ovarian cancer is the second most common gynecologic malignancy and the most common cause of gynecologic cancer death in the United States. The average age at diagnosis of ovarian cancer in the U.S. is 63 years. The National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) estimates that there will be 19,880 new cases of ovarian cancer and 12,810 deaths from the disease in 2022.[3,c] Most ovarian cancers (95%) are epithelial in origin. The most common histologic subtype of epithelial ovarian carcinoma is serous carcinoma, which is regarded as closely related to fallopian tube and peritoneal serous carcinoma based upon similar histology and clinical behavior. These carcinomas are collectively referred to as epithelial ovarian carcinoma (EOC).[4] Most serous epithelial carcinomas are diagnosed at Stage III (51%) or IV (29%), reflecting the aggressive nature of the disease. The 5-year survival rates of patients with Stage III or IV EOC are 41% and 20%, respectively.[5,d]

3.2 Description of Current Treatment Options

Despite an initial response to platinum therapy, most women with EOC will relapse and require additional treatment. Platinum-resistant EOC is not curable. There are multiple drugs with activity in platinum-resistant EOC including paclitaxel, pegylated liposomal doxorubicin, bevacizumab, gemcitabine, topotecan, and other agents. Combination chemotherapy, endocrine therapy such as tamoxifen, as well as treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor are also options for certain patients. Treatment selection decisions among these agents depend upon the clinician's experience, the toxicity profile, the patient's treatment history, and other considerations specific to the individual patient.[6] At this time, there are no treatments approved specifically for patients with FRα-positive, platinum-resistant ovarian cancer.

4 Benefit Assessment

The efficacy of Elahere was evaluated in Study 0417 (NCT04296890), a multicenter, international, open-label, single-arm study. The study enrolled 106 patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. The median age of the patients was 62 years (range 35 to 85). Patients had received 1 to 3 prior treatments, with 50% of patients

[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.*

having received three prior therapies. All patients had received prior bevacizumab. Patients received Elahere 6 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. Tumor response was assessed every 6 weeks for the first 36 weeks and every 12 weeks thereafter. The primary endpoint was the confirmed overall response rate (ORR) assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The duration of response (DOR) was a secondary endpoint. The ORR was 32% (95% C.I., 23%, 42%). Five percent (5%) of patients had a complete response and 27% of patients had a partial response. The median DOR was 6.9 months (95% C.I., 5.6, 9.7).[7,e]

The confirmatory study is an ongoing randomized Phase 3 clinical trial comparing Elahere to investigator's choice chemotherapy in patients with FRα positive, platinum-resistant EOC who have received 1-3 prior lines of systemic therapy. Interim ORR/DOR data from the confirmatory study were supportive of the results from Study 0417.

The draft multidisciplinary review notes that available chemotherapies for the treatment of advanced ovarian cancer have ORRs of 12-13% and median DORs of 4-7.4 months, and these data come from clinical trials where patients were less heavily pre-treated than the patients enrolled to Study 0417. Considering the limited therapeutic options for these patients, along with the results from Study 0417 and interim data from the confirmatory trial, the review team considers the efficacy of Elahere to represent a meaningful advantage compared to available therapies.

5 Risk Assessment & Safe-Use Conditions

The pooled safety population includes data from 464 patients with EOC who received at least one dose of Elahere. A subset of this population comprises the 106 patients who received Elahere in Study 0417. The median duration of treatment in the safety population was 4.3 months (range: 0.7 to 30.4).

5.1 Serious and Severe Adverse Events[f]

Serious adverse events (SAEs) occurred in 147 (32%) patients in the safety population. The most common SAEs by System Organ Class (SOC) were gastrointestinal disorders (15%), respiratory, thoracic, and mediastinal disorders (9%), infections and infestations (6%), and metabolism and nutrition disorders (3%). The most common SAEs by Preferred Term (PT) were pneumonitis (5%), small intestinal obstruction (4%), intestinal obstruction (3%); and abdominal pain, constipation, vomiting, pleural effusion, and dehydration (each 2%).

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[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.*

[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.*

Severe adverse events were reported in a total of 231 (50%) patients. The most common severe adverse events by SOC were Gastrointestinal disorders (20%), Eye disorders (9%), Metabolism and nutrition disorders (8%), and Investigations (6%). The most common severe adverse events by PT were abdominal pain, small intestinal obstruction, and cataract (each 4%).

