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DRUG EVALUATION

Evaluating trifluridine + tipiracil hydrochloride in a fixed combination (TAS-102) for the treatment of colorectal cancer

N. Mulet[a,b], I. Matos[a,c], A. Noguerido[a,c], G. Martini[c], M. E. Élez[a,c], G. Argilés[a,c] and J. Tabernero[a,c]

[a]Department of Medical Oncology, Vall D'Hebron University Hospital Barcelona/Universitat Autònoma de Barcelona, Barcelona, Spain; [b]Department of Medical Oncology, Institut Català d'Oncologia-IDIBELL, Universitat de Barcelona, Barcelona, Spain; [c]Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

ABSTRACT

Introduction: Despite major progress in treating advanced colorectal cancer (CRC), prognosis in this population after progression on standard treatment remains dismal and the development of new drugs represents an unmet need. Historically, fluoropyrimidines have played a major role in the treatment of metastatic CRC. TAS-102, a novel combination of trifluridine and tipiracil hydrochloride, has demonstrated improvement in overall survival in the refractory CRC setting, with a safe toxicity profile.

Areas covered: A literature review of published clinical studies was performed. Herein, the authors review the pharmacological and clinical data of TAS-102 when used in metastatic CRC, both as a single agent as well as in novel combinations under investigation.

Expert opinion: The addition of TAS-102 to the therapeutic armamentarium of metastatic CRC is an encouraging breakthrough considering the demonstrated survival benefit and favorable tolerability profile. Combinations with other agents are under clinical investigation in different settings in an attempt to widen its use. To optimize treatment in today's era of molecular oncology, efforts should be focused on understanding primary and secondary resistance mechanisms, along with the identification of potential biomarkers of response.

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Biomarker; colorectal cancer; combination therapy; RECOURSE; refractory setting; TAS-102; trifluridine; tipiracil hydrochloride

1. Introduction

Colorectal cancer (CRC) is the second most common malignancy worldwide, with close to 135,000 new cases and 50,000 related deaths reported in 2017 in the United States alone [1]. These dramatic figures are driven by the fact that 50% of patients diagnosed with CRC will become unresectable and subsequently incurable [1–3]. Major efforts have been made to raise the bar for efficient therapeutic approaches, which has seen the progressive introduction of new agents into routine clinical practice. As a result, survival of patients with metastatic CRC (mCRC) has increased dramatically over the past decade, notably thanks to the addition of agents targeting angiogenesis, either antibodies that bind to vascular endothelial growth factor (VEGF) or its receptor (VEGFR) and also agents inhibiting proliferation by blocking the epidermal growth factor receptor (EGFR). Combinations of these drugs with a FOLFOX or FOLFIRI chemotherapy backbone are standard treatments in both the first- and second-line setting [4–10].

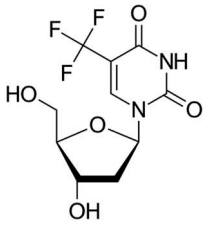
Nevertheless, the options in refractory-stage patients remain restricted. The anti-EGFR monoclonal antibodies, panitumumab and cetuximab, have demonstrated increased progression-free survival (PFS) versus best supportive care when given as monotherapy in patients with a wild-type *RAS* oncogene who have progressed on 5-fluorouracil (5-FU), oxaliplatin, and irinotecan [11,12]. Likewise, regorafenib, a multi-targeted kinase inhibitor, was approved for patients previously treated with a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, as well as cetuximab or panitumumab for patients without *KRAS* mutations in exon 2, on the basis of the phase III CORRECT and CONCUR studies [13,14]. The CORRECT trial, carried out in a mainly Caucasian population, demonstrated an increase in median overall survival (OS) in the regorafenib arm with 6.4 months (95% CI 3.6–11.8) versus 5.0 months (95% CI 2.8–10.4) for placebo, giving a hazard ratio (HR) of 0.77 (95% CI 0.64–0.94; $P = 0.0052$), but at the cost of a 33% rate of grade 3 and 4 adverse events. This outcome was subsequently confirmed in the CONCUR study for an Asian population [14]. This narrow risk/benefit ratio raises the need to develop new approaches with better tolerability profiles. In this regard, several clinical trials are currently ongoing to address this issue (NCT02368886 and NCT02835924).

