CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761115Orig1s000

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	761115
PDUFA Goal Date	June 2, 2020
OSE RCM #	2018-939 & 958
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader (Acting)	Elizabeth Everhart, MSN, RN,ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	March 30, 2020
Subject	Evaluation of Need for a REMS
Established Name	Sacituzumab govitecan-hziy
Trade Name	Trodelvy
Name of Applicant	Immunomedics
Therapeutic Class	An antibody-drug conjugate (ADC)
Formulation(s)	Lyophilized powder in single use vial containing 180 mg per vial
Dosing Regimen	10 mg/kg as intravenious infusion on days 1 and 8 of 21-day cycles

This is an addendum to the review by the Division of Risk Management (DRM) evaluated whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Trodelvy (Sacituzumab govitecan-hziy) was necessary to ensure the benefits outweigh its risks.[a] Immunomedics submitted a Biologic Licensing Application (BLA) 761115 for Trodelvy with the proposed indication for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. The applicant did not submit a proposed REMS or risk management plan with this application.

Trodelvy (sacituzumab govitecan-hziy), is an antibody drug conjugate (ADC), composed of 3 components that are sacituzumab, SN-38 (the active metabolite of irinotecan), and a hydrolysable linkder. Trodelvy is proposed to be given as an intravenious (IV) infusion at 10 mg/kg on days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.

The original BLA was submitted on 05/18/2018. The agency issued a complete response letter on 01/17/2019 due to multiple chemistry, manufacture, and control (CMC) deficiencies. The sponsor resubmitted the BLA application on 12/02/2019. The sponsor addressed the CMC deficiencies that were identified in the complete response letter issued on 1/17/2019. There were no new safety issues that arose with this resubmission. The clinical review team recommends approval based on the corrective action on the CMC issues, as well the efficacy and safety results analyzed in the original BLA submission on 5/18/2018.

DRM and the Division of Oncology 1 (DO1) agree that a REMS is not needed to ensure the benefits of Trodelvy outweigh its risks. Metastatic TNBC is a disease with a poor prognosis with no currently approved specific agent to treat it. There is an unmet medical need to manage patients with mTNBC who have received two or more prior therapies. The most concerning risks of Trodelvy are severe neutropenia and severe diarrhea. SN-38, one component of Trodelvy, is a topoisomerase I inhibitor which is the active metabolite of irinotecan. Irinotecan carries a boxed warning for diarrhea and myelosuppression. If approved, the prescribing information of Trodelvy will have a boxed warning communicating the risks of severe neutropenia and severe diarrhea. Product labeling will also include recommendations in the Dosage and Administration and Warnings and Precautions sections regarding management of these risks.

[a] Chen M. Evaluation of the need for a REMS. January 10,2019. DARRTS ID# 4374149.

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Division of Risk Management (DRISK)
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	761115
PDUFA Goal Date	January 18, 2019
OSE RCM #	2018-939 & 958
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	January 10, 2019
Subject	Evaluation of Need for a REMS
Established Name	Sacitumzumab govitecan-hziy
Trade Name	Trodelvy
Name of Applicant	Immunomedics
Therapeutic Class	An antibody-drug conjugate (ADC)
Formulation(s)	Lyophilized powder in single use vial containing 180 mg per vial
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Trodelvy (Sacitumzumab govitecan-hziy) is necessary to ensure the benefits outweigh its risks. Immunomedics submitted a Biologic Licensing Application (BLA) 761115 for Trodelvy with the proposed indication for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Oncology Product 1 (DOP1) agree that a REMS is not needed to ensure the benefits of Trodelvy outweigh its risks. Metastatic TNBC is a disease with a poor prognosis and no currently approved specific agent to treat it; there is an unmet medical need to manage patients with mTNBC who have received two or more prior therapies. The most concerning risks of Trodelvy are potentially life-threatening diarrhea and neutropenia. SN-38, one component of Trodelvy, is a topoisomerase I inhibitor which is the active metabolite of irinotecan. Irinotecan carries a boxed warning for diarrhea and myelosuppression. If approved, the prescribing information of Trodelvy will have a boxed warning communicating the risks of diarrhea and neutropenia. Product labeling will also include recommendations in the Dosage and Administration and Warnings and Precautions sections regarding management of these risks.

1 Introduction

This review by DRISK evaluates whether a REMS for the new molecular entity (NME) Trodelvy (sacituzumab govitecan-hziy) is necessary to ensure the benefits outweigh its risks. Immunomedics submitted BLA 761115 for Trodelvy with the proposed indication for the treatment of adult patients with mTNBC who have received at least two prior therapies for metastatic disease.