Of the 106 patients who received Elahere in Study 0417, there were 33 (31%) deaths. The clinical safety reviewer noted that the majority of deaths were due to disease progression. Three patients experienced adverse events that led to death, including intestinal obstruction (N=2) and interstitial pneumonitis with respiratory failure (N=1).[7]

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Ocular Adverse Reactions

Ocular adverse reactions occurred in 61% (N=283/464) of patients receiving Elahere. The most common ocular adverse reactions were visual impairment (49%), keratopathy (36%), dry eye (26%), cataract (15%), photophobia (13%), and eye pain (12%). The median time to onset for the first ocular adverse reaction was 1.2 months (range: 0.03 to 12.9). Nine percent (9%) of patients experienced Grade 3 (severe) ocular adverse reactions, including visual impairment, keratopathy/keratitis, dry eye, photophobia, and eye pain; one patient (0.2%) experienced Grade 4 keratopathy. Forty-nine percent (49%) of patients who experienced ocular adverse events had complete resolution and 39% had partial improvement, which was defined as a decrease in severity by one or more grades from the worst grade at last follow up. Ocular adverse reactions led to permanent discontinuation of Elahere in 0.6% of patients.

The clinical protocol for Study 0417 required an ophthalmic exam at baseline for all patients. Subsequent assessments of ocular symptoms only were performed by the treating physician or another qualified individual before the start of each cycle. If a patient reported > Grade 1 ocular symptoms, treatment was held until the patient was evaluated by an ophthalmologist for a complete examination, which was then performed every other cycle afterwards including 30 days beyond the end of treatment and/or until resolution.

Reviewer comments:

- *The clinical review team did not find the monitoring of ocular toxicity based on patient-reported symptoms to be adequate for the purpose of labeling because ocular toxicities may be asymptomatic until they are at a more advanced stage. Routine ophthalmologic examinations are recommended in the draft Prescribing Information, which includes a Boxed Warning that states visual acuity and slit lamp exams are to be conducted prior to initiation of Elahere, every other cycle for the first 8 cycles, and as clinically indicated. The Boxed Warning also indicates patients are to administer ophthalmic topical steroids and lubricating eye drops as instructed.*
- *The review team also determined that a post-marketing requirement was needed, mandating that the Applicant conduct or amend an ongoing clinical trial to incorporate a prospectively*

specified ocular monitoring approach. The monitoring will need to employ scheduled ocular assessments of patients throughout the trial, rather than utilizing symptom-based ocular examinations, only.

5.2.2 Pneumonitis

The Applicant reported that pneumonitis treatment-emergent adverse events occurred in 42 (9%) of 464 patients receiving Elahere. Severe adverse events of Grade ≥ 3 occurred in 4 (<1%) patients. Pneumonitis led to discontinuation of treatment in 2% (N=11) of patients.[8] One patient died due to respiratory failure in the setting of pneumonitis and lung metastases.[7]

The draft label includes a Warning and Precaution for pneumonitis that states patients are to be monitored for pulmonary signs and symptoms of pneumonitis, which may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams, and that other causes for such symptoms should be excluded. Prescribers are to withhold Elahere for patients who develop persistent or recurrent Grade 2 pneumonitis until symptoms resolve to ≤ Grade 1 and to consider dose reduction. Elahere is to be permanently discontinued in all patients with Grade 3 or 4 pneumonitis.

5.2.3 Peripheral Neuropathy

The clinical reviewer's analysis found that 167 patients (36%) had peripheral neuropathy and that most of the events were Grade 1 or 2 in severity, though most patients did not have resolution of their symptoms at last follow-up.[7] Nine patients (2%) experienced peripheral neuropathy events of ≥ Grade 3 in severity.

The draft labeling includes a Warning and Precaution to monitor patients for signs and symptoms of neuropathy. For patients experiencing new or worsening peripheral neuropathy, withhold treatment, reduce the dose, or permanently discontinue Elahere based on the severity.

5.2.4 Embryo-fetal Toxicity

No reproductive or developmental animal toxicity studies have been conducted with mirvetuximab soravtansine. Based on its mechanism of action, the cytotoxic component of Elahere disrupts microtubule function, is genotoxic, and can be toxic to actively dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

The draft labeling includes a Warning and Precaution to advise pregnant women of the potential risk to a fetus, and to advise females of reproductive potential to use effective contraception during treatment with Elahere and for 7 months after the last dose.

6 Expected Postmarket Use

Elahere will likely be prescribed by gynecologic oncologists who should be familiar with the management of the serious risks associated with the product. Elahere will likely be administered at outpatient infusion centers and practice sites that have experience in administering monoclonal antibody infusions to cancer patients.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or a risk management program with this application.