A recent arrival to this challenging scenario, TAS-102 (Lonsurf®; Taiho Oncology), an oral combination of trifluridine (a nucleoside analog) and tipiracil hydrochloride (a thymidine phosphorylase inhibitor), has demonstrated proven efficacy in the treatment of chemorefractory CRC, as described below. This review summarizes available pharmacological and clinical data on TAS-102 in advanced mCRC, along with new potential applications and combinations that are currently being evaluated in several clinical trials.

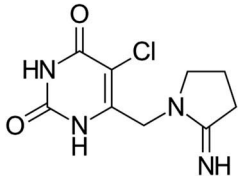
CONTACT J. Tabernero jtabernero@vhio.net. Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), P. Vall d'Hebron 119-129, Barcelona 08035, Spain

Box 1. Drug summary.

Drug name: TAS-102 (trifluridine and tipiracil hydrochloride)
Development phase: Launched
Indication: mCRC
Pharmacological description: Trifluridine is a thymidine-based nucleoside analog capable of inhibiting thymidylate synthase, a crucial enzyme in DNA synthesis. Tipiracil hydrochloride inhibits an enzyme involved in trifluridine degradation
Route of administration: Oral
Chemical structure:



Trifluridine



Tipiracil

Pivotal trial: RECOURSE [24]

mCRC: Metastatic colorectal cancer.

2. Drug chemistry

TAS-102 is a combination of trifluridine (FTD, a fluorinated thymidine analog) and tipiracil hydrochloride (TPI, a thymidine phosphorylase inhibitor) at a 1:0.5 molar ratio. The chemical names (IUAPC) of FTD and TPI are 1-[(2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-(trifluoromethyl)pyrimidine-2,4-dione and 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]-1*H*-pyrimidine-2,4-dione; hydrochloride, respectively. The molecular formula of TAS-102 is $C_{19}H_{23}Cl_2F_3N_6O_7$ and it has a molecular weight of 575.323 g/mol. The chemical structure of TAS-102 is shown in Box 1 along with the drug summary.

3. Mechanism of action and pharmacological parameters

FTD was synthesized in 1964 by Heidelberger et al. [15]. It is a thymidine-based nucleoside analog capable of inhibiting thymidylate synthase, a crucial enzyme in DNA synthesis. The FTD monophosphate metabolite F_3dTMP (trifluoromethyl deoxyuridine 5′-monophosphate) inhibits thymidylate synthase by binding to its active site, but unlike 5-FU, the inhibition is rapidly reversible. Phosphorylation of F_3dTMP results in the formation of F_3dTTP (trifluoromethyl deoxyuridine 5′-triphosphate) that is incorporated into DNA as a complimentary base to adenine. Importantly, the concentration of FTD incorporated into DNA is approximately 300-fold higher than that of 5-FU and furthermore is also higher in tumor tissues than in normal tissues [16].

In humans, FTD is rapidly degraded to its metabolite (5-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione) (18 min after intravenous administration) mainly during first-pass metabolism by the liver and intestines. However, TPI inhibits an enzyme involved in FTD degradation (thymidine phosphorylase) improving the bioavailability of FTD when administered orally [17].

Both FTD and TPI are rapidly absorbed, with a mean T_{max} of around 2 h [18]. Analysis of the food effect on TAS-102 pharmacokinetics revealed that postprandial administration is optimal with no effects on FTD area under the curve and thus no impact on efficacy. On the other hand, the rapid absorption derived from a fasting administration has been linked to higher C_{max} and thus higher rates of neutropenia [19,20]. Elimination half-life is about 2 h and neither FTD nor TPI are metabolized by the cytochrome pathway [18,19].