2 Background

2.1 PRODUCT INFORMATION

Trodelvy (sacituzumab govitecan-hziy), an NME,[a] is an antibody drug conjugate (ADC), composed of the following 3 components:

1. The humanized mococlonal antibody, hRS7 IgG1k (also called sacituzumab), which binds to Trop-2 (trophoblast cell-surface antigen-2).
2. The drug SN-38, a topoisomerase I inhibitor that is the active metabolite of irinotecan.
3. A hydrolysable linker (called CL2A), which links sacituzumab to SN-38.

Trop-2 is expressed on normal tissues including the epithelial/lining of epidermis, breast, cervix, epithelial secretory tissue of the endocrine and exocrine glands, esophagus, heart, kidneys, larynx, lung,

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

liver, pancrease, prostate, salivary gland, skin, thymus, tonsils, trachea, trophoblast cells, urothelium and uterus.[1]

Trop-2 is overexpressed in many epithelial cancers including metastases. It is a potential oncogene and is often found in aggressive tumors. Trodelvy binds to Trop-2 expressing cancer cells and is internalized into the cancer cells. After hydrolysis of the linker, SN-38 is released to interact with topoisomerase I and prevents single strand breaks. This results in DNA damage that leads to apotosis and cell death. Trodelvy decreased tumor growth in mouse xenograft models of TNBC. Trodelvy is administered as intravenious (IV) infusion at 10 mg/kg on days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.[b] Trodelvy is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA761115 relevant to this review:

- 12/22/2014: Fast track designation granted for the treatment of patients with TNBC who have failed no more than two prior therapies for metastatic disease.
- 2/4/2016: Breakthrough therapy designation granted.
- 9/25/2018: 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 was no plans for a REMS. The sponsor was also informed that their response to the 483 claiming “attorney client privilege” was unacceptable. The sponsor agreed to amend their response within a few days. Additional chemistry, manufacture, and control (CMC) deficiencies were to be discussed at a CMC specific conference.
- 11/2/2018: A type A meeting was held with the sponsor to dicsuss ongoing clinical deficiencies, incomplete response to a 483, data integrity and falsification issues at the Morris Plains manufacturing facility and the cancellation of Oncology Drug Advisory Committee meeting (ODAC). During the meeting, the sponsor agreed to a third-party audit report is due to the FDA by 12/14/2018. The sponsor was informed that a new inspectin would need to occur and that depending on the volume of information submitted on 12/14/2018, a mjor amendment may need to be issued.
- 11/26/2018: A late cycle meeting was held with the sponsor. The internal labeling discussions and CMC and facilities reviews are ongoing. FDA planned to request additional request for information related to hSR7 antibody intermediate, drug substance, drug product process control strategies, durg product method validation, lot release, and stability specifications.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

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

TNBC has been applied to cancers that are low in expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC is heterogenous and has different molecular subtypes that have differing natural histories and possibly different responses to therapy. Patients with TNBC have a poorer prognosis compared with other breast cancer subtypes. TNBC behaves more agrressively with rapid growth compared to other types of breast cancer.[2] Metastatic triple negative breast cancer is a disease with a particularly poor prognosis. The median age at diagnosis is approximately 50 years and median survival is about 13.3 months.[3, c]

TNBC accounts for about 15%-20% of breast cancers diagnosed worldwide. In 2018, it is estimated that there are over 150,000 patients in the United States (US) with metastatic breast cancer. This amounts to about 25,000 cases each year in US.[4,d] TNBC is more commonly diagnosed in women younger than 40 years compared with hormone-positive breast cancer. TNBC appears to be more common among black women compared with white women.

3.2 Description of Current Treatment Options

There is no agent approved specifically for mTNBC. The goals of treating mTNBC are palliative in nature with the aim of prolonging survival and reducing cancer-related symptoms. Treatment of mTNBC is typically with cytotoxic chemotherapy.[5] Multiple chemotherapies have been used to treat mTNBC including; taxanes, platinums, anthracyclines, gemcitabine, capecitabine, vinorelbine, ixabepiline, and eribulin. For the approximately 20% of patients with mTNBC who have a germline BRCA 1 or 2 mutation, the poly ADP-ribose polymerase (PARP) inhibitors, olaparib[6] and talozaparib[7], have been approved for pateints who have been previously treated with chemotherapy.

There is an unmet medical need to manage patients with mTNBC who have received two or more prior therapies.

4 Benefit Assessment[8]

The efficacy of Trodelvy was evaluated in study IMMU-132-01 (NCT 01631552). IMMU-132-01 was a multicenter, sigle-arm trial that enrolled 108 patients with mTNBC who had received at least 2 prior therapies. The median age of patients was 55 years (range: 31-80 years) with 87% of patients being younger than 65 years. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (29%) or 1 (71%). Seventy-six percent had visceral disease, 42% had hepatic metastases, 56% had lung/pleura metastates, and 2% had brain metastases. The median number of prior systemic therapies received in the metastatic setting was 3 (range: 2-10). Ninty-eight percent of patients had

[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.*

received prior taxanes and 86% had received prior anthracyclines either in the neoadjuvant or metastatic setting.

