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ORIGINAL ARTICLE

Trifluridine/tipiracil versus placebo for third or later lines of treatment in metastatic gastric cancer: an exploratory subgroup analysis from the TAGS study

J. Tabernero[1*], K. Shitara[2], A. Zaanan[3], T. Doi[4], S. Lorenzen[5], E. Van Cutsem[6], L. Fornaro[7], D. V. T. Catenacci[8], R. Fougeray[9], S. R. Moreno[10], P. Azcue[10], H.-T. Arkenau[11], M. Alsina[12] & D. H. Ilson[13]

[1]Department of Medical Oncology, Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain; [2]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [3]Department of Gastrointestinal Oncology, European Georges Pompidou Hospital, AP-HP Centre, University of Paris, Paris, France; [4]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan; [5]Third Department of Internal Medicine (Hematology/Medical Oncology), Klinikum Rechts der Isar, Technische Universitaet München, München, Germany; [6]Department of Gastroenterology and Digestive Oncology, University Hospital Gasthuisberg and University of Leuven, Leuven, Belgium; [7]Division of Oncology, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [8]Gastrointestinal Oncology Program, University of Chicago Medical Center, Chicago, USA; [9]Centre of EXcellence Methodology and Valorization of Data (CentEX MVD), Institut de Recherches Internationales Servier, Suresnes; [10]Global Medical and Patient Affairs, Les Laboratoires Servier SAS, Suresnes, France; [11]Drug Development Unit, Sarah Cannon Research Institute UK Limited, London, UK; [12]Department of Medical Oncology, Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), Barcelona, Spain; [13]Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, USA

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Background: Metastatic gastric cancer and cancer of the esophagogastric junction (GC/EGJ) is an aggressive disease with poor prognosis. In the TAGS study, trifluridine/tipiracil (FTD/TPI) improved overall survival (OS) compared with placebo in heavily pre-treated patients. This unplanned, exploratory subgroup analysis of the TAGS study aimed to clarify outcomes when FTD/TPI was used as third-line (3L) treatment and fourth- or later-line (4L+) treatment.

Patients and methods: Patients were divided into a 3L group (126 and 64 in FTD/TPI and placebo arms, respectively) and 4L+ group (211 and 106 in FTD/TPI and placebo arms, respectively). Endpoints included OS, progression-free survival (PFS), time to Eastern Cooperative Oncology Group performance status (ECOG PS) deterioration to $\geq$2, and safety.

Results: Baseline characteristics were generally well balanced between FTD/TPI and placebo for 3L and 4L+ treatment. Median OS (mOS) for FTD/TPI versus placebo was: 6.8 versus 3.2 months {hazard ratio (HR) [95% confidence interval (CI)] = 0.68 (0.47-0.97), $P = 0.0318$} in the 3L group; and 5.2 versus 3.7 months [0.73 (0.55-0.95), $P = 0.0192$] in the 4L+ group. Median PFS for FTD/TPI versus placebo was 3.1 versus 1.9 months [0.54 (0.38-0.77), $P = 0.0004$] in the 3L group; and 1.9 versus 1.8 months [0.57 (0.44-0.74), $P < 0.0001$] in the 4L+ group. Time to deterioration of ECOG PS to $\geq$2 for FTD/TPI versus placebo was 4.8 versus 2.0 months [HR (95% CI) = 0.60 (0.42-0.86), $P = 0.0049$] in the 3L group; and 4.0 versus 2.5 months [0.75 (0.57-0.98), $P = 0.0329$] in the 4L+ group. The safety of FTD/TPI was consistent in all subgroups.

Conclusions: This analysis confirms the efficacy and safety of FTD/TPI in patients with GC/EGJ in third and later lines with a survival benefit that seems slightly superior in 3L treatment. When FTD/TPI is taken in 3L as recommended in the international guidelines, physicians can expect to provide patients with an mOS of 6.8 months.