4. Clinical development of TAS-102

4.1. Phase I studies

Early clinical development of trifluridine was first implemented during the 1970s showing proficient antitumor activity; however, as discussed above, its poor pharmacokinetic properties blocked further development. It was only several years later that the combination of trifluridine with tipiracil was demonstrated to improve the bioavailability of trifluridine, leading to the initiation of the clinical development of TAS-102.

A Japanese phase I trial with a conventional 3 + 3 escalation design enrolled 21 patients with advanced solid tumors, 18 of whom had mCRC. The starting dose was 30 mg/m^2/day for 5 days a week for two consecutive weeks, followed by a 2-week rest, with 28-day cycles. One of the six patients who received the first dose level experienced dose-limiting toxicities (DLT) (grade 4 leucopenia, neutropenia, and thrombocytopenia); however, no further DLTs were described at the subsequently explored doses of 40, 50, and 60 mg/m^2. At the highest dose level tested, 70 mg/m^2, one of the six patients experienced a DLT (grade 4 neutropenia), and this dose was considered the recommended phase 2 dose without defining a maximum tolerated dose (MTD). In this trial, increasing doses of oral TAS-102 resulted in linear increases in the systemic concentration of the drug, accounting for the enhanced clinical activity of TAS-102 in terms of disease control rate and PFS at higher dose levels [19].

A second phase I trial was conducted in a Western population and was restricted to mCRC patients. The trial also used a conventional 3 + 3 dose-escalation design and was followed by an expansion cohort. The first three patients treated received TAS-102 at a dose of 30 mg/m^2 twice daily, a dose deemed to be safe, so in cohort 2, TAS-102 was explored at a dose of 35 mg/m^2 twice daily and included nine patients. In both cohorts, TAS-102 was administered on days 1–5 and 8–12 of each 4-week cycle. The dose of 35 mg/m^2 twice daily was selected for the expansion cohort, and 15 patients were treated. The only DLT observed during the dose-escalation part was grade 3 febrile neutropenia, seen in two out of the nine patients treated in cohort 2 (35 mg/m^2). The recommended dose was determined to be 35 mg/m^2 twice daily on days 1–5 and 8–12 of each 4-week cycle. The most frequent adverse events were grade 3/4 neutropenia and anemia (71% and 25% of patients, respectively). Only 7% of patients presented febrile neutropenia and no treatment-related deaths were observed. In terms

of efficacy, no partial responses were observed and 70% of patients treated at the recommended dose remained stable after 6 weeks of treatment. Median PFS in the overall population (N = 27) was 4.1 months (95% CI 2.7–9) and median OS was 8.9 months (95% CI 4.9–14.4), remarkable outcomes in a heavily pretreated population [21].

An additional phase I trial with TAS-102 was conducted to specifically evaluate cardiotoxicity in terms of QT prolongation, ischemia, syncope, seizure, or arrhythmia. The trial included 30 patients with advanced solid tumors and no cardiac events were observed. This established a clear differentiation of TAS-102 from other fluoropyrimidines that commonly present these events and which are a source of major concern in routine clinical practice [22].

4.2. Phase II study

In light of the encouraging results observed in the mCRC population, a phase II study was conducted in Japanese patients to evaluate the efficacy of the recommended dose (35 mg/m^2 twice daily with a 28-day cycle, days 1–5 and 8–12 of each 4-week cycle). In this multicentric, double-blinded, placebo-controlled trial, 169 patients were randomized to TAS-102 or placebo in a 2:1 fashion. The primary end point was OS, and secondary end points were PFS and safety in the overall study population. Median OS was 9.0 months in the TAS-102 arm versus 6.6 months in the placebo group (HR for death 0.56, 95% CI 0.39–0.81; P = 0.0011) [23]. Interestingly, this benefit was seen irrespective of performance status, primary tumor location, number of metastatic sites, organs involved, number of previous chemotherapy lines, *RAS* status, and pretreatment with biologic agents. However, median PFS according to an independent review committee was 2 months versus 1 month in the TAS-102 and placebo arms, respectively (HR 0.41, 95% CI 0.28–0.59; P < 0.0001). Similar to the phase I trial, only one patient in the TAS-102 arm had a partial response; however, the disease control rate was 43% with TAS-102 compared with 11% in the placebo arm. In this study, patients whose tumors harbored a *KRAS* mutation had a numerical trend toward better OS and PFS with TAS-102 compared to their *KRAS* wild-type counterparts.