Patients received Trodelvy 10 mg/kg IV on days 1 and 8 of a 21-day cycle. Patients were treated with Trodelvy until disease progression or intolerance to the therapy. Table 1 summarizes the efficacy results. Efficacy results based blinded, independent, central review audit were consistent with investigator assessment.

Table 1 Efficacy results for patients with mTNBC in IMMU-132-01

	Investigator Assessment	Blinded Independent Central Review (BICR)
Overall Response Rate (ORR) (95% confidence interval)	33.3% (24.6, 43.1)	34.3% (25.4, 44.0)
Complete response	2.8%	6.5%
Partial response	30.6%	27.8%
Response duration		
Number of responders	36	37
Median, month (95% CI)	7.7 (4.9, 10.8)	9.1 (4.6, 11.3)
Range, months	1.9+, 30.4+	3, 28.6+
% with duration≥ 6 months	55.6%	51.4%
% with duration ≥ 12 months	16.7%	16.2%

The clinical reviewer concluded that Trodelvy is considered an improvement over available therapy given the improved ORR. Eribulin was approved in 2010 for treatment of patients with metastatic breast cancer with an ORR 11% and duration of response 4.2 months. Ixabepilone was approved in 2007 for treatment of patient with metastatic or locally advanced breast cancer with an ORR by central assessment of 12.4%; investigator assessment 18.3%; and duration of response 6 month by central assessment.[9]

5 Risk Assessment & Safe-Use Conditions

The safety of Trodelvy was evaluated in a total of 408 patients. The safety data included study IMMU-132-01 and data from studies in other malignancies who had received prior systemic therapeutic

regimen. All patients received Trodelvy as an IV infusion once weekly on days 1 and 8 of 21-day treatment cycles at doses up to 10 mg/kg until disease progression or unacceptable toxicity.

Deaths:

In study IMMU-132-01, there were 20 deaths within 30 days of discontinuing study therapy at the time of the 90-day safety update (December 1, 2017) in the overall safety population. The medical reviewer concluded that there was one death in the safety population due to neutropenic typhilitis and agreed that the other deaths were due to disease progression. It is not likely that Trodelvy contributed to the deaths.[10]

With one death due to neutropenic typhilitis, along with the incidence of neutropenia and diarrhea, the medical reviewer concluded that a boxed warning for diarrhea and neutropenia is warranted.

5.1 THE SERIOUS RISKS ASSOCIATED WITH TRODELVY TREATMENT ARE LISTED IN THE SECTIONS BELOW. NEUTROPENIA

In clinical trials, Trodelvy caused severe or life-threatening neutropenia. SN-38, one component of Trodelvy, is a topoisomerase I inhibitor that is the active metabolite of irinotecan. Irinotecan carries a boxed warning for myelosuppression. Similar to irinotecan, if Trodelvy is approved, the risk of neutropenia will be communicated in a boxed warning in the product label.

The incidence of grade 1-4 neutropenia was 54% in all patients treated with Trodelvy, with 13% patients having grade 4 neutropenia. Febrile neutropenia occurred in 6% of patients treated with Trodelvy, including 9% patients with mTNBC after at least 2 prior therapies.

If approved, healthcare providers (HCPs) will be advised to monitor blood cell counts during therapy regularly and consider the growth factor, filgrastim, for secondary prophylaxis. Dose modification for neutropenia will also communicated in the Dosage and Administration section of the label.

5.2 DIARRHEA

In clinical trials, Trodelvy caused severe or life-threatening diarrhea because of the SN-38,component. Similar to irinotecan, which carries a boxed warning for diarrhea, if approved, diarrhea will be communicated in a boxed warning.

Diarrhea occurred in 62% of patients with mTNBC and 63% of all patients treated with Trodelvy. Grade 3-4 diarrhea occurred in 8% of mTNBC patients and 9% of all patients treated with Trodelvy. Three out of 408 patients (<1%) discontinued treatment because of diarrhea. Neutropenic colitis was reported in 4% of patients in the mTNBC patients and 1% of all patients treated with Trodelvy.

If approved, HCPs will be advised to hold Trodelvy for grade 3-4 diarrhea and resume when diarrhea resolved to ≤ grade 1. Additionally, they will be advised to evaluate for infectious causes and promptly start loperamide at the onset of diarrhea. The use of an appropriate premedication (e.g., atropine) will be advised for patients with an excessive cholinergic response for future therapies. Dosage modification recommendations for diarrhea will also be communicated in the Dosage and Administration section of product labeling.

