TAS-102: a novel antimetabolite for the 21st century

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TAS-102, a novel antimetabolite combination chemotherapy agent, consists of a rediscovered antimetabolite agent, trifluorothymidine (trifluridine) combined with the metabolic inhibitor of thymidine phosphorylase, tipiracil, in a 1:0.5 molar ratio. Mechanism of action studies suggest that this agent works by incorporation into DNA. Both preclinical and clinical studies demonstrate that this agent is noncross-resistant with 5-fluorouracil. Tipiracil may also have antiangiogenic effects through inhibition of thymidine phosphorylase. Recent randomized Phase II and III trials demonstrate clinical activity (improved progression-free survival, time to decrease in performance status, prolonged overall survival) in metastatic colorectal cancer refractory to all standard agents. Monotherapy with TAS-102 has now been approved for this indication in Japan and in the USA.

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TAS-102 is a novel oral combination drug that consists of an antineoplastic thymidine-based nucleoside analog, trifluorothymidine (TFT; trifluridine), and a potent thymidine phosphorylase (TP) inhibitor (TPI) (Figure 1). TFT was first synthesized more than 50 years ago, but its clinical development was halted because of unfavorable pharmacological profile with a human serum half-life of approximately 12 min. It reentered clinical research in early 2000s after the synthesis of TPI, which greatly improved bioavailability of the oral formulation of this drug. A combination of the two components known as TAS-102 has now been evaluated in multiple Phase I trials, as well as Phase II and III trials for its activity in metastatic colorectal cancer (mCRC). TAS-102 therapy has been shown to improve overall survival in heavily pretreated patients with mCRC, who have progressed on prior fluoropyrimidine-containing therapies. Monotherapy with TAS-102 was approved by the US FDA for the treatment of patients with refractory mCRC in September 2015 and is under regulatory review in Europe. TAS-102 also has potential to demonstrate enhanced activity when combined with other agents. Its role in the treatment of other malignancies and in combination with other drugs should be explored.

Fluoropyrimidines & colon cancer

Colon cancer is the third most common cancer in the USA, and it accounts for approximately 9% of all cancer deaths [1]. More than 100,000 new colon cancer cases were expected to be diagnosed in 2014, and about 20% of these cases are likely to have metastatic disease at presentation [1,2]. Unfortunately, only a small number of patients with stage IV disease can be cured with

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Figure 1. Structure of TAS-102.

multimodality therapy. Hence, systemic medical therapy is essential in management of these patients. Fluoropyrimidines have remained the cornerstone of therapy against colon cancer for decades [3]. Over the last decade, a number of available systemic treatments for colon cancer have increased significantly. They have improved both quality of life and overall survival, which now exceeds 2.5 years for stage IV disease [4]. In addition to fluoropyrimidines, these treatments include other chemotherapy agents (oxaliplatin and irinotecan), angiogenesis inhibitors (bevacizumab, aflibercept and ramucirumab), multitarget oral tyrosine kinase inhibitor (TKI) regorafenib and anti-EGFR antibodies (cetuximab and panitumumab). In the USA, FOLFOX (combination of 5-fluorouracil [5FU], leucovorin and oxaliplatin) or less frequently FOLFIRI (combination of 5FU, leucovorin and irinotecan) is used as initial backbone chemotherapy for metastatic disease. Both of these regimens have response rates of over 50% [5]. The addition of biologic agents (anti-VEGF or anti-EGFR antibodies) can increase this response rate even further.

Although the standard therapies are initially effective, most patients relapse due to the onset of drug resistance. Patients who have progressed through all of the available treatments frequently have adequate performance status to continue with palliative therapies. Therefore, there is an unmet need for alternative treatment strategies. Development of novel therapeutic agents, both chemotherapy and biologics, for this patient population is essential in hopes of extended survival for metastatic disease. TAS-102 is a new combination agent that has been demonstrated to have activity in heavily pretreated mCRC patients [6]. The combination agent consists of

a TFT, which acts as a nucleoside analog, and a TPI, which prevents degradation of TFT, as well as inhibits angiogenesis. Since its mechanism of action differs from other fluoropyrimidines and it possesses antiangiogenic properties on its own, it has activity against tumors with primary or secondary fluoropyrimidine resistance. As such, it has a role in management of mCRC and holds promise to be active in other diseases that tend to respond to fluoropyrimidines.