In terms of tolerability, 20% of patients in the TAS-102 arm required at least one dose reduction and 31% required treatment interruption, mainly due to hematologic toxicities [23]. This correlated with a tolerability profile characterized by hematologic toxicity, with half of the patients presenting grade 3/4 neutropenia, 17% had anemia (all grades), and 10% had lymphopenia. Nevertheless, non-hematologic grade 3/4 adverse events (fatigue, diarrhea, nausea, anorexia, and vomiting) were much less frequent, being reported in around 4–6% of patients.

4.3. Phase III study

The pivotal phase III RECOURSE trial led to the approval of TAS-102 for the treatment of chemo-refractory mCRC. This trial used a 2:1 randomized, double-blind design comparing TAS-102 versus placebo [24]. The TAS-102 dose of 35 mg/m^2 twice daily on days 1–5 and 8–12 of each 4-week cycle was explored based on the results of the aforementioned two phase I trials and the phase II trial. The population was composed of 800 patients with chemo-refractory or chemo-intolerant mCRC from Japan, USA, Europe, and Australia. Patients were stratified according to *KRAS* status, geographic region, and time from diagnosis of metastatic disease to randomization.

The study met its primary end point of OS, with an HR of 0.68 (95% CI 0.58–0.81; P < 0.001) for TAS-102 compared to placebo. Median OS was 7.1 months (95% CI 6.5–7.8) in the TAS-102 arm compared to 5.3 months (95% CI 4.6–6) in the placebo group. Of note, benefit was observed in all prespecified clinical and molecular subgroups. Median PFS for TAS-102 was 2.0 months (95% CI 1.9–2.1) compared to 1.7 months (95% CI 1.7–1.8) in the placebo group, with an HR of 0.48 (95% CI 0.41–0.57; P < 0.001).

In line with what was observed in the phase I and II trials, TAS-102 did not demonstrate superiority to placebo in terms of the objective response rate (1.6% in the TAS-102 arm); however, the disease control rate at week 6 was 44% versus 16% in the experimental and placebo groups, respectively (P < 0.001). Furthermore, patients treated with TAS-102 presented a significant delay in the worsening of ECOG performance status, accounting for a direct impact on patients' quality of life.

In-depth review of the data highlighted that TAS-102 was effective even after regorafenib treatment, regardless of mutational status of *KRAS*, and was particularly active when 5-FU was included in the last treatment administered before receiving TAS-102. No conclusions can be drawn however in terms of *BRAF* since only 15% of tumor samples were assessed for this molecular status.

TAS-102 tolerability profile was coherent with that of a cytostatic agent. Patients who received TAS-102 experienced more grade 3 or higher adverse events than those in the placebo group, most of which were hematologic disturbances (38% of patients had neutropenia, although only 4% had febrile neutropenia, 18% had anemia, and 5% had thrombocytopenia). One treatment-related death occurred and was caused by septic shock. Grade 3 or higher non-hematologic adverse events in the TAS-102 group were much lower, since fewer than 4% of patients suffered from gastrointestinal toxicity. Importantly, confirming the outcome of the phase I cardiotoxicity trial, less than 1% of patients treated with TAS-102 presented coronary spasm. As a consequence, the RECOURSE trial led to approval of TAS-102 for refractory mCRC by the Food and Drug Administration in September 2015 and the European Medicines Agency in April 2016.

