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pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Trifluridine-Tipiracil (Lonsurf) for Gastric Cancer

March 24, 2020

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List of Abbreviations

AE(s)	Adverse Events
BICR	Blinded independent central review
CI	Confidence interval
CGP	Clinical Guidance Panel
CR	Complete Response
DOR	Duration of Response
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICR	Independent Central Review
GC	Gastric Cancer
ORR	Overall response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
PFS	Progression free survival
PR	Partial Response
ECOG	Eastern Cooperative Oncology Group

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding trifluridine-tipiracil and gastric cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on a systematic review of the literature regarding trifluridine-tipiracil and gastric cancer conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on trifluridine-tipiracil for gastric cancer. and a summary of submitted Registered Clinician Input on trifluridine-tipiracil for gastric cancer and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of trifluridine-tipiracil, as monotherapy for the treatment of adult patients with metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior lines of chemotherapy including a fluropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate with HER2/neu-targeted therapy. The reimbursement request aligns with the approved Health Canada indication.[1]

Trifluridine-tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil (as tipiracil hydrochloride). The recommended dose of trifluridine-tipiracil (tablets) is a starting dose of 35 mg/m2/dose administered orally with water, twice daily, within one hour after completion of morning and evening meals, on days 1 to 5 and days 8 to 12 of each 28-day cycle. The treatment cycle is repeated every four weeks as long as benefit is observed or until unacceptability toxicity occurs.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized controlled trial (RCT), the TAGS trial (n=507), and the results are summarized below.

TAGS trial

TAGS was an international, double-blinded, phase III, randomized, placebo-controlled, superiority trial of trifluridine-tipiracil plus best supportive care (BSC) versus placebo plus BSC in patients with advanced gastric cancer, including those with adenocarcinoma of the gastroesophageal junction (GEJ), who were refractory or were intolerant to at least 2 prior therapies for their disease. Eligible patients were randomized in a 2:1 ratio to receive oral trifluridine-tipiracil at a dose of 35 mg/m^2 twice daily or matching placebo twice daily with best supportive care (BSC) on days 1 through 5 and days 8 through 12 of each 28-day

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treatment cycle until disease progression, unacceptable toxicity or withdrawal due to adverse events. There were 337 patients randomized to the trifluridine-tipiracil arm, of which 335 were treated, and 170 patients randomized to the placebo, of which 168 were treated.[2]

The primary endpoint of the TAGS trial was overall survival (OS), and secondary outcomes included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), time to deterioration to Eastern Oncology Group Performance Status (ECOG PS) ≥ 2. Health-related quality of life (HRQoL) was also explored and assessed using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 (QLQ-C30) and the EORTC gastric cancer module (EORTC-QLQ-STO22). Safety was monitored regularly throughout the study and included all patients who received at least 1 dose of the assigned treatment.[2]

The median age was 64 years in the trifluridine-tipiracil arm and 63 years in the placebo arm. Overall, the primary tumor site was gastric for 71% of patients had gastroesophageal junction for 29% of patients. All patients were previously treated with platinum and 99.8% were previously treated with a fluoropyrimidine. A number of demographic and disease characteristics were imbalanced which included a higher proportion of patients that were male (75% vs. 69%), had White ethnicity (72% vs. 66%), were ECOG PS 1 (64% vs. 60%), had HER2-positive disease (20% vs. 16%), and were previously treated with a taxane (92% vs. 87%) or immunotherapy (7% vs. 4%) in the trifluridine-tipiracil arm compared to the placebo arm, respectively. There were a higher proportion of patients with ≥3 metastatic sites (58% vs. 54%), ≥4 prior chemotherapy regimens (27% vs. 23%), and peritoneal metastases (31% vs. 26%) in the placebo arm compared to the trifluridine-tipiracil arm, respectively.[2]

Efficacy

The key efficacy outcomes are presented in Table 1.1, based on the final analysis with a data cut-off of March 27th, 2018 for OS (the date of the 384th death) and March 31st 2018 for all other endpoints.[3] The median duration of survival follow-up was 10.7 months (95% CI: 10.2, 13.1) in the overall ITT population, with a median duration of follow-up of 10.6 months (95% CI: 10.1, 13.1) in the trifluridine-tipiracil treatment arm and 10.7 months (95% CI: 9.9, 15.4) in the placebo arm.[4]

OS: The median OS was 5.7 months (95% CI: 4.8, 6.2) in the trifluridine-tipiracil treatment arm and 3.6 months (95% CI: 3.1, 4.1) in the placebo arm, with a 31% reduction in the risk of death in the trifluridine-tipiracil treatment arm relative to the placebo arm (HR: 0.69; 95% CI: 0.56, 0.86; p=0.0006). Subgroup analyses for OS were largely consistent with the primary results, except the following subgroups where the CIs crossed 1: patients that were female; of Asian ethnicity; from the United States or Japan region; had a primary site of GEJ; had diffuse tumor histology; had HER2-positive disease; had peritoneal metastases; had no previous gastrectomy; had 3 or 4 prior lines of chemotherapy regimens; had prior ramucirumab; had prior irinotecan; and patients that did not receive a prior taxane were suggested to be at increased risk for mortality (HR point estimate >1).[3]

PFS: The median PFS in the trifluridine-tipiracil arm was 2.0 months (95% CI: 1.9, 2.3) and 1.8 months (95% CI: 1.7, 1.9) in the placebo arm, with a 43% reduction in the risk of PD or death associated with the trifluridine-tipiracil arm relative to the placebo arm (HR: 0.57; 95% CI: 1.7, 1.9; p<0.0001). Subgroup analyses for PFS were largely consistent with the primary results, except for the following subgroups where the CI crossed 1: patients that were female; from the United States region; had no measurable disease; had mixed histology; and did not receive a prior taxane.[3]

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ORR: The ORR was 4.5% in the trifluridine-tipiracil treatment arm and 2.1% in the placebo arm.[3]

DCR: The DCR was 44.1% in the trifluridine-tipiracil treatment arm compared to 14.5% in the placebo, driven by the large proportion of patients achieving stable disease in the trifluridine-tipiracil treatment arm.[3]

Time to deterioration to ECOG PS ≥2: The median time to deterioration to ECOG PS ≥2 was 4.3 months (95% CI: 3.7, 4.7) in the trifluridine-tipiracil arm compared to 2.3 months (95% CI: 2.0, 2.8) in the placebo arm, representing a 31% reduction in the median time to deterioration to ECOG PS ≥2 relative to placebo (HR=0.69; 95% CI: 0.56, 0.85; p=0.0005).[2]

Health-related Quality of Life (HRQoL)

The mean baseline global health status (GHS) based on the EORTC QLQ-C30 was 58.4 for both treatment arms.[3] There were no clinically relevant changes (≥10 points) in GHS from baseline to up to cycle 3 in each treatment arm. There were no clinically relevant differences in the mean change in score from baseline for most of the functioning and symptom scales of the EORTC QLQ-C30, except for role functioning at cycle 3, where there was a difference of 10 points favouring placebo, and the pain scale at cycle 2, where there was a difference of 11.3 points favouring trifluridine-tipiracil. There were no clinically relevant changes in mean scores from baseline in the QLQ-STO22 scores.[5]

Harms

The median total treatment duration was 6.71 weeks in the trifluridine-tipiracil arm and 5.71 weeks in the placebo arm, and less than 50% of patients initiated treatment beyond cycle 2 in either treatment arm (43.3% in the trifluridine-tipiracil arm vs. 19.6% in the placebo arm initiated cycle 3). A total 58.2% of patients that required a dose modification (dose delay or dose reduction) in the trifluridine-tipiracil arm compared to 22.0% in the placebo arm. A total of 10.7% and 1.2% of patients required a dose reduction in the trifluridine-tipiracil and placebo arms, respectively.[3]

Any-grade AEs: There were a higher proportion of patients in the trifluridine-tipiracil arm (97.3%) who experienced at least 1 any-grade AE compared to the placebo arm (93.4%).[3] The most common any-grade AEs included anemia (44.5%), neutropenia (38.5%), nausea (37.0%), and decreased appetite (34.3%) in the trifluridine-tipiracil arm. In the placebo arm, the most common any-grade AEs included nausea (31.5%), fatigue (31.0%), asthenia (23.8%), and fatigue (20.8%).[6]

Grade ≥3 AEs: There were a higher proportion of grade ≥3 AEs that occurred in the trifluridine-tipiracil arm (79.7%) compared to the placebo arm (57.7%).[3] The most common grade ≥3 AEs in the trifluridine-tipiracil arm included neutropenia (23.3%) and anemia (18.8%), whereas in the placebo arm it was general physical health deterioration (8.9%), abdominal pain (8.9%), and anemia (7.7%).[6]

Serious adverse events (SAEs): SAEs occurred in a similar proportion between treatment arm, occurring in 42.7% of patients in the trifluridine-tipiracil arm and in 41.7% of patients in the placebo arm. In both treatment arms, general deterioration of health (6.3% and 8.9% in the trifluridine-tipiracil arms and placebo arms, respectively) and anemia (3.9% and 2.4%, respectively) were common SAEs.[6]

Withdrawal due to AEs (WDAEs): A total of 43 (12.8%) of patients discontinued treatment due to any AE in the trifluridine-tipiracil arm compared to 28 (16.7%) of patients in the placebo arm.[3]

Deaths: There were a total of 45 (13.4%) deaths due to AEs in the trifluridine-tipiracil arm compared to 19 (11.3%) in the placebo arm. General physical health deterioration was the

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most common AE in the trifluridine-tipiracil arm (n=17; 5%) and in the placebo arm (n=11; 7%) leading to death.[2]

Table 1.1. Highlights of Key Outcomes

	TAGS trial	
	Trifluridine-tipiracil Arm (N=337)	**Placebo Arm (N=170)**
Primary Outcome ᵻ		
Overall survival†		
Median months (95% CI)	5.7 (4.8, 6.2)	3.6 (3.1, 4.1)
HR (95%CI)	0.69 (0.56, 0.85)	
p-value**	0.00029	
Key Secondary Outcomes ᵀ		
Progression-free survival†		
Median months (95% CI)	2.0 (1.9, 2.3)	1.8 (1.7, 1.9)
HR (95%CI)	0.57 (0.47, 0.70)	
p-value***	<0.0001	
Objective response rate (ORR)		
ORR (CR+PR) % (95% CI)	4.5 (2.4, 7.5)	2.1 (0.4, 5.9)
p-value***	0.2833	
Disease control rate (DCR)		
DCR (CR+PR+SD) % (95% CI)	44.1 (38.3, 50.1)	14.5 (9.2, 21.3)
p-value***	<0.0001	
Time to deterioration to ECOG PS ≥ 2		
Median months (95% CI)	4.3 (3.7, 4.7)	2.3 (2.0, 2.8)
HR (95%CI)	0.69 (0.56, 0.85)	
p-value***	0.00053	
HRQoL	**Trifluridine-tipiracil Arm (N=337)‡**	**Placebo Arm (N=170)‡**
EORTC QLQ-C30 Mean Global Health Status Score (GHS)		
Baseline GHS score, sd	58.4 (20.2)	58.4 (19.7)
Cycle 3 sample size, n	121	23
Cycle 3 GHS score, sd	57.1 (20.74)	59.8 (18.7)
Cycle 3 change from baseline, sd	-4.1 (18.3)	-1.4 (22.0)
Harms Outcome, n (%)	**Trifluridine-tipiracil Arm (N=335)**	**Placebo Arm (N=168)**
AE (any grade)	326 (97.3)	157 (93.5)
AE grade ≥3	267 (79.7)	97 (57.7)
SAE§	143 (42.7)	70 (41.7)
TEAE	271 (80.9)	95 (56.6)
WDAE	43 (12.8)	28 (16.7)
Deaths¥	45 (13.4)	19 (11.3)

AE = adverse event, **CI** = confidence interval, **CR** = complete response, **ECOG PS** = Eastern Cooperative Oncology Group Performance Status, **EORTC QLQ-C30** = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, **HR** = hazard ratio, **HRQoL** = health-related quality of life, **PR** = partial response, **SAE** = serious adverse event, **SD** = stable disease, **sd** = standard deviation, **TEAE** = treatment-emergent adverse event, **WDAE** = withdrawal due to adverse event

*HR < 1 favours trifluridine-tipiracil arm

** one-sided p-value

*** two-sided p-value

ᵻ Data cut-off of March 27, 2018.

† Controlled for multiplicity.

‡ Sample sizes at each cycle of HRQoL varied.

ᵀ Data cut-off March 31, 2018

§ 38 (11.6%) SAEs were considered treatment-related in the trifluridine-tipiracil arm and 6 (3.6%) in the placebo arm

¥ 13 (4%) AEs were considered TEAEs in the trifluridine-tipiracil arm, and 2 (2%) in the placebo arm

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	TAGS trial
Sources: EPAR, 2019[3] Shitara et al., 2018[2] Taiho Oncology Inc. Clinical Study Report, 2018[6]	

Limitations:

- There were several imbalanced covariates between treatment arms, some of which may have confounded the efficacy results, including:
  - There were a slightly higher proportion of patients with an ECOG PS of 1 (64%) and HER2-positive disease (20%) in the trifluridine-tipiracil treatment arm compared to the placebo arm (ECOG PS 1: 60%; HER2-positive disease: 16%).[2] These were suspected to potentially bias the results in favour of the placebo arm.
  - There were a higher proportion of patients with ≥3 metastatic sites (58%) and patients with peritoneal metastases (31%) in the placebo arm compared to the trifluridine-tipiracil arm (≥3 metastatic sites: 54%; peritoneal metastases: 26%). This imbalance was suspected to bias in favour of the trifluridine-tipiracil treatment arm.
  - There were a higher proportion of patients in the placebo treatment arm that had 4 or more prior chemotherapy (27%) compared to the trifluridine-tipiracil treatment arm (23%), as well as a higher proportion of patients in the placebo arm that received 3 or more subsequent therapies post-treatment discontinuation (8%) compared to the trifluridine-tipiracil arm (4%).[2,3] The consensus was reached that it was difficult to determine the impact of the confounding by prior therapies and subsequent therapies post-treatment discontinuation, and thus the results may have been confounded in an unknown direction.
  - Imbalances in sex, ethnicity, prior taxane, or prior immunotherapy were not considered to confound the results.
- Secondary outcomes, such as PFS, were investigator-assessed, and thus may be subject to detection bias. Although the study was double-blind, the comparator was placebo and a higher proportion of AEs occurred in the trifluridine-tipiracil arm, which could be an indicator of active treatment and thus, could lead to differential assessment of outcomes by the investigators in either treatment arm. Additionally, specific AEs characteristic of trifluridine-tipiracil could also potentially indicate to investigators what treatment arm their patients were randomized to.
- The primary PFS analysis may have been subject to informative censoring, which may have introduced bias that overestimated PFS observed in the study. A number of sensitivity analyses were conducted to address these concerns including a sensitivity analysis including clinical progression as a PD event (HR: 0.55; 95% CI: 0.45, 0.67); clinical progression and initiation of new antitumor therapy as PD events (HR: 0.55; 95% CI: 0.45, 0.68); clinical progression, initiation of new antitumor therapy, and deaths included as events even if missed visits occurred (HR: 0.56; 95% CI: 0.46, 0.68).[3] Two additional analyses were requested, which were also consistent with the primary study results. Thus, the impact of informative censoring was considered to be minimal and confirmed the robustness of the study results.
- Although, HRQoL assessments were to be conducted prior to dosing initiation at each cycle, the exact time of the questionnaires' collection were not recorded in the case report form database.[7] HRQoL may have been subject to response bias if assessments were conducted following dosing and after significant interactions with study staff, (for example, if patients are informed of improvement or deterioration could affect how they respond to HRQoL assessments). However, the extent and impact of this potential bias is unknown as the time of data collection cannot be verified.

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1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, metastatic gastric cancer has a significant physical and psychological impact on their lives, limiting their ability to carry on with their daily lives. The most common concerns reported by patients included fatigue, loss of appetite, nausea, weight loss, anemia, and the psychological symptoms of anxiety and depression. Caregivers also expressed significant emotional challenges from fulfilling their duties of caring for patients with metastatic gastric cancer, with many reporting that they experience anxiety and depression. Current therapies available include FLOT, Folfiri, Capecitabine + cisplatin, Paclitaxel + Ramucirumab, Herceptin, Folfox, Docitaxel, Oxyplatin, Fluorouracil (5FU) and immunotherapy drugs such as Keytruda. Overall, the majority of patient (77.2%) and caregiver (86.5%) respondents had no knowledge of the drug under review. None of the patient respondents had direct experience with the trifluridine-tipiracil and only two caregivers reported that their patients had experience with the drug.. Overall, patients and caregivers value an improvement in quality of life and better management of side effects. The majority of respondents reported that they are willing to take a drug that improves their overall daily functioning, even if it does not extend overall survival.

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- No standard of care in this setting

Economic factors:

- Complex dosing schedule and multiple dose strengths required
- Additional pharmacy, nursing and clinic resources will be required

Registered Clinician Input

Two registered clinician input submissions were submitted for the review of trifluridine-tipiracil for patients with metastatic gastric cancer who have been previously treated with at least two prior systemic treatment regimens. One input was provided by an individual medical oncologist from Segal Cancer Centre, Jewish General Hospital, McGill University in Quebec, and one joint input submission was provided on behalf of seven clinicians from various institutions in Ontario and British Columbia, including Mount Sinai Hospital, Cross Cancer Institute, London Regional Cancer Program and the B.C Cancer Agency. Based on the favourable results of the TAGS trial, all clinicians agreed that trifluridine-tipiracil is a highly effective treatment for gastric cancer patients for whom two standard treatments have previously failed. The clinicians highlighted that trifluridine-tipiracil was associated with a significant increase in PFS and OS and was generally well-tolerated by patients compared to placebo. Furthermore, both inputs suggested that trifluridine-tipiracil could be an option for patients in earlier lines of treatment who are intolerant to, not candidates for or contraindicated to previous chemotherapies. Clinicians also

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suggested that the trifluridine-tipiracil could be extended to patients with an ECOG performance status of 2 and to patients who have received prior immunotherapy. Both groups of clinicians highlighted the convenience of trifluridine-tipiracil, as it an oral medication which makes it an effective treatment option for patients who want a low-intensity treatment, such as elderly patients.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2. Assessment of generalizability of evidence for trifluridine-tipiracil in advanced gastric cancer

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG PS	The TAGS trial included patients with ECOG PS 0-1. A total of 316 (62.2%) patients had ECOG PS 1 and a total of 191 (37.7%) patients had ECOG PS 0.[2]	Can the results be applied to patients with ECOG PS ≥1?	No, the trial excluded patients with ECOG PS>1.
	CNS metastases	Patients with known brain or leptomeningeal metastases were excluded from the TAGS trial.[2]	Can the results be applied to patients with brain metastases?	No, the trial excluded patients with brain metastases and therefore treatment with trifluridine-tipiracil should not be given to patients with CNS metastases.
	Prior therapy	A total of 32 (6.3%) patients received a prior immunotherapy (anti-PD-1 or anti-PD-L1) in the TAGS trial. An exploratory subgroup analysis of OS including only patients with a prior immunotherapy resulted in a 78% reduction in the risk of death in the trifluridine-tipiracil arm relative to placebo (HR: 0.22; 95% CI: 0.06, 0.86). Similarly, there was a 52% reduction in the risk of a PFS event (HR: 0.48; 95% CI: 0.47, 0.71). In patients that did not receive a prior immunotherapy (n=475), there was a 29% reduction in the risk of death (HR: 0.71; 95% CI: 0.57, 0.88) in the trifluridine-tipiracil arm relative to placebo, and a 42% reduction in the risk of a PFS event (HR: 0.58; 95% CI: 0.47, 0.71).[3]	Can the results be applied to patients with prior immunotherapies?	Yes, the mechanisms of action are different and prior immunotherapy should not influence safety or efficacy of trifluridine tipiracil. Thus, the results can be applied to patients treated with prior immunotherapy.

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<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Disease definition</td><td>Patients were included if they had histologically confirmed, non-resectable, metastatic gastric adenocarcinoma including adenocarcinoma of the GEJ as defined by the AJCC staging classification 7th edition, 2010.[2] There was an 8th edition of AJCC staging released in 2017, which primarily included major changes to stage III from the 7th to 8th edition.[8]

Summary of changes include:

<table>
<tr><th>TNM</th><th>7th edition stage</th><th>8th edition stage</th></tr>
<tr><td>T1N3bM0</td><td>IIB</td><td>IIIB</td></tr>
<tr><td>T2N3bM0</td><td>IIIA</td><td>IIIB</td></tr>
<tr><td>T3N3bM0</td><td>IIIB</td><td>IIIC</td></tr>
<tr><td>T4bN0M0</td><td>IIIB</td><td>IIIA</td></tr>
<tr><td>T4aN2M0</td><td>IIIB</td><td>IIIA</td></tr>
<tr><td>T4aN3aM0</td><td>IIIC</td><td>IIIB</td></tr>
<tr><td>T4bN2M0</td><td>IIIC</td><td>IIIB</td></tr>
<tr><td colspan="3">Source: Lu et al., 2017[8]</td></tr>
</table>

Additionally, the AJCC 8th edition defined GEJ tumors based on their epicentre, rather than upper edge (7th edition). The 7th edition staged all cancers of GEJ as esophageal cancer, whereas in the 8th edition adenocarcinomas with epicentres no more than 2 cm into the gastric cardia (Siewart I and II) are considered esophageal and tumors farther than 2 cm into the cardia (Siewart III) are staged as gastric cancer.[9]</td><td>Can the results be applied to patients with advanced gastric adenocarcinoma including adenocarcinoma of the GEJ as defined by the AJCC 8th edition, 2017? Would there be any impact on the eligible population?</td><td>Yes, for metastatic gastroesophageal cancer patients, there would be very little difference between eligible patients based on the differences between AJCC 7 and 8th edition. (Primary tumor location based on epicentre (AJCC 8th edition) versus the upper edge (7th edition)</td></tr>
<tr><td>Intervention</td><td>Line of therapy</td><td>Patients must have been refractory or unable to tolerate at least two prior systemic regimens for advanced disease in the TAGS trial. Patients who received preoperative neoadjuvant and/or postoperative adjuvant chemotherapy or chemoradiotherapy and had recurrence during or within 6 months of completion of the adjuvant chemotherapy were allowed to count this therapy as 1 prior regimen for advanced disease (only if the same regimen was administered both pre- and postoperatively).).[2] A total of 15 (3.0%) patients met this criteria.[3]</td><td>Can trifluridine-tipiracil be used in an earlier line of therapy if patients have a contraindication to chemotherapy?</td><td>Although only a small number of patients had recurrence within 6 months of adjuvant therapy on the TAGS trial, since it was an inclusion criteria, the data should be generalizable to that specific population. The efficacy of trifluridine-tipiracil in an earlier line of therapy, outside of that specific</td></tr>
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Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				instance, requires prospective evaluation.
Comparator	PAG noted that for patients with MSI-high metastatic gastric or GEJ adenocarcinomas and with private drug insurance, pembrolizumab is an option. PAG is seeking guidance on sequencing pembrolizumab with trifluridine-tipiracil.	The comparator used in the trial was best supportive care, which was appropriate for the indication. However, pembrolizumab is an option for patients who have MSI-H tumors (however, pembrolizumab is not SOC nor is MSI status routinely tested in Canada). As confirmed with the sponsor, no information on MSI-H status was collected during the study.[4]	For patients with MSI-H tumors, how would pembrolizumab and trifluridine-tipiracil be sequenced?	Data reflecting the optimal sequencing of trifluridine-tipiracil and immunotherapy is lacking. If MSI-H/dMMR patients can access immunotherapy, it should not preclude them from treatment with trifluridine-tipiracil if they are deemed suitable for ongoing treatment given the different mechanisms of action of these treatments.
Outcomes	Secondary outcomes	Secondary outcomes, such as PFS and ORR, were investigator-assessed. No BICR assessment of secondary outcomes was conducted. The study was double-blinded and a number of sensitivity analyses were conducted.[2]	Are there any concerns about bias related to investigator-assessed secondary outcomes?	Central radiology review may have changed the magnitude of difference between the two arms for PFS and ORR but not the direction (in favor of trifluridine tipiracil). Since these were secondary outcomes, it is of less importance.
Setting	Countries participating in the trial	The trial was conducted in 110 academic hospitals in 17 countries (Belarus, Belgium, Czech Republic, France, Germany, Ireland, Israel, Italy, Japan, Poland, Portugal, Romania, Russia, Spain, Turkey, UK, USA).[2] No Canadian patients or site were included.	Are there known differences in the practice patterns between countries? Could these affect the applicability of the results to the Canadian population or implementation of trifluridine-tipiracil in Canada?	Patients in France, Germany, Ireland, Italy, the UK, and USA would likely be treated similarly to Canadian patients; thus the data is generalizable to the Canadian setting.

