Pharmacological Mechanisms and Clinical Efficacy of TAS-102 in Colorectal Cancer Patients

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Abstract. Colorectal cancer (CRC) is ranked as the third most common cancer diagnosis and the second leading cause of cancer-related mortality globally; meanwhile, its patient population is primarily concentrated in the age group of 60 years and older. For now, the research about anticarcinogens against CRC already had magnificent results; among the findings, TAS-102 with its concomitant treatments was one of the most useful medicines, but it still needs to be improved. This review analyzes the latest research to elucidate the pharmacological mechanism of TAS-102 and compares the clinical data from different combination therapies to conclude with current achievements and future directions. In comprehensive words, TAS-102 plus panituzumab is the most effective TAS-102 combination treatment available, and the problems most urging to be resolved are optimising toxicity control and improving precision in patient selection. Against the backdrop of worldwide aging, this essay aims to provide a comprehensive review for researchers fresh to related topics and inform them of the importance of unsolved problems such as reducing the side effects and improving drug formulation.

Keywords: Colorectal cancer; pharmacological mechanism; TAS-102.

1. Introduction

CRC represents a formidable global health challenge, characterized by its anatomical division into colon cancer (CC) and rectal cancer (RC). The colon's architecture, featuring proximal and distal segments, serves as a conduit between the small intestine and the rectum. This disease poses a significant and growing public health challenge; global estimates for 2020 indicated over 1.9 million new CRC cases and 930,000 deaths. Furthermore, the burden is projected to rise to 3.2 million new cases and 1.6 million deaths by 2040, with the majority of cases predicted to occur in countries with high Human Development Index (HDI) [1].

Managing refractory metastatic CRC (mCRC) remains a particular clinical dilemma; for patients with mCRC who have tolerance to traditional fluoropyrimidines like fluorouracil, treatment options are limited. TAS-102 has emerged as a standard salvage therapy in this setting. It is a novel oral cytotoxic agent whose mechanism of action distinctively differs from fluoropyrimidines. This unique property allows TAS-102 to remain effective against certain fluoropyrimidine-resistant tumors, providing a crucial therapeutic option for this patient population.

The largest patient group of CRC is the elder people. In 2021, the age-standardized prevalence (ASPR) of CRC among individuals aged 60 and above worldwide reached 737.47/10 million, with an incidence rate (ASIR) of 149.16/10 million. Research predicts that by 2050, new cases of CRC in the elderly will reach 3.68 million, with China accounting for 28% of this increase [2]. This trend may cause some concern in countries like China, which face severe aging problems, since the population of CRC-related rates could have a significant increase for both incidence and mortality soon. According to moderate projections, the population aged 65 years or older in China is projected to increase from 14% to 20% of the total population by 2033 [3]. It is predictable that CRC will become a more concerning topic in aging countries, and to find a stable and reliable treatment would be essential.

TAS-102 is an oral combination anticancer drug containing trifluoro thymine (FTD) and tipiracil hydrochloride (TPI) in a 1:0.5 molar ratio. As a novel cytotoxic agent, it operates differently from fluorouracil-based drugs by overcoming 5-FU resistance [4]. The active component FTD's

phosphorylated product directly integrates into DNA strands, disrupting their function to exert antitumor effects. Although TAS-102 was widely used worldwide as a standard salvage therapy for mCRC, with proven survival benefits in phase III trials, there were still some disadvantages that needed to be improved. Firstly, the side effects of TAS-102 may affect the quality of life in elderly patients who are lacking. Current studies primarily focus on survival and objective response rates, while systematic evaluations of TAS-102's effects on functional status and QoL in the elderly are lacking. Secondly, TAS-102 combined with agents like bevacizumab shows synergistic effects, optimal dosing regimens, toxicity management strategies, and the best drug combinations for elderly patients require further investigation.

As a narrative review, this paper analyzes published data to evaluate the efficacy and safety of TAS-102 in patients aged more than 65 years, with a focus on its underlying pharmacological mechanisms and clinical trial outcomes.

2. Pharmacological Mechanisms

CRC is a formidable global health adversary, consistently ranking as the third most common and second deadliest malignancy worldwide. The core of its pathogenesis lies in abnormal signaling pathways that drive tumor development, sustain cancer cell proliferation, and enable metastatic dissemination. The core cause of CRC is genetic changes, and carcinogenesis involves three major genetic and epigenetic disruptions. That is the reason that TAS-102 is considered as a possible solution for CRC.