4.4. Expanded access program

A post-marketing surveillance study of TAS-102 in the Japanese population was recently published with the aim of determining the safety of the drug in the real-life setting. A total of 3420 patients were included in the analysis consolidating the already well-defined tolerability profile. Interestingly, no differences in terms of toxicity were identified between patients younger than 70 years versus older than 70 years. While seven patients developed interstitial lung disease, all of them recovered after treatment withdrawal; of note, three of

these patients had previously presented interstitial lung disease related to other chemotherapeutic agents [25].

5. The search for biomarkers of response

To date, no biomarkers of response to TAS-102 have been validated. Nonetheless, patients who develop neutropenia of at least grade 2 during the first month of treatment with TAS-102 have a better outcome, suggesting a potential role of neutropenia as a surrogate marker of drug exposure that could be exploited to individualize TAS-102 doses and follow-up [26,27]. Further studies are required to validate this hypothesis.

In another biomarker approach, a recent report of analysis of genomic DNA extracted from tumor samples of patients treated with TAS-102, associated polymorphisms in genes involved in the homologous recombination DNA repair system, such as ATM and XRCC, with a better clinical outcome with TAS-102 [28]. In preclinical models, FTD is incorporated into DNA and induces single-strand breaks followed by double-strand breaks, during the G2/M-phase of the cell cycle [28]. These double-strand breaks are repaired by homologous recombination mechanisms involving several proteins, including ATM, BRCA, CHECK, or XRCC. Genetic variants in homologous recombination pathways with different activity may predict response to TAS-102.

Polymorphisms in transporter genes have also been described as biomarkers for efficacy and toxicity in patients treated with TAS-102, mainly in two enzymes, organic cation transporter 2 (OCT2) and human multidrug and toxin extrusion 1 (MATE1). OCT2 and MATE1 are important in TPI excretion and renal clearance, so their activity may modulate levels of TPI in blood. On the other hand, genetic variants in human equilibrative nucleoside transporters may decrease FTD activity given that these cell membrane proteins are involved in the uptake and release of nucleosides and nucleoside analogues such as FTD [29].

6. New combinations with TAS-102 under development

To further exploit the potential of TAS-102, various combination therapy strategies have been launched. TAS-102 is currently being explored in other CRC settings than in refractory patients, mostly in combination with other drugs frequently used in mCRC. Table 1 summarizes the clinical trials that are currently ongoing with TAS-102 in mCRC.

Preclinical studies have shown that the combination of TAS-102 with irinotecan in xenograft mouse CRC models resulted in meaningful antitumor activity, including in tumors previously treated with 5-FU [30]. In the clinical setting, a phase I trial has been performed in a Japanese population, exploring the combination of TAS-102 with irinotecan. The recommended dose was defined as irinotecan 150 mg/m^2 on days 1 and 15 of a 28-day cycle combined with TAS-102 25 mg/m^2 every 12 h administered according to the day 1–5, 8–12 standard 28-day schedule. DLTs were grade 3 febrile neutropenia and grade 4 neutropenia. In terms of efficacy, two patients out of seven presented partial response. However, the early onset of DLTs makes continued development of the combination difficult using this same treatment schedule [31]. As a consequence, alternative schedules administering TAS-102 on only days 1–5 of a 14-day cycle are being explored to improve the tolerability of the combination (NCT01916447).

The efficacy of TAS-102 in combination with oxaliplatin has also been tested in mice xenografts derived from CRC cell lines [32]. Administration of both drugs resulted in significantly superior antitumor activity over each drug as single-agent therapy. Based on this observation, two studies are exploring the combination. A phase Ib trial has explored the safety of the combination in a dose-escalation phase using the MTD the labeled dose of both agents (NCT02848443). The combination was well tolerated and only one DLT was observed (grade 3 febrile neutropenia). The most common non-hematologic adverse events included nausea, asthenia, vomiting, diarrhea, and decreased appetite. Moderate-to-severe neutropenia occurred in five patients and thrombocytopenia in four

Table 1. Trials testing new therapeutic combinations with TAS-102 in mCRC.