Key words: metastatic gastric cancer, cancer of the esophagogastric junction, trifluridine/tipiracil, third line, fourth line, overall survival

INTRODUCTION

Gastric cancer (GC) is currently the third most frequent cause of cancer death globally.[1] Most patients with GC and cancer of the esophagogastric junction (EGJ) have metastatic disease at diagnosis, and are therefore not suitable for potentially curative surgery.[2] Metastatic GC/EGJ has a poor prognosis with a median overall survival (mOS), with first-line (1L) treatment, of ~1 year.[3]

*Correspondence to: Prof Josep Tabernero, Department of Medical Oncology, Vall d'Hebron University Hospital & Institute of Oncology (VHIO), Vall d'Hebron Hospital Campus, UVic-UCC, IOB-Quiron, P. Vall d'Hebron 119–129, 08035, Barcelona, Spain. Tel: +34 93 274 6085

E-mail: jtabernero@vhio.net (J. Tabernero).

According to the European Society for Medical Oncology (ESMO) guidelines,[4] 1L treatments of inoperable or metastatic GC/EGJ include doublet or triplet combinations of chemotherapy regimens containing a platinum agent (e.g. cisplatin) and a fluoropyrimidine (e.g. 5-fluorouracil or capecitabine), ± a taxane (e.g. docetaxel or paclitaxel) and triple combinations containing a taxane or anthracycline for human epidermal growth factor receptor 2 (HER2)-negative disease, and a platinum agent, a fluoropyrimidine, and trastuzumab for HER2-positive disease. These ESMO guidelines from 2016 also gave the recommendation of second-line (2L) chemotherapy, if the patient has an adequate Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, with a taxane or irinotecan, or treatment with ramucirumab as a single agent or in combination with paclitaxel.[4]

Studies have shown that between 12.2% and 18.1% of patients who receive 1L chemotherapy subsequently receive third-line (3L) treatment,[5-7] 7.9% receive fourth- or later-line (4L+) treatment,[5] and ∼38% of patients who receive 2L chemotherapy subsequently receive 3L treatment.[8] However, the results of the TAGS study showed that treatment with trifluridine/tipiracil (FTD/TPI) beyond 2L treatment resulted in an mOS of 5.7 months (versus 3.6 months with placebo; HR = 0.69, $P = 0.0006$),[9] and this led to updated guidelines for the use of FTD/TPI as 3L treatment in patients with advanced/metastatic GC/EGJ and a PS of 0-1.[10]

In another trial that recruited patients with unresectable, locally advanced or metastatic GC/EGJ (JAVELIN Gastric 300 trial), avelumab, irinotecan, and paclitaxel resulted in an mOS of 4.6, 5.4, and 4.7 months, respectively,[11] which are similar to the 5.7 months with FTD/TPI in the TAGS study.[9] However, in the TAGS study, 37% and 63% of patients received FTD/TPI as 3L and 4L+ treatment, respectively.[9] In contrast, in the JAVELIN Gastric 300 trial, 85%-86% of patients in the treatment arms received 3L treatment [and only 1 (0.5%) patient received 4L+ treatment].[11] It is therefore important to understand the efficacy and safety of FTD/TPI in the 3L setting.

Here we present an *ad hoc*, unplanned, exploratory subgroup analysis (not pre-planned) of the TAGS study that aimed to separately assess efficacy, safety and impact on quality of life (QoL) of FTD/TPI when used in the 3L setting or the 4L+ setting versus placebo.

PATIENTS AND METHODS

Study design

The study design and methodology of the TAGS study (ClinicalTrials.gov number: NCT02500043) have been previously described.[9] The study was approved by the relevant ethical review committees and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice. Patients provided written, informed consent to participate.

Briefly, TAGS was an international, randomised, double-blind, placebo-controlled, phase III trial of FTD/TPI in patients with metastatic GC/EGJ who had received at least two lines of previous therapy.

Patients were randomised 2 : 1 to receive either oral FTD/TPI 35 mg/m^2 twice daily plus best supportive care (BSC) or placebo twice daily plus BSC on days 1-5 and 8-12 of each 28-day cycle. Previous regimens must have included a fluoropyrimidine, a platinum agent, and a taxane or irinotecan, or both.[9]

Patients

The TAGS study included patients aged ≥18 years (≥20 years in Japan), with histologically confirmed, non-resectable metastatic GC/EGJ adenocarcinoma and an ECOG PS of 0-1.[9]

In this subgroup analysis, two patient groups were defined and assessed separately: patients who had received FTD/TPI or placebo after two lines of previous systemic therapy (3L group) and patients who had received FTD/TPI or placebo after three or more lines of previous systemic therapy (4L+ group).