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1.2.1 Interpretation

Burden of Illness and Need

In Canada, it is estimated that in 2019, gastric cancer will be diagnosed in 4,100 people and will lead to death in 1,950[10]. After progression on first and second line systemic therapy, there is no standard third line treatment for gastric cancer. The prognosis in this setting is poor and median survival is just over 3 months with best supportive care.[11] At the Royal Marsden, a quaternary referral centre in the United Kingdom, only 14% of gastroesophageal cancer patients received third line therapy. Thus, there is significant unmet need in this very small population of patients who are fit for third line therapy. The oral route of administration is preferred by patients and reduces resource utilization in cancer centres compared to intravenous agents. It is also advantageous for patients who live outside major urban centres.

Effectiveness

The primary endpoint of OS was significantly improved with trifluridine-tipiracil compared to placebo (median OS 5.7 months vs 3.6 months, HR 0.69; 95% CI: 0.56, 0.86; p=0.0006). One year OS was signficantly improved from 21% in the trifluridine-tipiracil arm compared to 13% in the placebo arm. There were no pertinent imbalances in baseline factors or co-interventions that would have influenced overall survival. Survival is the most clinically relevant outcome for trials evaluating third line treatments for metastatic gastric cancer. Input from patient groups emphasized the importance of survival and quality of life. The ESMO magnitude of clinical benefit scale (MCBS) is a standardized, validated tool to stratify the magnitude of clinical benefit for a novel therapy at the time of approval. The ESMO-MCBS Working Group evaluated the TAGS trial and determined the MCBS score was 3 (Form 2a), corresponding to a moderate benefit in a non-curative setting. [12] The ESMO practice guidelines for gastric cancer endorse third-line chemotherapy with trifluridine-tipiracil for patients with an ECOG PS 0-1 (level 1 evidence).[12]

In terms of quality of life, no differences were observed between patients treated with trifluridine-tipiracil and placebo. The mean baseline GHS based on the EORTC QLQ-C30 was 58.4 for both treatment arms.[3] There were no clinically relevant changes (≥10 points) in GHS from baseline to up to cycle 3 in each treatment arm. Additionally, there were no clinically relevant differences in the mean change in score from baseline for most of the functioning and symptom scales of the EORTC QLQ-C30, except for role functioning at cycle 3, where there was a difference of 10 points favouring placebo, and the pain scale at cycle 2, where there was a difference of 11.3 points favouring trifluridine-tipiracil. There were no clinically relevant changes in mean scores from baseline in the QLQ-STO22 scores.[5]

The improvement in median PFS in the trifluridine-tipiracil arm was 2.0 months and, in the placebo, arm it was 1.8 months (HR: 0.57; 95% CI: 1.7, 1.9; p<0.0001). The efficacy of trifluridine-tipiracil is largely driven by stable disease (ORR 4.5% with trifluridine-tipiracil vs 2.1% in the placebo; DCR 44.1% with trifluridine-tipiracil versus 14.5% with placebo). European patients would be expected to have similar outcomes to Canadian patients. Overall, the TAGS data should be generalizable to the Canadian population.

The results from the additional prespecified subgroup analyses conducted in patients with prior gastroectomy, patients 65 years or older, patients with metastatic gastroesophageal cancer and Japanese patients were consistent with the overall trial results and trifluridine-tipiracil would be an option in this patient population.

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Safety

The most common ≥ grade 3 treatment related AEs in the trifluridine-tipiracil arm were anemia (n=63; 18.8%) and neutropenia (n=78; 23.3%), which are common side effects that oncologists are very familiar with managing. These laboratory values are often asymptomatic, as reflected by neutral effect on quality of life for patients treated with trifluridine-tipiracil compared to placebo, and do not impact the patient's experience. The proportion of patients who discontinued treatment due to any AE was similar in the two arms (12.8% of patients treated with trifluridine-tipiracil arm vs 16.7% with placebo). SAEs occurred in a similar proportion between treatment arm, occurring in 42.7% of patients in the trifluridine-tipiracil arm and in 41.7% of patients in the placebo arm.[6] Clinical experience in the real-world setting supports tolerability of trifluridine-tipiracil in heavily pre-treated patients.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to trifluridine-tipiracil in the treatment of advanced gastric adenocarcinoma after progression on 2 prior lines of chemotherapy based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival for trifluridine-tipiracil compared with placebo. The two prior lines of therapy in the TAGS trial included a fluoropyrimidine, and either a taxane or irinotecan and if appropriate, HER2-neu targeted therapy. The adverse event profile for trifluridine-tipiracil was manageable and there was no difference in quality of life compared to placebo. The point estimates for improvements in median PFS and OS with trifluridine-tipiracil treatment are relatively small. However, the hazard ratio represents the difference between the treatment arms over the conduct of the trial and is a more relevant metric for the treatment effect for this agent in this disease. The Clinical Guidance Panel unanimously considered this to represent a clinically relevant, modest improvement in OS, especially in 1-year OS for Canadian patients.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Some metastatic gastric cancer patients maybe unsuitable for first line therapy with a platinum agent and are treated first line with FOLFIRI. Data from the TAGS trial could be extrapolated to patients who have previously received two lines of systemic therapy regardless of whether it included a platinum.
- The role of immunotherapy in this disease is evolving. Given the different mechanism of action, prior treatment with immunotherapy should not influence the clinical efficacy of trifluridine-tipiracil

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2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

The Canadian Cancer Society estimates that, for 2019, 4,100 Canadians were diagnosed with gastric cancer and another 2,300 Canadians were diagnosed with esophageal cancer with at least half attributable to distal esophageal or gastroesophageal junction (GEJ) adenocarcinomas. [10,13] Approximately 40% of these patients are expected to present with metastatic disease. [14] Globally, gastric and gastroesophageal cancer is the fifth most common cause of cancer mortality.[15] As such, the burden of advanced gastric/GEJ cancers is a concern and the need for improved treatments remains significant.

2.2 Accepted Clinical Practice

With respect to the locally advanced and/or metastatic setting, gastric and GEJ adenocarcinomas are treated similarly.[16] Adenocarcinomas represent over 90% of gastric and gastroesophageal cancers. Gastric cancers may be further histologically subdivided by Lauren classification to intestinal or diffuse. While this classification may have prognostic value, it does not inform systemic therapy decisions. Approximately 20% of gastric/GEJ adenocarcinomas overexpress the HER2 protein (a member of the EGFR family).

The goals for patients with advanced gastric and GEJ cancers are palliative – to reduce symptoms related to disease, improve quality of life and extend survival. The median survival for patients treated with best supportive care is less than 6 months (16). while patients treated with contemporary chemotherapies may be expected to reach a median survival of 9-11 months. [17] While selected patients may benefit from palliative radiation or surgery to relieve obstruction and/or bleeding, the primary treatment modality in this setting is chemotherapy which is considered suitable for patients with an ECOG PS of 2 or better. A network meta-analysis of systemic therapy for advanced gastric cancer demonstrated that anthracycline triplet chemotherapy and docetaxel, cisplatin, fluorouracil (5FU) triplets showed no benefit over fluoropyrimidine (FP: 5-fluorouracil (5FU) or capecitabine) doublets for overall survival (OS) or progression-free survival (PFS).[18] In Canada, the most commonly used regimens contain a combination of a fluoropyrimidine [(FP)] and a platinum (cisplatin or oxaliplatin) or irinotecan with infusional 5FU (FOLFIRI). For patients with HER2 positive disease, the addition of trastuzumab to first-line 5FU/platinum chemotherapy significantly extends survival and is current accepted practice. [19 20]

Immunotherapy has been evaluated in this patient population in multiple clinical trials, but it is not part of the standard therapeutic armamentarium in Canada (Table 1).

Table 1. Summary of relevant trials evaluating immunotherapy in advanced gastric or gastroesopheal adenocarcinoma

TRIAL	RESULT
KEYNOTE-62 No prior chemotherapy	Pembrolizumab non-inferior to cisplatin, FP for OS CPS $\geq$ 1: HR 0.91 (95% CI 0.69-1.18) CPS $\geq$ 10: HR 0.69(95% CI 0.49-0.97) Pembrolizumab,cisplatin,FP not superior to Placebo,cisplatin,FP for OS

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TRIAL	RESULT
	CPS ≥ 1 HR 0.85 (95% CI 0.70 to 1.03), p < 0.046 CPS ≥ 10 HR 0.85 (95% CI 0.62 to 1.17), p < 0.158
KEYNOTE 61 Gastric/GE junction Progressed after platinum,FP[21]	No significant improvement in OS for pembrolizumab compared to paclitaxel HR 0.82 (95% CI 0.66-1.03), one sided p value = 0.0421 Benefit seen in subset of patients with MMR deficiency HR 0·42, 95% CI 0·13–1·31; median overall survival not reached [95% CI 5·6 months–not reached] versus 8·1 months [2·0–16·7];
KEYNOTE 181 SCC or adenocarcinoma esophagus or Siewart type I GE junction Progressed after platinum,FP[22]	Significant improvement in OS for patients with CPS ≥ 10 with pembrolizumab versus placebo 9.3 versus 6.7 months
Le et al. Pembrolizumab in MMR deficient tumors[23]	5 patients had gastric/GE junction cancers Response rate was 54% in non-colorectal tumors
CHECKMATE 032 ≥ 1 prior line Esophageal GE junction and Gastric (n=160)[24]	Median OS 6.2 months Nivolumab 3 mg/kg IV q 2weks 6.9 months Nivolumab 1 mg/kg plus ipilimumab 3mg/kg IV q3 weeks 4.8 months Nivolumab 3mg/kg plus ipilimumab 1mg/kg IVq3 weeks

Second line therapy for Canadian patients with ECOG 0-1 is the combination of ramucirumab with paclitaxel (Table 2).[20] The efficacy of this regimen was demonstrated in the RAINBOW phase III trial, which randomized 665 patients with advanced gastric or GEJ adenocarcinoma to ramucirumab or placebo with paclitaxel. [25] The primary endpoint of overall survival (OS) significantly favoured the ramucirumab arm (median 9.6 months vs 7.4 months, HR 0.807, p=0.017). For patients who maintain an ECOG PS <=2 and/or who have contraindications to this combination, clinical trials have demonstrated a modest survival benefit over best supportive care with single agent docetaxel, paclitaxel, or irinotecan respectively.[26 27-29] Duration of disease control with second-line treatment is short, and there are few evidence based options for third- and later-line therapy.[30]

Table 2. Summary of Current Canadian Treatment Algorithm for Advanced Gastric/Gastroesophageal Cancer

Patients with Advanced Gastric or Gastroesophageal cancer		
Line of Therapy	Patient Characteristics in 1st-Line	
	HER2 positive	HER2 negative
1st-Line	Trastuzumab, FP, platin	FP plus cisplatin +/- Epirubicin or FP plus oxaliplatin or

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Patients with Advanced Gastric or Gastroesophageal cancer		
		FOLFIRI
	Patient Characteristics in 2nd-Line	
	ECOG 0-1	ECOG 2 or contraindication to either paclitaxel or ramucirumab
2nd-Line	Paclitaxel plus ramucirumab	Paclitaxel Irinotecan (if no prior FOLFIRI) Docetaxel

Table 3. Landmark randomized trials evaluating third or later lines of therapy for advanced gastric/GE junction adenocarcinoma

Trial	Outcome
ATTRACTION 2 Nivolumab vs placebo Asia Gastric or GE junction Failed 2 or more standard regimens (n=493)[31]	Nivolumab was superior to placebo for OS 5.3 vs 4.1 months (HR 0.63, 95% CI 0.51-0.78) p < 0.0001
JAVELIN Failed two or more standard regimens Gastric Asian patients (n=371)[32]	Avelumab was not superior to treatment of physician's choice for OS (either weekly paclitaxel or irinotecan monotherapy) median, 4.6 versus 5.0 months; hazard ratio (HR)=1.1 [95% confidence interval (CI) 0.9–1.4]; P = 0.81]
Rivoceranib (Apatinib) Gastric [33,34]	Rivoceranib treatment demonstrated a survival benefit compared to placebo in a phase III trial conducted in Asian patients (n=267) OS was significantly improved 6.5 vs 4.7 months (HR 0.71; p = 0.015)
	In a phase III confirmatory trial conducted in Asia, North America, and Europe (n=460), treatment with rivoceranib did not significantly improve overall survival in the overall population. Median overall survival in ≥ 3rd-line patients did not show statistical difference for rivoceranib vs placebo (5.78 versus 5.13 months; HR = 0.93; 95% CI 0.74–1.15; p = 0.4850). In ≥ 4th-line patients (rivoceranib n = 122, placebo n = 63) median OS was improved with rivoceranib versus placebo (6.43 vs 4.73 months; HR = 0.65; 95% CI 0.46–0.92; p = 0.0195)
TAGS	Improvement in OS in patients treated with trifluridine-tipiracil versus placebo. Median OS 5.7 months with trifluridine-tipiracil

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Trial	Outcome
Gastric and GE junction adenocarcinoma (n=507)[35]	versus 3.6 months with placebo (HR 0.69; [95% CI 0·56–0·85]; one-sided p=0·00029, two-sided p=0·00058)

Currently in Canada, there is no evidence-based standard third line chemotherapy for patients with advanced gastric or gastroesophageal cancer (Table 3). Kang et al compared chemotherapy with irinotecan or docetaxel (physician choice) vs best supportive care, including patients with prior treatment with 1 or 2 previous chemotherapy regimens.[28]Median OS was significantly improved to 5.3 months for patients randomized to chemotherapy compared to 3.8 months in the best supportive care arm (HR 0.66; p = 0.007), however, no significant benefit was seen for the subgroup of patients receiving third line chemotherapy. Chan et al performed a systematic review and metaanalysis of third-line systemic treatments (apatanib, regorafenib, everolimus, docetaxel, irinotecan).[36] They included 5 trials (N=890 patients) of which 587 were assigned to receive third line treatment and 303 to best supportive care. There was a significant improvement of OS from 3.2 to 4.8 months when comparing third line treatment to best supportive care or placebo (HR 0.63; p=0.006), a magnitude of benefit which was not significantly different when considering Asian patients only. Canadian patients with good performance status after 2 prior lines of systemic therapy for advanced or metastatic disease are encouraged to participate in clinical trials. In the absence of a trial, patients are sometimes offered an agent that they have not previously been treated with (e.g. irinotecan for patients previously treated with FP/platin and paclitaxel).

Trifluridine-tipiracil (FTD/TPI, TAS-102), is an oral therapy comprised of the thymidine analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil, which inhibits trifluridine degradation. [37] In the TAGS trial, 507 patients with unresectable or metastatic gastric/GEJ adenocarcinoma; previously treated with ≥ 2 regimens for advanced disease; ECOG PS ≤ 1; were randomized to trifluridine-tipiracil or placebo. Patients had previously been treated with a fluoropyrimidine, platinum, and taxane and/or irinotecan, along with anti-HER2 therapy if HER2 positive, and either experienced radiologic progression within 3 months of final dose of, or were unable to tolerate last therapy. Treatment with trifluridine-tipiracil was associated with a significant improvement in the primary endpoint of overall survival compared to placebo [Median OS with trifluridine-tipiracil vs placebo arm: 5.7 vs 3.6 months; HR: 0.69 (95% CI: 0.56-0.85); 1-sided P = 0.00029, 2-sided P = 0.00058].

The use of trifluridine-tipiracil is currently endorsed in the guidelines of the National Comprehensive Cancer Network (NCCN) as a Category 1 recommendation for third-line therapy ("based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[16]

2.3 Evidence-Based Considerations for a Funding Population

Based upon the TAGS trial eligibility criteria, the population under consideration is patients with advanced gastric or gastroesophageal adenocarcinoma, previously treated with at least 2 lines of therapy for advanced disease consisting of fluoropyrimidine, platinum, and taxane and/or irinotecan with an ECOG PS of 0 to 1.

In a review of advanced esophago-gastric adenocarcinoma patients treated at the Royal Marsden over a 6-year period ending in 2015, 39% of patients received second line therapy

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and 14% received third line therapy. [38]In one large retrospective South Korean study of a single institution (2008-2011), of 1435 patients, 53% and 27% of advanced gastric or gastroesophageal junction cancer patients were treated in the second and third line setting respectively. [39]An analysis of a South Korean national health insurance database found that for 1078 patients undergoing first line chemotherapy in 2010, uptake of second and third line treatment was 47% and 21% respectively.[40]

Assuming 2,100 new cases of advanced esophago-gastric adenocarcinoma in Canada, and 20% uptake of third line therapy, roughly 420 Canadians would be considered eligible for treatment with trifluridine-tipiracil annually.

Currently, there are no biomarkers that predict for a response to trifluridine-tipiracil. Patients with a histologic subtype of squamous carcinoma would not be considered eligible.

2.4 Other Patient Populations in Whom the Drug May Be Used

None.

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3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient input on trifluridine-tipiracil for metastatic gastric cancer was provided by My Gut Feeling (MGF) - Stomach Cancer Foundation of Canada. MGF is the first non-profit organization in Canada dedicated to providing support, awareness, education, information and advocacy to stomach cancer patients, survivors and caregivers.

MGF conducted online patient and caregiver surveys, and telephone interviews from September 13 to September 25, 2019. Survey links were shared through email to members on the MGF database and were also posted on MGF's Facebook account. MGF also posted the survey links in online support groups such as Stomach Cancer Warrior and Caregiver Family and reached out to No Stomach for Cancer who shared the links to its members.

Fifty-seven patients and 39 caregivers completed the survey for a total of 96 respondents. From the 96 respondents, MGF conducted one-on-one interviews with 5 respondents. MGF explained that these 5 respondents were selected to provide a representation of the voices of patients and caregivers who were currently in treatment as well as those who were no longer in treatment. The interviews were conducted over a period of 8 days. MGF commented that although the recommended number of respondents was 6-8, they strongly believed that their interviews were in-depth, with each interview lasting for an average of 30 minutes. In addition to asking about their caregiving experiences, the caregivers were asked the same questions as the patients, to which they were requested to respond on behalf of the patients they were caring for. 78% of the total respondents were female and 22% were male. Out of the 57 patient responses, 20 were from Canada (from Ontario, British Columbia, Alberta, Manitoba and Nova Scotia), 26 were from the U.S. and the remaining 11 were international. Out of the caregiver responses, 14 were Canadian (with 12 being from Ontario), 1 from British Columbia and 1 from Alberta, 21 were from the U.S. and the other 4 were from other countries. Responses indicated that 81.25% of respondents had experienced gastric cancer under the age of 60.

From a patient's perspective, metastatic gastric cancer has a significant physical and psychological impact on their lives, limiting their ability to carry on with their daily lives. Some of the most common concerns reported by patients included fatigue, loss of appetite, nausea, weight loss, anemia, and the psychological symptoms of anxiety and depression. Caregivers also expressed significant emotional challenges from fulfilling their duties of caring for patients with metastatic gastric cancer, with many reporting that they experience anxiety and depression. Current therapies used by patients included FLOT, Folfiri, Capecitabine + cisplatin, Paclitaxel + Ramucirumab, Herceptin, Folfox, Docitaxel, Oxyplatin, Fluorouracil (5FU) and immunotherapy drugs such as Keytruda. Overall, the majority of patient (77.2%) and caregiver (86.5%) respondents had no knowledge of the drug under review. None of the patient respondents had direct experience with the trifluridine-tipiracil and only two caregivers reported that their patients had experience with the drug. Although the patients of the caregivers had to discontinue trifluridine-tipiracil, both caregivers responded that they would recommend the drug to be made available to other patients. Overall, patients and caregivers value an improvement in quality of life and better management of side effects. 86% of patients and 94.6% of caregivers reported that they are willing to take a drug that improves their overall daily functioning, even if it does not extend overall survival.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

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3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Metastatic Gastric Cancer

Respondents were asked to report what stage they were in when they were diagnosed with gastric cancer. The results are shown in Table 1.

Table 1: Staging

Stage	Number of People (out of 96)	%
0	1	0.01%
I	12	12.5%
II	22	23%
III	23	24%
IV	35	36.5%
Did not know staging	3	0.03%

MGF noted that later stage diagnosis occurred in over 55% of cases, with the highest percentage of patients being diagnosed at Stage IV.

Fatigue was the most common side-effect experienced by respondents, with 82 respondents (85%) reporting having experienced it. 75 respondents (77%) reported experiencing weight-loss and 68 respondents (77%) reported loss of appetite. Anemia, vitamin B12 deficiency and dumping syndrome were also reported. The following are patient comments regarding side effects:

- *"I am unable to gain weight as most food is difficult to digest. Currently weight is 87lbs and I have very little energy."*
- *"My daily life has completely changed - many of the things I was easily able to do before my surgery and treatments, I cannot do at all now. My biggest issues are fatigue and eating."*

Respondents were asked to report any additional impacts of gastric cancer on their lives. 66% (38 out of 57) of patient respondents reported that the disease had a significant impact on their quality of life. 40% (23 out of 57) of the patients reported that they are no longer able to work and 25% (14 out of 57) reported not being able to fulfill familial obligations anymore. 56% (32 out of 57) of the patient respondents cited fatigue as the biggest barrier to their daily functioning. Patients also reported a significant psychological impact, as 96.5 % (55 out of 57) of them reported anxiety or depression.

