RETRO-TAS, a Retrospective Observational Study of Trifluridine/ Tipiracil in Chemorefractory Metastatic Colorectal Cancer

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Number: P-50

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WORLD CONGRESS ON Gastrointestinal Cancer

INTRODUCTION

Trifluridine/tipiracile (FTD/TPI; TAS-102) is an oral combination of the antineoplastic nucleoside analogue trifluridine (FTD) and the thymidine phosphorylator inhibitor tipiracil (TPI). The primary cytotoxic mechanism is DNA dysfunction through incorporation of triphosphorylated FTD into DNA. This mechanism of action is distinct from the inhibition of thymidylate synthase caused by 5-FU and other fluoropyrimidines[1]. Reducing degradation of FTD, TPI improves the bioavailability and ensures sufficient blood concentrations of FTD. FTD/TPI is indicated for patients with metastatic colorectal cancer (mCRC) who have been treated with fluoropyrimidine-,oxaliplatin-, or irinotecan-based chemotherapies and antibodies targeting vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). FTD/TPI was approved for refractory mCRC in Japan (March 2014) [2] and subsequently, the RECOURSE trial led to approval in the United States (September 2015) and Europe (April 2016) [3]. The efficacy and safety of FTD/TPI monotherapy in adults with refractory mCRC has been demonstrated in a Japanese phase II trial by Yoshino et al [4] and later in the pivotal phase III RECOURSE trial [5]. The latter study showed that compared with placebo, FTD/TPI increased median overall survival (mOS) from 5.3 to 7.1 months (p<.001) and median progression free survival (mPFS) from 1.7 to 2.0 months (p<.001). Recently, a phase IIIb trial PRECONNECT, confirmed these results [6].

AIM

Study design: We conducted an investigator initiated retrospective analysis in patients with chemorefractory mCRC treated with TAS-102 (RETRO-TAS study NCT04965870) to record clinical practice and to collect real world data on the clinical efficacy of TAS-102 in the Greek population.

Main objectives: To assess physician's choice of treatment in chemoresistant metastatic colorectal cancer with FTD/TPI in third line and beyond. In addition, the clinicopathologic features related to metastatic colorectal cancer (focus on molecular profile, sideness), duration of treatment, dose modification and toxicity were analysed.

Study Endpoints: The primary endpoint was the Progression Free Survival (PFS) and as secondary endpoints the Overall Survival (OS), the PFS rate at 6 months and 8 months, the Duration of treatment with FTD/TPI, the Objective Responses, Disease Control Rate (DCR) and the efficacy endpoint: PFS and OS in relation to i) mutational status and ii)the number of metastasis and time from metastatic progression in three scenarios as follows: A) ≤2 metastatic sites, low metastatic burden and >18 months from first diagnosis of metastasis; B) ≤2metastatic sites, low metastatic burden and <18 months from first metastasis but no liver metastasis; C) >3 metastatic sites with high mutational burden and <18 months from first metastasis

METHODS

Patients: Data of patients with metastatic colorectal cancer, treated in 8 Cancer Centres, were collected to assess physician's choice of treatment in chemoresistant mCRC with TAS-102 in third line and beyond. Selection Criteria: Patient' s selection inclusion criteria were age > 18 years, histologically confirmed metastatic colorectal cancer, treatment according to the approved dose of TAS-102 in adults of 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle, and available data on previous chemotherapy lines. No exclusion criteria have been established for this observational and retrospective study. Statistics: The clinicopathologic features related to mCRC (focus on molecular profile), duration of treatment, dose modification and toxicity were analysed. The PFS, the OS, the 6-/8-month PFS rate and the disease control rate were calculated. Prognostic factors were evaluated by Cox regression model and Kaplan-Meier curves, along with log-rank tests using Stata/MP 16.0 for Windows.