Fluorinated antimetabolites

Fluoropyrimidines have long been a cornerstone in the treatment of multiple solid tumors and of gastrointestinal malignancies in particular. Fluoropyrimidines are DNA base or nucleoside analogs, with a fluorine substitution. In 5FU, the most widely used fluoropyrimidine, a hydrogen atom in C-5 position is substituted by a fluorine. 5FU was first synthesized by Heidelberg in 1957 [7]. More than 50 years after its synthesis, 5FU remains widely used in the management of multiple tumor types with the most notable footprint in the treatment of colorectal and other GI cancers.

5FU may be considered the earliest targeted therapy in cancer care. It specifically inhibits thymidylate synthase (TS), an enzyme that plays a central role in DNA synthesis [8]. TS catalyzes a rate-limiting step in pyrimidine production and is crucial for cellular production of deoxythymidine triphosphate (dTTP). In the absence of TS, cells are depleted of dTTP, which results in the accumulation of deoxyuridine monophosphate (dUMP). Resultant imbalance in cellular nucleotide pools leads to uracil (and fluorouracil) misincorporation into the DNA and RNA, impaired DNA synthesis and ultimately disruption of cell cycle (Figure 2). TS is overexpressed in multiple tumor types and is frequently associated with poor clinical outcomes [9–12]. Moreover, TS has been shown to possess oncogenic activity on its own [13]. The TS enzyme consists of a homodimer with each subunit possessing a binding site for a nucleotide and a reduced folate. As a result, two classes of drugs are able to disrupt its cellular activity – fluoropyrimidine and folate analogs.

The earliest fluoropyrimidine, 5FU, is generally administered intravenously, either as a bolus or as continuous infusion. Oral administration of 5FU is plagued by erratic absorption due to intestinal dihydropyrimidine dehydrogenase (DPD) activity. To simplify treatment

regimens, a number of oral 5FU analogs have been developed as an alternative (**Table 1**). Tegafur (or ftorafur) is an oral prodrug of 5FU, which is metabolized in the liver by CYP450 to 5FU [14]. It was synthesized more than 30 years ago and is now used in combination with other compounds that improve its bioavailability and toxicity profile [8]. UFT consists of a combination of tegafur and uracil, which is a substrate for DPD, an enzyme that degrades 5FU. S-1 is a combination of tegafur with 5-chloro-2,4-dihydroxypyridine (CDHP) and oteracil potassium (OXO). CDHP is a DPD inhibitor, and OXO decreases gastrointestinal toxicity associated with tegafur. Capecitabine is a prodrug of 5FU, which requires three enzymatic steps to be converted to 5FU. It is widely used in the USA and has antitumor activity equivalent to 5FU in colon cancer. TAS-102 is a more recent oral fluoropyrimidine, which is a combination of a thymidine analog TFT and an inhibitor of TP that rapidly metabolizes TFT. Its mechanism of action, however, differs from other fluoropyrimidines, and TS is not its main target.

Inhibition of cell cycle by TAS-102

TAS-102 is a novel functional antitumor nucleoside. It is a combined form of 1 M TFT (2'-deoxy-5-(trifluoromethyl)uridine, trifluridine) and 0.5 M tipiracil hydrochloride, which is a TPI (**Figure 1**). TFT is an antineoplastic antimetabolite, which was first synthesized in 1964 by Dr Charles Heidelberger, who also synthesized 5FU and FU deoxyribonucleoside (FUDR) a few years earlier [21]. TFT is a nucleoside derivative, in which a 5'-methyl group of thymidine is substituted with the trifluoromethyl group (**Figure 1**). Intracellularly TFT is phosphorylated to the monophosphorylated form of TFT, F3TMP, by thymidine kinase [22]. F3TMP can also be further phosphorylated to a triphosphate form, F3TTP.

