

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207981Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: August 24, 2015

Reviewer(s): Mona Patel, Pharm.D.  
Division of Risk Management

Acting Team Leader: Naomi Redd, Pharm.D.  
Division of Risk Management

Acting Division Director: Cynthia LaCivita, Pharm.D.  
Division of Risk Management

Subject: Review to determine if a REMS is necessary

Established Drug Name(s): Trifluridine/tipiracil hydrochloride (TAS-102)

Proprietary Drug Name: Lonsurf

Therapeutic Class: Anti-tumor nucleoside

Dosing Regimen: 35 mg/m<sup>2</sup> orally twice daily for 5 days, and 2 days of rest,  
for 2 weeks followed by 14 days of rest, every 4 weeks

Proposed Indication (s): Unresectable advanced or recurrent colorectal cancer

Division: Division of Oncology Products – 2 (DOP-2)

Application Type/Number: NDA 207981

Applicant/sponsor: Taiho Oncology, Inc.

OSE RCM #: 2014-2487  
2014-2490

## CONTENTS

1	INTRODUCTION .....	1
2	MATERIALS REVIEWED.....	1
	2.1 DATA AND INFORMATION SOURCES .....	1
3	REGULATORY HISTORY .....	1
4	ASSESSMENT OF NEED FOR A REMS .....	1
	4.1 RATIONALE FOR DRUG DEVELOPMENT.....	1,2
	4.2 CLINICAL DEVELOPMENT PROGRAM .....	3
	4.2.1 Efficacy.....	3,4
	4.2.2 Safety .....	4,5,6
	4.3 ASSESSMENT OF RISK.....	6,7,8
5	PROPOSED POST MARKETING REQUIREMENTS/COMMITMENTS .....	8
6	CONCLUSION.....	8

## 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME) Lonsurf [(trifluridine (FTD)/tipiracil (TPI) or TAS-102]. The applicant, Taiho Oncology Inc., submitted a New Drug Application (NDA) 207981 with the proposed indication for treatment of patients with metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.

DRISK requested on January 16, 2015 for Taiho Oncology Inc., to submit a Risk Management Plan (RMP). Taiho Oncology Inc., informed FDA on January 26, 2015 that it would submit a RMP (b) (4) by the end of February 2015. A RMP was received on February 27, 2015. The RMP identified risks of bone marrow suppression, gastrointestinal symptoms (nausea, vomiting and diarrhea), and infection. A potential risk associated with TAS-102 identified in the RMP was the use of the drug in moderate renal impairment. Taiho Oncology's submission included a pharmacovigilance plan, which proposed to manage these events through routine pharmacovigilance and product labeling. Taiho Oncology did not submit a REMS.

## 2 MATERIALS REVIEWED

### 2.1 DATA AND INFORMATION SOURCES

- Taiho Oncology Clinical Modules (sections 2.5, 2.7.3 and 2.7.4)
- Taiho Oncology Nonclinical Module (section 4.2.3)
- Applicant Orientation Presentation, February 2, 2015
- Risk Management Plan, February 27, 2015
- Midcycle Slides, May 13, 2015
- Draft Clinical Review by Dr. Leigh Marcus (v. 7.30.15)
- Lonsurf [trifluridine/tipiracil hydrochloride (TAS-102)] draft label, August 6, 2015

## 3 REGULATORY HISTORY

The review timeline for this application is Standard. Listed below are the pertinent regulatory history milestones for this NDA:

- November 17, 2008 – IND 57674 submitted for TAS-102
- July 31, 2014 – Type B Pre-NDA Meeting
- September 12, 2014 – Fast track designation
- October 16, 2014 – Part 1 of Rolling NDA Submission
- November 7, 2014 – Part 2 of Rolling NDA Submission
- December 19, 2014 – Part 3 of Rolling NDA Submission
- February 2, 2015 – Applicant Orientation Presentation
- May 13, 2015 – Midcycle meeting
- May 15, 2015 – Midcycle teleconference with the sponsor
- **December 18, 2015 – PDUFA (Action) date**