Outcomes

Collection of all outcome data has been described.[9] Tumour assessments were done by computed tomography of the chest and abdomen (and pelvis if clinically indicated) within 28 days before day 1 of treatment cycle 1 and every 8 weeks during treatment until radiologically confirmed disease progression.[9]

In this analysis, we report the following data for the 3L and 4L+ groups: baseline characteristics; mOS (defined as time from randomisation until death); median progression-free survival (mPFS; time from randomisation until investigator-assessed radiological disease progression or death); time from randomisation to deterioration of ECOG PS to ≥2; frequency of adverse events (AEs; graded according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03); QoL [measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30), according to the methods reported in Tabernero et al.[12]].

Statistics

Efficacy endpoints were analysed in the intention-to-treat (ITT) population with a stratified log-rank test using the three stratification factors as outlined in the primary publication,[9] with hazard ratios (HRs) and two-sided 95% confidence intervals (CIs) based on a stratified Cox model. As this was an unplanned, exploratory analysis, no formal statistical hypotheses were formulated. *P* values are shown for exploratory purposes and were not adjusted for multiple testing.

Treatment effect was analysed in the following subgroups within the 3L and 4L+ groups: age (<65 years or ≥65 years), sex, ethnicity, geographical region, ECOG PS (0 or 1), primary tumour site, measurable disease, histology (diffused, intestinal, or mixed), HER2 status, number of

metastatic sites (1-2 or ≥3), peritoneal metastases, and previous gastrectomy.

Data on AEs were collected in the safety analysis population (all patients who received at least one dose of study treatment).

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.4.0 software (R Foundation, Vienna, Austria).

RESULTS

Patients

In the TAGS study, the ITT population consisted of 507 patients (337 in the FTD/TPI arm and 170 in the placebo arm).[9] Of these, 190 had received two previous lines of therapy (126 in the FTD/TPI arm and 64 in the placebo arm) and 317 had received three or more lines of therapy (211 in the FTD/TPI arm and 106 in the placebo arm).

In both the 3L and 4L+ groups, baseline characteristics were generally well balanced between the FTD/TPI arm and placebo arm (Table 1). In the 3L group, more patients had peritoneal metastasis at baseline in the placebo arm than in the FTD/TPI arm (36% and 26%, respectively; Table 1). In the FTD/TPI arm, there were more patients with previous gastrectomy at baseline in the 4L+ group than in the 3L group (52% and 29%, respectively; Table 1). FTD/TPI appeared to be reserved for 4L+ treatment more frequently in Japan and the USA than in Europe (Table 1).

Efficacy

Overall survival. The mOS was longer in patients treated with FTD/TPI than with placebo in both the 3L group and the 4L+ group (Figures 1 and 2A). In the 3L group, mOS was 3.6 months [HR = 0.68 (95% CI 0.47-0.97), $P = 0.0318$] longer in the FTD/TPI group than in the placebo group (6.8 versus 3.2 months, respectively). In the 4L+ group, mOS was 1.5 months [HR = 0.73 (95% CI 0.55-0.95), $P = 0.0192$] longer with FTD/TPI (5.2 versus 3.7 months, respectively). In the ITT population, the difference in mOS between treatment groups was 2.1 months (5.7 versus 3.6 months, respectively;[9] Figure 1).

The magnitude of the FTD/TPI treatment effect on OS was maintained in most subgroups in both 3L and 4L+ groups (Figure 3). For the subgroup of patients with peritoneal metastases, mOS was prolonged with FTD/TPI compared with placebo and the benefit was more pronounced in 3L [mOS of 6.0 (3.3-9.5) months with FTD/TPI versus 3.1 (1.9-4.8) months with placebo] than in 4L+ [mOS of 4.1 (3.1-6.1) months with FTD/TPI versus 3.4 (2.3-5.6) months with placebo].

In patients who underwent gastrectomy before treatment randomisation in the TAGS study, mOS was prolonged with FTD/TPI versus placebo in the 3L group [7.0 and 2.2 months, respectively; HR = 0.51 (95% CI 0.25-1.02)] and the 4L+ group [6.0 and 3.7 months, respectively; HR = 0.59 (95% CI 0.41-0.87)].