TAS-102 is an oral combination anticancer drug consisting of trifluridine (FTD) and tipiracil hydrochloride (TPI) in a 1:0.5 molar ratio. As illustrated in Fig. 1, the active cytotoxic component, FTD, is phosphorylated intracellularly. This phosphorylated product is then directly incorporated into DNA, which activates the caspase-9-mediated endogenous apoptosis pathway and triggers a p53-independent cell death program, thereby inhibiting cellular proliferation. Meanwhile, TPI potently blocks FTD's degradation in the liver and intestines through inhibition of thymidine phosphorylase (TPase) activity, thereby slowing down the rapid degradation of FTD in the liver and significantly enhancing its bioavailability and gastrointestinal tract [5]. FTD/TPI (TAS-102) was established as a standard third-line treatment for mCRC based on the pivotal results of the worldwide Phase III RECOURSE trial [6].

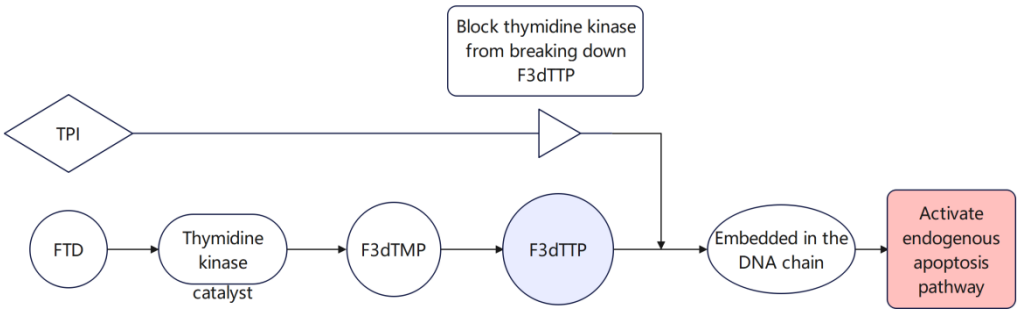


Fig. 1 The flow graph demonstrates the mechanism of the two ingredients cooperating when patients are having TAS-102 [5].

Although TAS-102 is a well-established treatment for mCRC, its toxicity profile remains a critical consideration in treatment decisions. The most common serious adverse events associated with TAS-102 are hematologic, such as grade 3-4 neutropenia, leukopenia, and anemia, among others. It is important to note that while fluoropyrimidines as a class are associated with cardiotoxicity, the risk profile of TAS-102 differs. This safety concern is underscored by data from a study of 110 patients, which found that 19% of those in the TAS-102 group experienced serious adverse events, compared to 9% in the placebo group [7].

However, for patients with previously treated metastatic CRC, the combination of TAS-102 plus bevacizumab (thereafter, BEV) has shown promising efficacy and a manageable safety profile.

Preclinical studies suggested that BEV may help increase FTD accumulation and its subsequent phosphorylation in tumors by normalizing tumor vasculature. In CRC xenografts, combination of TAS-102 plus BEV would increase the phosphorylated FTD levels and ability of inhibiting tumor growth was significantly enhanced with TAS-102 plus BEV compared with either single agent [8].

This preclinical promise was supported by a randomized, investigator-initiated, phase 2 trial conducted across four oncology centres in Denmark. The trial demonstrated a notably higher disease control rate in the combination group: 67% (31 of 46 patients) in the TAS-102 plus bevacizumab group versus 38% (18 of 47 patients) in the TAS-102 monotherapy group. Importantly, the addition of bevacizumab did not lead to a substantial increase in severe toxicity; serious adverse events were observed in 41% of patients in the combination group, compared to 45% in the monotherapy group [9].

Beyond the general metastatic CRC population, the TAS-102 plus bevacizumab regimen is particularly relevant for elderly patients, who often require efficacious yet tolerable therapies. For this demographic, chemotherapy must balance efficacy with the preservation of quality of life. The TAS-102 plus Bev combination has emerged as a favorable option due to its manageable safety profile. Clinical evidence suggests that this regimen can prolong survival while maintaining a good quality of life in older adults with mCRC.

3. Clinical Efficacy

3.1. Monotherapy

This section focuses on the efficacy and safety profile of TAS-102 monotherapy, thereby exploring the rationale for its use in combination strategies.

The efficacy of TAS-102 was established in a multicenter, double-blind, phase 2 trial in Japan, patients were randomized in a 2:1 ratio to receive either TAS-102 plus best supportive care or placebo [7]. The results demonstrated a significant survival benefit: median overall survival(MOS) was 9.0 months in the TAS-102 group versus 6.6 months in placebo group. Furthermore, based on an independent review, the disease control rate was markedly higher with TAS-102 (43%) than with placebo (11%); this included 1% partial response and 42% stable disease in the TAS-102 arm.