## 4 ASSESSMENT OF NEED FOR A REMS

### 4.1 RATIONALE FOR DRUG DEVELOPMENT<sup>1</sup>

Colorectal cancer is the third most frequently diagnosed cancer worldwide, with more than 1.4 million new cases diagnosed in 2012 and representing 9.7% of all cancers.<sup>2</sup> In 2013, it was estimated that 102,480 new cases of colon cancer and 40,340 cases of rectal cancer would occur in the United States, and that an estimated 50,830 people would die of colon and rectal cancer combined during that year. According to the American Cancer Society, African Americans have the highest colorectal cancer *incidence* and *mortality* rates in the United States while Jews of Eastern European descent have one of the highest colorectal cancer *risks* of any ethnic group in the world.<sup>3</sup> Statistics show that not only are more than 90 percent of tumors of the large intestine adenocarcinomas, but that 90% people with colorectal cancer are diagnosed after age 50 with the average age at diagnosis of 72 years.<sup>4,5</sup> According to the National Cancer Institute's SEER database, between 2005-2011, the 5-year survival rate for patients diagnosed with colorectal cancer was close to 65%.<sup>6</sup>

The current treatment options for metastatic colorectal cancer (mCRC) are mainly palliative rather than curative. For resectable metastasis, surgery is employed while chemotherapy is used for unresectable disease. First line treatment for mCRC is combination chemotherapy with the addition of a monoclonal antibody. The primary chemotherapy for mCRC is a combined regimen containing fluoropyrimidine, such as 5-FU or capecitabine, along with other agents such as leucovorin, irinotecan and oxaliplatin. Monoclonal antibodies or proteins such as bevacizumab or ziv-aflibercept against vascular endothelial growth factor (VEGF) and monoclonal antibodies against endothelial growth factor receptor (EGFR; cetuximab and panitumumab) may be employed. Second-line and third line treatment options will be contingent on the first-line regimen used. For third-line treatment, cetuximab or panitumumab in combination with irinotecan are recommended in patients with wild type RAS tumors if either were not used in previous therapies. Despite the available chemotherapy options, limited treatment options exist for patients who have exhausted all initial therapies.

**TAS-102** – TAS-102 is an oral antineoplastic thymidine-based nucleoside analog (trifluridine) combined with a thymidine phosphorylase inhibitor (tipiracil). The first approval of TAS-102 in the world was in Japan on March 24, 2014 for the treatment of patients with unresectable advanced or recurrent colorectal cancer (only if refractory to standard therapies).

According to the applicant's submission, trifluridine is incorporated into deoxyribonucleic acid (DNA) in tumor cells following phosphorylation while tipiracil inhibits degradation of

<sup>1</sup> Clinical Overview (section 2.5), TAS-102

<sup>2</sup> Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403.

<sup>3</sup> <http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-risk-factors>. Accessed 7/31/15

<sup>4</sup> DiPiro, Joseph T. *Pharmacotherapy: A Pathophysiologic Approach*. New York: McGraw-Hill Medical, 2008.

<sup>5</sup> <http://www.cancer.gov/colorectalcancerrisk/def-age-range.aspx>. Accessed 8/4/15

<sup>6</sup> <http://seer.cancer.gov/statfacts/html/colorect.html>. Accessed 8/12/15

trifluridine by inhibiting thymidine phosphorylase. The proposed indication for TAS-102 is for the treatment of patients with metastatic colorectal cancer who have been previously treated with, (b)(4) fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.

The recommended dose of TAS-102 for adults is at 35 mg/m<sup>2</sup>/dose administered orally twice daily after meals on days 1 - 5 and 8 - 12 of each 28 day cycle, repeated every 4 weeks (b)(4) until disease progression or unacceptable toxicity.

## 4.2 CLINICAL DEVELOPMENT PROGRAM

Efficacy data of TAS-102 for the treatment of patients with refractory metastatic colorectal cancer was derived from the pivotal Phase 3 study, Study TPU-TAS-102-301 and the Phase 2 supportive study, Study J003-10040030

### 4.2.1 Efficacy

At the time of this writing, the FDA clinical reviewer, Dr. Leigh Marcus, was still completing analysis of the safety and efficacy of the studies outlined below. The summary below provides a high level overview of the studies submitted to support this application.

**Key Efficacy Findings:**<sup>7,8,9</sup> Please refer to the clinical review by Dr. Leigh Marcus for the full review on efficacy and safety. The following is a summary of the key findings from labeling discussions for TAS-102 as of **August 6, 2015**.