Progression-free survival. In the 3L group, mPFS was 3.1 versus 1.9 months in the FTD/TPI group versus placebo group, with a difference of 1.2 months [HR = 0.54 (95% CI 0.38-0.77), $P = 0.0004$; Figure 1D], and in the 4L+ group, mPFS was 1.9 versus 1.8 months, respectively, with a difference of 0.1 months [HR = 0.57 (95% CI 0.44-0.74), $P < 0.0001$; Figure 1F]. In the overall study, mPFS was 2.0 versus 1.8 months, respectively, with a median gain of 0.2 months [HR = 0.57 (95% CI 0.47-0.70), $P < 0.0001$; Figures 1B and 2B].

In patients who underwent gastrectomy before treatment, mPFS was 2.2 and 1.7 months in 3L for the FTD/TPI and placebo groups, respectively [HR = 0.37 (95% CI 0.19-0.72)], and 2.2 and 1.8 months in 4L+ for the FTD/TPI and placebo groups, respectively [HR = 0.52 (95% CI 0.36-0.76)].

Time from randomisation to deterioration of ECOG PS. The median time for patients to deteriorate to ECOG PS ≥2 was significantly extended in patients treated with FTD/TPI compared with placebo in both the 3L group and the 4L+ group (Figure 2C). The improvement in median time to deterioration to ECOG PS ≥2 with FTD/TPI compared with placebo was numerically higher in the 3L group (2.8 months) than in the 4L+ group (1.5 months) or the ITT population (2.0 months).[9] The proportion of patients with an ECOG PS of 0-1 at treatment discontinuation in the FTD/TPI and placebo arms was: 74% and 63%, respectively, in the ITT population; 77% and 54%, respectively, in the 3L group; and 73% and 68%, respectively, in the 4L+ group.

Quality of life

The median (95% CI) time to deterioration of the QLQ-C30 Global Health Status score by ≥5 points was 2.4 (2.1-3.3) and 2.8 (2.1-3.8) months in the 3L group ($n = 259$) and 4L+ group ($n = 163$), respectively [HR = 1.29 (95% CI 0.87-1.92), $P = 0.1907$]. However, the mean change from baseline in the QLQ-C30 Global Health Status score and the QLQ-C30 subscale scores was not deemed clinically significant in either group.

Safety

Dose exposure was similar between the two subgroups and the overall study population. Median treatment duration in the 3L and 4L+ groups was 160.8 and 161.5 days, respectively. In the 3L group, mean [standard deviation (SD)] dose intensity of FTD/TPI was 147.2 (24.7) mg/m^2/week, and the mean (SD) relative dose intensity (ratio to planned) was 0.84 (0.14). In the 4L+ group, mean (SD) dose intensity of FTD/TPI was 148.8 (28.0) mg/m^2/week and the mean (SD) relative dose intensity was 0.85 (0.16). The mean (SD) relative dose intensity in the overall population receiving FTD/TPI was 0.85 (0.15).[9]

The frequency of any treatment-emergent AE (TEAE) in the placebo group was similar to the frequency in the 3L and 4L+ groups (Table 2). Specific AEs occurred at similar rates in the 3L and 4L+ groups, but due to the low incidences in each group, firm conclusions are not possible

Table 1. Baseline patient and disease characteristics of the 3L and 4L+ groups from the TAGS study