3.1.2 Patients' Experiences with Current Therapy for Gastric Cancer.

Out of the 57 patients that responded, 33 patients had late-stage metastatic gastric cancer and out of those 33 patients, 16 had been treated with at least two prior regimens. Out of the 39 caregivers that responded, 25 cared for patients that had late-stage metastatic gastric cancer and out of those 25 patients, 15 had been treated with at least two prior regimens.

Respondents had varying responses on whether they agreed that current treatments help manage their symptoms. When asked on a scale of 1 to 7 on agreeing or disagreeing with the following statement: "*Current treatments are able to manage my/my loved one's gastric cancer symptoms*," 73% of patients, and 41% of caregivers responded with a rating of 5 or higher. MGF commented that many caregivers had lost their loved ones to gastric cancer.

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MGF reported that 16 of the 57 patient respondents (28%) did not have any drug therapy for their cancer, all of whom were at very early stages of the disease. All 39 caregivers responded that their patients had experience with drug therapies including FLOT, Folfiri, Capecitabine + cisplatin, Paclitaxel + Ramucirumab, Herceptin, Folfox, Docitaxel, Oxyplatin, Fluorouracil (5FU) and Immunotherapy drugs such as Keytruda.

The patients who underwent drug therapy reported many side effects including diarrhea, nausea, hair loss, vomiting, loss of appetite, weight loss, mouth sores, anemia, low white blood cell count, fatigue, general body pain, skin rash, hand and foot syndrome, abdominal cramping. Patients reported fatigue, nausea and weight loss as the most difficult side effects to manage. MGF reported that in almost all cases, patients were prescribed medications to help manage the side effects including anti-nausea medication such as Ondancetron (Zofran) and Stemetil, anti-anxiety medication (Ativan), and anti-pain medication such as Tramedol and Percocet. 34% of the patient respondents (19 out of 57) reported that they had to pay out of pocket for the drug therapies and medications related to treatment.

The following are comments shared by the respondents about current available treatments.

- Patient: *"In going forward, I do not see many options after 3rd line. This is very scary. The only option for curative intent is to have a TG which when you are stage IV is not always there. So what do we have to offer as a curative intent for stage IV? Nothing but the hope that research trials will find the next drug to keep us alive until we can have something done with a curative intent."*

- Patient: *"I am currently in a clinical trial. I am feeling great and experiencing very few side effects."*

- Caregiver: *"There are very few options for gastric cancer. If you don't have a complete response from the first line chemotherapy, the rest is just trying to give you more time."*

- Caregiver: *"Although many things were tried, nothing really seemed to alleviate the symptoms at all."*

3.1.3 Impact of Gastric Cancer and Current Therapy on Caregivers

MGF noted the relationship of the caregiver respondents to the patients, as shown in Table 2.

Table 2: Caregiver Relationship to Patient

Relationship	Number of People (n= 39)	%
Spouse/Partner	17	43.6%
Child	12	30.8%
Sibling	4	10.3%
Parent	4	10.3%
Immediate family relative (aunt, uncle, cousin, niece, nephew)	2	5.1%

97% (38 out of 39) of the caregiver respondents indicated experiencing emotional drain, 82% (32 out of 39) answered that it took an emotional toll on family life, and 79.5% (31 out of 39) also suffered from anxiety or depression.

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The following are comments of caregivers when asked to describe the impact of gastric cancer on their life:

"Challenging, sad, emotionally draining, time consuming, it puts your life on hold."

"…the role of caregiver changed me forever. I suffer post traumatic stress, anxiety attacks, and insomnia. People want to believe we are strong …"

"Right now I feel like there is nothing in the world more difficult and painful than caring for your loved one who was diagnosed with gastric cancer, especially know the prognosis, limitations of treatments and poor management of side effects."

Additionally, MGF reported that many caregiver respondents had lost their loved ones to gastric cancer.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Trifluridine-tipiracil or New Therapies

The majority of patients and caregivers reported that they value improvement in quality of life and better management of side-effects. MGF further emphasized the importance of managing side effects since they can be quite debilitating as patients have little or no stomach. Many side-effects were considered to be very important to all respondents such as hair loss, diarrhea, mouth sores, skin rashes, anemia, and low white blood cell count. The most important side effects that patients expected a new drug to control were nausea, vomiting and fatigue and for caregivers, the most important side-effects were loss of appetite, weight loss and nausea. MGF asked both patients and caregivers, on a scale of 1 to 7, "How important is it that new therapies bring about improvement in quality of life, such as a sense of wellness and relief from side effects?"100% of patients and 97% of caregivers provided a rating higher than 5. When asked about the importance of understanding the overall survival benefit of a new drug therapy, 55 patients (97%) said it was important to very important, and 33 (85%) caregivers said it was important to very important. 37 caregivers (94.6%) and 49 patients (86%) responded that they want a drug that has been proven to provide better quality of life, even if it did not extend overall survival.

3.2.2 Patient Experiences to Date with Trifluridine-tipiracil

None of the patient respondents had experience with trifluridine-tipiracil and only two caregivers reported experience with trifluridine-tipiracil. The survey also revealed that there is little patient and caregiver knowledge of the drug under review as 77.2 % of patients (44 out of 57) and 86.5 % of caregivers (34 out of 39) reported having no knowledge of trifluridine/tipiracil.

Both patients of the two caregivers that responded received trifluridine-tipiracil as a 4th line treatment. One patient accessed to the drug through an insurance plan and the other patients had access through a special access program. Neither of the two caregivers that responded were Canadian – one was from the U.S and the other was from Austria. The American caregiver was a wife of a 42-year-old male who had passed away and the Austrian caregiver was a daughter of a 78-year-old female. Both patients had used trifluridine-tipiracil for 1 to 6 months. The female patient was initially diagnosed at Stage III which later became Stage IV; the 42-year old male was diagnosed at stage IV.

The caregiver of the 42-year old patient described the treatments and medications as follows:

"On Folfox and Folfiri my husband had cold sensitivity for the first 3 days each round so everything had to be room temperature for him to eat, otherwise he said it felt like pins sticking him in the throat. The side

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effects he had on Taxol & Cyramza was high blood pressure, in the 200/100 range at times. He ended up on 3 different blood pressure meds to keep it normal. He also got a skin rash from those two but he started taking a Claritin each day and that took care of it. Lonsurf also caused a loss of appetite which was hard because you have to eat each time you take that drug."

The treatments and therapies used by the 78-year-old female patient were as follows: Herceptin and 5Fu for 4 months, Folfox for 4 months; Paclitaxel & Ramucirumab for 3 months; trifluridine-tipiracil for 2 months. This patient also had surgery to remove ¾ of her stomach, as well as radiation. Side effects experienced by this patient, as described by her caregiver were diarrhea, nausea, loss of appetite, weight loss, hair loss, mouth sores, anemia and fatigue. The caregiver noted that low blood pressure and severe fatigue were next to impossible to manage. When asked about the side effects that the patient experienced on trifluridine-tipiracil, the caregiver noted: *"it gave her a much needed rest after paclitaxel and cyramza. She got stronger, gained weight, her energy levels normalized, she was eating well. The doctors stopped the Lonsurf because tests results showed the cancer had continue to spread while on Lonsurf."* Additionally, the caregiver mentioned that her mother became quite upset that she was not able to continue on the trifluridine-tipiracil regimen as she had gained 3 kilograms of weight, had more energy and began to revamp her social lie.

Both caregivers stated that they would recommend trifluridine-tipiracil as a treatment for other patients. Both emphasized that although the drug did not work for their loved one, it could potentially work for other patients given that gastric cancer is a very complex disease and many factors determine whether or not the patients will respond to the drug.

3.3 Additional Information

The author of the patient input report is a gastric cancer survivor and a patient advocate who provided some additional comments to be emphasized. The author stressed the high mortality rate of gastric cancer. The majority of gastric cancer patients do not survive which the author believes is a result of the following factors: lack of knowledge about the disease, lack of early preventative screening and drug therapies that often have worse side effects than the disease itself. Additionally, the author commented that for those fortunate enough to survive, the effects of the disease do not stop once the patients are cancer free. The author asserted that more research needs to be done, more awareness of the disease and treatments needs to be promoted and more effective therapies are still yet to be discovered. These comments indicate that patients not only value the prolonging of their life, but also better quality of life during the course of their treatment. Earlier screening leading to earlier diagnosis can significantly delay the progression of the disease. Continuing, effective therapies are needed even for those who have survived the cancer to not only ensure a state of remission, but to also enable them to return to a normal life.

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4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- No standard of care in this setting

Economic factors:

- Complex dosing schedule and multiple dose strengths required
- Additional pharmacy, nursing and clinic resources will be required

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that for patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease, there is no standard of care and patients may receive best supportive care (BSC).

Prior first-line therapies include combinations of a fluoropyrimidine (e.g., 5-fluorouracil, capecitabine), platinum agent (e.g., cisplatin), taxane (e.g., docetaxel), and for HER2-positive patients the addition of trastuzumab. Second-line treatments include taxanes, epirubicin, irinotecan, and ramucirumab in combination with paclitaxel. Ramucirumab plus paclitaxel is funded in almost all jurisdictions for patients after first-line chemotherapy.

4.2 Eligible Patient Population

PAG is seeking guidance on whether the following subgroups of patients would be eligible for trifluridine-tipiracil:

- ECOG PS of 2
- CNS metastases
- In earlier lines if patients have contraindication to chemotherapy
- Prior immunotherapy

If recommended for reimbursement, PAG noted that patients who are currently receiving BSC or third-line treatment would need to be addressed on a time-limited basis.

There is a potential for indication creep to first- or second-line treatment or other GI cancers.

4.3 Implementation Factors

PAG had concerns with the complex dosing schedule and that multiple dose strengths would be required, as this may lead to dosing or dispensing errors. Additional pharmacy resources would be required for dispensing trifluridine-tipiracil as well as supports to

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ensure patient compliance.

PAG noted that the blister packaging of the tablets is an enabler to implementation as it would minimize drug wastage and also minimize exposure of hazardous drugs to health care providers and caregivers. However, blister packaging is a significant increase in workload for pharmacies that dispense oral chemotherapy and given current work volumes for IV chemotherapy. Drug wastage can also occur if patients develop adverse events (e.g., neutropenia) and need to discontinue treatment with trifluridine/tipiracil. PAG noted that performance status in these patients can decline quickly.

Trifluridine-tipiracil is available in two strengths and dose is based on body surface area. PAG noted that some patients will require two different strengths of tablets to make up their dose and thus, may have two dispensing fees in those provinces where the access to oral therapies is through pharmacare.

Additional resources (e.g., nursing and clinic visits) are required to monitor and treat severe (grade 3 to 4) myelosuppression including anemia, neutropenia, thrombocytopenia and febrile neutropenia as well as monitor complete blood count. The cost of supportive therapy (e.g. anti-emetics, G-CSF) also needs to be considered in implementation.

PAG noted that trifluridine-tipiracil is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

Trifluridine-tipiracil would be an additional line of therapy. PAG noted that trifluridine-tipiracil provides an option for patients who are fit enough to receive therapy and fills the treatment gap where BSC would be the alternate option.

PAG noted that for patients with MSI-high metastatic gastric or GEJ adenocarcinomas and with private drug insurance, pembrolizumab is an option. PAG is seeking guidance on sequencing pembrolizumab with trifluridine/tipiracil.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

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5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two registered clinician input submissions were submitted for the review of trifluridine-tipiracil for patients with metastatic gastric cancer who have been previously treated with at least two prior systemic treatment regimens. One input was provided by an individual medical oncologist from Segal Cancer Centre, Jewish General Hospital, McGill University in Quebec, and one joint input submission was provided on behalf of seven clinicians from various institutions in Ontario and British Columbia, including Mount Sinai Hospital, Cross Cancer Institute, London Regional Cancer Program and the B.C Cancer Agency. Based on the favourable results of the TAGS trial, all clinicians agreed that trifluridine-tipiracil is a highly effective treatment for gastric cancer patients for whom two standard treatments have previously failed. The clinicians highlighted that trifluridine-tipiracil was associated with a significant increase in progression-free survival and overall survival and was generally well-tolerated by patients compared to placebo. Furthermore, both inputs suggested that trifluridine-tipiracil could be an option for patients in earlier lines of treatment who are intolerant to, not candidates for or contraindicated to previous chemotherapies. Clinicians also suggested that the trifluridine-tipiracil could be extended to patients with an ECOG performance status of 2 and to patients who have received prior immunotherapy. Both groups of clinicians highlighted the convenience of trifluridine/tipiracil, as it an oral medication which makes it an effective treatment option for patients who want a low-intensity treatment, such as elderly patients.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Metastatic Gastric Cancer

Both groups of clinicians confirmed that there is currently no standard of care for third-line therapy. The joint clinician input asserted that there is a significant unmet medical need for therapy for patients in this setting. The clinicians suggested that the use of irinotecan-based treatment can be considered if it was not received in earlier lines of treatment.

Furthermore, the joint group of clinicians stated the following for current therapies for first and second-line treatment:

- 1st line: The most common chemotherapy regimen used in the first-line is platinum-based treatment (cisplatin or oxaliplatin) in combination with 5FU. The clinicians also mentioned that irinotecan-based treatment can also be used by patients who cannot receive or are intolerant to platinum.

- 2nd line: The clinicians stated that second-line treatment depends on previous therapy and baseline performance status. Once a patient progresses on first-line treatment, second-line treatment is usually a combination of ramucirumab (a vascular endothelial growth factor receptor (VEGFR-2) antibody with paclitaxel. The clinicians noted that this also may be used in the first-line setting if patients have recently relapsed from platinum-based peri-operative treatments in the curative setting.

5.2 Eligible Patient Population

Clinicians were asked if there is evidence to extend the use of trifluridine-tipiracil to particular subgroups of interests provided that all other eligibility criteria are met.

a) ECOG Performance Status of 0-2: Both groups of clinicians agreed that it would be reasonable to extend the use of trifluridine-tipiracil to patients with an ECOG status of 2. The clinician from Segal Cancer Centre stated that since trifluridine-tipiracil has predictable toxicities , it can be used for patients with an ECOG status of 0, 1 and 2. Similarly, the joint

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group of clinicians stated that since patients currently have no third-line treatment options, it would be acceptable to extend the use of trifluridine-tipiracil to patients with an ECOG status of 2, considering that the drug has manageable adverse events and toxicities. The clinicians further referred to the favourable results of the TAGS trial in which patients in the treatment arm, with an ECOG performance status of 0 and 1 achieved a statistically significant reduced risk of ECOG performance status deterioration, a statistically significant reduction of progressive disease, and experienced similar health-related quality of life (HrQoL) compared to placebo. The clinicians suggested that these favourable results observed for patients with an ECOG performance status of 0 and 1 would also be observed for patients with an ECOG performance status of 2 in clinical practice.

b) **Patients with CNS Metastase**s: The joint clinician input noted that currently there is no evidence that supports the use of trifluridine-tipiracil in patients with CNS metastases. These patients were excluded from the TAGS trial.

c) **In earlier lines if patients have contraindication to chemotherapy:** Both groups of clinicians suggested that it would be reasonable to use trifluridine-tipiracil in earlier lines of patients that have a contraindication to chemotherapy.

d) **Prior immunotherapy:** The clinicians providing the joint input concluded that trifluridine-tipiracil can be offered to patients with prior immunotherapy, since the TAGS trial protocol included patients who had been previously treated with immunotherapy. The clinicians also noted that many patients may have had immunotherapy from clinical trials or through private means.

5.3 Relevance to Clinical Practice

Both clinician groups stated that the TAGS trial demonstrated a clinically meaningful OS benefit for metastatic gastric cancer patients who have previously received at least two prior treatment regimens. The clinician from Segal Cancer Centre commented that this group of patients would also include those treated with trastuzumab in HER2 positive. Additionally, both clinician inputs highlighted that trifluridine-tipiracil is a convenient oral treatment option for patients. The clinician from Segal Cancer Centre commented that this is an option for elderly patients who often prefer a low-intensity treatment. The clinician mentioned that he has treated elderly patients, who have reported acceptable tolerance and a similar quality of life when compared to other regimens. The clinician also shared that many of his patients have reached 6 to 8 active cycles of trifluridine-tipiracil with manageable adverse events.

5.4 Sequencing and Priority of Treatments with Trifluridine-Tipiracil

When asked if there is evidence to support the optimal treatment sequencing with trifluridine-tipiracil in patients with MSI-high metastatic gastric or GEJ adenocarcinomas who may be treated with a PD-1 inhibitor such as pembrolizumab, the clinicians noted that immunotherapy can be given to these patients.

The clinician from Segal Cancer Centre noted that patients who received immunotherapy (anti-PD-1 or anti-PD-L1) as first or second line of treatment were included in the trial. The clinician noted that patients with MSI-high metastatic gastric or GEJ adenocarcinomas should receive immunotherapy in earlier lines of treatment, if there are no contraindications, as there is some evidence that has demonstrated an overall survival benefit for these patients. The clinician further advised that treatment sequencing should be reviewed on an individual basis.

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Similarly, the group of joint clinicians also advised immunotherapy (pembrolizumab) could be given to patients with MSI-high metastatic gastric or GEJ adenocarcinomas. The clinicians mentioned that MSI-high and MMR are considered good biomarkers for predicting response to pembrolizumab treatment. However, they noted that outside of clinical trials, pembrolizumab is not available to patients with gastric cancer. The clinicians asserted that patients with MSI-high gastric cancer should have access to pembrolizumab and trifluridine-tipiracil. Additionally, the clinicians acknowledged some data that was presented at the 2018 Gastrointestinal Cancers Symposium that demonstrated the efficacy of immunotherapies in some settings of gastric and gastroesophageal junction cancers. The clinicians concluded that further trials can help determine the role of immunotherapy and sequencing of treatments.

5.5 Companion Diagnostic Testing

No companion diagnostic testing is required for trifluridine-tipiracil.

5.6 Implementation Questions

N/A

5.7 Additional Information

The joint clinician input commented on some implementation considerations of trifluridine-tipiracil for all stakeholders. The clinicians mentioned that as an oral medication, the reimbursement of trifluridine-tipiracil would primarily affect pharmacy resources. Although the drug is overall well-tolerated and has a favourable toxicity profile, it could potentially increase drug-related visits to medical clinics or emergency departments. Overall, the clinicians concluded that the implementation of trifluridine-tipiracil into clinical practice should be relatively simple and uncomplicated.

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6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this systematic review is to evaluate the safety and efficacy of trifluridine-tipiracil in adult patients with advanced, metastatic gastric cancer (including adenocarcinoma of the gastroesophageal junction), who have been previously treated with at least two systemic therapies.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

Table 6.1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of trifluridine-tipiracil should be included.	Adult patients (≥18 years of age) with advanced stage, metastatic gastric cancer who have received 2 or more previous lines of therapy <u>Subgroups:</u> - Age - Sex - ECOG PS - Number of previous lines of therapy - Stage - Primary tumor site - Histology - Previous type of therapy - Number of metastases - HER2 status	Trifluridine-tipiracil	Best supportive care	<u>Primary:</u> - **OS** - **HRQoL** <u>Secondary:</u> - PFS - ORR - DCR <u>Safety:</u> - **AEs** - **SAEs** - **WDAEs**
Abbreviations: **AE** = adverse event; **HER2** = human epidermal growth factor receptor 2; **HRQoL**= health-related quality of life; **OS** = overall survival; **PFS** = progression-free survival; **RCT** = randomized controlled trial; **SAE** = serious adverse event; **WDAE** = withdrawal due to adverse event				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

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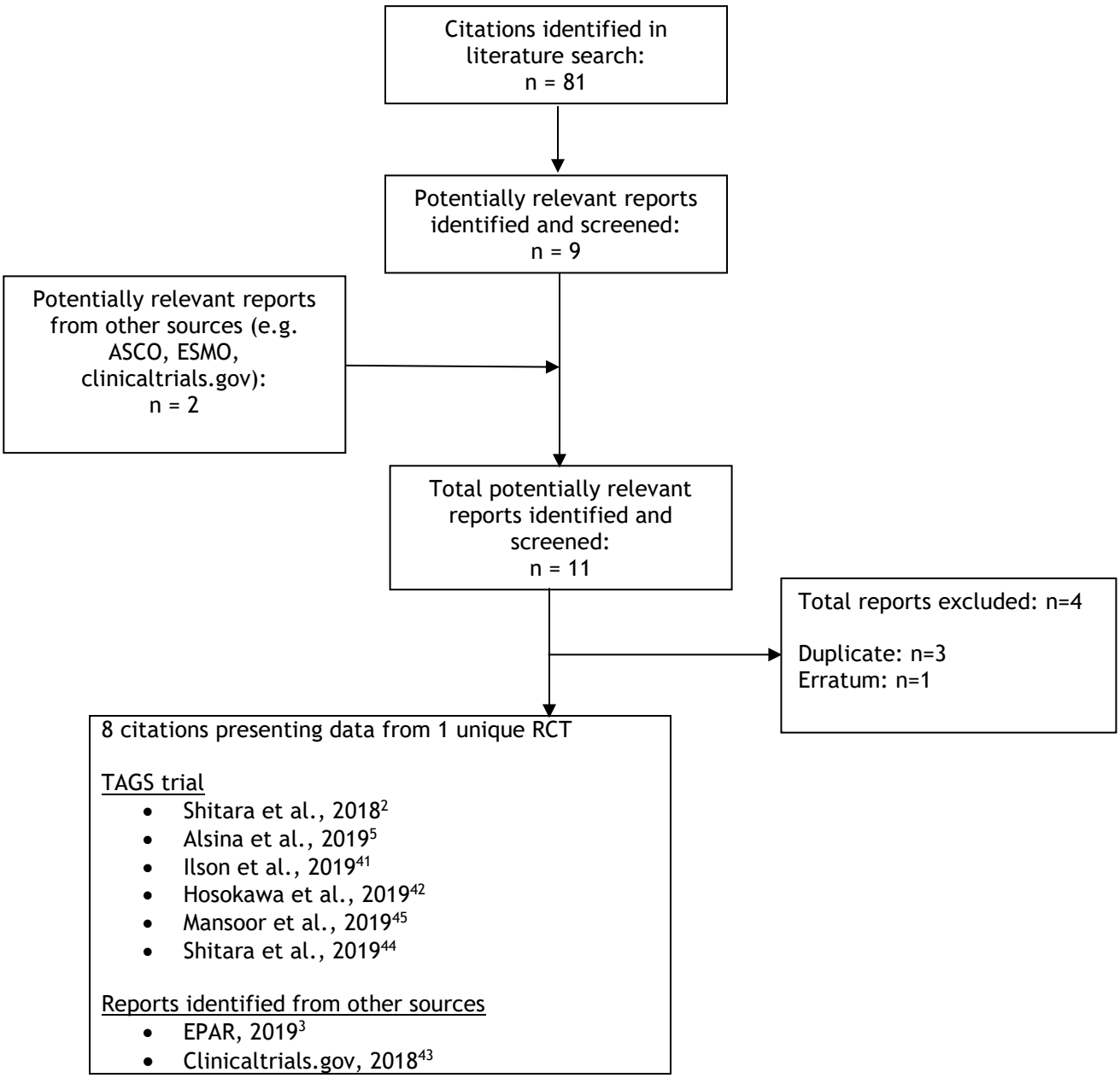
6.3 Results

6.3.1 Literature Search Results

Of the 13 potentially relevant reports identified, 8 citations reporting data from one controlled trial (RCT) were included in the pCODR systematic review[2,3,5,41-45], and 4 citations were excluded[35,46-48]. Citations were excluded because they included duplicate data available from the other sources[35,47,48] and were an erratum[46].

Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the TAGS trial was also obtained through requests to the sponsor by pCODR.[4,6,7,49-51]

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6.3.2 Summary of Included Studies

One randomized controlled trial (RCT), the TAGS trial, met the selection criteria for this systematic review. Key trial characteristics including study design, eligibility criteria, intervention details, and trials outcomes are summarized in Table 6.2.

6.3.2.1 Detailed Trial Characteristics

Table 6.2. Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study:[2,3] TAGS NCT02500043 **Characteristics:** Phase III, superiority, double-blinded, randomized (2:1), placebo-controlled trial N=507 randomized (trifluridine-tipiracil: n=337; placebo: n=170) N=503 treated (trifluridine-tipiracil: n=335; placebo: n=168) **Setting:** 110 academic hospitals in 17 countries (Belarus, Belgium, Czech Republic, France, Germany, Ireland, Isreal, Italy, Japan, Poland, Portugal, Romania, Russia, Spain, Turkey, UK, USA) **Patient Enrolment Dates**: February 24th, 2016 – January 5th, 2018 **Data cut-off (OS) – final analysis:** March 27th, 2018 **Data cut-off all other endpoints – final analysis:** March 31st, 2018 **Funding:** Taiho Oncology Inc.	<u>Key Inclusion Criteria:</u> - Adults ≥18 years of age (≥20 years in age in Japan) - Histologically confirmed non-resectable, metastatic, gastric adenocarcinoma including GEJ as defined by the AJCC staging classification (7th ed., 2010) - Previously received 2 therapies, with at least 1 cycle per regimen for advanced disease and were refractory or unable to tolerate last prior therapy - Prior therapy must have included fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; HER2+ patients must have received prior anti-HER2+ therapy - Patients must have progressed based on imaging during or within 3 months of last administration of last prior therapy - Measurable or non-measurable disease as per RECIST 1.1. - ECOG PS 0 or 1 - Adequate organ function <u>Key Exclusion Criteria:</u> - Concurrent active malignancies excluding those disease-free for ≥5 years or cured carcinoma in-situ - Known brain metastases or leptomeningeal metastases - Active infection including active or unresolved pneumonia/pneumonitis - Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or cerebrovascular disorder - Uncontrolled diabetes - Myocardial infarction within 12 months prior to randomization, severe/unstable angina, symptomatic CHF NYHA class III or IV - GI hemorrhage grade ≥3 within 2 weeks prior to randomization - Known HIV or AIDS-related illness - Chronic or acute HBV or HCV	<u>Intervention</u> Trifluridine-tipiracil administered orally (tablet) at a dose of 35 mg/m^2 of BSA, twice daily, in 28 day cycles plus BSC For each cycle, trifluridine-tipiracil is taken on days 1-5 and 8-12 <u>Comparator</u> Matching placebo to trifluridine-tipiracil taken orally (tablet) in 28 day cycles (dose/tablets determined as per BSA dose for intervention) plus BSC For each cycle, placebo is taken on days 1-5 and 8-12	<u>Primary:</u> - OS <u>Secondary:</u> - PFS - Safety <u>Tertiary:</u> - ORR - DCR - Time to ECOG PS deterioration to score of 2 or higher - HRQoL

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Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	- Autoimmune disorders or history of organ transplantation who require immunosuppressive therapy - Psychiatric disease that may increase risk of with study participation or study drug administration - Other serious illness or medical conditions - Following treatments prior to study drug initiation: major surgery within 4 weeks; anticancer therapy within 3 weeks; extended field radiation within 4 weeks or limited field radiation within 2 weeks; investigational agent/device within 4 weeks - Prior treatment with trifluridine-tipiracil - Unresolved toxicity from prior therapies that is grade ≥2 (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity)		

Abbreviations:
AIDS = acquired immunodeficiency syndrome; AJCC = American Joint Committee on Cancer; BSA = body surface area; BSC = best supportive care; CHF = congestive heart failure; DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GEJ = gastroesophageal junction; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; m^2 = square metre; mg = milligram; NYHA = New York Heart Association; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors; UK = United Kingdom; USA = United States of America

Table 6.3. Select quality characteristics of included studies of trifluridine-tipiracil in patients with advanced gastric cancer

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
TAGS	Trifluridine/ tipiracil vs. placebo	OS	500	507	2:1 via IXRS using dynamic allocation method (biased coin)	Yes	Yes	Yes	Yes	No	Yes

Abbreviations: IXRS = interactive voice/web response system; OS = overall survival

a) Trials

TAGS was an international, double-blinded, phase III, randomized, placebo-controlled, superiority trial of trifluridine-tipiracil plus best supportive care (BSC) versus placebo plus BSC in patients with advanced gastric cancer, including those with adenocarcinoma of the gastroesophageal junction (GEJ), who were refractory

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or were intolerant to at least 2 prior therapies for their disease. This study was conducted at 110 academic hospitals, which are listed in Table 6.2, and did not include any Canadian sites or patients in the trial.[2]

Trial Design

Screening and Randomization

Patients were assessed for eligibility during a 28-day screening period, and key inclusion and exclusion criteria are outlined in Table 6.2. Eligible patients must have been randomized by day 29 of screening, with a first dose of study treatment received within 3 calendar days or randomization. Patients were randomized in a 2:1 ratio to trifluridine-tipiracil plus BSC or placebo plus BSC using a dynamic allocation method (biased coin) with an interactive voice/web response system (IXRS). Randomization was stratified by:

- Region (Japan vs. the rest of the world)
- Previous treatment with ramucirumab (yes vs. no)
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (0 vs. 1)[2]

Treatment

Patients assigned to trifluridine-tipiracil received 35 mg/m^2 of body surface area (BSA) orally twice a day plus best supportive care (BSC) and patients assigned to placebo received placebo matched to trifluridine-tipiracil plus BSC. After the final analysis, the study was unblinded and patients from the placebo arm had the option to crossover to open-label trifluridine-tipiracil.[2]

Treatment Discontinuation

Treatment was continued until any of the following a discontinuation criterion was met or until completion of the primary endpoint analysis, whichever was sooner:

- Radiological progressive disease (PD) as per Response Evaluation Criteria In Solid Tumors (RECIST)
- Patient withdrawal
- Clinical progression
- Patient experienced an irreversible, treatment-related Grade 4, clinically relevant, non-hematologic event
- Unacceptable adverse event (AE) or change in underlying condition such that the patient could no longer tolerate therapy (including a maximum dose delay of >28 days or need for more than 3 dose reductions)
- Physician's decision including need for other anticancer therapy, surgery, or radiotherapy to the only site(s) of disease being evaluated in this protocol
- Pregnancy[2]

Follow-Up

Patients who discontinued blinded study treatment within 2 weeks of their last treatment visit, and end of treatment (EOT) visit was not required unless clinically necessary as determined by the investigator. If the decision to discontinue study treatment was over 2 weeks since the last study treatment visit, an EOT was required and could be combined with a 30 day safety follow-up visit if the EOT was within 2 weeks of 30 days since the patient's last dose of study medication. Assessments to be performed at the EOT or safety follow-up visit included physical examination, vital signs, ECOG PS, blood samples for chemistry and hematology, pregnancy test, concomitant medication information (including any new anticancer

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therapies), AES and serious adverse events (SAEs). At the EOT visit, if patients discontinued for reasons other than PD, efforts to perform an EOT tumor assessment prior to the start of a new anticancer therapy was recommended. At the 30-day safety follow-up visit, HRQoL assessments were conducted if not performed within the previous 4 weeks.

Patients who discontinued treatment for reason other than radiologic PD were followed for tumor response every 8 weeks until radiologic PD, death or initiation of new anticancer therapy, whichever occurred first. Following PD, patients were followed for survival every 4 weeks until death or the target number of events for the final analysis was reached, whichever occurred first. Survival follow-up included collection of information on antitumor therapies, SAEs, and survival status. Patients were able to request discontinuation from study treatment, but agree to survival follow-up, which was not considered withdrawal of consent from the trial.[2]

Tumor Assessments

Tumors were assessed by imaging through computed tomography (CT) of the chest and abdomen (pelvis only if clinically indicated) within 28 days prior to the first cycle/dose of study treatment, and then every 8 weeks during study treatment thereafter. Patients who discontinue for other reasons apart from radiologic PD were to be followed every 8 weeks until radiologic PD or initiation of a new anticancer therapy. All evaluations were investigator/local radiologist assessed. Participants with clinical progression, in the absence of radiological progression, were recommended to stop treatment, but to continue to be followed for radiological PD.[2]

Sample Size

The study was powered at 90% to detect a hazard ratio (HR) of 0.70 (30% risk reduction) in the trifluridine-tipiracil arm compared to the placebo arm with an overall 1-sided type I error of 0.025. A total of 500 patients were required based on a treatment allocation of 2:1 of trifluridine-tipiracil to placebo, and the assumptions of a variable accrual period of 18 months and 5% loss to follow-up, with a target of 384 deaths for the final analysis of overall survival (OS).[2]

Study Endpoints and Statistical Analyses

Primary Endpoint – Overall Survival (OS)

OS was defined as the time from randomization to the date of death due to any cause. Patients who were alive or in the absence of confirmation of death at the time of the OS data cut-off date were censored at the date of last study follow-up or the cut-off date, whichever was earlier. The cut-off date was defined by the date of the 384th death, survival status after this time was censored.

OS was assessed using the intention to treat (ITT) population; patients were assessed according to the treatment arm they were randomized to. A stratified log-rank test was used to compare the two treatment groups including one and two-sided p-values. If the one-sided p-value was <0.0245, the primary objective was declared to have been met. The HR and 2-sided 95% confidence interval (CI) were provided using Cox proportional hazards (PH) model, which included the 3 stratification factors as per IXRS assignment in the model. The Kaplan-Meier (K-M) curves and median survival probability at 3, 6, 9, and 12 months, along with corresponding 2-sided 95% CIs were summarized.[3]

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Subgroup analyses of OS were conducted for each of the stratification factors as per IXRS, in addition to: gender, age, race, region, ECOG PS, prior treatment with ramucirumab, prior treatment with irinotecan, prior treatment with taxane, prior immunotherapy, number of prior regimens, time from confirmed metastases to randomization, previous gastrectomy, primary cancer type, tumor grade, presence of peritoneal metastases, presence of live metastases, presence of lung metastases, number of metastatic sites, measurable disease, histology subtype, and HER2 status.[49]

The following supportive analyses for the primary efficacy endpoint were also conducted, which included:

1. The unstratified log-rank test and a Cox PH model with only the treatment effect included in the model.
2. Multivariate analysis using the Cox PH model including the 3 stratification factors, in addition to potential prognostic/predictive factors: age group (<65, ≥65 years), race (White, Asian, other), gender, number of prior regimens (2, 3+), prior therapy (taxane: yes, no; irinotecan: yes, no), previous gastrectomy, GEJ involvement, presence of peritoneal metastases, presence of liver metastases, presence of lung metastases, number of metastatic sites (≤2, 3+), measurable disease, histology subtype (diffuse, intestinal), and HER2 status at the baseline. Factors included the model were assessed for collinearity and stepwise selection process was used to identify factors in the model.[3] Factors significant at a 10% level were added to the final model the effect was assessed in the presence of identified covariates.[49] An exploratory analysis of treatment by factor interaction using the Cox PH model was also conducted using the factors identified from the final model.[3]
3. Additional sensitivity analyses were also conducted and include the following:
    - Patients who did not have documented refractory metastatic gastric cancer excluded (as per protocol inclusion criteria).
    - Primary efficacy analysis excludes/adjusts for all major protocol violations.
    - Stratified test analysis using the case report form (CRF) designation instead of IXRS, if there was a difference.
    - OS analysis as per the primary OS efficacy analysis, but excluding sites with high accrual (>25 patients)
    - OS analysis using the as-treated (AT) population
    - OS analysis as per the primary OS efficacy analysis, but using all events (deaths) and survival status as of April 30th, 2018[3]
        - This was the database lock date, and thus for completeness and transparency deaths reported between March 27th and April 30th, 2018 were used in the sensitivity analysis[50]

Secondary Endpoints

Progression-free survival (PFS)

PFS was defined as the time from randomisation until the date of investigator-assessed radiologic PD or death due to any cause. Patients alive with no PD at the time of data analysis cut-off were censored at the date of last tumor assessment. Patients who received non-study anticancer treatment before PD or with clinical, but not radiologic, PD were censored at the date of last radiologic tumor

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assessment before non-study cancer treatment is initiated.[3] Please see Table 6.4 for the full list of PFS censoring rules.

PFS analysis was conducted in a similar manner to the OS analysis. Comparisons were made at the 2-sided 0.05 significance level. Subgroup analysis was conducted in a similar manner to the OS subgroup analysis. In line the Federal Drug Agency (FDA) guidance, the following sensitivity analysis were conducted:

1. Clinical progression was included as a PFS event, in addition to the radiological PD.
2. Clinical progression and initiation of non-study antitumor therapy as a PFS event.
3. All deaths and response assessments (without censoring missed visits) count as an event if there is radiological PD, clinical PD, initiation of non-study anticancer therapy, and death through to the data cut-off sate for the survival analysis.
4. Analysis of time to first, second, and third radiological tumor assessments from date of randomization (K-M curves of times were depicted and the corresponding supporting tables were created; long-rank tests to compare two groups was applied).[3]

Table 6.4. Censoring rules for PFS in the TAGS trial

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Situation	End Date	Censored	Assignment in PFS table
Documented radiological PD	Date of the first assessment of the series of the tests that determined PD	No	
Death during the study before PD	Date of death	No	
Treatment discontinuation for other than radiologic PD or death with no post-baseline tumor assessments	Date of randomization	Yes	Discontinued Follow Up
Treatment discontinuation for other than radiologic PD or death with post-baseline tumor assessments	Date of last adequate tumor assessment prior to initiation of non-study anti-tumor treatment	Yes	Discontinued Follow Up
Subjects still followed without radiologic PD as of cut-off date	Date of last adequate tumor assessment prior to cut-off date	Yes	Ongoing
Non-study anti-tumor treatment initiated before radiologic PD	Date of last adequate tumor assessment prior to initiation of non-study anti-tumor treatment	Yes	Initiated anti-tumor therapy
Non-study anti-tumor treatment initiated on date of radiologic PD	Date of radiologic PD (= date of initiation of non-study anti-tumor treatment)	No	
Death or radiologic PD after a missed tumor assessment	Date of last adequate tumor assessment prior to missed tumor assessment	Yes	Missed Visit
Death or radiologic PD after 91 days period since first dose (no post-baseline tumor assessments during this period)	Date of randomization	Yes	Missed Visit
Only NE tumor assessments after CR, PR, or SD	Date of last adequate tumor assessment prior to NE tumor assessments	Yes	Missed Visit
Ongoing patients with no post-baseline tumor assessments	Date of randomization	Yes	Ongoing
No baseline tumor assessment	Date of randomization	Yes	Depends on the discontinuation status and post-baseline tumor scan status – anyone of the 4 categories can take place

Source: EPAR, 2019; Table 4; p. 23/88[3]

Overall Response Rate (ORR)

The investigator-assessed ORR was defined as the proportion of patients with objective evidence of complete response (CR) and partial response (PR) as per RECIST criteria.[3] The primary analysis was conducted using the tumor response (TR) population, which was a subset of the intention to treat (ITT) population that was restricted to patients with measurable disease at baseline with at least 1 post-baseline evaluation or early disease progression (or cancer-related death).[2,3] The

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comparison was conducted using Fisher's exact test.[2,3] Treatment estimates and differences were presented with associated 95% CIs, which were constructed using the Clopper-Pearson approximation to the exact binomial proportion for individual estimates within group and the normal approximation for the difference between groups.[49]

Disease Control Rate (DCR)

DCR was defined as the proportion of patients with objective evidence of CR, PR, or stable disease (SD), following the same assessment methodology as ORR.[3]

Time to Deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS)

The time to deterioration of ECOG PS is defined as time from randomization to the first date on which an ECOG PS status score of 2 or higher is observed; patients not reaching an ECOG PS of 2 or higher were censored at the last recorded ECOG assessment on the study. The same methodology was used as for the primary efficacy analysis of OS. A sensitivity analysis was conducted where deaths during survival follow-up (when ECOG PS was not measured) were not counted and only on-study ECOG assessments were used for analysis.[3]

Interim Analyses and Multiplicity

One interim analysis for efficacy and futility was planned for the study after half of the total number of target deaths were observed (192 deaths). The Lan-DeMets alpha-spending approach was used with the O'Brien Fleming stopping boundaries to guide the efficacy evaluation at the interim and final OS analysis and to account for multiple testing to preserve the overall 1-sided study significance level of 0.025. A fixed HR boundary of ≥0.95 when conditional power was less than 2% was used to assess futility at the interim analysis. Stopping the study for efficacy at the time of the interim analysis was recommended if the calculated 1-sided p-value was less than 0.0015, which corresponded with a HR of 0.63 and improvement in median OS of 5 to 7.9 months. The final analysis of OS was considered significant if the 1-sided p-value was <0.0245, which corresponded to a HR of <0.808 associated with an improvement of median OS from 5 to 8 months. All secondary endpoints were assessed at the 2-sided 0.05 significance level and were not controlled for multiplicity, with the exception of PFS (if OS was demonstrated to be significant at the 1-sided 0.025 level).[3]

Safety

Patients who received at least one dose of study treatment were included in the safety analyses and were analyzed based on the treatment received; patients were referred to as the as-treated (AT) population or the safety population. Safety assessments included evaluation of laboratory test results, vital signs measurements, physical examination findings and changes in ECOG PS score. Standard safety and tolerability monitoring was performed and adverse events (AEs) were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[3] Simple descriptive statistics were provided for safety endpoints and demographic/baseline characteristics.[2]

Health-related Quality of Life (HRQoL)

HRQoL was measured using the European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire (QLQ), core 30 (EORTC QLQ-C30), which is a validated and reliable self-report measure that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and

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social); three symptom scales (fatigue, nausea, vomiting, and pain; and the global health/quality of life), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The EORTC gastric cancer module (QLQ-STO22) is meant for use among gastric patients varying in disease stage and treatment modality. Assessments were conducted within 7 days prior to randomization and on day 1 of every cycle starting at cycle 2, as well as at the safety follow-up visit (if not performed within prior 4 weeks of the visit).[2]

For both the EORTC QLQ-C30 and QLQ-STO22 a deterioration in quality of life (QoL) of 5 points from baseline will be considered a small, but meaningful, change in QoL. The proportion of patients with deteriorating, stable, or improving, scores at weeks 4, 8, and 12 were compared using the Fisher's exact test and were summarized in a table. The main QoL analysis was time to first deterioration in QoL and was evaluated using K-M estimates and treatment arms were compared using the log-rank test. Cox PH model adjusting for the baseline value of the EORTC QLQ-C30 and QLQ-STO22 score, country, and primary tumor type was conducted. Patients with no deterioration in QoL scores were censored at the end of study, data cut-off, or death.

A sensitivity analysis was conducted as per the main QoL analysis, however a deterioration of 10 points in QoL was used for the analysis.[49]

Protocol Amendments

Protocol amendments are summarized in Table 6.5.

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Table 6.5. Summary of protocol amendments in the TAGS trial

Amendment No.	Date	Key Changes
Original	30 Jun 2015	Not applicable
Version 0.1 Rest of World	16 Jul 2015	Administrative; change in Medical Monitor
Version 1.0 Japan	10 Jul 2015	Added Appendix E: Supplemental Requirements for Japan Only Added Appendix F: Summary of Changes to Protocol
Version 1.1 Japan	16 Jul 2015	Administrative; change in Medical Monitor
Version 1.0 Rest of World Version 2.0 Japan	19 Feb 2016 22 Feb 2016	• Added Quality of Life to secondary endpoints • Revised footnote in the Study Schedule and throughout the document to clarify timing of screening period, randomization, and study treatment start. • Revised footnote in the Study Schedule to clarify timing of Eastern Cooperative Oncology Group (ECOG) performance status score collection. • Revised survival follow-up to exclude patients who have withdrawn consent from the study unless they request discontinuation of study treatment but agree to survival follow-up (this was not considered withdrawal of consent). • Revised inclusion/exclusion criteria definition of contraception to comply with Health Authority Request. Minor clarification was made to inclusion criterion #3d to allow patients who received postoperative adjuvant chemotherapy **or** chemoradiotherapy to continue the adjuvant therapy. • Clarified resumption criteria for patients with decreases in neutrophils. • Clarified Quality of Life assessments were to be performed prior to dose administration in each cycle. Clarified reference points of Quality of Life assessments from Weeks to Cycles. • Added definition of serious adverse reaction, and reporting requirements for serious adverse events, serious adverse reactions and suspected unexpected serious adverse reactions (SUSARs) per Health Authority request. • Clarified reporting requirements for medication errors and SUSARs.
Version 1.0 Germany	22 Feb 2016	The same changes were made as for Version 1.0 Rest of World amendment. **In addition** the following change was made: • Added new assessment: 12-lead electrocardiogram (ECG) was to be performed within 28 days prior to randomization.
Version 2.0 Rest of World Version 2.0 Germany Version 3.0 Japan	05 May 2016	• Clarified that steroids at doses ≤ 20 mg of prednisone equivalent per day for ≤ 2 weeks are permitted during the study. • Added dose interruption/resumption guidelines for febrile neutropenia per Health Authority Request. • Revised terminology pertaining to related adverse events: "related" was changed to "reasonably possible" and "not related" was changed to "not reasonably possible."
Version 4.0 Japan	23 Apr 2018	Appendix E: Supplemental requirements for Japan Only • The study period was changed from Jun 2018 to Dec 2018 to extend the planned study duration.