TFT is known to inhibit the cell cycle via at least two mechanisms. The monophosphorylated form of TFT can bind and inhibit TS [23,24] (**Figure 2**). This binding, in contrast to 5FU binding, does not require folates and is reversible. The triphosphorylated form of TFT is incorporated into DNA [24,25]. Once TFT–triphosphate is incorporated into DNA, it leads to abnormal DNA synthesis and inhibition of cell division. The two mechanisms of action are dependent on the mode of TFT delivery and exposure time, similarly to 5FU. While continuous infusion of

TFT results in significant TS inhibition, interrupted pulsed dosing, which is currently utilized in clinical trials, results in greater DNA incorporation and disruption of DNA synthesis [26]. In cell culture, repeat dosing of TAS-102 resulted in much higher DNA incorporation of TFT than with single daily dosing, which increased further with administration of TAS-102 on consecutive days [26]. Moreover, TFT appears to be incorporated into DNA to a significantly greater degree than either 5FU or FdUrd (more than 300-fold higher when compared with 5FU in HeLa cells) [27]. In preclinical models with human

Figure 2. The mechanism of action of TAS-102. TAS-102 consists of TFT and TPI.

TFT is intracellularly phosphorylated. TFT-MP can inhibit TS. Inhibition of TS is not the main mechanism of action when TFT is orally administered as part of TAS-102. The majority of TFT is phosphorylated further into the TFT-TP, which is incorporated into DNA resulting in DNA dysfunction and cell cycle arrest. TPI inhibits TP, which metabolizes TFT, and thus increases bioavailability of TFT. TPI also possesses antiangiogenic properties.

TFT: Trifluorothymidine;

TFT-MP: Monophosphorylated form of TFT;

TFT-TP: Triphosphorylated form of TFT;

TP: Thymidine phosphorylase; TPI: Thymidine phosphorylase inhibitor; TS: Thymidylate synthase.

Table 1. Oral fluorinated antimetabolites.			
Drug	Chemical composition	Mode of action	Indications
Tegafur–uracil	Uracil and tegafur in a 4:1 ratio	Tegafur is converted to 5FU Uracil: competitive substrate for DPD, which increases bioavailability of tegafur	Colon/rectum, lung, breast, stomach, head and neck, liver, gallbladder, bile duct, pancreas, bladder, prostate and cervix Not approved in the USA
S-1 (tegafur + CDHP + oteracil potassium)	Tegafur, CDHP and oteracil potassium in a 1:0.4:1 M ratio	Tegafur is converted to 5FU CDHP inhibits metabolism of 5FU Oteracil potassium decreases gastrointestinal toxicity	Gastric cancer, CRC, breast, pancreatic, bile duct, lung cancer and head and neck Not approved in the USA
Capecitabine	Fluoropyrimidine prodrug of 5'-DFUR	Prodrug of 5FU	Colon cancer and breast cancer
TAS-102	TFT and TPI in a 1:0.5 M ratio	TFT is phosphorylated and incorporated into DNA TPI inhibits angiogenesis and TP, which metabolizes TFT	Metastatic CRC Awaiting approval in the USA
5FU: 5-Fluorouracil; CDHP: 5-Chloro-2,4-dihydroxypyridine; CRC: Colorectal cancer; DFUR: Deoxyfluorouridine; DPD: Dihydropyrimidine dehydrogenase; M: Molar; TFT: Trifluorothymidine; TPI: Thymidine phosphorylase inhibitor.			

cancer xenografts, higher amount of TFT was incorporated into DNA with divided oral dosing, which also resulted in stronger antitumor effects and better tolerability than intravenous administration via continuous infusion [26,28].

There are now sufficient preclinical data suggesting that inhibition of TS does not appear to be the main mode of action of oral form of TFT when administered as TAS-102 in the clinic [28]. Inhibition of TS does not correlate with the antitumor activity of FTD but there is a positive correlation between the antitumor activity of TAS-102 and the amount of TFT incorporated into human cancer xenograft DNA [26,28]. It has been shown previously that DNA incorporation of TFT results in increased DNA fragmentation due to single- and double-stranded DNA breaks [29,30]. However, the mechanisms underlying this process have not been fully elucidated. Triphosphorylated form of TFT is a weak competitor for thymidine triphosphate, suggesting that DNA polymerases are not its main targets [27]. TFT also does not appear to be a substrate for DNA glycosylases when it is paired with adenine and incorporated into the T sites of DNA helix as it was not subject to excision by uracil DNA glycosylases (UDG), thymine DNA glycosylase (TDG) and methyl-CpG-binding domain 4 (MBD4) [27]. TDG and MBD4 glycosylases were able to excise the TFT paired to guanine in DNA but the pairing with guanine occurs much less frequently than with adenine [30]. Cells deficient in the TDG and MBD4 glycosylases have been reported to be resistant to 5FU. Excision of DNA-incorporated 5FU by these glycosylases results in DNA-strand