Variable	Population					
	3L group		4L+ group		ITT (from Shitara et al.[9])	
	FTD/TPI (n = 126)	Placebo (n = 64)	FTD/TPI (n = 211)	Placebo (n = 106)	FTD/TPI (n = 337)	Placebo (n = 170)
Mean (SD) age, years	61.9 (10.8)	60.4 (10.9)	63.3 (10.7)	63.0 (9.4)	62.8 (10.8)	62.0 (10.0)
Age, *n* (%)						
<65 years	76 (60)	41 (64)	107 (51)	55 (52)	183 (54)	96 (56)
≥65 years	50 (40)	23 (36)	104 (49)	51 (48)	154 (46)	74 (44)
Mean (SD) BSA, m^2	1.8 (0.2)	1.7 (0.2)	1.7 (0.2)	1.8 (0.2)	1.7 (0.2)	1.8 (0.2)
Sex, *n* (%)						
Male	89 (71)	37 (58)	163 (77)	80 (75)	252 (75)	117 (69)
Female	37 (29)	27 (42)	48 (23)	26 (25)	85 (25)	53 (31)
Ethnicity, *n* (%)						
White	104 (83)	49 (77)	140 (66)	64 (60)	244 (72)	113 (66)
Asian	12 (10)	4 (6)	39 (18)	25 (24)	51 (15)	29 (17)
Other	2 (2)	1 (2)	2 (1)	3 (3)	4 (1)	4 (2)
Not available	8 (6)	10 (16)	30 (14)	14 (13)	38 (11)	24 (14)
Region, *n* (%)						
EU	111 (88)	60 (94)	159 (75)	78 (74)	270 (80)	138 (81)
USA	6 (5)	0 (0)	15 (7)	5 (5)	21 (6)	5 (3)
Japan	9 (7)	4 (6)	37 (18)	23 (22)	46 (14)	27 (16)
ECOG PS, *n* (%)						
0	50 (40)	20 (31)	73 (35)	48 (45)	123 (36)	68 (40)
1	76 (60)	44 (69)	138 (65)	58 (55)	214 (64)	102 (60)
Mean (SD) QLQ-C30 Global Health Status score	59.4 (20.52)	57.5 (19.53)	57.8 (20.07)	58.9 (19.91)	58.4 (20.2)	58.4 (19.7)
Previous gastrectomy, *n* (%)	37 (29)	18 (28)	110 (52)	56 (53)	147 (44)	74 (44)
Primary site, *n* (%)						
Gastroesophageal	25 (20)	16 (25)	73 (35)	31 (29)	239 (71)	121 (71)
Gastric	101 (80)	47 (73)	138 (65)	74 (70)	98 (29)	47 (28)
Peritoneal metastases, *n* (%)	33 (26)	23 (36)	54 (26)	30 (28)	87 (26)	53 (31)
Number of metastatic sites, *n* (%)						
1-2	55 (44)	28 (44)	100 (47)	44 (42)	155 (46)	72 (42)
≥3	71 (56)	36 (56)	111 (53)	62 (59)	183 (54)	98 (58)
HER2 status, *n* (%)						
Positive	18 (14)	6 (9)	49 (23)	21 (20)	67 (20)	27 (16)
Negative	63 (50)	34 (53)	144 (69)	72 (68)	207 (61)	106 (62)
Measurable disease, *n* (%)	109 (87)	57 (89)	197 (93)	93 (88)	306 (91)	150 (88)
Histology subtype, *n* (%)						
Diffused	22 (17)	7 (11)	31 (15)	14 (13)	53 (16)	21 (12)
Intestinal	27 (21)	14 (22)	76 (36)	38 (36)	103 (31)	52 (31)
Mixed	6 (5)	3 (5)	8 (4)	5 (5)	14 (4)	8 (5)

3L, third-line treatment; 4L+, fourth or more lines of treatment; BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, Europe; FTD/TPI, trifluridine/tipiracil; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD, standard deviation.

and data are not presented in full here. In the primary publication of the TAGS study, grade ≥3 neutropenia, anaemia, and leukopenia of any cause were observed more frequently in the FTD/TPI group than in the placebo group.[9] In this subgroup analysis, there were similar findings for both groups compared to placebo. However, in the 3L FTD/TPI group, neutropenia and leukopenia were reported in 31% and 19% of patients, respectively, whereas in the 4L+ FTD/TPI group, the frequencies were 10% and 5%, respectively. Details of treatment-related serious AEs and deaths related to TEAEs in the TAGS study were described previously.[9]

DISCUSSION

This analysis of the TAGS study[9] confirms the efficacy of FTD/TPI versus placebo for third- and later-line treatment of GC/EGJ. These results suggest a superior survival benefit with FTD/TPI in patients treated in the 3L setting than in later lines, with an expected mOS of 6.8 months and HR of 0.68 in 3L treatment. While cross-study comparisons are unreliable, this is a longer mOS in 3L treatment than with other recently assessed treatments (mOS ranging from 4.6 to 5.4 months).[11,13]

PFS and time to deterioration to ECOG PS ≥2 were also improved with FTD/TPI versus placebo in both 3L and 4L+ treatment. Despite the inevitably lower patient numbers in each subgroup and lower statistical validity, the differences in mOS for FTD/TPI versus placebo were consistent with the overall study population[9] and had P values <0.05. Indeed, independently of the line of treatment, FTD/TPI showed a P value <0.05 in all three efficacy endpoints versus placebo.

