Published OnlineFirst February 17, 2017; DOI: 10.1158/1078-0432.CCR-16-2157

CCR Drug Updates

Clinical Cancer Research

FDA Approval Summary: TAS-102

Leigh Marcus, Steven J. Lemery, Sachia Khasar, Emily Wearne, Whitney S. Helms, Weishi Yuan, Kun He, Xianhua Cao, Jingyu Yu, Hong Zhao, Yaning Wang, Olen Stephens, Erika Englund, Rajiv Agarwal, Patricia Keegan, and Richard Pazdur

Abstract

The FDA approved TAS-102 (Lonsurf; Taiho Oncology, Inc.) for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF biological therapy; and if RAS wild type, an anti-EGFR therapy. In an international, multicenter, double-blinded, placebo-controlled trial (TPU-TAS-102-301, herein referred to as RECOURSE), 800 patients with previously treated mCRC were randomly allocated (2:1) to receive either TAS-102 35 mg/m^2 orally twice daily after meals on days 1 through 5 and 8 through 12 of each 28-day cycle (n = 534) or matching placebo (n = 266). The trial demonstrated a statistically significant improvement in overall survival for those randomized to receive TAS-102, with a median survival of 7.1 months in the TAS-102 arm [confidence interval (CI), 6.5–7.8] and 5.3 months in the placebo arm [CI, 4.6–6.0; hazard ratio (HR), 0.68; 95% CI, 0.58–0.81; $P < 0.001$, stratified log-rank test]. The trial also demonstrated a statistically significant prolongation of progression-free survival (HR, 0.47; 95% CI, 0.40–0.55; $P < 0.001$). The most common adverse reactions, in order of decreasing frequency, observed in the patients who received TAS-102 were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. Adverse events led to discontinuation of TAS-102 in 3.6% of patients, and 13.7% required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea. *Clin Cancer Res; 23(12); 2924–7. ©2017 AACR.*

Introduction

This article summarizes the FDA's independent review of the data submitted in the New Drug Application (NDA) for TAS-102, the issues identified during the review, and the basis for FDA approval. Following the review of the data in the application, the FDA approved TAS-102 for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF biological therapy; and if RAS wild type (wt), an anti-EGFR therapy (1). TAS-102 is now the second drug approved for this population following the approval of regorafenib in 2012.

Chemistry, Manufacturing, and Control

TAS-102 is an orally administered drug, which is a fixed combination (1:0.5) of trifluridine (FTD) and tipiracil hydrochloride (TPI; ref. 1). TAS-102 tablets are provided in two strengths: 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil (1). The drug substances for FTD and TPI were determined to be highly soluble, and both drug substances are manufactured via chemical synthesis (2). On the basis of stability data in the application, 24 months expiration was granted; however, tablets should be discarded if stored outside the original bottle for more than 30 days (1, 2).

Nonclinical Pharmacology and Toxicology

FTD is a thymidine nucleoside analogue. Following uptake into cancer cells, FTD is phosphorylated by thymidine kinase, further metabolized in cells to a DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation (3, 4). TPI is a specific inhibitor of thymidine phosphorylase. When TPI is not present, the bioavailability of FTD after oral administration is extremely low due to a first-pass effect by thymidine phosphorylase, which results in the rapid degradation of FTD to its major metabolite, 5-trifluoromethyl-2,4 (1H,3H)-pyrimidinedione (FTY; ref. 5). Coadministration of TPI with FTD, therefore, increases exposure to FTD and enables the attainment of effective and consistent levels of FTD that could not be reached by administration of higher doses of oral FTD alone.