RESULTS

Table 1. Baseline patient and disease characteristics

	N (%) 200 (100%)
Female Gender	84 (42.0)
Metastatic at diagnosis	116 (58.0)
ASA Score	
Normal healthy patient	109 (54.5)
Mild systemic disease	78 (39.0)
Severe systemic disease	12 (6.0)
Constant threat to life	1 (0.5)
Tumor Site	
Right	37 (18.5)
Left	90 (45.0)
Rectum	73 (36.5)
Presence of Mucus>50%	25 (12.5)
Molecular Markers	
Her2 Positive	7 (3.5)
MSI High	18 (9.0)
KRAS Mut	104 (52.0)
NRAS Mut	10 (5.0)
BRAF Mut	7 (3.5)
Patients with	
No marker	73 (36.5)
Any marker detected	127 (63.5)

Table 2. Patient and disease characteristics on TAS-102 initiation

	N (%) 200 (100%)
Performance Status (ECOG)	
0 or 1	135 (67.5)
2 or 3	65 (32.5)
Liver Metastatic Sites	
No	46 (23.0)
Yes	154 (77.0)
Lung Metastatic Sites	
No	95 (47.5)
Yes	105 (52.5)
Bone Metastatic Sites	
No	172 (86.0)
Yes	28 (14.0)
Other Metastatic Site	
No	141 (70.5)
Yes	59 (29.5)
Metastatic sites	
1 or 2	28 (14.0)
3 or more	172 (86.0)
>18 months from diagnosis	
No	60 (30.0)
Yes	140 (70.0)

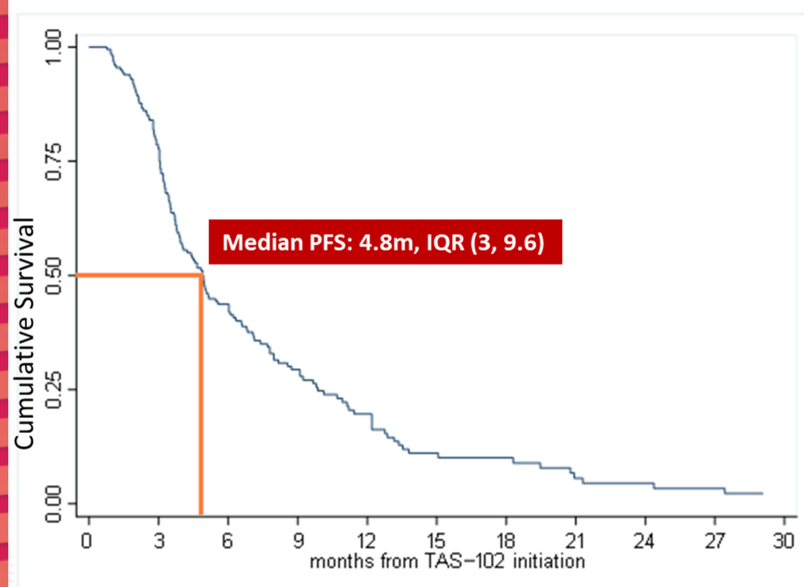
Table 3. Multivariable Cox Regression for Progression- Free Survival

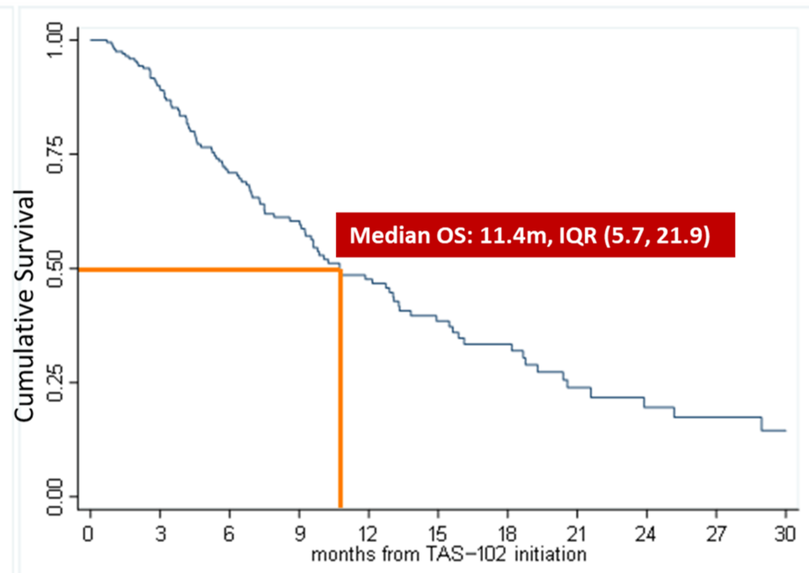
	HR	95%CI	P
Performance Status (ECOG)			
0 or 1	1		
2 or 3	2.686	1.893 – 3.813	0.001
Metastatic Sites			
Other	1		
Liver & Lung	1.536	1.108-2.128	0.010