breaks and activation of DNA damage signaling cascades, which ultimately inhibits cell cycle progression [31]. However, siRNA-mediated knockdown of TDG or MBD4 had no effect on TFT-mediated cytotoxicity, suggesting that the inhibitory effects of TFT on DNA replication and repair enzymes differ from those of 5FU and FdUrd [27]. There are also now conflicting data regarding TFT-induced DNA fragmentation. While Suzuki *et al.* demonstrated that TFT incorporation into DNA resulted in single- and double-strand breaks and subsequent activation of DNA repair cascades, DNA fragmentation was not observed with a more recent study by Matsuoka *et al.* [30,32]. Both studies, however, demonstrated that TAS-102 treatment resulted in massive TFT incorporation into DNA and in activation of similar DNA damage response pathways, which involve phosphorylation of Chk1 and cycle arrest during the G2/M-phase. At present time, the exact mechanisms underlying the cytotoxicity of TAS-102 are still under investigations, but TFT activity appears to be most dependent on its DNA incorporation and resultant cell cycle arrest.

Antiangiogenic properties of TAS-102

TPI is an essential component of TAS-102, and it has two different functions. It enhances bioavailability of TFT by reducing its degradation to trifluorothymine, and possesses antiangiogenic properties. Hence, TAS-102 likely exhibits some of its antitumor affects through inhibition of angiogenesis. TP is identical to PDEGF, which is a known proangiogenic agent that has been shown to promote tumor growth [33,34].

TP protects cells from hypoxia-induced apoptosis [35]. Hypoxia, low pH, chemotherapeutic agents and radiation can increase TP protein levels in human tumors [36–38]. TP is expressed at higher levels in a wide variety of solid tumors compared with the adjacent non-neoplastic tissues [39]. Higher levels of tumor TP expression have been correlated with the more aggressive nature of disease and poor prognosis [40–44].

Over the last two decades, TP has emerged as an attractive target for antiangiogenic agents, and TPI has demonstrated antitumor activity in a number of preclinical models both as a single agent and in combination with TFT [45,46]. TPI has also been suggested to have a role as a radiosensitizer as it enhanced radiation potency in colorectal cancer cell lines and mouse models. This effect was at least partially attributable to the inhibition of angiogenesis and activation of DNA repair cascades [47].

TAS-102 activity in 5FU-resistant tumors

A number of preclinical studies demonstrated that TAS-102 retains its antitumor effects irrespective of sensitivity to other fluoropyrimidines. Murakami *et al.* has previously shown that TFT was cytotoxic to 5FU-resistant DLD-1 colon cancer cells despite the amplification of TS mRNA in these cells [48]. These data support the idea that TS inhibition is not essential for TFT activity and that TS activation does not underlie TFT resistance. TFT sensitivity was also seen in 5FU-resistant esophageal, pancreatic and gastric cell lines [29]. Exposure of these cells to high concentration of TAS-102 for short periods of time resulted in significant TFT incorporation into DNA and associated DNA fragmentation [29]. In a xenograft model of colon cancer, TAS-102 had similar antitumor activity against cells from 5FU-resistant tumors and cells from their parental 5FU-sensitive tumors [49]. In Phase II and III clinical trials, which are detailed below, TAS-102 demonstrated activity in patients with mCRC who had previously progressed on 5FU, oxaliplatin and irinotecan-containing regimens [6,50].