As expected, on the basis of the mechanism of action, the primary targets of FTD/TPI in toxicology studies in rats and monkeys were the bone marrow and gastrointestinal tract (6). Following administration, both FTD and TPI were present in the milk of lactating rats (6). These data were described in product labeling. In addition, FTD/FTP administration resulted in embryo–fetal lethality as well as structural anomalies at FTD exposures approximately equivalent to those in humans at the clinically recommended dose of TAS-102 (6). For this reason, labeling advises pregnant women of the potential risk to a fetus. Similarly, labeling advises females of reproductive potential to use effective contraception during treatment with TAS-102. Consistent with its mechanism of action, FTD/TPI is also genotoxic; therefore, labeling also advises males with female partners of

Center for Drug Evaluation and Research, U.S. Food and Drug Administration, White Oak, Maryland.

Corresponding Author: Leigh Marcus, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0004. Phone: 240-402-4936; Fax: 301-796-9849; E-mail: leigh.marcus@fda.hhs.gov

doi: 10.1158/1078-0432.CCR-16-2157

Published OnlineFirst February 17, 2017; DOI: 10.1158/1078-0432.CCR-16-2157

reproductive potential to use effective contraception during treatment with TAS-102 and for 3 months after the final dose (6).

Clinical Pharmacology

In clinical studies, administration of TAS-102 35 mg/m^2 increased the $AUC_{0\text{-last}}$ of FTD by 37 times and C_{max} by 22 times compared with administration of FTD 35 mg/m^2 alone (7). The mean elimination half-life at steady state was 2.1 hours for FTD and 2.4 hours for TPI (7). FTD is primarily eliminated via thymidine phosphorylase in the liver and gastrointestinal tract, and the major inactive metabolite is excreted, unchanged, in the urine (7). On the basis of the results of a food-effect study indicating that a high-fat meal decreases FTD C_{max}, but not AUC, and that C_{max} is correlated with neutropenia, it is recommended that patients take TAS-102 within 1 hour after completion of the morning and evening meals (1, 7).

Data collected in the RECOURSE study were not sufficient to allow for accurate analyses of exposure–response relationships for TAS-102. On the basis of population pharmacokinetic analyses, there were no clinical relevant effects of age, sex, or race on the pharmacokinetics of FTD or TPI; however, comparisons of the pharmacokinetics for race were limited by the numbers of patients who were not White or Asian (7). Mild hepatic impairment did not result in clinically relevant differences in exposure in the RECOURSE study. On the basis of population pharmacokinetic analyses, the AUC of FTD was 31% higher in patients with mild renal impairment and 43% higher in patients with moderate renal impairment than that in patients with normal renal function (7). Although labeling does not recommend dose adjustment in patients with mild or moderate renal impairment, labeling does state that patients with moderate renal impairment may require dose modification for increased toxicity (1).

Clinical Data

A single randomized controlled trial (RECOURSE) and a supportive randomized trial (Japanese study, Study J003/10040030; ref. 8), along with a safety database of patients who were exposed to TAS-102 in various clinical trials, were submitted to support the approval of TAS-102 in the United States. The results of RECOURSE have been published (9).

RECOURSE was a multicenter, randomized (2:1), double-blind, placebo-controlled trial that enrolled 800 patients with previously treated mCRC. Randomization stratification factors were geographic region (Japan vs. United States and Europe), KRAS status (wt vs. mutant), and time since diagnosis of first metastasis (<18 months vs. ≥18 months). Eight hundred patients at 101 sites in 13 countries were randomized to receive 35 mg/m^2 TAS-102 (based on trifluridine component) orally twice daily for 5 days, and 2 days of rest, for 2 weeks followed by 14 days of rest, every 4 weeks (n = 534) plus best supportive care (BSC) or placebo (n = 266) plus BSC; of these, one in each group did not receive TAS-102 or placebo, respectively, thus, 798 patients were included in the safety analysis (533, TAS-102; 265, placebo). In general, treatment continued until disease progression, unacceptable toxicity, or death. The prespecified primary endpoint was overall survival (OS). The study was designed to require a total of 571 deaths to detect with 90% power a hazard ratio (HR) of 0.75 (25% risk reduction) for OS with a one-sided type I error of 0.025. Assessment of progression-free survival (PFS) was a secondary endpoint. RECOURSE was monitored by an independent data monitoring committee.