A preplanned exploratory analysis suggested that the efficacy of TAS-102 was particularly pronounced in patients with mutant KRAS tumors. KRAS, a key protein in the EGFR signaling pathway, drives tumor development upon mutation by encoding abnormal proteins that stimulate uncontrolled growth and metastasis [10]. In this subgroup, patients receiving TAS-102 achieved a MOS of 13.0 months, compared to 6.9 months in the placebo group, indicating a potential predictive role for the KRAS mutation status [7].

However, this clinical benefit was accompanied by a significant burden of adverse events. Grade 3 or 4 hematological toxicities, including but not limited to neutropenia, leukopenia were frequently observed in the TAS-102 group but were uncommon in the placebo group. This safety profile was corroborated by a larger study (N=553), which reported grade 3/4 neutropenia in 38% of patients (with 11% grade 4) and grade 3/4 thrombocytopenia in 5% (with 1% grade 4) [11]. Serious events included febrile neutropenia (3.8%) and one treatment-related death due to neutropenic infection (0.2%). Notable non-hematologic reactions included alopecia (7% vs. 1%) and pulmonary embolus (2% vs. 0%) (Table 1).

Table 1. Comparison of the ratio of main adverse events between TAS-102 administered alone and placebo only [11].

Adverse Reaction / Laboratory Abnormality	TAS-102 Group Incidence	Placebo Group Incidence
Hematologic Toxicity		
Anemia (grade 3-4)	77%	33%
Neutropenia	67%	1%
Thrombocytopenia	42%	8%
Non-Hematologic Toxicity		
Fatigue/Asthenia	52%	35%
Nausea	48%	24%
Decreased Appetite	39%	29%
Diarrhea	32%	12%
Vomiting	28%	14%
Abdominal Pain	21%	18%
Pyrexia (Fever)	19%	14%

In conclusion, TAS-102 monotherapy demonstrated efficacy in improving OS and disease control in patients with CRC, particularly in those with KRAS mutations. However, its use was associated with substantial toxicities. To mitigate these adverse events, combination therapies have been explored as a promising strategy.

3.2. Combination Treatment

The exploration of TAS-102 combination therapies has yielded several promising candidates, notably with bevacizumab, cetuximab, and panitumumab. To preclinically evaluate these strategies, an animal study on SW48 CRC xenografts compared them across three key metrics: weight change rate (indicating tolerability), relative tumor volume, and tumor growth inhibition rate (TGI) [8]. As demonstrated in Fig. 2, the combination of TAS-102 with bevacizumab emerged as the most favorable regimen, exhibiting the best overall profile: the highest tumor growth inhibition rate (86.1%), the smallest relative tumor volume (4.66), and a minimal weight change (0.40%) that suggested superior tolerability and a wider therapeutic window compared to other targeted combinations.