NCT ID	Stage of development	Drugs	Population
NCT02613221	Phase I/II	TAS-102 + panitumumab	Patients with *RAS* wild-type mCRC refractory to standard chemotherapy
NCT02654639	Phase II	TAS-102 + bevacizumab	Maintenance with TAS-102 plus bevacizumab after induction chemotherapy in mCRC
NCT02860546	Phase II	TAS-102 + nivolumab	Patients with microsatellite stable refractory mCRC
NCT02848079	Phase I/II	TAS-102 + oxaliplatin	Patients with mCRC whose cancer has progressed or recurred after FOLFOX chemotherapy
NCT02602327	Phase I	TAS-102 + SIR-Sphere	Patients with chemotherapy-refractory liver-dominant chemotherapy-refractory mCRC
NCT02848443	Phase I	TAS-102 + oxaliplatin + nivolumab or bevacizumab	Patients with mCRC progressing on standard therapy (dose escalation)
NCT02743221	Phase II	TAS-102 + bevacizumab vs. capecitabine + bevacizumab	Frail patients not able to receive doublet chemotherapy in front-line
NCT01916447	Phase I	TAS-102 + irinotecan	mCRC patients who have progressed on at least one treatment line
NCT03368963	Phase I/II	TAS-102 + nanoliposomal irinotecan	mCRC patients who have progressed on at least one treatment line
NCT03305913	Phase I	TAS-102 + regorafenib	Third-line mCRC
NCT03223779	Phase I/II	TAS-102 + stereotactic body radiotherapy	mCRC patients with liver involvement suitable for stereotactic body radiotherapy
NCT03317119	Phase I	TAS-102 + trametinib	*RAS* mutant or unresectable mCRC who progressed on standard therapy

mCRC: Metastatic colorectal cancer; *KRAS*: Kristen rat antigen sarcoma gene.

patients (all grade 1). Interestingly in this oxaliplatin pretreated population, neurotoxicity grade ≥2 was observed in only two patients [33]. This trial is currently exploring the addition of bevacizumab or nivolumab to the combination in the two expansion cohorts. Another phase I/II trial is currently exploring this combination in patients previously progressing on FOLFOX (NCT02848079). In addition, two phase II trials are evaluating treatment with TAS-102 plus bevacizumab, one as maintenance therapy after first-line induction chemotherapy (FOLFOX or FOLFIRI; NCT02613221) and the other as front-line therapy for frail patients unable to receive doublet chemotherapy combinations (NCT02743221).

In the refractory setting, TAS-102 with panitumumab is being evaluated in a phase I/II trial in *RAS* wild-type patients (NCT02613221). The combination approach with the PD-1 immune checkpoint inhibitor nivolumab is under evaluation in patients with microsatellite-stable and refractory mCRC, based on the idea that TAS-102 may generate new neoantigens which could be recognized by lymphocytes, thereby being synergistic with nivolumab (NCT02860546).

Finally, TAS-102 has been tested with ionizing radiation in preclinical models. Matsuoka et al. showed that FTD sensitizes colorectal cells to ionizing radiation using an *in vitro* clonogenic survival assay [34]. These outcomes are particularly encouraging and clinical trials exploring and improved chemoradiation using TAS-102 are underway (NCT03223779).

7. Conclusion

The search for effective treatments for mCRC patients who have progressed after standard therapies is a major and urgent unmet need given the dismal prognosis of these patients. TAS-102 has a number of advantages over 5-FU, with its notably improved stability and allowing dramatically higher concentrations to be incorporated into DNA and localized to tumor tissues. Likewise, TAS-102 has demonstrated a significant OS benefit in this setting with a manageable toxicity profile mostly consisting of hematologic adverse events, leading to its approval worldwide in the refractory mCRC setting. Although the median absolute survival benefit of TAS-102 is around 2 months compared with placebo, it clearly contributes to the prolongation of CRC patients' life, which today is often in the order of 30 months.