TAS-102 has unique mechanisms of action compared with other fluorinated antimetabolites, which is why it is not surprising that this compound is active in tumors resistant to 5FU and similar drugs. Extensive DNA incorporation of TFT, which underlies its cytotoxic effects, appears to be a very important pharmacological distinction between TFT and 5FU, and it likely explains why cross-resistance is not an

issue when the two drugs are used sequentially. The process of autophagy has also been linked to the development of 5FU resistance but it has not been elicited by TFT in cancer cell lines, suggesting that this mechanism of 5FU resistance can be overcome by TFT treatment as well [51]. In addition, the TPI portion of TAS-102 possesses antiangiogenic properties, which are not a feature of other antimetabolites.

TAS-102 activity in combination with other antineoplastic agents

The efficacy of TAS-102 in combination with other antineoplastic agents has been evaluated in a number of preclinical studies. TFT preincubation of colorectal cancer cell lines enhanced cytotoxicity induced by SN38, the active metabolite of irinotecan [52]. The combination of TFT with the third-generation platinum agent, oxaliplatin, resulted in a dose- and schedule-dependent synergism between these drugs as well [53]. TFT was also synergistic with erlotinib in EGFR expressing colon cancer cells, even in the presence of *K-Ras* mutation [54]. TAS-102 activity against colorectal cancer xenografts was further enhanced by combining it with bevacizumab, cetuximab or panitumumab [55]. All of the above preclinical combination studies suggest that antitumor activity of TAS-102 can be further enhanced with other agents, a concept that should be explored further in clinical trials.

Clinical experience with TAS-102

• Phase I data with TAS-102

The first clinical trials with TFT were published in 1971, in which repeat intravenous administration of this compound led to size reduction of human colon and mammary tumors [56]. However, further clinical development of this compound was halted because of unfavorable pharmacokinetics and associated toxicities, primarily on the bone marrow. TFT was found to be rapidly cleared from bloodstream with half-life of less than 20 min after intravenous administration [57]. When TFT is taken orally, it is largely degraded to an inactive form (5-trifluoromethyluracil) by TP. This enzyme is present in gastrointestinal tract, liver and tumor tissue. The TPI, tipiracil, was first synthesized in 2000. TPI effectively blocked the activity of TP and significantly increased the levels of circulating TFT in primates and also enhancing antitumor activity of TFT in cancer xenografts [58]. The optimal molar drug ratio resulting in maximal TFT

plasma levels in monkeys was determined to be 1:0.5 (TFT:TPI). This combination was subsequently developed as TAS-102, which included 1 M TFT and 0.5 M TPI [45]. This formulation has been shown to not only increase TFT-related cytotoxicity in human tumor xenografts but also to decrease TFT-associated adverse effects [45].

A number of Phase I clinical trials have been completed with TAS-102 to established optimal dose and schedule of administration (Table 2). In the first Phase I trial, TAS-102 was given orally once a day for 14 consecutive days of a 21-day cycle [15]. Fourteen patients with solid tumors were enrolled in this study. The initial dose of 100 mg/m², which was based on preclinical studies, resulted in grade 3 and grade 4 bone marrow suppression, particularly granulocytopenia and anemia. Maximum-tolerated dose (MTD) was established at 50 mg/m² per day because of hematologic dose-limiting toxicities (DLTs). At this dose, there were no DLTs but progressive myelotoxicity was seen later in the course of therapy with pharmacokinetic analysis demonstrating progressive accumulation of TFT. Out of 12 evaluable for response patients, four had stable disease but no objective responses were seen.

Subsequent Phase I studies concentrated on establishing optimal dosing interval to decrease previously observed progressive hematologic toxicity. Overman *et al.* published the results of

the two Phase I studies that looked at different schedule of oral daily TAS-102 administration [16]. In schedule A, TAS-102 was administered once daily for five consecutive days per week for 2 weeks (days 1–5 and 8–12) of a 28-day cycle. Based on a previous study, a starting dose of 50 mg/m² per day was chosen. In schedule B, TAS-102 was administered once daily for five consecutive days per week during week 1 (days 1–5) of a 21-day cycle. Given that the previous Phase I study had demonstrated that a total dose of 700 mg/m² (50 mg/m² per day for 14 days) over a 3-week cycle was tolerable, a starting dose level of 100 mg/m² per day (500 mg/m² total dose over 3 weeks) was chosen. Pharmacokinetic analysis performed during these studies demonstrated that TFT reached peak concentration in plasma in 0.53–3.15 h and had elimination half-life of 1.46–4.20 h. Both treatment schedules resulted in increased accumulation of TFT by the last day of treatment, similar to the original Phase I study by Hong *et al.* [15]. In the heavily pretreated patient population enrolled, no objective responses were seen. In total, 30% of patients were demonstrated to have stable disease.