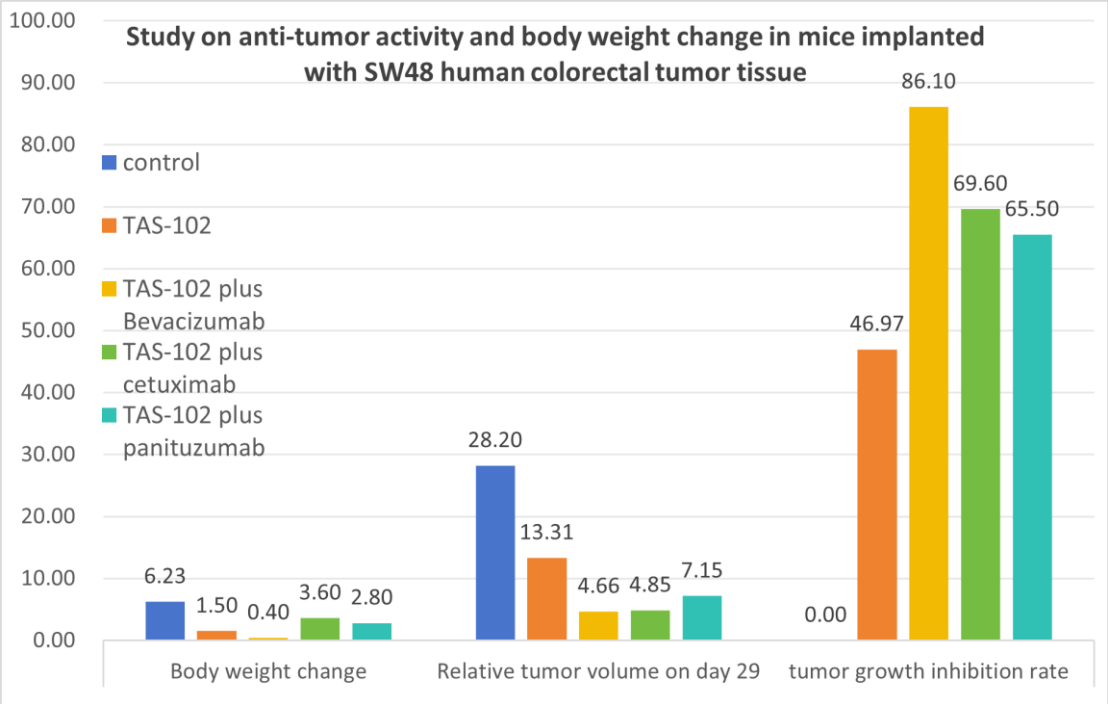


Fig. 2 The animal study aimed to compare the effect of three usual concomitant treatments and monotherapy [8].

The compelling preclinical data for TAS-102 plus bevacizumab found definitive validation in the phase 3 SUNLIGHT trial, which marked a significant advancement for patients with previously treated mCRC [12].

The trial's outcomes were striking: the combination therapy extended median overall survival to 10.8 months, compared to 7.5 months with TAS-102 monotherapy. This translated to a robust 39% lower risk of death (HR 0.61; P<0.001). An increased objective response rate (6.1% vs. 1.2%) further supported the combination's superiority. Importantly, subgroup analyses revealed that the survival benefits were universal across all patient categories (Fig. 3), a finding that aligns with the consistent efficacy observed in animal studies and highlights the reliability of this combination approach.

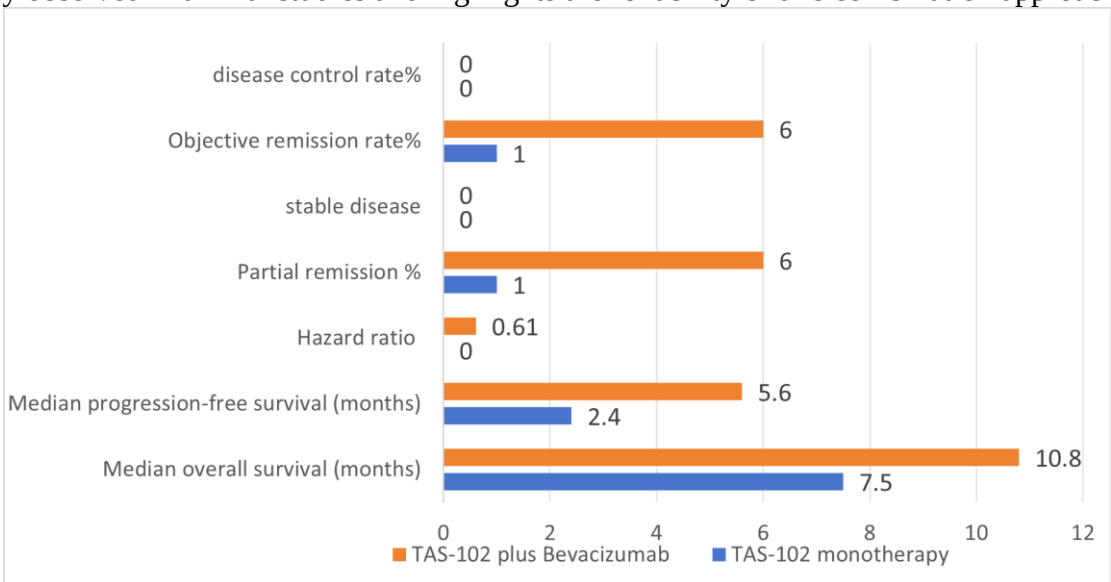


Fig. 3 Clinical data comparison between TAS-102 alone and plus BEV therapy [12].