**Study TPU-TAS-102-301** (RECOURSE) was a multi-national, double-blind, two-arm, parallel group, randomized, Phase 3 study evaluating the efficacy and safety of TAS-102 plus best supportive care (BSC) versus placebo plus BSC in Western and Japanese patients with refractory metastatic colorectal cancer who had failed previous treatment with standard chemotherapies. The primary objective of this study was evaluation of overall survival (OS). Median OS was 7.1 months for the TAS-102 arm and 5.3 months for the placebo group. Secondary objectives were progression-free survival (PFS), safety/tolerability, time to treatment failure (TTF), overall response rate (ORR), disease control rate (DCR), and duration of response (DR). The median PFS was 2 months for patients treated with TAS-102 compared 1.7 months for patients on the placebo arm.

The baseline demographics and disease characteristics of the intention-to-treat (ITT) population were balanced between both arms. The median age for patients in this study was 63 years. Close to 61% of patients were men, 57% were Caucasian, 35% were Asian, and all patients had baseline Eastern Cooperative Oncology Group (ECOG) of 0 or 1. Sixty-two percent of mCRC patients had the colon as the primary site of disease. All patients received prior treatment with a fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received prior treatment with bevacizumab, and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab.

---

<sup>7</sup> Draft clinical review by Dr. Leigh Marcus (v. 7/30/15)

<sup>8</sup> Lonsurf (TAS-102) draft label, August 6, 2015

<sup>9</sup> Lonsurf Summary of Clinical Efficacy Section 2.7.3

A total of 800 patients were randomized to receive either TAS-102 at 35 mg/m<sup>2</sup>/dose administered orally twice daily after meals on days 1 - 5 and 8 - 12 of each 28 day cycle, repeated every 4 weeks (b) (4) until disease progression or unacceptable toxicity.

**Study J003-10040030** was a randomized, double-blind, placebo-controlled, multi-centre, Phase 2 study in Japan evaluating the efficacy and safety of TAS-102 versus placebo in patients with mCRC who had failed two or more chemotherapeutic regimens including fluoropyrimidine, irinotecan, and oxaliplatin. The primary objective of this study was OS. The median OS was 9 months in the TAS-102 arm and 6.6 months in the placebo arm. The result was consistent with those obtained in the RECURSE study. Secondary objectives were PFS, ORR, duration of response, DCR, TTF, safety and tolerability of TAS-102, and the relationship between the effect of TAS-102 and KRAS gene status. The median PFS was 2 months in the TAS-102 arm and 1 month in the placebo arm. The ORR was 0.9% in the TAS-102 arm versus 0% in the placebo arm and the DCR was 43.8% in the treatment arm vs. 10.5% in the placebo arm.

Demographic and baseline characteristics were similar in both trials, with the exception of only Asian subjects enrolled in the Japanese trial.

A total of 172 patients were randomized on a 1:1 basis to receive either TAS-102 at the same dosage regimen as those patients in RECURSE or placebo and like in the RECURSE study, patients in both the treatment and control arm were to receive study therapy until disease progression or unacceptable toxicity.

#### **4.2.2 Safety<sup>7, 8, 10</sup>**

Safety results obtained for all patients receiving TAS-102 in the integrated studies and for all patients treated in the placebo-controlled studies were consistent with results obtained in Study TPU-TAS-102-301. The safety of TAS-102 is based on analysis of data from the 798 patients in Study TPU-TAS-102-301 who received at least one dose of study medication. Of those 798 patients, 533 patients received TAS-102 and 265 patients received placebo. In Study TPU-TAS-102-301, 4.1% of patients had entry criteria violations and 1.8% of patients received other anticancer therapy (surgery or radiotherapy) during study drug administration constituting a protocol violation.<sup>11</sup>

In Study TPU-TAS-102-301, the mean duration of treatment for patients treated with TAS-102 was 12.7 weeks for patients in the TAS-102 group and 6.8 weeks for patients in the placebo group.<sup>9</sup> In the TAS-102 group, 87.4% of patients initiated at least 2 cycles of treatment, 43.3% initiated Cycle 3, and 11.7% initiated Cycle 4.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) (Version 16.0) and were categorized by system organ class (SOC) and preferred term (PT), and the safety events were classified by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria (Version 4.03).