8 Discussion of Need for a REMS

The review team recommends accelerated approval of Elahere for the treatment of patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Platinum resistant EOC is not curable and patients with this condition have a poor prognosis. Elahere demonstrated a confirmed ORR of 32% (95% C.I., 23%, 42%) and median DOR of 6.9 months (95% C.I., 5.6, 9.7), which represent an improvement compared to available treatments for patients with FRα-positive, platinum-resistant ovarian cancer who have received 1-3 prior lines of systemic treatment, including one line containing bevacizumab. ORR and DOR results are reasonably likely to predict clinical benefit.[7]

The serious risks of Elahere include ocular toxicity, pneumonitis, peripheral neuropathy, and embryo-fetal toxicity. The risks of pneumonitis, peripheral neuropathy, and embryofetal toxicity will be communicated in the Warnings and Precautions section of the label. With respect to ocular toxicity, 61% (N=283/464) of patients in the safety population experienced an ocular adverse reaction. Forty-nine percent (49%) of these patients had complete resolution of the event, and 39% of patients experienced partial improvement, which was defined as a decrease in severity by one or more grades from the worst grade at last follow up. Grade 3 ocular adverse reactions occurred in 9% of the 464 patients, including visual impairment, corneal disorders, and other eye symptoms, and one patient (0.2%) experienced Grade 4 keratopathy. Ocular adverse reactions led to permanent discontinuation of Elahere in 3 of 464 (0.6%) patients. The Elahere draft label includes a Boxed Warning for the risk of ocular toxicity. Recommendations in the Boxed Warning include instructing healthcare providers to conduct an ophthalmic exam including visual acuity and slip lamp exam prior to initiation of treatment, every other cycle for the first 8 cycles, and as clinically indicated; to administer prophylactic ophthalmic topical steroids and lubricating eye

drops; to withhold Elahere for ocular toxicities until improvement, and to resume at the same or reduced dose, and to discontinue Elahere for Grade 4 ocular toxicities.

The likely prescribers will be gynecologic oncologists who should be familiar with managing the serious risks reported with Elahere, including the risk of ocular toxicities. For example, Tivdak (tisotumab vedotin), an antibody-drug conjugate approved in September 2021 for the treatment of recurrent or metastatic cervical cancer in adults with disease progression on or after chemotherapy, also carries a risk of ocular toxicity. Ocular adverse reactions occurred in 60% of patients with cervical cancer treated with Tivdak across clinical trials. In the patients who experienced ocular toxicity, 55% of these patients had complete resolution, and 30% had partial improvement, which was defined as a decrease in severity by one or more grades from the worst grade at last follow-up. Grade 3 ocular adverse reactions occurred in 4% of patients, including severe ulcerative keratitis in 3% of patients. Ocular adverse reactions led to discontinuation of Tivdak in 10 of 158 (6%) patients, and one patient experienced ulcerative keratitis with perforation requiring corneal transplantation.[9,10] Approval of Tivdak did not require a REMS to mitigate the risks of ocular toxicity, as it was determined the risks could be mitigated through the label, including a Boxed Warning. Similarly to the risk management approach for Tivdak, DRM and DO1 agree that the risk of ocular toxicity for Elahere can be mitigated with the recommendations outlined in the labeling. Further, we expect that the likely prescribers for both Tivdak and Elahere will be oncologists including gynecologic oncologists who are expected to be familiar with the management of adverse reactions associated with these products.

Given the limited therapeutic options and reasonably likely clinical benefit, the review team concluded the safety and tolerability of Elahere is acceptable for this patient population. The adverse reactions are manageable through monitoring, pretreatment, and supportive care and can be communicated through labeling. Therefore, at this time, DRM and DO1 have determined a REMS is not necessary to ensure the benefits outweigh the risks of Elahere.

Of note, the risk of ocular toxicity must be further evaluated in a Postmarketing Requirement of the Applicant to conduct a clinical trial, or amend existing clinical trials, of Elahere to incorporate prospectively specified, scheduled ophthalmologic assessments in all patients (symptomatic or asymptomatic) to further characterize the incidence and severity of Elahere-related ocular adverse events and evaluate additional risk mitigation strategies for ocular adverse events.

9 Conclusion & Recommendations

Based on the available data, the review team concluded the benefit-risk profile was favorable for this patient population. Therefore, a REMS is not necessary to ensure the benefits of Elahere outweigh the risks. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

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