However, a nuanced analysis of the clinical safety data reveals a more complex picture than the preclinical models suggested. While the animal study pointed to improved tolerability, the clinical data show that the enhanced efficacy comes with a manageable yet increased burden of specific adverse events. As shown in Fig. 4, A numerical increase in the incidence of grade ≥3 or higher

adverse events was observed with the combination regimen (72.4%) versus monotherapy (69.5%). Notably, the combination therapy was associated with expected increases in rates of hypertension (10.2% vs. 2.0%), nausea (37.0% vs. 27.2%), and neutropenia (62.2% vs. 51.2%), including severe neutropenia (43.1% vs. 32.1%). This increase in hematologic toxicity may be pharmacodynamically explained by bevacizumab's potential to promote the increased accumulation of phosphorylated trifluridine, thereby potentiating both its cytotoxic and myelosuppressive effects.

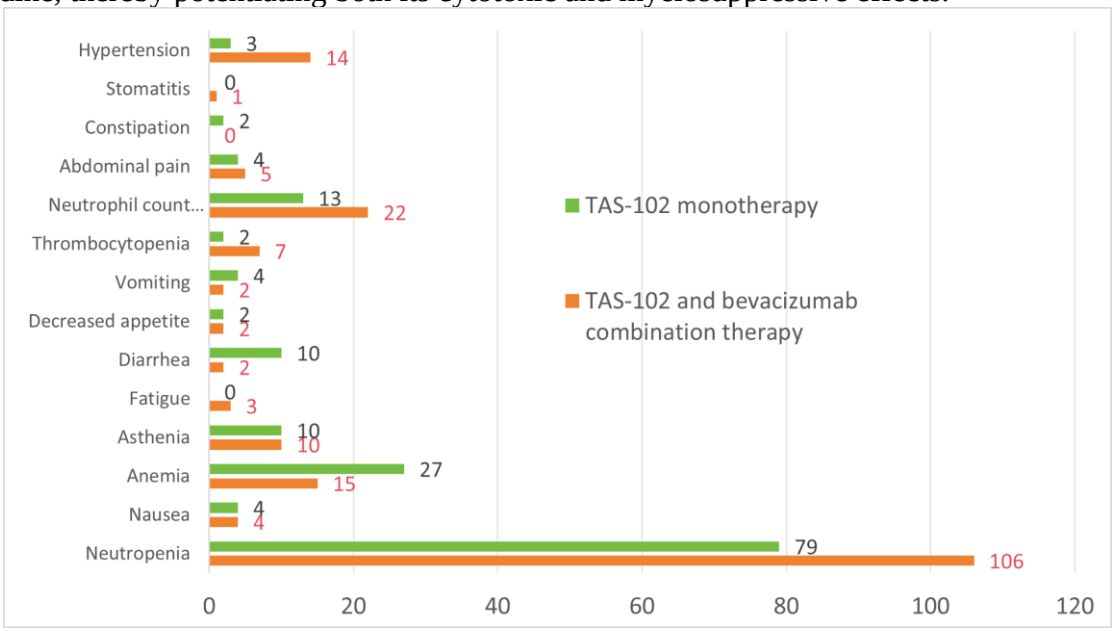


Fig. 4 Comparison of the number of serious adverse events between TAS-102 monotherapy and BEV combination regimen [12].

In conclusion, the journey from bench to bedside for the TAS-102/BEV regimen demonstrates a successful translation of preclinical promise into tangible clinical benefit. Despite eliciting a predictable increase in manageable toxicities, the regimen delivers a significant and robust improvement in survival outcomes for patients with mCRC. This favorable risk-benefit profile solidifies its role as a valuable therapeutic strategy in the later-line treatment setting.

4. Conclusion

As an oral combination of TFT and TPI, TAS-102 has demonstrated improved survival with a manageable safety profile in patients with refractory mCRC, including those with fluoropyrimidine-resistant disease. Beyond its current indication, TAS-102 presents undeniable potential for expanded clinical applications. This includes evaluation in combination with agents like bevacizumab for mCRC, as well as exploration of its efficacy in other tumor types and in earlier lines of therapy.

Since TAS-102 plus bevacizumab has emerged as a superior option for suitable patients, the treatment paradigm for elderly patients has evolved. However, significant challenges remain. Precision in patient selection still needs to be improved. Predictive biomarkers, rather than imperfect clinical metrics such as age and performance status, would allow for better selection. This makes it more difficult to identify individuals who are fit and those who are at risk but may still benefit from treatment. Optimizing toxicity control is also essential for preserving quality of life and treatment compliance in this susceptible group, especially for fatigue and neutropenia.

The future directions must fill these gaps through dedicated research. A primary focus should be on discovering and validating biomarkers, to enable personalized therapy and predict efficacy. Ultimately, the goal is to move beyond a one-size-fits-all approach and forge a path toward truly personalized and sustainable management of elderly mCRC with TAS-102.

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