Source: EPAR, 2019; Table 6; p. 27/88[3]

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authors reported financial support from the sponsor in the form of research funding, consultancy fees, honoraria, and/or advisory fees. One of the eight authors reported support from the sponsor outside the submitted work. One of the eight authors were directly employed and had travel, accommodations, and expenses covered by the sponsor.[2]

b) Populations

Disease and demographic characteristics are presented in Table 6.6. A total of 507 patients were randomly assigned to receive trifluridine-tipiracil (n=337) or placebo (n=170). The median age was 64 years (IQR: 56-70) in the trifluridine-tipiracil treatment arm and 63 years in the placebo arm (IQR: 56-69). Overall, the majority of patients had a primary tumor site of gastric (n=360; 71%), were from Europe (n=408; 80.4%), had measurable disease (n=456; 90%), and were previously treated (neoadjuvant, adjuvant, or metastatic setting) with platinum therapy (n=507; 100%) and fluoropyrimidine (n=506; 99.8%). Tumor histology was balanced between treatment arms. Overall, there were 44% (n=221) of patients who had a previous gastrectomy, 55% (n=281) received previous irinotecan, 33% (n=169) were previously treated with ramucirumab, and 17% (n=84) were previously treated with anti-HER2 therapy. A number of factors were imbalanced between treatment arms and are highlighted below:

- There were a higher proportion of males in the trifluridine-tipiracil treatment arm (n=252; 75%) compared to the placebo arm (n=117; 69%), and there were a higher proportion of females in the placebo arm (n=53; 31%) compared to the trifluridine-tipiracil arm (n=85; 25%).
- There were more patients reporting a White ethnicity in the trifluridine-tipiracil arm (n=244; 72%) compared to the placebo arm (n=113; 66%).
- There was a slightly higher proportion of patients reporting an ECOG PS of 1 (n=214; 64%) in the trifluridine-tipiracil treatment arm compared to the placebo arm (n=102; 60%).
- There was a slightly higher proportion of patients with HER2 positive disease in the trifluridine-tipiracil (n=67; 20%) arm compared to the placebo arm (n=27; 16%).
- There was a slightly higher proportion of patients with ≥3 metastatic sites in the placebo arm (n=98; 58%) compared to the trifluridine-tipiracil arm (n=182; 54%).
- There were a higher proportion of patients who had 3 previous chemotherapy regimens in the trifluridine-tipiracil arm (n=134; 40%) compared to the placebo treatment arm (n=60; 35%); whereas a higher proportion of patients in the placebo had 4 or more prior chemotherapy (n=46; 27%) compared to the trifluridine-tipiracil treatment arm (n=77; 23%).
- A higher proportion of patients in the placebo arm had peritoneal metastases (n=53; 31%) compared to the trifluridine-tipiracil arm (n=87; 26%).
- There were a higher proportion of patients who were previously treated with a taxane in the trifluridine-tipiracil treatment arm (n=311; 92%) compared to the placebo arm (n=148; 87%). A slightly higher proportion of

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patients were previously treated with an immunotherapy in the trifluridine-tipiracil arm (n=25; 7%) compared to placebo (n=7; 4%).[2]

Table 6.6. Baseline demographic and disease characteristics in the TAGS trial

	Trifluridine/tipiracil group (n=337)	Placebo group (n=170)
Age, years		
Median (IQR)	64 (56–70)	63 (56–69)
<65	183 (54%)	96 (56%)
≥65	154 (46%)	74 (44%)
Sex		
Male	252 (75%)	117 (69%)
Female	85 (25%)	53 (31%)
Ethnicity		
White	244 (72%)	113 (66%)
Asian	51 (15%)	29 (17%)
Other	4 (1%)	4 (2%)
Not available	38 (11%)	24 (14%)
Region		
USA	21 (6%)	5 (3%)
Europe	270 (80%)	138 (81%)
Japan	46 (14%)	27 (16%)
ECOG performance status		
0	123 (36%)	68 (40%)
1	214 (64%)	102 (60%)
Primary site		
Gastric	239 (71%)	121 (71%)
Gastroesophageal junction	98 (29%)	47 (28%)
Both	0	2 (1%)
Measurable disease	306 (91%)	150 (88%)
Histology		
Diffuse	53 (16%)	21 (12%)
Intestinal	103 (31%)	52 (31%)
Mixed	14 (4%)	8 (5%)
Unknown	132 (39%)	69 (41%)
Not available	35 (10%)	20 (12%)

(Table 1 continues in next column)

	Trifluridine/tipiracil group (n=337)	Placebo group (n=170)
(Continued from previous column)		
HER2 status		
Positive	67 (20%)	27 (16%)
Negative	207 (61%)	106 (62%)
Not assessed or unknown	63 (19%)	37 (22%)
Number of metastatic sites		
1–2	155 (46%)	72 (42%)
≥3	182 (54%)	98 (58%)
Peritoneal metastases	87 (26%)	53 (31%)
Previous gastrectomy	147 (44%)	74 (44%)
Number of previous chemotherapy regimens		
2	126 (37%)	64 (38%)
3	134 (40%)	60 (35%)
≥4	77 (23%)	46 (27%)
Previous systemic anticancer agents		
Platinum	337 (100%)	170 (100%)
Fluoropyrimidine	336 (>99%*)	170 (100%)
Taxane†	311 (92%)	148 (87%)
Irinotecan†	183 (54%)	98 (58%)
Ramucirumab	114 (34%)	55 (32%)
Anti-HER2 therapy	60 (18%)	24 (14%)
Immunotherapy (anti-PD-1 or anti-PD-L1)	25 (7%)	7 (4%)
Other	77 (23%)	41 (24%)

Data are n (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. *One patient did not receive a fluoropyrimidine. †All patients received irinotecan or taxane or both.

Table 1: **Baseline characteristics of the intention-to-treat population**

Source: Shitara et al., 2018; Table 1

Reprinted from The Lancet Oncology, Vol 19, Shitara K. et al, Trifluridine-tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial, 1437-48, 2018, Copyright (2018), with permission from Elsevier.[2]

c) Interventions

Of the 507 randomly assigned patients, a total of 503 (99.2%) were treated including 335 in the trifluridine-tipiracil arm and 168 in the placebo arm. There were 2 patients not treated in the trifluridine-tipiracil arm due to one death and one protocol violation, and 2 patients withdrew consent in the placebo arm.[2]

Trifluridine-tipiracil was available in two strengths: 15 mg and 20 mg tablets. It was administered orally at a dose of 35 mg/m^2 of body surface area, twice daily, within 1 hour of completing morning and evening meals and was to be taken with water. Dose and tablet calculations are presented in Table 6.7. One cycle was 28 days, and treatment was administered from days 1-5, followed with a 2 day rest,

and then from days 8-12, followed by a rest period for the remainder of the cycle (days 13-28). Study medication was only given on the days outlined between days 1-12, regardless of missed or held doses. Study treatment was not permitted on the rest days of days 6-7 and days 13-28.[2]

Table 6.7. Study drug and tablet calculation and administraion in the TAGS trial

TAS-102 dose (twice daily)	Body surface area (m^2)	Dose in mg (twice daily)	Total daily dose (mg)	Tablets per dose (twice daily)	
				15 mg	20 mg
35 mg/m^2	<1.07	35	70	1	1
	1.07 - 1.22	40	80	0	2
	1.23 - 1.37	45	90	3	0
	1.38 - 1.52	50	100	2	1
	1.53 - 1.68	55	110	1	2
	1.69 - 1.83	60	120	0	3
	1.84 - 1.98	65	130	3	1
	1.99 - 2.14	70	140	2	2
	2.15 - 2.29	75	150	1	3
	≥2.30	80	160	0	4

Source: EPAR, 2019; Table 3; p. 17/88[3]

Previous Anticancer Therapies

Previous systemic anticancer therapies were discussed in the previous section (Table 6.6). Briefly, most types of prior systemic therapies (neoadjuvant, adjuvant, and metastatic setting) were balanced between treatment arms except for a slightly higher proportion of patients that were treated with a taxane and/or immunotherapy in the trifluridine-tipiracil treatment arm compared to the placebo arm.[2]

All patients were required to have at least one prior systemic therapy in the metastatic setting, and a total of 13 (3.9%) in the trifluridine-tipiracil arm and 2 (1.2%) patients in the placebo arm had only 1 prior regimen for metastatic disease. Overall, most patients had 2 (n=232; 45.8%) or 3 (n=182; 35.9%) prior treatments for metastatic disease. The median number of prior treatment regimens for metastatic disease was 3 in both treatment arms. Similar to the overall types of prior systemic therapies, there were more patients in the trifluridine-tipiracil arm that received a previous taxane (n=306; 90.8%) and HER2 targeted therapy (n=59; 17.5%) compared to the placebo arm (taxane: n=146, 85.9%; HER2 targeted therapy: n=23, 13.5%), with the latter likely due to more patients that were HER2 positive in the trifluridine-tipiracil arm (20%) compared to the placebo arm (16%). All patients who received a prior immunotherapy received it in the metastatic setting.

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The most frequently reported last line of treatment prior to randomization in the ITT population was taxane (48.7%), fluoropyrimidine (32.3%), irinotecan (32.9%), and platinum (20.3%). Most patients were refractory to their last treatment prior to randomization, ranging from 85.4% to 98.2% across the most common last prior treatments.[3]

Table 6.8. Prior anticancer therapies by treatment arm for metastatic disease in the TAGS trial, ITT population

Parameter	TAS-102 (N=337)	Placebo (N=170)	Total (N=507)
Number of Prior Regimens for Metastatic Cancer n (%)			
1	13 (3.9)	2 (1.2)	15 (3.0)
2	151 (44.8)	81 (47.6)	232 (45.8)
3	120 (35.6)	62 (36.5)	182 (35.9)
≥4	53 (15.7)	25 (14.7)	78 (15.4)
Prior Systemic Cancer Therapeutic Agents to Treat Metastatic Cancer [1] , n (%)			
Yes	337 (100.0)	170 (100.0)	507 (100.0)
Fluoropyrimidine [3]	327 (97.0)	163 (95.9)	490 (96.6)
Platinum [4]	317 (94.1)	160 (94.1)	477 (94.1)
Taxane [5]	306 (90.8)	146 (85.9)	452 (89.2)
Irinotecan [6]	183 (54.3)	98 (57.6)	281 (55.4)
HER2i [8]	59 (17.5)	23 (13.5)	82 (16.2)
Immunotherapy (PD1/PDL1) [7]	25 (7.4)	7 (4.1)	32 (6.3)
Other	76 (22.6)	38 (22.4)	114 (22.5)

[1] Patients with multiple levels are counted in each applicable category. [2] Includes all prior systemic therapies (Neoadjuvant, Adjuvant, Metastatic
[3] Fluoropyrimidine includes 5-FU (Fluorouracil), Capecitabine, Doxifluridine, S-1, Tegafur and UFT and some agents that were collected as 'Other and re-mapped later to Fluoropyrimidine.
[4] Platinum includes Oxaliplatin, Cisplation, Carboplatin and some agents that were collected as 'Other' and re-mapped later to Platinum.
[5] Taxane includes Docetaxel, Paxlitaxel, Nub-Paclitaxel (abraxane), and same agents that were collected as =Other| and re-mapped later to Taxane.
[6] Irinotecan includes Irinotecan and CPT-11, and same agents that were collected as =Other| and re-mapped later to Irinotecan.
[7] Immunotherapy includes all PD1/PDL1 agents. [8] HER2i includes Trastuzumab, Pertuzumab and TDM-1. Data Source: ADSL, ADCM

Source: EPAR, 2019; Table 11; p. 32/88[3]

Concomitant Medications

Other investigational, anticancer therapies, or palliative radiotherapy were not permitted during the study treatment period. Megestrol acetate and steroids at doses ≤ 20 mg of prednisone equivalent per day for ≤2 weeks were allowed.

Caution was recommended to be exercised when using antiviral drugs that were human thymidine kinase substrates and had to be monitored for decreased drug efficacy of the human thymidine kinase substrate or switched to an alternative agent.

Hematologic support (e.g. blood transfusions, granulocyte colony stimulating factor, erythropoietin, etc.) was permitted if medically indicated according to institutional site standards. Management of diarrhea was according to standard therapy was recommended or prophylactic treatment if clinically indicated. Infection prophylaxis with oral antibiotics was considered for patients with persistent diarrhea beyond 24 hours, or coincident with grade ≥3 neutropenia.[2]

Concomitant medication use was reported by 90.1% of patients in the trifluridine-tipiracil group and 84.5% in the placebo group. Use of any supportive blood product or growth factor was reported for 30.7% of patients in the trifluridine-tipiracil arm and 7.1% in the placebo arm for the management of neutropenia, thrombocytopenia, and anemia. Other frequently reported concomitant

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medications were in the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) level III categories of opioids (31.0%), drugs for peptic ulcer and gastroesophageal reflux disease (28.8%), other analgesics and antipyretics (21.1%), and propulsives (20.1%).[3]

Subsequent Anticancer Therapies

A similar proportion of patients received post-discontinuation anticancer treatments, as outlined in Table 6.9. Approximately a quarter of patients received a systemic therapy in both treatment arms, 24.6% and 26.5% in the trifluridine-tipiracil and placebo arms, respectively, which was followed by surgery (13.9% and 16.5% in the trifluridine-tipiracil and placebo arms, respectively) and radiotherapy (2.4% and 2.9%, respectively).

Of those that received a subsequent systemic anticancer therapy, most patients received 1 subsequent therapy in the trifluridine-tipiracil (n=53; 15.7%) and placebo (n=25; 14.7%) arms.[3] There was a slightly higher proportion of patients in the placebo arm that received 4 or more subsequent therapies (n=9; 5.3%) compared to the trifluridine-tipiracil arm (n=5; 1.5%).[4] Similar proportions of patients received a subsequent anticancer therapy containing ramucirumab or immunotherapy.[3]

Table 6.9. Subsequent anticancer therapies following discontinuation in the TAGS trial, ITT population

Treatment, n (%)	TAS-102 N = 337	Placebo N = 170
Surgery	47 (13.9)	28 (16.5)
Radiotherapy	8 (2.4)	5 (2.9)
Any systemic Therapy	83 (24.6)	45 (26.5)
Number of regimens:		
1	53 (15.7)	25 (14.7)
2	16 (4.7)	7 (4.1)
≥3	14 (4.2)	13 (7.6)
Any regimen containing ramucirumab	11 (3.3)	4 (2.4)
Any regimen containing immunotherapy	15 (4.5)	8 (4.7)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of patients in arm; n = number of patients in group

Source: EPAR, 2019; Table 12; p. 33/88[3]

d) Patient Disposition

The patient disposition diagram is outlined in Figure 6.2. A total of 625 patients were screened for eligibility, and 118 (18.9%) were ineligible.[2] The majority were screen failures (n=111; 17.8% of those screened). Of the 111 ineligible for study, 32.4% (n=36) did not have adequate organ function (including 11 patients that did not meet platelet count and 10 patients that did not meet absolute neutrophil count requirements), 23.4% (n=26) were excluded due to ECOG PS >2, and 19.8% (n=22) did not meet the prior regimen requirements (including 7 patients who did not have at least 2 prior regimens with at least 1 cycle per regimen and were refractory or unable to tolerate their last line of therapy; and another 7 patients who did not have a prior regimen that included a fluoropyrimidine, platinum, and

either a taxane- and/or irinotecan-containing regimen and/or anti-HER2-positive therapy if applicable).[51] Of the 507 patients randomized (ITT population), 337 were assigned to trifluridine-tipiracil and 170 were assigned to placebo. Four patients (2 patients in each treatment group) did not receive study treatment, and thus a total of 335 were treated in the trifluridine-tipiracil arm and 168 were treated in the placebo arm. At the time of data cut-off, most patients had discontinued treatment (94.3% and 98.2% in the trifluridine-tipiracil and placebo arms, respectively), with 19 (5.7%) patients ongoing treatment in trifluridine-tipiracil arm and 3 (1.8%) patients ongoing treatment in the placebo arm.[2]

There were a higher proportion of patients in the placebo arm that discontinued treatment due to radiological PD (n=110; 65.5%) or clinical PD (n=35; 20.8%) compared patients in the trifluridine-tipiracil arm that discontinued due to radiological PD (n=192; 57.3%) or clinical PD (n=54; 16.1%). There were more patients who permanently discontinued the study due to death in the placebo arm (n=141; 83.9%) compared to the trifluridine-tipiracil arm (n=252; 75.2%).[3]

Protocol Deviations

Protocol deviations are summarized in Table 6.10. Major protocol deviations that occurred in the trial overall were low (n=13; 2.6%), and occurred in a similar proportion of patients in the trifluridine-tipiracil arm (n=9; 2.7%) and the placebo arm (n=4; 2.4%). Numerically, there were more patients in the trifluridine-tipiracil arm who received fewer than 2 prior regimens (n=7; 2.1%) compared to the placebo arm (n=1; 0.6%). The single patient in the placebo who was administered another concurrent chemotherapy while on study treatment was administered ramucirumab.[3]

Non-major protocol deviations occurred in a higher proportion of patients in the trifluridine-tipiracil arm (n=60; 17.8%) compared to the placebo arm (n=14; 8.2%). This was largely due to more patients in the trifluridine-tipiracil arm that received the wrong treatment or incorrect dose (n=39; 11.6%) compared to the placebo arm (n=4; 2.4%). Of these 43 patients, 31 (in 2 of whom the event occurred twice), the dose of the study medication was not held even though the absolute neutrophil count was below 1.5 x 10^9/L, and thus was considered a 'wrong' treatment. There were 6 patients who took the wrong dose, 4 patients where the height and weight was recorded incorrectly leading to a wrong BSA calculation, 2 patients were given the wrong kit, and 2 patients did not return kits (of note, for 2 patients more than 1 reason for a wrong or incorrect dose was assessed).[3] Of the patients with an incorrect dose (n=5, all from the trifluridine-tipiracil arm), the duration of the incorrect dose ranged from 1-5 days and was a dose difference of less than 10%, and thus, was considered to have minimal impact efficacy or safety results.[7]

Other non-major reportable deviations were balanced between treatment arms and included did not meet entry criteria (overall: n=19; 3.7%); developed withdrawal criteria but were not withdrawn (n=5; 1.0%); received an excluded medication (n=3; 0.6%); or critical ICF, GCP, and other protocol deviations (n=8; 1.6%).[3]

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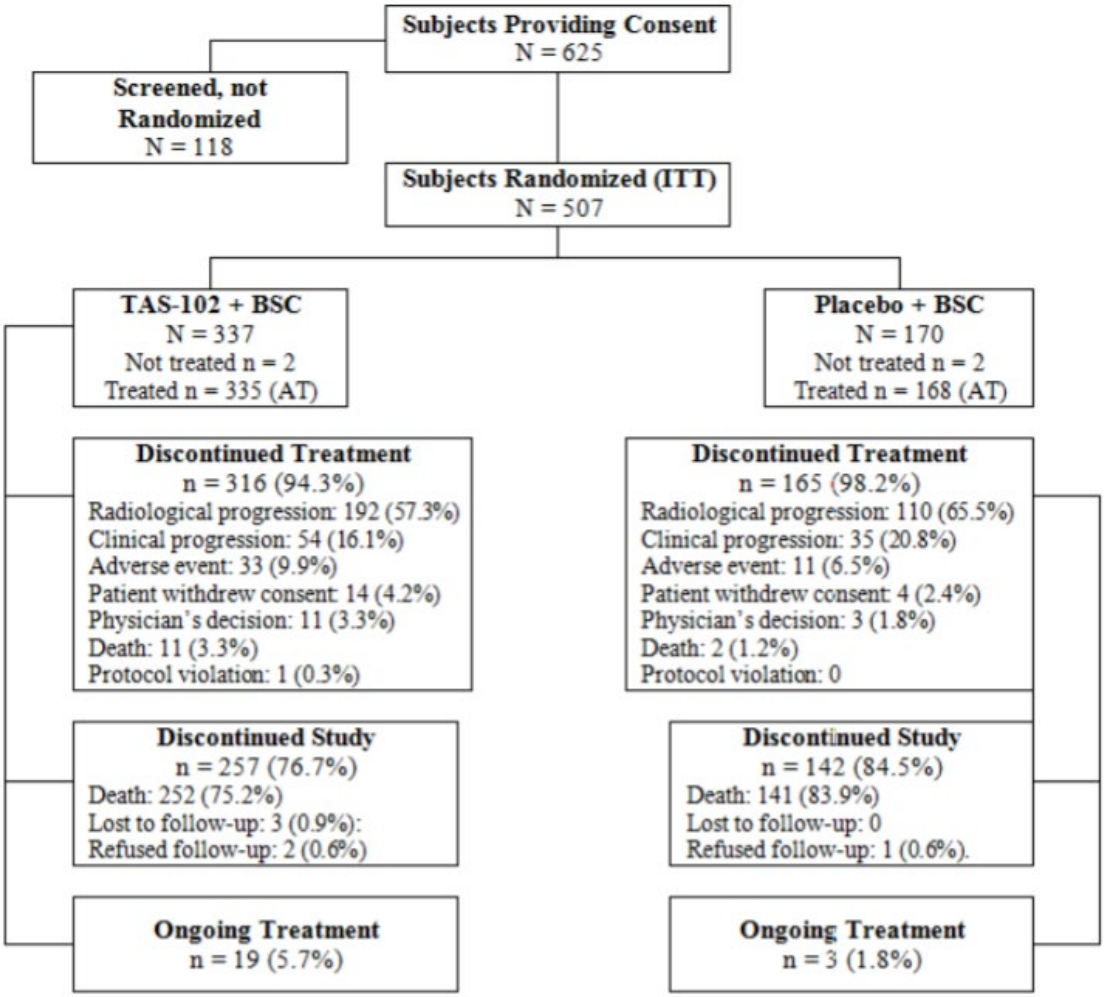
Figure 6.2. Patient disposition diagram in the TAGS trial



Source: EPAR, 2019; Figure 2; p. 26/88[3]

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Table 6.10. Summary of protocol deviations in the TAGS trial

Deviation	Number (%) of Patients		
	TAS-102 (N=337) n (%)	Placebo (N=170) n (%)	Total (N=507) n (%)
Major CSR Reportable Deviations			
Any criteria	9 (2.7)	4 (2.4)	13 (2.6)
MRD1 – No histological confirmation of gastric adenocarcinoma including adenocarcinoma of the gastroesophageal junction	0	0	0
MRD2 – No metastatic disease	0	0	0
MRD3 – No measurable or non-measurable disease per RECIST v1.1	0	0	0
MRD4 – Received fewer than 2 prior regimens	7 (2.1)	1 (0.6)	8 (1.6)
MRD5 – Prior anticancer therapy within 3 weeks prior to study treatment administration	2 (0.6)	2 (1.2)	4 (0.8)
MRD6 – Previously received TAS-102	0	0	0
MRD7 – Received incorrect treatment (ie, randomized to 1 arm but received the other treatment)	0	0	0
MRD8 – Other concurrent chemotherapy or radiotherapy administered while receiving study treatment	0	1 (0.6)	1 (0.2)
CSR Reportable Deviations			
Any criteria	60 (17.8)	14 (8.2)	74 (14.6)
RD1 – Did not meet entry criteria	13 (3.9)	6 (3.5)	19 (3.7)
RD2 – Developed withdrawal criteria but were not withdrawn	4 (1.2)	1 (0.6)	5 (1.0)
RD3 – Received the wrong treatment or incorrect dose	39 (11.6)	4 (2.4)	43 (8.5)
RD4 – Received an excluded medication	2 (0.6)	1 (0.6)	3 (0.6)
RD5 – Critical ICF, GCP and other protocol deviations	6 (1.8)	2 (1.2)	8 (1.6)

Abbreviations: CSR = clinical study report; GCP = Good Clinical Practice; ICF = Informed Consent Form; MRD = major reportable deviation; RD = reportable deviation; RECIST = Response Evaluation Criteria in Solid Tumours

Source: EPAR, 2019; Table 7; p. 28/88[3]

e) Limitations/Sources of Bias

Limitations:

- There were several imbalanced covariates between treatment arms, some of which may have confounded the efficacy results, which are discussed below:
  - Specifically, there was a slightly higher proportion of patients with an ECOG PS of 1 (64%) and HER2-positive disease (20%) in the trifluridine-tipiracil treatment arm compared to the placebo arm (ECOG PS 1: 60%; HER2-positive disease: 16%).[2] These were suspected to potentially bias the results in favour of the placebo arm. As discussed with the CGP, patients with a worse performance status were considered to have a worse prognosis. Additionally, while earlier studies reported mixed results on the prognosis of patients with HER2-positive gastric cancer, recent systematic reviews support that patients with HER2-positive gastric cancer have a

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worse prognosis, and thus, the combination of these factors could have confounded the efficacy results.[52,53]
    - There were a higher proportion of patients with ≥3 metastatic sites (58%) and patients with peritoneal metastases (31%) in the placebo arm compared to the trifluridine-tipiracil arm (≥3 metastatic sites: 54%; peritoneal metastases: 26%). This imbalance was suspected to bias in favour of the trifluridine-tipiracil treatment arm. As discussed with the CGP, patients with a higher number of metastatic sites would generally be considered to have a worse prognosis. There is also evidence to suggest patients with peritoneal metastases have shorter survival, and thus the combination of these factors could have confounded the efficacy results.[54]
    - There were a higher proportion of patients in the placebo treatment arm that had 4 or more prior chemotherapy (27%) compared to the trifluridine-tipiracil treatment arm (23%), as well as a higher proportion of patients in the placebo arm that received 3 or more subsequent therapies post-treatment discontinuation (8%) compared to the trifluridine-tipiracil arm (4%).[2,3] Per discussion with the CGP, heavily pre-treated patients could have a worse prognosis due to toxicities from previous treatments, however, these patients may also be "healthier" or unique due to the ability to tolerate so many lines of treatment. Patients in the placebo group also had more subsequent therapies, which could potentially support the latter point. The consensus was reached that it was difficult to determine the impact of the confounding by prior therapies and subsequent therapies post-treatment discontinuation, and thus the results may have been confounded in an unknown direction.
    - Imbalances in sex, ethnicity, prior taxane, or prior immunotherapy were not considered to confound the results. There was limited literature available on the prognosis of patients with gastric cancer by sex. There was some literature to support patients with Asian ethnicity may have better survival outcomes, however Asian ethnicity was balanced between treatment arms within the trial.[55] Though White ethnicity was imbalanced, there was a significant proportion of patients who did not report ethnicity, thus confounding based on ethnicity was considered to be limited. A recent trial comparing taxane versus irinotecan in the second-line for patients with metastatic gastric cancer did not find either treatment to be superior, thus, the imbalance in taxane therapy was not suspected to confound the trial results.[56] As per discussion with the CGP, the role of immunotherapy in this patient setting is unclear, and thus it is uncertain how the imbalance in prior immunotherapies may have affected trial results.
- Secondary outcomes, such as PFS, were investigator-assessed, and thus may be subject to detection bias. Although the study was double-blind, the comparator was placebo and a higher proportion of AEs occurred in the trifluridine-tipiracil arm, which could be an indicator of active treatment and thus, could lead to differential assessment of outcomes by the investigators in either treatment arm. Additionally, specific AEs characteristic of trifluridine-tipiracil could also potentially indicate to investigators what treatment arm their patients were randomized to.
- The primary PFS analysis may have been subject to informative censoring, which may have introduced bias that overestimated PFS observed in the study. Specifically, patients who discontinued treatment for reasons other than radiologic PD (for reasons such as clinical PD, unacceptable toxicity, or voluntary withdrawal), patients who initiated non-study anti-tumor treatment

before the date of radiologic PD, and patients with radiologic PD or death after missed tumor assessments were censored at various time points, however these patients may have been at a different risk for treatment failure than those who remained on the study. A number of sensitivity analyses were conducted to address these concerns including a sensitivity analysis including clinical progression as a PD event (HR: 0.55; 95% CI: 0.45, 0.67); clinical progression and initiation of new antitumor therapy as PD events (HR: 0.55; 95% CI: 0.45, 0.68); clinical progression, initiation of new antitumor therapy, and deaths included as events even if missed visits occurred (HR: 0.56; 95% CI: 0.46, 0.68).[3] An additional analysis was requested to count patients who had initiated a new anti-cancer therapy and experienced a PD event as having a PD event, which was also consistent with the primary analysis results (HR: 0.57; 95% CI: 0.47, 0.70). Time to treatment failure (discontinuation of treatment for any reason counted as a PD event) was also consistent with the primary study results (HR: 0.55; 95% CI: 0.45, 0.77).[50] Thus, the impact of informative censoring was considered to be minimal and confirmed the robustness of the study results.

- Although, HRQoL assessments were to be conducted prior to dosing initiation at each cycle, the exact time of the questionnaires' collection were not recorded in the case report form database.[7] HRQoL may have been subject to response bias if assessments were conducted following dosing and after significant interactions with study staff, (for example, if patients are informed of improvement or deterioration could affect how they respond to HRQoL assessments). However, the extent and impact of this potential bias is unknown as the time of data collection cannot be verified.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed using the ITT population, which included 507 patients. The cut-off date for overall survival was March 27th, 2018. The cut-off date for all other endpoints was March 31st, 2018.[3] The median duration of survival follow-up was 10.7 months (95% CI: 10.2, 13.1) in the overall ITT population, with a median duration of follow-up of 10.6 months (95% CI: 10.1, 13.1) in the trifluridine-tipiracil treatment arm and 10.7 months (95% CI: 9.9, 15.4) in the placebo arm.[4]

Primary Endpoint – Overall Survival

The primary endpoint of the study was met at the time of the final analysis of OS. At the time of the planned interim analysis (~220 deaths), the efficacy or futility boundaries were not met and thus the study continued as per the data monitoring committee recommendation until completion. The interim analysis was reported on August 31st, 2017 when 200 events were observed, and the HR was 0.73 (95% CI: 0.55, 0.97; P = 0.0138) with an associated median OS in the trifluridine-tipiracil arm of 5.7 months and 3.8 months in the placebo arm. An additional sensitivity analysis was conducted on the date of the 192nd death, which had a corresponding efficacy boundary of a 1-sided p-value of 0.0016 and neither the efficacy or futility boundaries were met. The alpha-spending of these interim analyses resulted in an efficacy boundary of a 1-sided p-value of 0.0215 for the final analysis.[3]

The median overall survival was 5.7 months (95% CI: 4.8, 6.2) in the trifluridine-tipiracil treatment arm and 3.6 months (95% CI: 3.1, 4.1) in the placebo arm at the time of the final analysis and is summarized in Table 6.11. A total of 244 (72.4%) deaths occurred in the trifluridine-tpiracil arm and 140 (82.4%) deaths occurred in

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the placebo arm. As illustrated in Figure 6.3, there was a 31% reduction in the risk of death in the trifluridine-tipiracil treatment arm compared to the placebo arm (HR: 0.69; 95% CI: 0.56, 0.86; 1-sided p=0.0003), which was statistically significant and met the efficacy boundary of the final analysis.[2] Survival at 3, 6, 9, and 12 months in the trifluridine-tipiracil arm was 72.4%, 46.7%, 30.3%, 21.2% compared to 60.3%, 33.1%, 23.3%, and 13.0% in the placebo arm.[3]

Subgroup analyses for OS were largely consistent with the primary results (Figure 6.4), however the following subgroups had CIs that crossed 1: female; Asian ethnicity; United States or Japan region; primary site of GEJ; diffuse tumor histology; HER2 positive status; peritoneal metastases; no previous gastrectomy; 3 or 4 prior lines of chemotherapy regimens; prior ramucirumab; and prior irinotecan. The subgroup analysis for prior immunotherapy is not shown in Figure 6.4., and was reported as:

- Yes: events/patients = 18/25 vs. 6/7; HR=0.22 (95% CI: 0.06, 0.86); mOS 6.0 versus. 3.5 months.
- No: events/patients = 226/312 vs. 134/163; HR=0.71 (95% CI: 0.57, 0.88); median OS 5.7 versus 3.6 months.

Patients that did not receive a prior taxane were suggested to be at increased risk for mortality (HR: 1.14; 95% CI: 0.55, 2.35).[3] However, all subgroup analyses are exploratory, and thus should be interpreted with caution. Some subgroups were limited by small sizes.

All sensitivity analyses conducted were consistent with the primary efficacy results, confirming the robustness of the results and are shown in Table 6.12. For the multivariate model, the final model included the following covariates: treatment arm, region, ECOG PS at baseline, prior treatment with ramucirumab, age group (<65 vs. ≥65 years), number of prior regimens, number of metastatic sites, histology subtype, and HER2 status at baseline. None of the listed factors were shown to modify the effect of treatment (all interaction p-values were >0.24) in the Cox PH model. The multivariate model estimate for the HR was 0.69 (95% CI: 0.560, 0.851; p = 0.0005), which was consistent with the primary efficacy analysis of OS.[3]

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Table 6.11. Summary of overall survival in the TAGS trial, ITT population

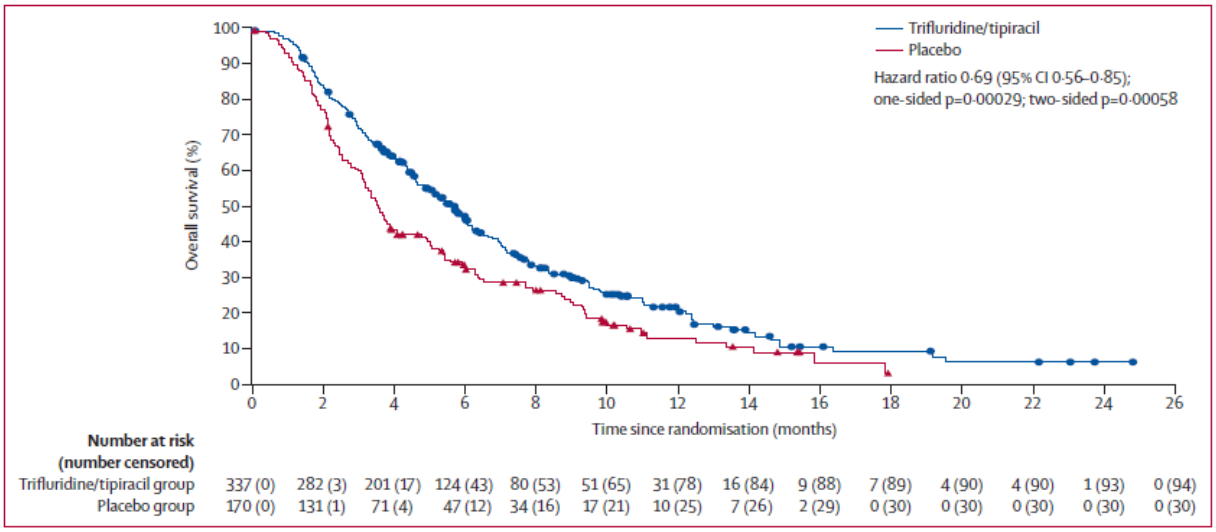
	TAS-102 N = 337	Placebo N = 170
Number of events (deaths), n (%)	244 (72.4)	140 (82.4)
Censored	93 (27.6)	30 (17.6)
Overall survival		
Median, months	5.7	3.6
95% CI, months	4.8, 6.2	3.1, 4.1
Hazard ratio	0.69 (0.560, 0.855)	
1-sided p-value[a]	0.0003	
2-sided p-value	0.0006	
Survival at 3 months, % (95% CI)	72.4 (67.3, 76.9]	60.3 (52.4, 67.2)
Survival at 6 months, % (95% CI)	46.7 (41.1, 52.2)	33.1 (25.9, 40.3)
Survival at 9 months, % (95% CI)	30.3 (24.9, 35.8)	23.3 (16.8, 30.3)
Survival at 12 months, % (95% CI)	21.2 (16.1, 26.7)	13.0 (7.7, 19.8)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of patients in arm; n = number of patients in group

[a] boundary for final analysis 1-sided alpha = 0.0215

Source: EPAR, 2019; Table 14; p. 34/88[3]

Figure 6.3. Kaplan-Meier curve for overall survival in the TAGS trial, ITT population (n=507)



Source: Shitara et al., 2018 ; Figure 2

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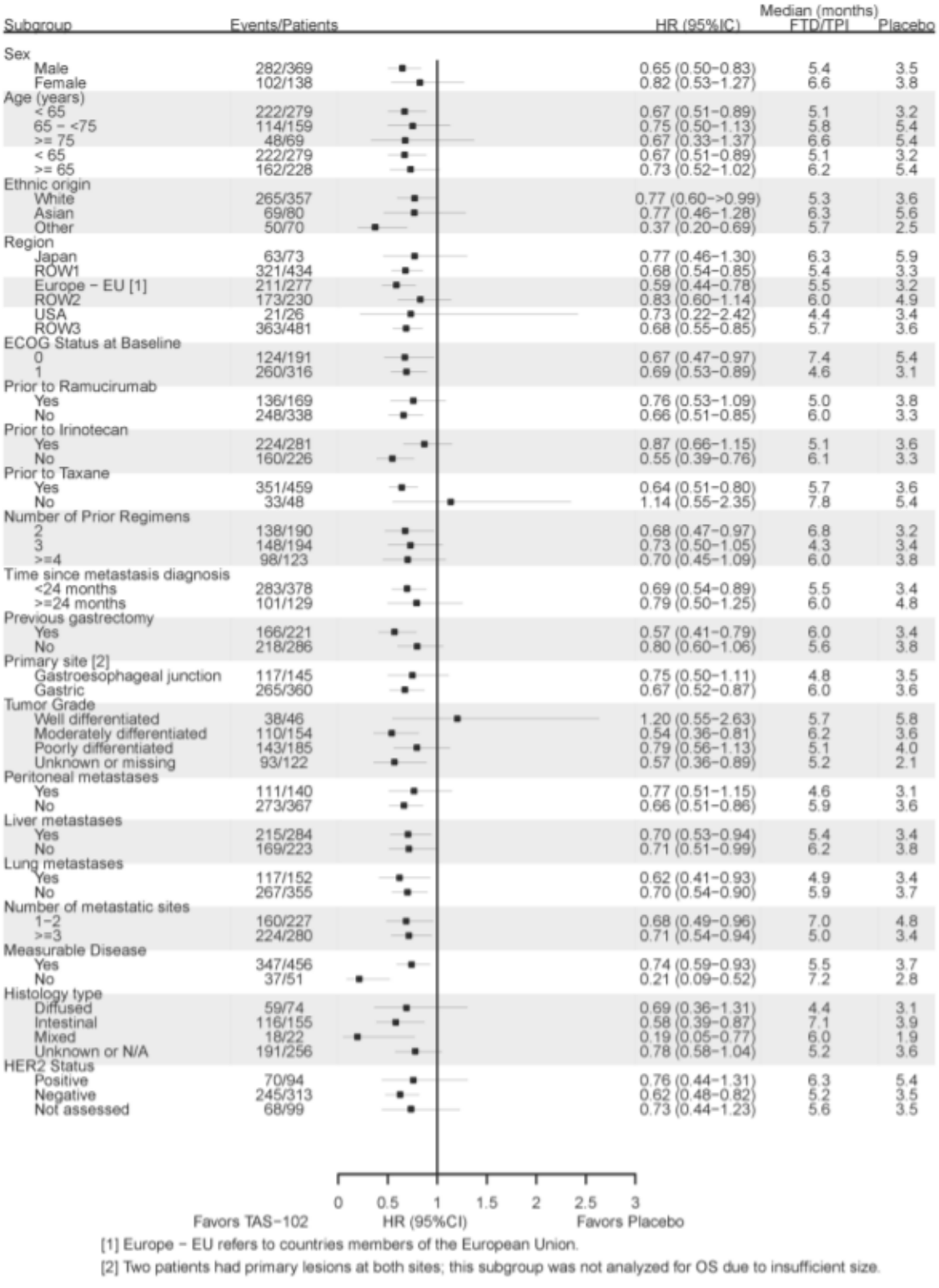
Figure 6.4. Subgroup analyses of overall survival in the TAGS trial, ITT population (n=507)



[1] Europe − EU refers to countries members of the European Union.

[2] Two patients had primary lesions at both sites; this subgroup was not analyzed for OS due to insufficient size.

Source: EPAR, 2019; Figure 4; p. 37/88[3]

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Table 6.12. Results of the sensitivity analyses for overall survival in the TAGS trial

	Trifluridine-tipiracil		Control arm			
Analysis	N	Median OS (months)	N	Median OS (months)	HR (95% CI)	p-value*
A1: Non-stratified log-rank test, ITT popualtion	337	5.7	170	3.6	0.71 (0.58, 0.88)	0.0007
A2: Excluding patients who did not meet inclusion criteria of disease requirements (#2) or prior lines requirements (#3)	333	5.7	169	3.6	0.70 (0.57, 0.87)	0.0005
A3: Excluding patients with major protocol deviations	330	5.7	169	3.6	0.70 (0.57, 0.87)	0.0005
A4: Based on CRF stratification factors for the AT population	335	5.7	168	3.6	0.68 (0.55, 0.85)	0.0002
A5: By AT population/treatment group	335	5.7	168	3.6	0.69 (0.56, 0.86)	0.0003
A6: Excluding sites with high accrual	304	5.7	149	3.4	0.60 (0.48, 0.75)	<0.0001
A7: Using date of collected events and survival status as of 30-Apr-2018	337	5.6	170	3.6	0.71 (0.58, 0.87)	0.0006

Abbreviations: A= analysis number; AT = as-treated; CI = confidence interval; CRF = case report form; HR = hazard ratio; ITT = intention to treat; PD = progressive disease; OS = overall survival
* 1-sided p-value
Source:
EPAR, 2019; p. 35/88[3]

Secondary Endpoints

Progression-free survival

The median PFS in the trifluridine-tipiracil arm was 2.0 months (95% CI: 1.9, 2.3) and in the placebo arm it was 1.8 months (95% CI: 1.7, 1.9), and is summarized in Table 6.13. A total of 287 (85.2%) PFS events occurred in the trifluridine-tipiracil arm and 156 (91.8%) PFS events occurred in the placebo arm. As illustrated in Figure 6.5, there was a 43% reduction in the risk of PD or death associated with the trifluridine-tipiracil arm relative to the placebo arm (HR: 0.57; 95% CI: 0.47, 0.70; p<0.0001). PFS at 2, 4, 6, and 8 months in the trifluridine-tipiracil arm was 49.7%, 26.8%, 14.6%, and 9.4% compared to 25.3%, 7.7%, 6.4%, and 2.8% in the placebo arm.[3]

Subgroup analyses for PFS were largely consistent with the primary PFS analysis (Figure 6.6), with the exception of the following subgroups where the CI crossed 1: female; United States region; no measurable disease; mixed histology; and did not receive a prior taxane. The subgroup analysis for prior immunotherapy was not shown in Figure 6.6., however it was reported as:

- Yes: events/patients = 22/25 versus. 7/7; HR= 0.4782 (95% CI: 0.1413, 1.6184); median PFS 2.4 versus. 1.9 months
- No: events/patients = 265/312 versus. 149/163; HR= 0.5774 (95% CI: 0.4690, 0.7110); median PFS 2.0 versus. 1.8 months.[3]

All subgroup analyses are exploratory, and thus should be interpreted with caution. Some subgroups were limited by small sizes.

The sensitivity analyses to address potential informative censoring concerns associated with the primary PFS analysis were highly consistent with the primary

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PFS results and are shown in Table 6.14. A sensitivity analysis of time to first, second and third radiological tumour assessments from the date of randomization was also conducted (results not shown), and the results confirmed that the assessments were performed to schedule and that timing was similar between the two treatment arms.[3]

Two additional sensitivity analyses to assess for the robustness of the results were requested. One analysis included patients who had initiated a new anti-cancer therapy and experienced a PD event as having a PD event, which was consistent with the primary analysis results (HR: 0.57; 95% CI: 0.47, 0.70). Time to treatment failure (discontinuation of treatment for any reason counted as a PD event) was also consistent with the primary study results (HR: 0.55; 95% CI: 0.45, 0.77).[50]

Table 6.13. Summary of progression-free survival in the TAGS trial, ITT population (n=507)

	TAS-102 N = 337	Placebo N = 170
Number of events, n (%)		
Progression	209 (62.0)	113 (66.5)
Death	78 (23.1)	43 (25.3)
Censored	50 (14.8)	14 (8.2)
Discontinued follow-up	12 (3.6)	1 (0.6)
Initiated antitumor therapy	8 (2.4)	6 (3.5)
Missed visit (>91 days since last contact)	10 (3.0)	3 (1.8)
Follow-up ongoing	20 (5.9)	4 (2.4)
Progression-free survival		
Median, months	2.0	1.8
95% CI, months	1.9, 2.3	1.7, 1.9
Hazard ratio (95% CI)	0.57 (0.467, 0.701)	
2-sided p-value	<0.0001	
PFS at 2 months, % (95% CI)	49.7 (44.1, 55.1)	25.3 (18.9, 32.1)
PFS at 4 months, % (95% CI)	26.8 (21.9, 31.9)	7.7 (4.2, 12.5)
PFS at 6 months, % (95% CI)	14.6 (10.7, 19.0)	6.4 (3.2, 10.9)
PFS at 8 months, % (95% CI)	9.4 (6.2, 13.3)	2.8 (0.8, 6.8)

Abbreviations: ITT = intent-to-treat; CI = confidence interval; N = number of patients in arm; n = number of patients in group; PFS = progression-free survival

Source: EPAR, 2019; Table 16; p. 38/88[3]

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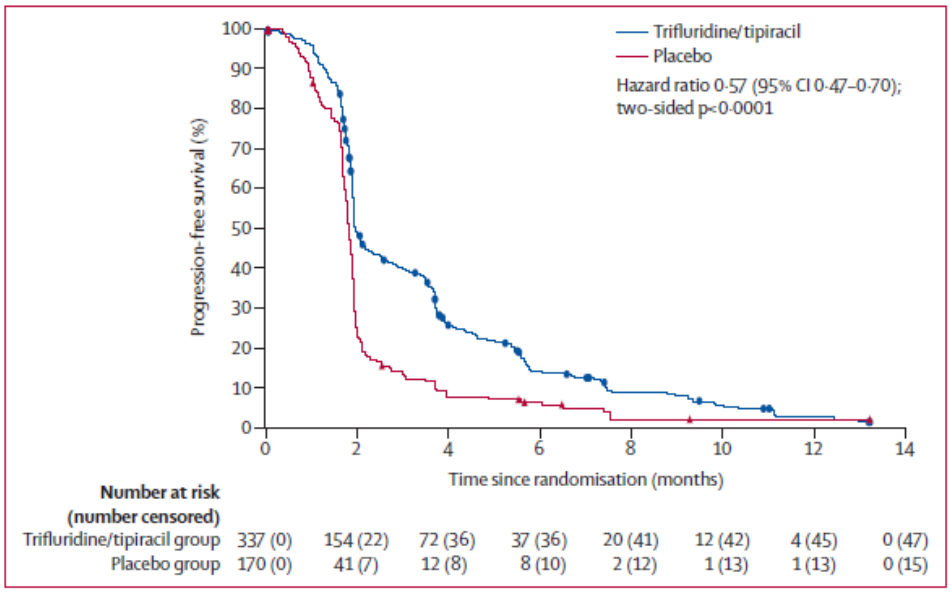
Figure 6.5. Kaplan-Meier curve for progression-free survival in the TAGS trial, ITT population (n=507)