While TAS-102 has recently been added to the medical armamentarium against refractory CRC, it is not the only new agent in the setting. Regorafenib is another oral drug that inhibits several kinases involved in angiogenesis and oncogenesis (*VEGFR 1–3, TIE2, KIT, RET, RAF1, BRAF, PDGFR*, and *FGFR*). In its pivotal trial, regorafenib also demonstrated significantly longer OS and PFS compared with placebo.

A trial comparing both drugs head to head is lacking; however, retrospective analysis – that should be interpreted with caution – did not identify any differences between these two agents in terms of efficacy but did in terms of safety, creating nonequivalent benefit/risk ratios [35]. Unlike TAS-102, regorafenib significantly induces higher ratios of hand–foot syndrome and liver enzyme alterations, an observation that could be relevant for therapeutic decisions due to the lack of well-established biomarkers to guide treatment choice in the refractory setting.

8. Expert opinion

Metastatic and unresectable CRC represents a major challenge for clinicians, since their main goal is to prolong OS without impairing quality of life. Several front-line strategies are approved for these patients as well as in the second- and third-line setting, including class chemotherapy drugs in combination with anti-EGFR antibodies or antiangiogenic agents when molecularly and clinically indicated. However, less than 30% of patients are suitable for receiving second-line therapy and beyond and furthermore most of them present symptoms or laboratory alterations that give them a small chance of being eligible for a clinical trial. The availability of new drugs with an acceptable toxicity profile and improvement in OS in the refractory setting, such as TAS-102, represent a small but important step forward in the continued care of these patients.

TAS-102 is currently the only chemotherapy agent approved for the refractory setting in mCRC, its main feature being a favorable safety/efficacy ratio including in heavily pretreated patients who have progressed on regorafenib (an oral multikinase inhibitor that shares this indication with TAS-102), and its better cardiac safety compared to fluoropyrimidines. However, the absolute numerical improvement in OS remains modest, at only 1.8 months increase over placebo. Clinicians and researchers need to use a two-pronged approach to improve patient selection and maximize patient outcomes. On the one hand, mechanisms of primary resistance to TAS-102 or positive biomarkers that could predict greater efficacy with this drug should be investigated. On the other hand, a search for secondary resistance mechanisms that could be detected early during treatment is essential to avoid potential toxicity, while possible therapies to counter such resistances need to be identified in parallel. Until now, only neutropenia has been postulated as a potential biomarker of response, but in daily clinical practice, not all patients with prolonged benefit on TAS-102 experienced this toxicity. Further studies evaluating polymorphisms or molecular alterations acquired in thymidine phosphorylase, thymidylate synthase, or in the pathways in which they are involved are necessary to locate robust biomarkers of response to TAS-102. In addition, data analysis taking into consideration other less thoroughly explored molecular and clinical features, such as BRAF mutations, microsatellite instability status, and sidedness, may also help to select patients.

Clinical trials assessing the efficacy of TAS-102 (mostly in combination) in earlier lines of treatment for mCRC are currently ongoing. In this regard, we may need to wait for new combination studies focused on combinations with other chemotherapies and agents targeting VEGF and EGFR to define in the coming years the ultimate role of TAS-102 in the treatment of mCRC. Immunotherapy agents are also good potential candidates for combination with TAS-102, since they induce DNA damage and the possibility of neoantigen formation and,

as a consequence, increase the chance of response to immunotherapy.

TAS-102 is without question a very promising drug for continuing to improve the outcome in mCRC patients, notably in the development of different combinations and in alternative settings. Essential next steps in this development program will involve further analyses to determine the optimal sequence of treatment and biomarker research to guide patient selection in the current era of molecular oncology.

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