5.3 HYPERSENSITIVITY

Hypersensitivity reactions, including anaphylaxis, occurred in 35% of patients treated with Trodelvy, with grade 3-4 occurred in 1% of patients. Hypersensitivity reactions leading to permanent discontinuation of Trodelvy was seen in 1% of patients in clinical trials.

If approved, the Warnings and Precautions section of labeling will advise HCPs to premedicate patients prior to infusion. Labeling will also advise HCPs to observe patients closely during each infusion and for at least 30 mintues after completion of the infusion.

5.4 NAUSEA AND VOMITING

Trodelvy is moderately emetogenic. Nausea occurred in 67% of patients with mTNBC and 67% of all patients treated with Trodelvy. Grade 3 nausea reported in 6% and 5% of these treated patients, respectively. Forty-nine percent of patients with mTNBC and 44% of all patients treated with Trodelvy reported to have vomiting; grade 3-4 vomiting occurred in 6% and 4% of these treated patients, respectively.

If approved, the Warnings and Precautions section of the product label will advise HCPs to give premedications with a 2 or 3 drug combination. Dosage modification for nausea/vomiting will also be communicated in Dosage and Administration (section 2.3).

5.5 USE IN PATIENTS WITH REDUCED UGT1A1 ACTIVITY

Based on genotyping done in clinical trials of Trodelvy, patients who were homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele were at increased risk for neutropenia, and may be at increased risk for other adverse events. In the clinical trials, the incidence of grade 4 neutropenia was 27% in patients homozygous for the UGT1A1*28 allele, 6% in patients heterozygous for the UGT1A1*28 allele, and 5% in patients homozygous for the wild-type allele.

If approved, the Warnings and Precautions section of the product labeling will advise HCPs to monitor patients with reduced UGT1A1 activity for severe neutropenia. Retrospective UGT1A1 genotype results were available in 82% of patients who received Trodelvy.

5.6 EMBRYO-FETAL TOXICITY

SN-38, a component of Trodelvy, is genotoxic and targets rapidly dividing cells. Therefore, Trodelvy can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. If approved, HCPs will be advised to communicate the potential risk to a fetus in the Warnings and Precautions section of the product label.

6 Expected Postmarket Use

Trodelvy is likely to be prescribed and administered as an out-patient treatement or in the hospital settings under the supervision of oncologists, who should have training and experience in managing the toxicities associated with Trodelvy.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The clinical reviewerer recommends approval of Trodelvy on the basis of the efficacy and safety information currently available.[11]

The most concerning risks of Trodelvy are severe and/or life-threatening neutropenia and diarrhea. To mitigate these risks, if approved, the prescribing information of Trodelvy will likely have a boxed warning to communicate risks of neutropenia and diarrhea. Additionally, the Dosage and Administration and Warnings and Precautions sections of the label will convey these risks and advice for their mitigation.

If approved, the other risks of Trodelvy that will be communicated in the labeling in the Warnings and Precautions section of the label are hypersentivity, nausea and vomiting, use in patients with reduced UGT1A1 activity, and embryo-fetal toxicity.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable. If approved , a REMS is not necessary for Trodelvy to ensure the benefits outweigh the risks. The risks associated with Trodelvy will be communicated through product label. At the time of this review, evaluation of CMC, facilities, and labeling were ongoing.

Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Howe, L Medical Reviewer, executive summary in multidisciplinary review, in DARRTS December 31, 2018

[2] Anders, C & Carey, L Epidemiology, risk factors and the clinical approach to Triple negative breast cancer, UpToDate accessed May 10, 2018

[3] Howe, L Medical Reviewer, multidisciplinary review, in DARRTS December 31, 2018

[4] Howe, L Medical Reviewer, multidisciplinary review, in DARRTS December 31, 2018

[5] Burstein, H Adjuvant chemotherapy for HER-2 negative breast cancer, UpToDate accessed May 10, 2018

[6] Olaparib (Lynparza) prescribing information, 12/2018

[7] Talazoparib (Talzenna) prescribing information, 10/2018

[8] Proposed Trodelvy Labeling, December 27, 2018

[9] Howe, L Medical Reviewer, 8.2.4 safety results in multidisciplinary review, in DARRTS December 31, 2018

[10] Howe, L Medical Reviewer, multidisciplinary review, in DARRTS December 31, 2018

[11] Howe, L Medical Reviewer, multidisciplinary review, in DARRTS December 31, 2018

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/s/

MEI-YEAN T CHEN
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ELIZABETH E EVERHART
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I concur.

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