Source: Shitara et al., 2019; Figure 4

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Figure 6.6. Subgroup analyses of progression-free survival in the TAGS trial, ITT population (n=507)

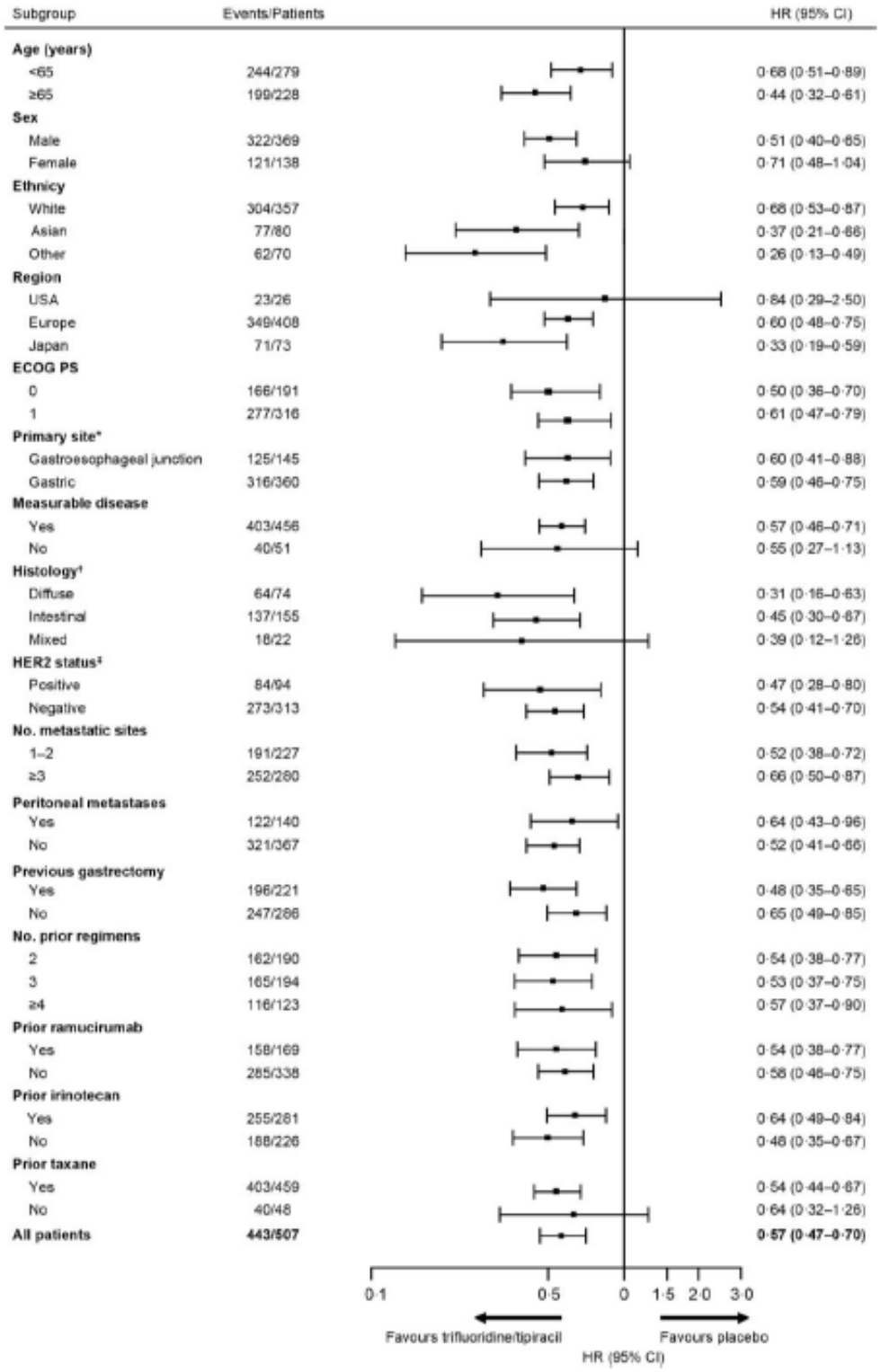

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Table 6.14 Sensitivity analyses for progression-free survival in the TAGS trial

	Trifluridine-tipiracil arm		Control arm			
Analysis	N	Median PFS (months)	N	Median PFS (months)	HR (95% CI)	p-value*
A1: Including clinical PD as PFS event	337	1.9	170	1.8	0.55 (0.45, 0.67)	<0.0001
A2: Including clinical PD and initiation of new antitumor therapy as PFS event	337	1.9	170	1.8	0.55 (0.45, 0.68)	<0.0001
A3: Including clinical PD, initiation of new antitumor therapy, and deaths without censoring missed visits	337	1.9	170	1.8	0.56 (0.46, 0.68)	<0.0001
A4: Excluding sites with high accrual	304	1.9	149	1.8	0.48 (0.38, 0.59)	<0.0001

Abbreviations: A= analysis number; CI = confidence interval; HR = hazard ratio; PD = progressive disease; PFS = progression-free survival
* 2-sided p-value
Source: EPAR, 2019; p. 39/88[3]

Objective Response Rate (ORR) and Disease Control Rate (DCR)

The ORR was 4.5% (n=13) in the trifluridine-tipiracil treatment arm and 2.1% (n=3) in the placebo arm (Table 6.15). The difference in ORR between treatment arms was 2.4% (95% CI: -0.9, 5.7, p=0.2833). The DCR was 44.1% (achieved in 128 patients) in the trifluridine-tipiracil treatment arm compared to 14.5% (achieved in 21 patients) in the placebo arm, driven by the large proportion of patients achieving stable disease in the trifluridine-tipiracil treatment arm. The difference in the DCR between treatment arms was 29.7% (95% CI: 21.6, 37.7, p<0.0001).[2,3]

Table 6.15. Best overall response, objective response rate, and disease control rate in the TAGS trial, TR population (n=435)

	TAS-102 N = 290	Placebo N = 145
Best overall response, n (%)		
Complete response (CR)	1 (0.3)	0
Partial response (PR)	12 (4.1)	3 (2.1)
Stable disease (SD)	115 (39.7)	18 (12.4)
Progressive disease (PD)	120 (41.4)	90 (62.1)
Not evaluable	42 (14.5)	34 (23.4)
Objective response rate, %	4.5	2.1
95% CI	2.4, 7.5	0.4, 5.9
p-value[c]	0.2833	
Disease control rate, %	44.1	14.5
95% CI	38.3, 50.1	9.2, 21.3
p-value[c]	<0.0001	

Abbreviations: CI = confidence interval; N = number of patients in arm; n = number of patients in group; TR = tumour response

[c] Fisher's exact test (2-sided)

Source: EPAR, 2019; Table 18; p. 42/88[3]

Time to deterioration of ECOG PS ≥ 2

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The median time to deterioration to ECOG PS ≥2 was 4.3 months (95% CI: 3.7, 4.7) in the trifluridine-tipiracil arm compared to 2.3 months (95% CI: 2.0, 2.8) in the placebo arm. There was significant increase in the median time to deterioration to ECOG PS ≥2 compared to placebo (HR=0.69; 95% CI: 0.562, 0.854; p=0.0005). A sensitivity analysis was performed, using only on therapy ECOG assessments for analysis (excluding deaths during the survival follow-up period). There were 214 (63.5%) patients in the trifluridine-tipiracil arm that were censored and 90 (52.9%) patients in the placebo arm. The median time to ECOG PS ≥2 was 5.5 months (95% CI: 4.4, 6.9) in the trifluridine-tipiracil arm vs. 2.2 months (95% CI: 1.9, 3.0) in the placebo arm (HR=0.54; 95% CI: 0.404, 0.721; 2-sided p<0.0001).[3]

Health-related Quality of Life (HRQoL)

The rate of questionnaire compliance was, overall, higher in the trifluridine-tipiracil treatment arm compared to the placebo arm for the EORTC QLQ-C30 (86.9% vs. 78.2% compliance, respectively), as well as for the EORTC QLQ-STO22 (86.6% vs. 78.2% compliance, respectively). By cycle 3 compliance dropped to 37.3% and 36.7% for the QLQ-C30 and QLQ-STO22, respectively, in the trifluridine-tipiracil treatment arm and dropped even lower in the placebo treatment arm to 14.0% compliance for both questionnaires.[5]

Baseline global health status (GHS) data from the EORTC QLQ-C30 were available for 330 (97.9%) of patients in the trifluridine-tipiracil treatment arm and for 163 (95.9%) of patients in the placebo arm.[57] The mean baseline global health status (GHS) based on the EORTC QLQ-C30 was 58.4 for both treatment arms. By cycle 3, the mean GHS score was 57.1 in the trifluridine-tipiracil arm and 59.8 in the placebo arm, representing a mean change from baseline of -4.1 in the trifluridine-tipiracil arm and -1.4 in the placebo arm.[3] There were no clinically relevant changes (≥10 points) in GHS from baseline to up to cycle 3 in each treatment arm, as illustrated in Figure 6.7.[57] There were no clinically relevant differences in the mean change in score from baseline for most of the functioning and symptom scales of the EORTC QLQ-C30, except for role functioning at cycle 3, where there was a difference of 10 points favouring placebo, and the pain scale at cycle 2, where there was a difference of 11.3 points favouring trifluridine-tipiracil. There were no clinically relevant changes in mean scores from baseline in the QLQ-STO22 scores.[5]

The median time to deterioration (≥5 points) in GHS was 2.6 months (95% CI: 2.3, 3.3) in the trifluridine-tipiracil arm compared to 2.3 months (95% CI: 1.4, NA) in the placebo arm (HR: 1.27; 95% CI: 0.85, 1.88, P=0.2350). A sensitivity analysis using a decrease of ≥10 points showed similar results with a median time to deterioration of 5.6 months (95% CI: 3.8, NA) in the trifluridine-tipiracil treatment arm vs. 4.6 months (95% CI: 2.2, NA) in the placebo arm (HR: 0.97; 95% CI: 0.64, 1.47; p=0.8709). Both analyses included 288 patients in the trifluridine-tipiracil treatment arm and 130 patients in the placebo treatment arm.[3] An additional sensitivity analysis that included death or PD as an event (i.e., as a decrease of ≥10 points in GHS score) resulted in a statistically significant 35% reduction in time to clinically relevant deterioration in GHS score (HR: 0.65; 95% CI: 0.52, 0.81), which coincided with a median time to deterioration of 64 days (~2.1 months) in the trifluridine-tipiracil treatment arm and 57 days (~1.9 months), which was considerable lower overall than not including PD or death as QoL deterioration events.[5]

An analysis to explore the association between QoL and time to ECOG PS deterioration was conducted in a QoL deterioration time-dependent univariate

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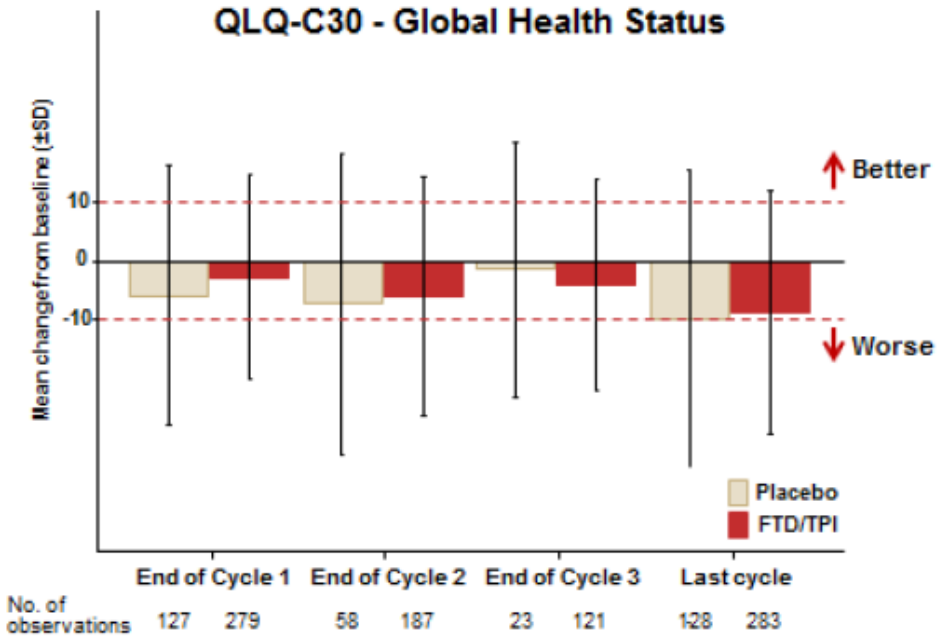
model, and a reduction in the QLQ-C30 GHS score of ≥10 point was significantly associated with a deterioration in ECOG PS of ≥2 (HR: 1.51; 95% CI: 1.22, 1.88), which was consistent with what was expected.[5,57]

Figure 6.7. Change from baseline in the mean EORTC QLQ-C30 Global Health Status score across treatment cycles, TAGS trial



Source: Alsina et al., 2018; Figure 1[57]

Harms Outcomes

Treatment Exposure

The median total treatment duration in the tipiracil/trifluridine arm was 6.71 weeks (95% CI: 0.4, 62.7) and 5.71 weeks (95% CI: 0.1, 63.0) in the placebo arm. As illustrated in Table 6.16., less than 50% of patients initiated treatment beyond cycle 2. The median dose intensity was 156.72 mg/m^2 per week for trifluridine-tipiracil patients and 166.15 mg/m^2 per week for placebo patients. The median relative dose intensity (the ratio of actual administered dose to planned dose) was 90% in the trifluridine-tipiracil arm. and 95% in the placebo arm, which was close to the entire planned dose intensities. Over the entire treatment period, 95.8% in the trifluridine-tipiracil treatment arm and 92.3% in the placebo arm received ≥90% of their target cycle dose.[3]

A total of 195 (58.2%) and 37 (22.0%) patients in the trifluridine-tipiracil and placebo arms, respectively, had an AE that resulted in a dosing modification (dose delay or dose reduction). In the trifluridine-tipiracil arm, a total of 36 (10.7%) patients had a dose reduction, and 2 (1.2%) in the placebo arm due to AEs.[3] Most of dose reductions, for any reason, were single dose reductions.[6] The most common AE leading to a dose modification was neutropenia and/or decreased neutrophil count in the trifluridine-tipiracil arm (n=123; 37%) compared to the placebo arm (n=1; 1%). Additional factors are outlined in Table 6.18.[2]

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A total of 43 (12.8%) of patients discontinued treatment due to any AE in the trifluridine-tipiracil arm compared to 28 (16.7%) of patients in the placebo arm.[3] A total of 13 (4%) discontinued due to a treatment-related AE (TEAE) in the trifluridine-tipiracil arm, with the most common reason of thrombocytopenia, compared to 2 (2%) patients in the placebo arm where the most common reason was vomiting (see Table 6.18).[2]

Adverse Events

There were more patients in the trifluridine-tipiracil arm who experienced at least 1 any-grade AE (n=326; 97.3%) compared to the placebo arm (n=157; 93.5%). There were 271 patients (80.9%) in the trifluridine-tipiracil arm with any treatment-related AE compared to 95 patients (56.6%) in the placebo arm. Grade ≥3 AEs occurred in a higher proportion of patients in the trifluridine-tipiracil arm (n=267; 79.7%) than in the placebo arm (n=97; 57.7%).[3]

As shown in Table 6.19, the most common any-grade AEs included anemia (n=149; 44.5%), neutropenia (n=129; 38.5%), nausea (n=124; 37.0%), and decreased appetite (n=115; 34.3%) in the trifluridine-tipiracil arm. In the placebo arm, the most common any-grade AEs included nausea (n=53; 31.5%), decreased appetite (n=52; 31.0%), asthenia (n=40; 23.8%), and fatigue (n=35; 20.8%).[6]

The most common TEAEs in the trifluridine-tipiracil arm included neutropenia (n=126; 37.6%), anemia (n=104; 31.0%), and nausea (n= 85; 25.4%). In the placebo arm, the most common TEAEs included nauseas (n=26; 15.5%), decreased appetite (n=19; 11.3%), and fatigue (n=17; 10.1%). See Table 6.20 for more details. [6]

The most common grade ≥3 AEs in the trifluridine-tipiracil arm included neutropenia (n=78; 23.3%) and anemia (n=63; 18.8%), whereas in the placebo arm it was general physical health deterioration (n=15; 8.9%), abdominal pain (n=15; 8.9%), and anemia (n=13; 7.7%). See Table 6.21 for more details.[6]

Serious Adverse Events

Serious adverse events (SAEs) occurred in a similar proportion between treatment arm, occurring in 42.7%; n=143) in the trifluridine-tipiracil arm and in 41.7% (n=70) in the placebo arm. In both treatment arms, general deterioration of health (6.3% and 8.9% in the trifluridine-tipiracil arms and placebo arms, respectively) and anemia (3.9% and 2.4%, respectively) were common SAEs. Decrease appetite (3.3%) and vomiting (2.7%) were additional SAEs occurring often in the trifluridine-tipiracil arm, whereas ascites (4.2%) and abdominal pain (3.6%) occurred often in the placebo arm. See Table 6.22 for more details.[6]

Treatment-related SAEs occurred in 12% and 4% of patients in the trifluridine-tipiracil and placebo arms, respectively. Pancytopenia was the only treatment-related SAE that occurred in more than 2% of patients, occurring in 2.1% of patients in the trifluridine-tipiracil arm and in no patients in the placebo arm.[2]

Deaths

There were a total of 45 (13.4%) deaths due to AEs in the trifluridine-tipiracil arm compared to 19 (11.3%) in the placebo arm. General physical health deterioration was the most common AE in the trifluridine-tipiracil arm (n=17; 5%) and in the placebo arm (n=11; 7%) leading to death. Additional AEs leading to death in the trifluridine-tipiracil arm included pulmonary embolism (n=3; 1%), septic shock (n=3; 1%), acute coronary syndrome (n=2; 1%), hemorrhagic shock (n=2; 1%), hepatic failure (n=2; 1%), and pleural effusion (n=2; 1%). In the placebo arm, other AEs leading to death included failure to thrive (n=1; 1%), pleural effusion (n=1; 1%),

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ascites (n=1; 1%), bacterial peritonitis (n=1; 1%), gastrointestinal obstruction (n=1; 1%), and toxic hepatitis (n=1; 1%). The full list is provided in Table 6.23.[2]

Table 6.16. Summary of treatment exposure by treatment arm in the TAGS trial, AT population (n=503)

	TAS-102 N = 335	Placebo N = 168
Total number of weeks of exposure[a]	4038	1191
Mean (SD)	12.05 (11.47)	7.09 (7.84)
Median	6.71	5.71
Min, Max	0.4, 62.7	0.1, 63.0
Cycles initiated per patient[b]		
Total cycles initiated	1108	394
Mean (SD)	3.3 (2.50)	2.3 (1.92)
Median	2.0	2.0
Min, Max	1,14	1,16
Cycle initiated, n (%)[b]		
1	335 (100)	168 (100)
2	282 (84.2)	125 (74.4)
3	145 (43.3)	33 (19.6)
4	116 (34.6)	18 (10.7)
>4	65 (19.4)	15 (8.9)

Abbreviations: AT = as-treated; N = number of patients in arm; n = number of patients in group; SD = standard deviation

[a] (Date of last dose of study medication – date of first dose of study medication +1) / 7
[b] Patients counted in each cycle initiated (at least 1 dose administered)

Source: EPAR, 2019; Table 22; p.52/88[3]

Table 6.17. Adverse events leading to dosing modification or discontinuation of treatment by treatment arm and grade (any grade and grade ≥3) in the TAGS trial, AT population (n=503)

	Trifluridine/tipiracil (n=335)†		Placebo (n=168)†	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Adverse events of any cause leading to dosing modification				
Any event	195 (58%)	148 (44%)	37 (22%)	29 (17%)
Most common events‡				
Neutropenia and/or decreased neutrophil count	123 (37%)	85 (25%)	1 (1%)	0
Anaemia and/or decreased haemoglobin level	29 (9%)	15 (4%)	3 (2%)	3 (2%)
Leucopenia and/or decreased white blood cell count	19 (6%)	11 (3%)	0	0
Treatment-related adverse events leading to discontinuation of treatment				
Any event	13 (4%)	13 (4%)	2 (1%)	2 (1%)
Thrombocytopenia	3 (1%)	3 (1%)	0	0
Diarrhoea	2 (1%)	1 (<1%)	1 (1%)	1 (1%)
Nausea	2 (1%)	2 (1%)	1 (1%)	1 (1%)
Neutropenic sepsis	2 (1%)	2 (1%)	0	0
Anaemia	1 (<1%)	1 (<1%)	0	0
Cerebrovascular accident	1 (<1%)	0	0	0
Decreased appetite	1 (<1%)	1 (<1%)	0	0
Fatigue	1 (<1%)	1 (<1%)	0	0
General physical health deterioration	1 (<1%)	1 (<1%)	0	0
Ileus	1 (<1%)	1 (<1%)	0	0
Neutropenia	1 (<1%)	1 (<1%)	0	0
Vomiting	0	0	2 (1%)	1 (1%)

Data are n (%).*Per Common Terminology Criteria for Adverse Events. †All treated patients. ‡Adverse events of any grade that occurred in 5% or more of patients in either treatment group.