---

<sup>10</sup> Lonsurf (TAS-102) Summary of Safety

<sup>11</sup> February 2, 2015 Lonsurf (TAS-102) Applicant Orientation Presentation

The most frequently reported Grade 3-4 treatment-related adverse events (TEAEs) in patients treated with TAS-102 were neutropenia (23.8%), decreased neutrophil count (18.9%), anemia (15.6%), decreased WBC count (10.9%), fatigue (3.9%), increased blood bilirubin (3.8%), febrile neutropenia (3.8%), decreased appetite (3.6%), asthenia (3.4%), and increased blood alkaline phosphatase (3.2%) and gamma-glutamyltransferase (3%).

Dose reductions due to an adverse reaction occurred in 70 patients in the TAS-102 arm versus 2 patients in the placebo arm. The majority of dose reductions in the TAS-102 arm were due to myelosuppression, specifically neutropenia (8.9% vs. 0.4% in placebo arm). Fatigue (1.5%), nausea (0.9%), vomiting (0.8%), and diarrhea (1.3%) were also reasons cited for dose reduction in the TAS-102 arm. In the placebo group, the most frequent AEs leading to a dose reduction were decreased appetite (1.9%), abdominal pain (1.2%), and pyrexia (0.9%).

The adverse events seen were generally managed by dose interruptions, cycle delays, dose reduction, and/or standard medical therapy. According to the study protocol for RECURSE, a complete blood count was to be obtained prior to initiation of each 28-day cycle of TAS-102. TAS-102 was to be withheld if the absolute neutrophil count (ANC) was less than 500/mm<sup>3</sup> or febrile neutropenia was evident, platelets were less than 50,000/mm<sup>3</sup>, or Grade 3 or 4 non-hematological adverse events were evident. After patient recovery, TAS-102 could be resumed after reducing the dose by 5 mg/m<sup>2</sup>/dose from the previous dose level if the following occurred:

- Febrile neutropenia,
  - Uncomplicated Grade 4 neutropenia (which resolved to greater than 1500/mm<sup>3</sup>) or thrombocytopenia (which has resolved to greater than 75,000/mm<sup>3</sup>) that resulted in more than 1 week delay in start of next cycle,
- or,
- Non-hematologic Grade 3 or Grade 4 adverse event except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication.

A maximum of 3 dose reductions would be permitted to a minimum dose of 20 mg/m<sup>2</sup> twice daily and once TAS-102 was reduced, the dose was not to be increased for subsequent cycles. In addition, patients who required more than a 28-day delay in the scheduled start date of the next cycle would have study medication discontinued.

Permanent discontinuation due to an adverse reaction occurred in 55 (10.3%) patients on TAS-102 and 36 (13.6%) patients on placebo. Fatigue was indicated as the primary reason for discontinuation in the TAS-102 arm.

The adverse event of concern was severe myelosuppression. This adverse event will be managed in labeling under a separate subsection of Warnings and Precautions. Fertility and embryo-fetal toxicity was a concern based on nonclinical safety findings and will also be addressed in the Warnings and Precautions section of the labeling.

**Deaths:** Thirty-five patients in the TAS-102 group and 33 patients in the placebo group died within 30 days of the last dose of study medication. Of these patients, 29 of the 35 patients in the TAS-102 arm and 31 of the 33 patients in the placebo arm died due to disease progression. For the patients in the TAS-102 arm and the placebo group who died due to reasons other than disease progression, patients died of a related AE (i.e., hepatic and renal failure, dyspnea, and pulmonary embolism) considered not related to study treatment.

### **Clinical Assessment Based on Pharmacology/Toxicology Findings**

**Embryo-fetal toxicity<sup>8</sup>:** Based on the drug's mechanism of action and findings from animal reproduction studies, TAS-102 can cause fetal harm when administered to a pregnant woman. TAS-102 caused embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose exposure levels lower than the clinical exposure at the recommended human dose. Inhibition of fetal growth was observed after administration at doses of 50 mg/kg or higher and a teratogenic effect was observed at 150 mg/kg. Females of reproductive potential are advised to use effective contraception during treatment with TAS-102 and for 2 weeks following the final dose.

The applicant proposed to communicate all safety events through labeling and therefore did not submit a REMS.

### **4.3 ASSESSMENT OF RISK**

Despite the available chemotherapy options, limited treatment options exist for patients who have exhausted all initial therapies (i.e., fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy and, for patients with KRAS wild-type tumors, an anti-EGFR antibody). The indication for TAS-102 will include patients for the treatment of metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.