Results

The median age of the 800 patients that constituted the intention-to-treat population was 63 years; 61% were men, 58% and 35% were White and Asian, respectively, and all patients had baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1. Sixty-two percent of patients had primary colon cancer, and 38% had primary rectal cancer. Forty-nine percent had KRAS wt mCRC, and 51% had KRAS-mutant CRC. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab, and all but two patients with KRAS wt tumors received panitumumab or cetuximab.

Efficacy

A statistically significant improvement in OS was observed in patients randomized to receive TAS-102 compared with placebo. Median survival was 7.1 months in the TAS-102 arm [confidence interval (CI), 6.5–7.8] and 5.3 months in the placebo arm (CI, 4.6–6.0; HR, 0.68; 95% CI, 0.58–0.81; $P < 0.001$, stratified log-rank test; see Fig. 1 and Table 1). In addition, there was a statistically significant prolongation of PFS in patients randomized to receive TAS-102 (HR, 0.47; 95% CI, 0.40–0.55; $P < 0.001$). The objective response rate was 1.5% for the TAS-102 arm versus 0.4% for the placebo arm.

Safety

The safety database contained data from 761 patients who received TAS-102 at a dose of 35 mg/m^2 twice daily in one of eight clinical trials. The majority (533) of these patients were enrolled in the RECOURSE trial. In general, safety results in all patients exposed to TAS-102 were consistent with the results observed in RECOURSE. In RECOURSE, the most common adverse drug reactions or laboratory abnormalities in patients treated with TAS-102 versus placebo were (grade 3–4) anemia, 77% versus 33% (18% vs. 3%); neutropenia, 67% versus 1% (38% vs. 0%); asthenia/fatigue, 52% versus 35% (7% vs. 9%); nausea, 48% versus 24% (2% vs. 1%); thrombocytopenia, 42% versus 8% (5% vs. <1%); decreased appetite, 39% versus 29% (4% vs. 5%); diarrhea, 32% versus 12% (2% vs. <1%); vomiting, 28% versus 14% (2% vs. <1%); abdominal pain, 21% versus 18% (2% vs. 4%); and pyrexia, 19% versus 14% (1% vs. <1%). Grade 4 neutropenia occurred in 11% and grade 4 thrombocytopenia occurred in 1% of patients treated with TAS-102. Grade 3 or 4 neutropenia (48% vs. 30%) and thrombocytopenia (9% vs. 2%) occurred more frequently among patients 65 years or older compared with younger patients. Granulocyte-colony stimulating factors were administered to 9.4% of patients treated with TAS-102.

Other potentially important but less commonly occurring non-hematologic adverse reactions included alopecia (7% vs. 1%) and pulmonary embolus (2% vs. 0%). Febrile neutropenia occurred in 3.8% of patients treated with TAS-102, and one patient (0.2%) died due to neutropenic infection.

In RECOURSE, 54.2% of patients receiving TAS-102 had an adverse event leading to a dose interruption, dose delay, or dose reduction. Most of these patients required only a dose interruption/delay, with 13.7% requiring a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea. Adverse events led to discontinuation of TAS-102 in 3.6% of patients.