Source: Reprinted from The Lancet Oncology, Vol 19, Shitara K. et al, Trifluridine-tipiracil versus placebo in patients with heavily pretreated metastatic gastric

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cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial, 1437-48, 2018, Copyright (2018), with permission from Elsevier.[2]

Table 6.18. Summary of any-grade adverse events by treatment arm occurring in ≥5.0% of patients in the TAGS trial, AT population (n=503)

Preferred Term	TAS-102 (N=335) n (%)	Placebo (N=168) n (%)
Number of Patient with at Least 1 TEAE	**326 (97.3)**	**157 (93.5)**
Anaemia	149 (44.5)	32 (19.0)
Neutropenia	129 (38.5)	6 (3.6)
Nausea	124 (37.0)	53 (31.5)
Decreased appetite	115 (34.3)	52 (31.0)
Fatigue	89 (26.6)	35 (20.8)
Vomiting	83 (24.8)	34 (20.2)
Diarrhoea	76 (22.7)	24 (14.3)
Asthenia	65 (19.4)	40 (23.8)
Leukopenia	57 (17.0)	3 (1.8)
Abdominal pain	55 (16.4)	31 (18.5)
Neutrophil count decreased	51 (15.2)	1 (0.6)
Constipation	45 (13.4)	25 (14.9)
Thrombocytopenia	33 (9.9)	2 (1.2)
Blood alkaline phosphatase increased	30 (9.0)	14 (8.3)
Platelet count decreased	28 (8.4)	6 (3.6)
Back pain	25 (7.5)	11 (6.5)
Pyrexia	25 (7.5)	8 (4.8)
Dyspnoea	24 (7.2)	17 (10.1)
General physical health deterioration	23 (6.9)	17 (10.1)
White blood cell count decreased	23 (6.9)	0
Abdominal pain upper	22 (6.6)	15 (8.9)
Hypoalbuminaemia	22 (6.6)	10 (6.0)
Aspartate aminotransferase increased	21 (6.3)	13 (7.7)
Weight decreased	20 (6.0)	12 (7.1)
Dysphagia	20 (6.0)	8 (4.8)
Lymphopenia	20 (6.0)	8 (4.8)
Ascites	19 (5.7)	16 (9.5)
Oedema peripheral	17 (5.1)	12 (7.1)
Blood bilirubin increased	17 (5.1)	7 (4.2)
Abdominal distension	13 (3.9)	9 (5.4)
Insomnia	11 (3.3)	10 (6.0)
Malaise	9 (2.7)	9 (5.4)

Abbreviations: TEAE = treatment-emergent adverse event
Note: At each level of summation (overall, system organ class, preferred term), patients were only counted once.
Source: Table 14.3.1.5.1

Source: Taiho Oncology Inc., Clinical Study Report, 2018; Table 34, p. 107/160[6]

Table 6.19. Summary of any-grade treatment-related adverse events by treatment arm occurring in ≥5.0% of patients in the TAGS trial, AT population (n=503)

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System Organ Class Preferred Term	TAS-102 (N=335) n (%)	Placebo (N=168) n (%)
Number of patients with at least 1 treatment-related TEAE	**271 (80.9)**	**95 (56.5)**
Blood and Lymphatic System Disorders	**180 (53.7)**	**21 (12.5)**
Neutropenia	126 (37.6)	6 (3.6)
Anaemia	104 (31.0)	15 (8.9)
Leukopenia	52 (15.5)	3 (1.8)
Thrombocytopenia	28 (8.4)	1 (0.6)
Lymphopenia	18 (5.4)	6 (3.6)
Gastrointestinal Disorders	**138 (41.2)**	**50 (29.8)**
Nausea	85 (25.4)	26 (15.5)
Diarrhoea	54 (16.1)	16 (9.5)
Vomiting	36 (10.7)	12 (7.1)
General Disorders and Administration Site Conditions	**117 (34.9)**	**37 (22.0)**
Fatigue	63 (18.8)	17 (10.1)
Asthenia	31 (9.3)	13 (7.7)
Investigations	**97 (29.0)**	**16 (9.5)**
Neutrophil count decreased	50 (14.9)	1 (0.6)
Platelet count decreased	24 (7.2)	5 (3.0)
White blood cell count decreased	23 (6.9)	0
Metabolism and Nutrition Disorders	**72 (21.5)**	**21 (12.5)**
Decreased appetite	61 (18.2)	19 (11.3)

Abbreviations: TEAE = treatment-emergent adverse events
Note: At each level of summation (overall, system organ class, preferred term), patients were only counted once.
Source: Table 14.3.1.3

Source: Taiho Oncology Inc., Clinical Study Report, 2018; Table 36, p. 109/160[6]

Table 6.20. Summary of grade ≥3 adverse events by treatment arm occurring in ≥5.0% of patients in the TAGS trial, AT population (n=503)

Preferred Term	TAS-102 (N=335) n (%)	Placebo (N=168) n (%)
Number of Patient with at Least 1 ≥ Grade 3 TEAE	**267 (79.7)**	**97 (57.7)**
Blood and Lymphatic System Disorders	**137 (40.9)**	**16 (9.5)**
Anaemia	63 (18.8)	13 (7.7)
Neutropenia	78 (23.3)	0
Leukopenia	23 (6.9)	0
Gastrointestinal Disorders	**70 (20.9)**	**48 (28.6)**
Abdominal pain	14 (4.2)	15 (8.9)
Ascites	12 (3.6)	11 (6.5)
General Disorders and Administration Site Conditions	**59 (17.6)**	**36 (21.4)**
Fatigue	23 (6.9)	10 (6.0)
Asthenia	16 (4.8)	11 (6.5)
General physical health deterioration	22 (6.6)	15 (8.9)
Investigations	**73 (21.8)**	**11 (6.5)**
Neutrophil count decreased	38 (11.3)	0
Metabolism And Nutrition Disorders	**40 (11.9)**	**22 (13.1)**
Decreased appetite	29 (8.7)	11 (6.5)

Abbreviations: TEAE = treatment-emergent adverse events
Note: At each level of summation (overall, system organ class, preferred term), patients were only counted once.

Source: Taiho Oncology Inc., Clinical Study Report, 2018; Table 35, p. 108/160[6]

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Table 6.21. Summary of serious adverse events by treatment arm occurring in ≥1.0% of patients in the TAGS trial, AT population (n=503)

System Organ Class Preferred Term	TAS-102 (N=335) n (%)	Placebo (N=168) n (%)
Number of patients with at least 1 serious adverse event	**143 (42.7)**	**70 (41.7)**
Blood and lymphatic system disorders	**25 (7.5)**	**4 (2.4)**
Anaemia	13 (3.9)	4 (2.4)
Pancytopenia	7 (2.1)	0
Febrile neutropenia	4 (1.2)	0
Neutropenia	4 (1.2)	0
Gastrointestinal disorders	**55 (16.4)**	**31 (18.5)**
Vomiting	9 (2.7)	1 (0.6)
Abdominal pain	8 (2.4)	6 (3.6)
Diarrhoea	6 (1.8)	0
Dysphagia	6 (1.8)	2 (1.2)
Gastrointestinal haemorrhage	4 (1.2)	1 (0.6)
Intestinal obstruction	4 (1.2)	3 (1.8)
Ascites	3 (0.9)	7 (4.2)
Gastric haemorrhage	3 (0.9)	3 (1.8)
Small intestinal obstruction	3 (0.9)	2 (1.2)
Upper gastrointestinal haemorrhage	2 (0.6)	2 (1.2)
General disorders and administration site conditions	**28 (8.4)**	**21 (12.5)**
General physical health deterioration	21 (6.3)	15 (8.9)
Asthenia	1 (0.3)	3 (1.8)
Infections and infestations	**20 (6.0)**	**9 (5.4)**
Neutropenic sepsis	4 (1.2)	0
Pneumonia	4 (1.2)	2 (1.2)
Metabolism and nutrition disorders	**18 (5.4)**	**7 (4.2)**
Decreased appetite	11 (3.3)	4 (2.4)
Musculoskeletal and connective tissue disorders	**1 (0.3)**	**3 (1.8)**
Back pain	0	3 (1.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**8 (2.4)**	**4 (2.4)**
Malignant ascites	1 (0.3)	2 (1.2)
Respiratory, thoracic and mediastinal disorders	**15 (4.5)**	**4 (2.4)**
Pleural effusion	5 (1.5)	1 (0.6)
Pulmonary embolism	5 (1.5)	2 (1.2)
Dyspnoea	4 (1.2)	2 (1.2)

Note: At each level of summation (overall, system organ class, preferred term), patients were only counted once at the highest toxicity grade

Source: Taiho Oncology Inc., Clinical Study Report, 2018; Table 39, p. 114/160[6]

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Table 6.22. Adverse events leading to death by treatment arm in the TAGS trial, AT population (n=503)

Adverse event of any cause leading to death	Trifluridine/tipiracil (n=335)†	Placebo (n=168)†
Any adverse event of any cause leading to death	45 (13%)	19 (11%)
General physical health deterioration	17 (5%)	11 (7%)
Pulmonary embolism	3 (1%)	0
Septic shock	3 (1%)	0
Acute coronary syndrome	2 (1%)	0
Failure to thrive	2 (1%)	1 (1%)
Haemorrhagic shock	2 (1%)	0
Hepatic failure	2 (1%)	0
Pleural effusion	2 (1%)	1 (1%)
Altered state of consciousness	1 (<1%)	0
Cardiorespiratory arrest	1 (<1%)	0
Cerebral haemorrhage	1 (<1%)	0
Escherichia sepsis	1 (<1%)	0
Gastrointestinal haemorrhage	1 (<1%)	0
Increased blood bilirubin	1 (<1%)	0
Lymphangiosis carcinomatosa	1 (<1%)	0
Malignant neoplasm	1 (<1%)	0
Metastases to CNS	1 (<1%)	0
Pneumonia	1 (<1%)	0
Respiratory failure	1 (<1%)	0
Upper gastrointestinal haemorrhage	1 (<1%)	0
Transient ischaemic attack	1 (<1%)	0
Ascites	0	1 (1%)
Bacterial peritonitis	0	1 (1%)
Disease progression	0	1 (1%)
Gastrointestinal obstruction	0	1 (1%)
Hypotension	0	1 (1%)
Intestinal obstruction	0	1 (1%)
Toxic hepatitis	0	1 (1%)

Data are n (%). *Per Common Terminology Criteria for Adverse Events. †All treated patients.

Source: Reprinted from The Lancet Oncology, Vol 19, Shitara K. et al, Trifluridine-tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial, 1437-48, 2018, Copyright (2018), with permission from Elsevier.[2]

Additional Information

Subgroup analysis in patients with prior gastrectomy

A pre-specified subgroup analysis in patients with prior gastrectomy was conducted. As presented in the earlier section on patient disease characteristics, a total of 221 (43.6%) had undergone prior gastrectomy and a total of 286 (56.4%) had not. Also illustrated in the earlier section on efficacy, OS (HR: 0.57; 95% CI: 0.41, 0.79) and PFS (HR; 0.48; 95% CI: 0.35-0.65) of patients randomized to the trifluridine-tipiracil arm relative to placebo in the gastrectomy subgroup were consistent with the primary analysis, and the HR estimates suggest a slightly enhanced benefit for this subgroup compared to the overall trial results. In the no prior gastrectomy subgroup, OS (HR: 0.80; 95% CI: 0.60, 1.06) and PFS (HR: 0.65; 95% CI: 0.49, 0.85) and) were generally consistent with the primary trial results, however, the benefit was less pronounced particularly in reference to the point estimate of OS and the confidence interval crossed 1. With regards to safety, there were a higher proportion of grade ≥3 AEs in the gastrectomy subgroup (84.1%) compared to the no gastrectomy subgroup (76.3%). There were a higher proportion of patients in the gastrectomy subgroup compared to the no prior gastrectomy subgroup that had grade ≥3 neutropenia (44.1% vs. 26.3%, respectively); anemia (21.4% vs. 17.4%); and leukopenia (14.5% vs. 5.3%). In the gastrectomy subgroup,

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64.8% had dosing modifications and 10.3% discontinued treatment due to AEs, compared to 53.2% of patients that had dosing modific

ations and 14.7% that discontinued treatment due to AEs in the no prior gastrectomy subgroup.[41]

Subgroup analysis in patients 65 years of age or older

Another pre-planned subgroup analysis in patients ≥65 years of age was conducted, which included 228 (45%) patients from the total population. The patient subgroup aged ≥65 years was similar to the overall population, except for a higher incidence of moderate renal impairment in the elderly subgroup (31% vs 17% in the overall trial). For patients aged ≥65 years, baseline characteristics were generally balanced between treatment arms, however a higher proportion of patients had ECOG PS 1 in the trifluridine-tipiracil arm (69%) than the placebo arm (59%). As presented in the earlier section on efficacy, the subgroup analysis of OS (HR: 0.73; 95% CI: 0.52, 1.02) and PFS (HR: 0.44; 95% CI: 0.32, 0.61), were generally consistent with the overall trial results, however there less pronounced benefit for OS (and the confidence interval crossed 1), yet an enhanced benefit for PFS in the ≥65 years age group compared to the overall trial results. The proportion of patients with grade ≥3 AEs were similar between the trifluridine-tipiracil arm in the overall trial and ≥65 years of age subgroup (80% for both), whereas there were a slightly higher proportion of patients in the placebo arm in the overall trial (58%) that had a grade ≥3 AE compared to the ≥65 years age subgroup (51%). There was a higher proportion of patients in the trifluridine-tipiracil arm in the ≥65 years of age subgroup with neutropenia grade ≥3 neutropenia (40%) compared to the overall trial (34%), and a similar proportion of patients had anemia in the overall trial compared to the ≥65 years of age subgroup in the trifluridine-tipiracil arms (19% in the overall trial and 18% in the ≥65 years of age) and placebo arms (8% in both the overall trial and ≥65 years of age subgroup).[44]

Subgroup analysis in patients with metastatic gastroesophageal cancer

Finally, a prespecified subgroup analysis in patients with metastatic gastroesophageal junction cancer (mGEJc) was conducted, which included 145 (29%) patients with GEJ as the sole primary disease site. Of patients with mGEJc, 85% were male and 83% were White, compared to 73% male and 70% White in the overall trial. Baseline characteristics were generally balanced between treatment arms in the mGEJc subgroup, however in the trifluridine-tipiracil arm compared to the placebo arm, a smaller proportion of patients had prior gastrectomy (40% vs. 55%, respectively) and a higher proportion of patients had received ≥3 prior regimens (74% vs. 66%, respectively). As shown in the earlier section of efficacy, OS (HR: 0.75; 95% CI: 0.50, 1.11) and PFS (HR: 0.60; 95% CI: 0.41, 0.88) in the mGEJc subgroup were generally consistent with the overall trial results, however, there was less pronounced benefit in terms of OS, and it was not statistically significant (CI crossed 1). The proportion of patients with grade ≥3 AEs were similar between the trifluridine-tipiracil arm in the overall trial and the mGEJc subgroup (80% vs. 77%, respectively) and for the placebo arm in the overall trial and the mGEJc subgroup (58% vs. 59%, respectively). There were a small proportion of patients in the trifluridine-tipiracil arm (25%) that experienced neutropenia in the mGEJc subgroup compared to the overall trial (34%). There was a smaller proportion of patients in the trifluridine-tipiracil arm in the mGEJc subgroup that experience grade ≥3 anemia (13%) compared to the trifluridine-tipiracil arm in the overall trial (19%), similar to the placebo arm in the mGEJc arm (4%) compared to the overall

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trial (8%). Similar proportions of patients in the mGEJc subgroup and overall population had dose modifications and discontinued treatment due to AEs.[45]

Subgroup analysis in Japanese patients

A subgroup analysis including 73 (14.4% of the total TAGS trial population) Japanese patients enrolled across 9 sites in Japan was conducted, which included 46 (13.6% of total 337 trifluridine/tipiracil arm) patients in the trifuridine/tipiracil arm and 27 (15.9% of total 170 placebo arm) patients in the placebo arm. Median OS was 6.3 months in the trifluridine/tipiracil arm and 5.9 months in the placebo arm, representing a 23% reduction in risk of death with trifluridine-tipiracil, which was consistent with the direction of the results of the primary analysis, however the CI was very wide and crossed 1 and thus, the result is not statistically significant with a degree of uncertainty (HR: 0.77; 95% CI: 0.46, 1.30). Median PFS was 2.0 months in the trifluridine-tipiracil arm and 1.7 months in the placebo arm, representing a 67% reduction in the risk of PD or death in the trifluridine-tipiracil arm (HR: 0.33; 95% CI; 0.19, 0.59), which was consistent with and suggestive of enhanced benefit of delaying progression or death compared to the primary analysis (47% reduction in progression or death).[2,42] Grade ≥3 AEs occurred in 80.4% of trifluridine-tipiracil patients, which was comparable to the overall trial results. Grade ≥3 AEs occurred in 33.3% of placebo patients, which was lower than observed in the placebo arm of the TAGS trial overall (57.7%).[3,42] Grade 3-4 hematological AEs in the trifluridine-tipiracil arm included neutropenia (52.2%), anemia (41.3%), and leucopenia (6.5%), and 3 patients experienced febrile neutropenia.[42] Neutropenia and anemia occurred in a higher proportion of patients in the trifluridine/tipiracil arm in the Japanese subpopulation than the overall patient population included in the trifluridine/tipiracil arm of TAGS trial (23.3% and 18.8% experiencing neutropenia and anemia, respectively).[3,42]

6.4 Ongoing Trials

There were no ongoing clinical trials that met the systematic review protocol criteria.

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7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

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8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

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9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on trifluridine-tipiracil for gastric cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Gastrointestinal Clinical Guidance Panel is comprised of 3 oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

#	Searches	Results
1	(lonsurf* or TAS 102 or TAS102 or "Viroptic mixture with 5-CIMU").ti,ab,ot,kf,kw,hw,nm,rn.	781
2	Trifluridine/	2308
3	(Trifluridin* or RMW9V5RW38 or trifluorothymidine* or trifluorothymine deoxyriboside* or thilol* or triflumann* or virophta* or viroptic* or tft ophtiole* or viromidin* or "BRN 0568095" or BRN0568095 or CCRIS 2348 or CCRIS2348 or F3DThd or F3T or F3TDR or HSDB 8126 or HSDB8126 or NSC 529182 or NSC529182 or NSC 75520 or NSC75520 or TFDU or Trifluoromethyldeoxyuridine* or aflomin* or bephen or ocufridine* or thriherpine* or trifluor thymidine* or trifluoro thymidine* or trifluorodeoxythymidine* or trifuridine* or triherpin*).ti,ab,ot,kf,kw,hw,rn,nm.	3655
4	or/2-3	3655
5	(Tipiracil* or NGO10K751P or 5-CIMU or MA 1 or MA1 or TPI or tas 1-462 or tas1462 or tas1-462 or 4H59KLQ0A4).ti,ab,ot,kf,kw,hw,rn,nm.	6664
6	4 and 5	950
7	1 or 6	1136
8	Stomach neoplasms/ or Linitis Plastica/ or linitis plastica*.ti,ab,kf,kw.	105215
9	((gastric* or stomach or epigastr* or digest* or gut or ventricul*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcin* or lymphoma* or cyst* or adenocarcin* or malig* or metasta*)).ti,ab,kf,kw.	282353
10	or/8-9	305361
11	7 and 10	100
12	11 use cctr	22
13	11 use medall	24
14	*tipiracil plus trifluridine/	287
15	(lonsurf* or TAS 102 or TAS102 or "Viroptic mixture with 5-CIMU").ti,ab,kw,dq.	778

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16	or/14-15	848
17	*trifluridine/	1114
18	(Trifluridin* or trifluorothymidine* or trifluorothymine deoxyriboside* or thilol* or triflumann* or virophta* or viroptic* or tft ophtiole* or viromidin* or "BRN 0568095" or BRN0568095 or CCRIS 2348 or CCRIS2348 or F3DThd or F3T or F3TDR or HSDB 8126 or HSDB8126 or NSC 529182 or NSC529182 or NSC 75520 or NSC75520 or TFDU or Trifluoromethyldeoxyuridine* or aflomin* or bephen or ocufridine* or thriherpine* or trifluor thymidine* or trifluoro thymidine* or trifluorodeoxythymidine* or trifuridine* or triherpin*).ti,ab,kw,dq.	1758
19	or/17-18	2284
20	*tipiracil/ or (Tipiracil* or 5-CIMU or MA 1 or MA1 or TPI or tas 1-462 or tas1462 or tas1-462 or 4H59KLQ0A4).ti,ab,kw,dq.	6201
21	19 and 20	629
22	16 or 21	991
23	exp Stomach cancer/ or linitis plastica*.ti,ab,kw,dq.	208269
24	((gastric* or stomach or epigastr* or digest* or gut or ventricul*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcin* or lymphoma* or cyst* or adenocarcin* or malig* or metasta*)).ti,ab,kw,dq.	279021
25	or/23-24	325987
26	22 and 25	88
27	26 use oemezd	45
28	27 not (Conference abstract or conference review).pt.	26
29	27 and (Conference abstract or conference review).pt.	19
30	13 or 28	50
31	limit 30 to english language	50
32	12 or 31	72
33	remove duplicates from 32	53
34	limit 29 to english language	19
35	limit 34 to yr="2014 -Current"	18

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36	33 or 35	71

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#12	Search #10 AND #11	2
#11	Search publisher[sb]	405591
#10	Search #6 AND #9	27
#9	Search #7 OR #8	192332
#8	Search (gastric*[tiab] OR stomach[tiab] OR epigastr*[tiab] OR digest*[tiab] OR gut[tiab] OR ventricul*[tiab]) AND (cancer*[tiab] OR neoplas*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR carcin*[tiab] OR lymphoma*[tiab] OR cyst[tiab] OR cysts[tiab] OR cystic*[tiab] OR adenocarcin*[tiab] OR malig*[tiab] OR metasta*[tiab])	175202
#7	Search Stomach neoplasms[mh] OR linitis plastica[mh] OR linitis plastica*[tiab]	93323
#6	Search #2 OR #5	256
#5	Search #3 AND #4	169
#4	Search tipiracil [Supplementary Concept] OR NGO10K751P[rn] OR Tipiracil*[tiab] OR 5-CIMU[tiab] OR MA 1[tiab] or MA1[tiab] OR TPI[tiab] OR tas 1-462[tiab] OR tas1462[tiab] OR tas1-462[tiab] OR 4H59KLQ0A4[tiab]	2657
#3	Search Trifluridine[mh] OR RMW9V5RW38[rn] OR Trifluridin*[tiab] OR trifluorothymidine*[tiab] OR trifluorothymine deoxyriboside*[tiab] OR thilol*[tiab] OR triflumann*[tiab] OR virophta*[tiab] OR viroptic*[tiab] OR tft ophtiole*[tiab] OR viromidin*[tiab] OR BRN 0568095[tiab] OR BRN0568095[tiab] OR CCRIS 2348[tiab] OR CCRIS2348[tiab] OR F3DThd[tiab] OR F3T[tiab] OR F3TDR[tiab] OR HSDB 8126[tiab] OR HSDB8126[tiab] OR NSC 529182[tiab] OR NSC529182[tiab] OR NSC 75520[tiab] OR NSC75520[tiab] OR TFDU[tiab] OR Trifluoromethyldeoxyuridine*[tiab] OR aflomin*[tiab] OR bephen[tiab] OR ocufridine*[tiab] OR thriherpine*[tiab] OR trifluor thymidine*[tiab] OR trifluoro thymidine*[tiab] OR trifluorodeoxythymidine*[tiab] OR trifuridine*[tiab] OR triherpin*[tiab]	842
#2	Search trifluridine tipiracil [Supplementary Concept] OR lonsurf*[tiab] OR TAS 102[tiab] OR TAS102[tiab] OR "Viroptic mixture with 5-CIMU"[tiab]	207

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

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Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials

http://www.canadiancancertrials.ca/

Search: Lonsurf/trifluridine-tipiracil, gastric cancer

Select international agencies including:

US Food and Drug Administration (FDA)

https://www.fda.gov/

European Medicines Agency (EMA)

https://www.ema.europa.eu/

Search: Lonsurf/trifluridine-tipiracil, gastric cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)

https://www.asco.org/

European Society for Medical Oncology (ESMO)

https://www.esmo.org/

Search: Lonsurf/trifluridine-tipiracil, gastric cancer — last five years

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Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[58]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Lonsurf (trifluridine-tipiracil) and gastric cancer.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of January 22, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[59] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

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Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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