Beneficial effects of FTD/TPI on OS in the subgroup of patients with peritoneal metastases were observed in both groups in this analysis, although the benefit was considerably more pronounced in 3L treatment. In both 3L and 4L+ groups, gastrectomy before FTD/TPI treatment did not have

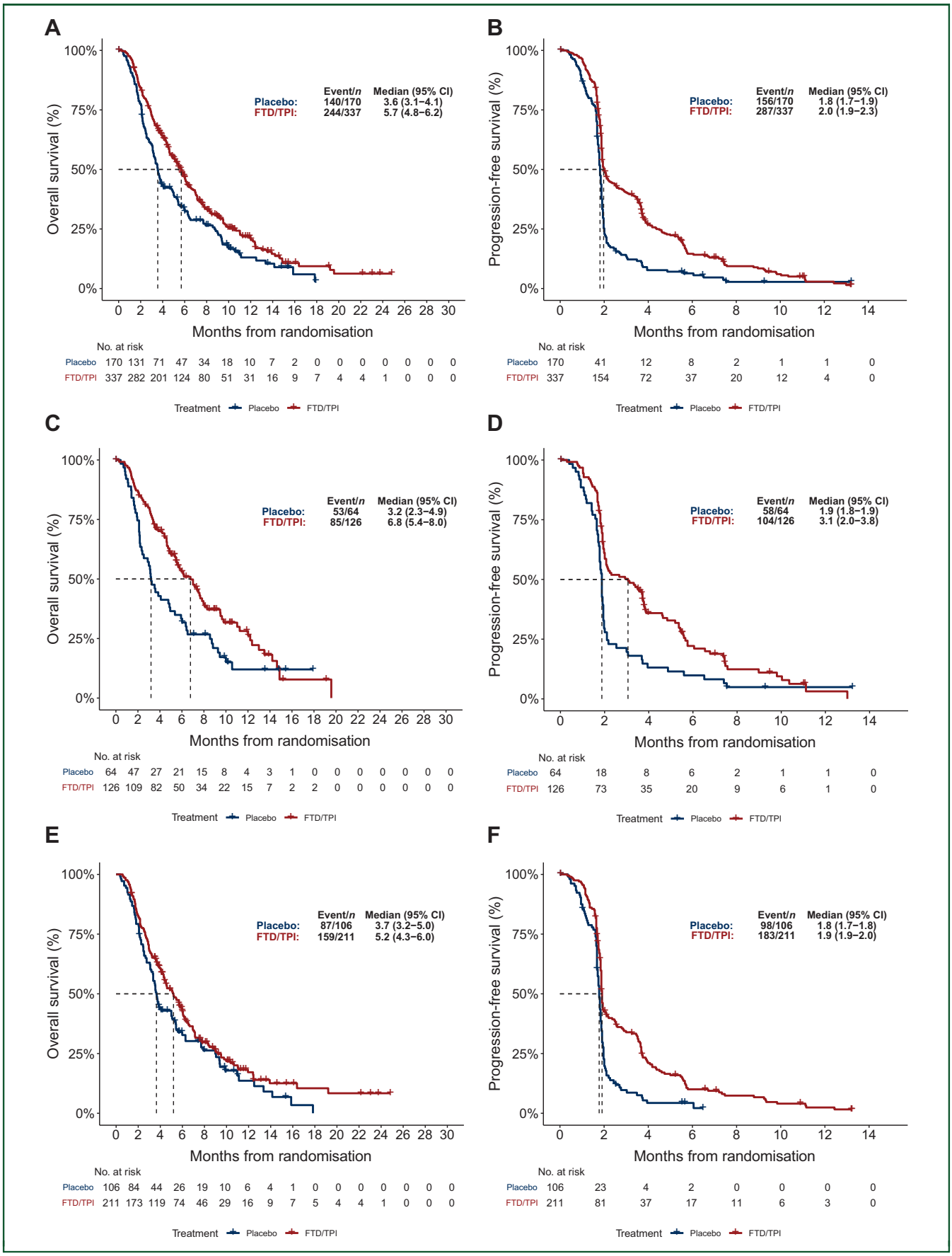

Figure 1. Kaplan–Meier overall survival and progression-free survival curves for FTD/TPI and placebo by months from randomisation in (A and B) the overall study population, (C and D) the 3L subgroup, and (E and F) the 4L+ subgroup, of the TAGS study.