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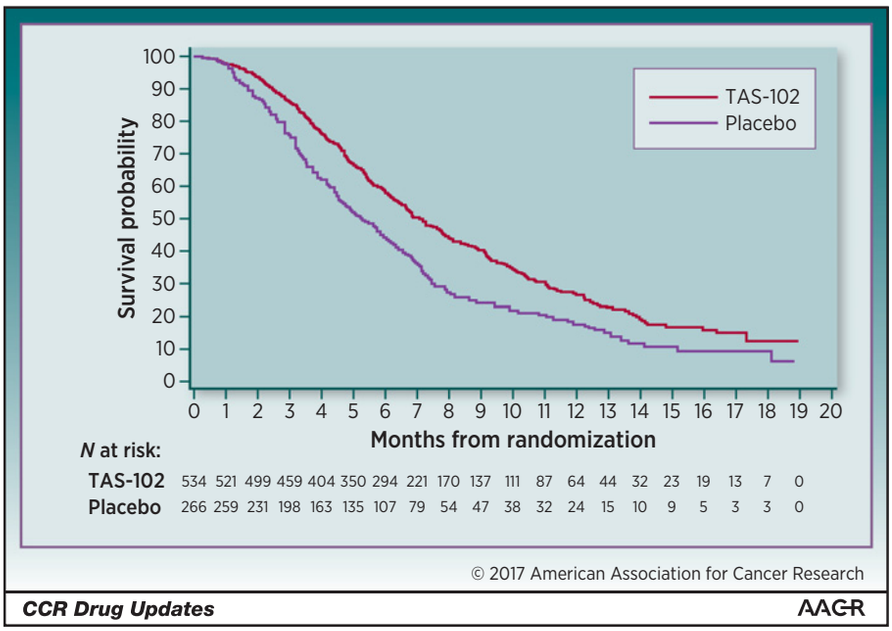

Figure 1.
Kaplan–Meier curves of OS.

Infections occurred in 27% of patients treated with TAS-102 compared with 15% of patients who received placebo in RECOURSE. The most commonly reported infections were nasopharyngitis (4% TAS-102 vs. 2% placebo) and urinary tract infections (4% TAS-102 vs. 2% placebo).

Fifteen (0.2%) patients developed interstitial lung disease among approximately 7,000 patients exposed to TAS-102 in clinical studies or clinical practice settings in Asia; three of the 15 cases were fatal.

Discussion

The primary issues identified during the review of the NDA for TAS-102 were whether both compounds (FTD and TPI) were necessary to achieve the intended effect, whether the results of a single adequate and well-controlled trial demonstrated substantial evidence of effectiveness, and whether the risk–benefit profile of TAS-102 was favorable for the intended population.

TAS-102, an antitumor nucleoside, is a fixed combination of FTD and TPI. FTD, an antineoplastic antimetabolite, is a thymidylate synthase inhibitor. TPI is a specific inhibitor of thymidine phosphorylase that inhibits the metabolism of FTD in the intestinal tract and liver.

Table 1. Primary efficacy results

	TAS-102 $n = 534$	Placebo $n = 266$
OS		
Median OS (months)[a] (95% CI)[b]	7.1 (6.5–7.8)	5.3 (4.6–6.0)
HR (95% CI)	0.68 (0.58–0.81)	
P[c]	<0.001	
PFS		
Median PFS (95% CI)	2.0 (1.9–2.1)	1.7 (1.7–1.8)
HR (95% CI)	0.47 (0.40–0.55)	
P[c]	<0.001	

[a]Kaplan–Meier estimates.
[b]Methodology of Brookmeyer and Crowley.
[c]Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region).

Prior to issuing Guidance for Industry in 2013, existing regulatory pathways focused primarily on assessment of the safety and effectiveness of single drugs acting alone. Because co-development of two investigational drugs provides less information regarding each drug, the FDA described criteria that should be met in order to proceed with co-development of two investigational drugs. These criteria include serious disease or condition, strong biological rationale, adequate nonclinical characterization, and a compelling reason why the investigational drugs cannot be developed independently (10).

Demonstration of the contribution of each agent could not be achieved by demonstrating superior antitumor activity of the combination as compared with each drug as a single agent, as TPI does not have antitumor activity. In this instance, the FDA relied on evidence that administration of TPI altered the pharmacokinetics of FTD such to reliably achieve an effective dose. When orally administered, FTD is rapidly degraded to an inactive form, 5-trifluoromethyluracil by thymidine phosphorylase, which is present in gastrointestinal tract, liver, and tumor tissue (7). The NDA contained clinical study data demonstrating that the FTD plasma concentrations ($AUC_{0\text{-last}}$) were approximately 37-fold higher when administered in combination with TPI compared with when administered without TPI. Large variability exists in the pharmacokinetics of FTD when administered at high doses, resulting in unacceptable hematologic toxicity. The NDA also contained nonclinical data that indicated that based on AUC, the estimated dose of FTD alone would be higher than the dose of FTD predicted to exceed the lethal dose for humans based on primate toxicology studies. Thus, the contribution of TPI was demonstrated, resulting in consistent concentrations of FTD to achieve improvements in OS and PFS.