Table 4. Multivariable Cox Regression for Overall Survival

	HR	95%CI	P
Performance Status (ECOG)			
0 or 1	1		
2 or 3	2.648	1.765-3.972	0.001
Metastatic Sites			
Other	1		
Liver & Lung	1.501	1.010-2.229	0.044
Metastatic at diagnosis			
No	1		
Yes	1.561	1.049-2.322	0.028

Figure 1. The median of progression free survival (PFS) and overall survival (OS) of patients treated with TAS-102





RESULTS

From October 2018 to October 2021, 200 patients with a median age at diagnosis of 63.7 years (IQR 54.2, 72.1) and at TAS-102 treatment initiation was 67.0 (IQR 58.0, 75.0). At the time of the analysis the median follow-up time was 14 months (IQR 7, 23), 158 PDs and 106 deaths were recorded. Patient clinicopathologic characteristics at diagnosis and on TAS-102 initiation are shown in **Table 1** and **Table 2** respectively.

Adjuvant chemotherapy and radical surgery was delivered in 39.5% and 51.5% respectively. TAS-102 was administered as a third (70.5%), fourth (17.0%) or fifth line (12.5%) of therapy. Patients received TAS-102 as monotherapy (71.5%), in combination with bevacizumab (24.5%) or with an anti-EGFR agent (4.0%).

Serious adverse events reported were neutropenia (4pts), anemia (2pts), thrombocytopenia (1pt), diarrhea (1pt), nausea (1 pt) and fatigue (8 pts).

Dose reduction, delay of initiation of the next cycle and shorter duration of therapy was reported in 25%, 31% and 14.5% of patients respectively.

RESULTS

The median duration of TAS-102 therapy was 119.5 days and 81% of patients discontinued therapy due to progressive disease.

Objective responses during TAS-102 therapy included 0.5% CR, 25% PR, 20% SD and 47% PD, while 7.5% of patients were not evaluable. The median PFS time was 4.8 and the median OS was 11.4 months (**Figure 1**). The 6 and the 8-month PFS rate was 41.4% and 31.5% respectively. In the multivariable analysis PS>1 and metastatic disease in the liver and lung were adversely associated with survival (**Table 3 and Table 4**) whereas tumor sidedness and mutational status were not.

CONCLUSIONS

This real-world observational study confirms and adds on the findings of the RECOURSE phase III study in relation to the toxicity and the effectiveness of TAS-102 in all subgroups of patients with chemotherapy refractory mCRC, regardless of mutational status and sidedness.

REFERENCES

1.Sunakawa Y. et al. Profile of trifluridine/tipiracil hydrochloride in the treatment of metastatic colorectal cancer:efficacy, safety, and place in therapy. Onco Targets Ther. 2017;10:4599–4605. 2.Yoshino T. et al. TAS-102 safety in metastatic colorectal cancer: results from the first postmarketing surveillance study. Clin Colorectal Cancer. 2016;15:205–211. 3.Mulet N. et al. Evaluating trifluridine/tipiracil hydrochloride in a fixed combination (TAS-102) for the treatment of colorectal cancer. Expert OpinPharmacother. 2018;19:623–629. 4.Yoshino T. et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 2012;13: 993–1001.5.Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372:1909–1919. 6.Bachet JB, et al. Safety, efficacy and patient-reported outcomes with trifluridine/tipiracil in pretreated metastatic colorectal cancer: results of the PRECONNECT study. ESMO Open 2020;5(3):e000698.

ACKNOWLEDGEMENT

The authors are grateful to SERVIER for supporting this research activity. The study sponsor had no interference in the study design, data collection or writing of the manuscript.

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