The anticipated duration of use for TAS-102 is 35 mg/m<sup>2</sup>/dose administered orally twice daily after meals on days 1 - 5 and 8 - 12 of each 28 day cycle, repeated every 4 weeks (b) (4) until disease progression or unacceptable toxicity.

The current first line treatment for mCRC is combination chemotherapy with the addition of a monoclonal antibody. The primary chemotherapy for mCRC is a combined regimen containing fluoropyrimidine, such as 5-FU or capecitabine, along with other agents such as leucovorin (LV), irinotecan and oxaliplatin. Monoclonal antibodies or proteins such as bevacizumab or ziv-aflibercept against vascular endothelial growth factor (VEGF) and monoclonal antibodies against endothelial growth factor receptor (EGFR; cetuximab and panitumumab) may be employed.

For patients who have exhausted all initial therapies (i.e., fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy and, for patients with KRAS wild-type tumors, an anti-EGFR antibody), an alternate treatment option to TAS-102 that has demonstrated survival benefit is regorafenib. It has been shown that 50% of patients receiving regorafenib will progress by the end of 2 cycles of therapy.<sup>1</sup>

The most serious adverse event with regorafenib is hepatotoxicity which required a Boxed Warning. Regorafenib also caused an increased incidence of hemorrhage, skin and subcutaneous tissues, hypertension, cardiac ischemia and infarction, reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation, and wound healing complications. Compared to TAS-102, both agents had embryo-fetal toxicity as a Warning & Precaution. Fatigue, nausea, decreased appetite, diarrhea, abdominal pain, and fever were also common between both agents and listed as adverse events.

In comparison with first and second line treatments, TAS-102 had embryo-fetal toxicity in common with irinotecan and bevacizumab. Myelosuppression was common between TAS-102 and irinotecan; however, the myelosuppression seen with TAS-102 did not rise to a level of a Boxed Warning as it did with irinotecan. A Boxed Warning was seen with a few agents. Capecitabine had a Boxed Warning for altered coagulation issues, panitumumab for dermatologic toxicities, and bevacizumab had a Boxed Warning for GI perforation, surgery, wound healing, and hemorrhage. Nausea, vomiting, diarrhea, and fatigue were common amongst all these agents. Only for irinotecan did diarrhea rise to the level of a Boxed Warning. In comparison with other agents for treatment of mCRC, TAS-102 appeared to have less side effects that rose to the level of a Boxed Warning or Warnings & Precautions section of the label. None of these agents required a REMS.

TAS-102 is another potential treatment option for refractory patients. In the pivotal trial, TAS-102 showed improvement in OS (7.1 vs. 5.3) by ~2 months and a slight improvement in PFS (2 versus 1.7) compared to placebo. Compared to regorafenib, an alternate treatment option to TAS-102, TAS-102 showed a median overall survival close to 1.5 months longer than regorafenib (6.4) and a similar PFS.<sup>12</sup> In looking at the efficacy data for first and second line treatments used to treat mCRC, TAS-102 did well for refractory treatment. In capecitabine, OS was close to 30 days better than the control arm (407 vs. 380) and PFS was similar between both arms (128 days versus 131).<sup>13</sup> Irinotecan had a better result when compared to capecitabine with OS at 14.8 months versus 12.6 months and PFS at 7 months vs. 4.3.<sup>14</sup> Panitumumab and cetuximab showed no significant difference in OS compared to these other therapies.

The adverse event of concern was severe myelosuppression. The Division determined this event to be adequately addressed under the Warnings & Precautions section of the label.

The prescribing population for TAS-102 will be managed by prescribers who are familiar with the disease and adverse events seen with drugs used for the treatment of colorectal cancer.

## **5 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS**

PMR's and PMC's have not been finalized at the time of this writing.

---

<sup>12</sup> Stivarga (regorafenib) US Package Insert (4/2015)

<sup>13</sup> Xeloda (capecitabine) US Package Insert (3/2015)

<sup>14</sup> Camptosar (irinotecan) US Package Insert (12/2014)

## 6 CONCLUSION

DRISK and DOP-2 concur that, at this time, a REMS is not necessary to ensure that the benefits outweigh the risks for the treatment of patients with metastatic colorectal cancer who have been previously treated with, [REDACTED]<sup>(b) (4)</sup> fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy. The risks associated with TAS-102 will be communicated through professional labeling and routine pharmacovigilance. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

MONA G PATEL  
08/24/2015

CYNTHIA L LACIVITA  
08/24/2015  
I concur