FDA Guidance for Industry ("Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," published May 1998) describes the conditions under which it is acceptable to rely on the results of a single study (11). These include an effect on a clinically important endpoint such as mortality or major morbidity, large multicenter study, consistency

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across subsets, multiple studies in a single study, multiple endpoints involving different events, and a statistically very persuasive finding (11). RECOURSE met its primary endpoint of OS, with a $P < 0.001$ (9). Furthermore, the results of RECOURSE were consistent with the supportive randomized trial (Japanese study, Study J003/10040030; ref.8). The FDA determined that it would not be ethical to require an additional trial given the favorable risk–benefit profile with an improvement in OS, statistically robust findings observed in RECOURSE, which are consistent with the results in the smaller trial conducted in Japan.

The last major issue pertinent to this application was whether the risk–benefit profile of TAS-102 was favorable for the intended population. RECOURSE demonstrated a statistically significant improvement in survival, with an increase in median survival time of 1.8 months in the TAS-102 arm. This is comparable with the effect size demonstrated in a clinical study investigating regorafenib for the treatment of patients with third-line mCRC. This improvement in survival is achieved with only 3.6% of patients requiring treatment discontinuation for adverse reactions and only 13.7% of patients requiring dose reductions for toxicity. Oncologists are experienced in the management of toxicities caused by TAS-102 (e.g., hematologic and gastrointestinal), thus the FDA concluded that the benefits of improvements in OS and PFS with TAS-102 35 mg/m^2 twice daily in a patient population with advanced mCRC who have limited treatment options outweighs its risks. Overall, the incidence rate of adverse events of any grade (98% TAS-102 vs. 93% placebo) was similar to placebo, although there was a higher incidence of grade 3 to 4 adverse events (49% vs. 10%) in patients receiving TAS-102, most of which were based on hematologic laboratory abnormalities rather than clinical adverse reactions. Grade 3 or 4 myelosuppression was also more common in patients older than 65 years of age compared with younger patients.

On the basis of recent changes to the panitumumab and cetuximab product labels, the indication for TAS-102 references previous anti-EGFR treatment for patients with RAS wt tumors rather than KRAS wt tumors even though RECOURSE enrolled patients based on KRAS mutation status. Residual uncertainty exists regarding whether TAS-102 is safe or effective in the following populations because TAS-102 has not been studied in these populations or because minimal data exist for these populations: patients with moderate to severe hepatic impairment, severe renal impairment, ECOG PS $\geq$2, brain metastases, or ascites requiring drainage within 4 weeks of enrollment. Taiho is required to complete studies to investigate the pharmacokinetics of TAS-102 in patients with moderate to severe hepatic impairment and in patients with severe renal impairment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The Deputy Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

Authors' Contributions

Conception and design: L. Marcus, Y. Wang, R. Pazdur
Development of methodology: R. Pazdur
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Pazdur
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Marcus, S.J. Lemery, E. Wearne, W. Yuan, K. He, X. Cao, J. Yu, Y. Wang, E. Englund, R. Agarwal, P. Keegan, R. Pazdur
Writing, review, and/or revision of the manuscript: L. Marcus, S.J.Lemery, S. Khasar, E. Wearne, W.S. Helms, K. He, X. Cao, H. Zhao, Y. Wang, O. Stephens, R. Agarwal, P. Keegan, R. Pazdur
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Marcus, R. Pazdur

Received August 29, 2016; revised October 3, 2016; accepted January 7, 2017; published OnlineFirst February 17, 2017.

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