Lack of clinical response in these trials, as well as pharmacokinetic profile of the drug, suggested that the once-daily schedule of TAS-102 administration may underutilize the drug’s antitumor

Study (year)	Patients (n)	Dosing	MTD (mg/m ²)	DLT	Antitumor efficacy	Ref.
Hong <i>et al.</i> (2006)	14	Daily on days 1–14 of a 21-day cycle	50 per day	Grade 4 granulocytopenia	No objective responses, four patients with stable disease	[15]
Overman <i>et al.</i> (2008)	24	Daily on days 1–5 and 8–12 of a 28-day cycle	110 per day	Grade 3–4 granulocytopenia	No objective responses; 29% with stable disease	[16]
Overman <i>et al.</i> (2008)	39	Daily on days 1–5 of a 21-day cycle	160 per day	Grade 3–4 granulocytopenia, grade 3 nausea	No objective responses; 30% with stable disease	[16]
Green <i>et al.</i> (2006)	19	b.i.d. on days 1–5 and 8–12 of a 28-day cycle	50 per day	Grade 3–4 granulocytopenia and thrombocytopenia	No objective responses, seven patients with stable disease	[17]
Overman <i>et al.</i> (2008)	15	t.i.d. on days 1–5 and 8–12 of a 28-day cycle	70 per day	Grade 4 granulocytopenia and grade 3 fatigue	No objective responses, nine patients with stable disease	[18]
Doi <i>et al.</i> (2012)	21	b.i.d. on days 1–5 and 8–12 of a 28-day cycle	70 per day	Grade 4 granulocytopenia, leucopenia and thrombocytopenia	No objective responses; 11 patients with stable disease	[19]
Patel <i>et al.</i> (2012)	12	b.i.d. on days 1–5 and 8–12 of a 28-day cycle	70 per day	Grade 3 febrile neutropenia	Not available	[20]

b.i.d.: Twice daily; DLT: Dose-limiting toxicity; MTD: Maximum-tolerated dose; t.i.d.: Three-times daily.

effects. Subsequent studies concentrated on exploring divided daily administration of TAS-102 to maximize exposure to the drug. This idea originated from Phase I studies with TFT conducted back in 1971. While no responses were seen in patients treated with various daily doses of TFT ranging from 1.5 to 30 mg/kg per day, when TFT was administered every 3 h at a dose of 2.5 mg/kg per day, 28% of patients demonstrated more than 50% reduction in tumor size [56]. Hence, in subsequent Phase I trials with TAS-102, multiple daily dosing schedules were studied. Nineteen patients with metastatic breast cancer were given TAS-102 twice a day on days 1–5 and 8–12 of a 28-day cycle [17]. An MTD of 50 mg/m² per day was established with bone marrow toxicity seen as the main DLT. Seven patients had prolonged stable disease for more than 3 months. Concurrently, three-times per day administration of TAS-102 was studied in a different trial [18]. Fifteen 5FU refractory patients received TAS-102 three-times a day on days 1–5 and 8–12 every 4 weeks. MTD was established at 70 mg/m² per day. Similarly to other studies, granulocytopenia was the primary toxicity associated with this schedule. No objective responses were seen but nine patients had prolonged stable disease and five patients had radiographic reductions in tumor burden that did not meet objective response criteria by the RECIST. A Phase I study in Japanese population further evaluated twice daily dosing of TAS-102 and established an MTD of 70 mg/m² per day when given twice a day on days 1–5 and 8–12 of a 28-day cycle [19]. Again, no objective responses were seen but stable disease was achieved in more than 50% of heavily pretreated patients. The same MTD was confirmed in the western population as well [20]. One DLT (febrile neutropenia) was seen at the goal dose of 70 mg/m² per day. A dose of 35 mg/m² given twice a day on days 1–5 and 8–12 of a 28-day cycle was subsequently taken to Phase II and III trials.

• Randomized Phase II data with TAS-102

The initial Phase II clinical trial exploring the antitumor efficacy of TAS-102 was conducted in Japan [50]. This was a multicenter, double-blinded randomized, placebo-controlled study. Patients with mCRC who have progressed on at least two lines of approved therapy and who were refractory or intolerant to fluoropyrimidines, irinotecan and oxaliplatin were eligible for participation. Enrolled patients were randomized

2:1 to either TAS-102 plus best supportive care or placebo plus best supportive care. TAS-102 was taken orally twice a day at 35 mg/m² dose on days 1–5 and 8–12 of a 28-day cycle. This dosing was based on the previously described Phase I trials. A total of 112 patients were enrolled into the TAS-102 cohort and 57 into the placebo cohort. This study demonstrated significant improvement in overall survival (primary end point) in TAS-102-treated subjects compared with the placebo-controlled group (9.0 vs 6.6 months with HR: 0.56; $p = 0.0011$). Median progression-free survival was longer in the TAS-102 group as well (2.7 vs 1.0 months with HR: 0.35 and $p < 0.0001$). The most common grade 3 and 4 toxicities associated with TAS-102 therapy were neutropenia, leucopenia, anemia, fatigue and diarrhea. This trial demonstrated promising activity of TAS-102 in refractory colorectal cancer patients. Based on the results of this trial, TAS-102 was approved in March 2014 in Japan for advanced colorectal cancer refractory to standard therapies.

• Randomized Phase III data with TAS-102

A global randomized Phase III study (RECOURSE) enrolled patients with mCRC who had progressed on at least two lines of standard therapy that included fluoropyrimidines, oxaliplatin, irinotecan, angiogenesis inhibitors and anti-EGFR agents for *RAS* wild-type tumors [6]. Similar to the Japanese randomized Phase II trial, subjects were randomized in a 2:1 fashion to either TAS-102 or placebo. The TAS-102 cohort enrolled 534 patients, and the placebo cohort enrolled 266 patients, for a total of 800 patients. In total, 93% of patients receiving TAS-102 and 90% of those receiving placebo had disease refractory to fluoropyrimidines. TAS-102 therapy resulted in significant improvement in overall survival compared with the placebo group (7.1 vs 5.3 months with HR: 0.68; $p < 0.0001$). In addition, treatment with TAS-102 resulted in the delay in the deterioration of Eastern Cooperative Oncology Group (ECOG) performance status to 2 or higher when compared with placebo. Overall, TAS-102 therapy was well tolerated. Only 14% of patients required dose reductions, and adverse events resulted in study withdrawal of 4% of patients receiving treatment (2% in placebo group). The most common grade 3–4 toxicities observed were bone marrow suppression (neutropenia, anemia and thrombocytopenia), but mainly

delayed marrow recovery, similar to what has been reported in previous studies. The most common nonhematological toxicities of any grade included fatigue, nausea, vomiting and diarrhea. Based on the results of this trial, TAS-102 was approved by FDA for the treatment of refractory mCRC in September 2015.

TAS-102-associated toxicities

TAS-102 has been demonstrated to have a favorable toxicity profile even in heavily pretreated patient population. The main DLT in Phase I trials was bone marrow suppression with granulocytes as the main cell line effected. Similar observations were seen in larger Phase II and III trials. In the Phase II trial conducted in Japan, grade 3–4 neutropenia, leukopenia, anemia, fatigue and diarrhea were the most frequently observed toxicities in the TAS-102 group (Table 3). Febrile neutropenia occurred in five (4%) subjects in the TAS-102 group and was the most common serious adverse event. Myelosuppression was successfully managed with treatment delays or dose adjustments. No treatment-related deaths occurred in this Phase II trial, and only four (4%) patients discontinued treatment because of the treatment-related side effects.

A very similar toxicity profile of TAS-102 was observed in the global Phase III RECURSE trial (Table 3) [6]. Again, bone marrow suppression was the most commonly observed grade 3 toxicity. The most common nonhematological toxicities of any grade included nausea, vomiting, decreased appetite, fatigue and diarrhea. Only 4% of subjects receiving TAS-102 discontinued treatment because of the adverse events. There was one treatment-related death secondary to septic shock. This trial also evaluated subjects for

changes in their ECOG performance status as a result of the treatment. Subjects in the TAS-102 group experienced a significant delay in ECOG performance status deterioration from 0 or 1 to 2 or worse compared with the placebo group (5.7 vs 4.0 months with HR of 0.66 and $p < 0.001$) again pointing toward good tolerability of this agent.

The toxicity profile of TAS-102 compares favorably to that of regorafenib, a small-molecule tyrosine kinase inhibitor approved for use in mCRC in a similar setting. Regorafenib provides similar benefit on overall survival to TAS-102 with a different toxicity profile as seen in the Phase III randomized, placebo-controlled clinical trial (CORRECT) [59]. A total of 67% of patients required dose modifications of regorafenib in the CORRECT study, compared with 14% of patients treated with TAS-102 [6,59]. In a comparable patient population with mCRC that has progressed on standard chemotherapy regimens and approved biological therapies excluding regorafenib, TAS-102 appears to provide a valuable alternative to regorafenib.

The results of the completed clinical trials with TAS-102 demonstrated favorable toxicity profile of this agent. TAS-102 is safe to use in heavily pretreated patient population. Moreover, this agent may be amenable to safe combination with other chemotherapeutic or biological agents in the future studies.

Conclusion

TAS-102 has demonstrated activity in heavily pretreated mCRC, including patients who have previously progressed on fluoropyrimidines. Preclinical and clinical data demonstrate that this agent can overcome resistance to standard fluoropyrimidines. Since fluoropyrimidines are widely used in oncological practice and are particularly active against GI cancers, TAS-102 has the potential to be effective against a variety of tumors, including those previously exposed to fluoropyrimidine-based therapies. Given a favorable toxicity profile, future clinical trials will explore the possibility of introducing this drug during earlier lines of mCRC therapy. TAS-102 is also being studied in combination with other chemotherapy and biological agents based on the preclinical data that indicate potential synergism between these compounds. All evidences suggest that TAS-102 has broad applicability in chemotherapy backbone regimens utilizing antimetabolite anticancer drugs.

Table 3. Toxicity profile of TAS-102 in the Phase II and III studies.				
Toxicity	Phase II study		Phase III study	
	Any grade (%)	Grade 3–4 (%)	Any grade (%)	Grade 3–4 (%)
Neutropenia	72	50	67	38
Leukopenia	76	28	77	21
Anemia	73	17	77	18
Thrombocytopenia	39	4	42	5
Fatigue	58	6	35	4
Diarrhea	38	6	32	3
Nausea	65	4	48	2
Febrile neutropenia	4	4	4	4
Vomiting	34	4	28	2
Anorexia	62	4	39	4

Adapted with permission from [6,50].

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employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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EXECUTIVE SUMMARY**Mechanism of action**

- TAS-102 is a combination drug that consists of an antineoplastic thymidine-based nucleoside trifluridine (trifluorothymidine [TFT]) and a thymidine phosphorylase inhibitor.
- Phosphorylated form of TFT is incorporated into DNA resulting in DNA dysfunction and cell cycle arrest.
- Thymidine phosphorylase inhibitor inhibits degradation of TFT and inhibits angiogenesis.

Dosage & administration

- TAS-102 is an oral combination agent.
- TAS-102 is administered at a dose of 35 mg/m² twice a day on days 1–5 and 8–12 of a 28-day cycle.
- TAS-102 should be taken within 1 h after completion of morning and evening meals.

Clinical efficacy

- TAS-102 improved overall survival when compared with placebo (7.1 vs 5.3 months; hazard ratio: 0.68) in patients with metastatic colorectal cancer who have been previously treated with at least two prior regimens of standard chemotherapy in the global RECURSE Phase III trial.
- TAS-102 delayed deterioration of Eastern Cooperative Oncology Group performance status in patients with metastatic colorectal cancer refractory to standard therapies.

Safety & tolerability

- TAS-102 is generally well tolerated.
- The most common grade ≥3 adverse event in clinical trials was myelosuppression, which was managed with treatment delays, dose reductions and, rarely, growth factor support.

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