3L, third-line treatment; 4L+, fourth or more lines of treatment; CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio.

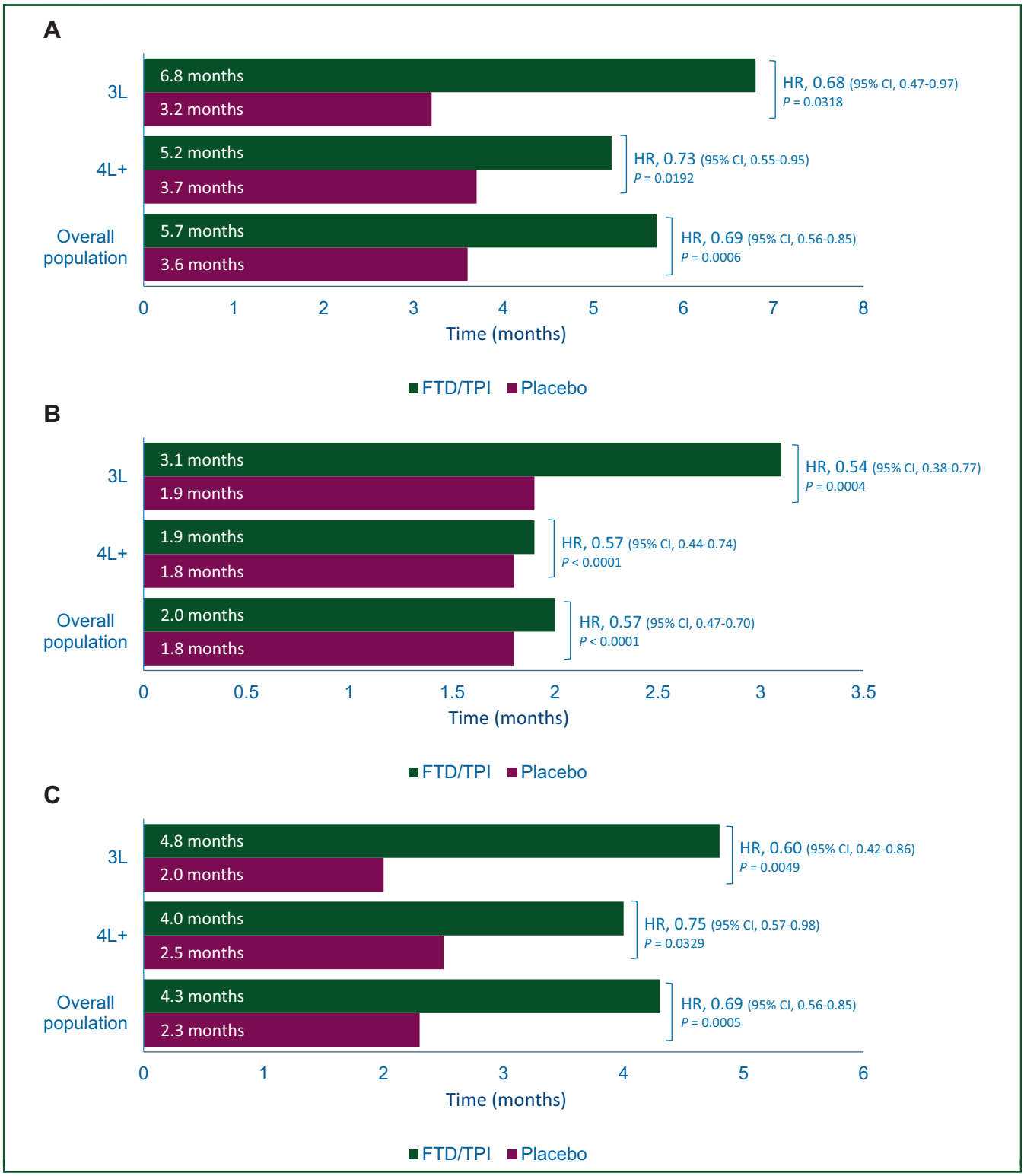

Figure 2. Comparison of (A) median overall survival, (B) median progression-free survival, and (C) median time to deterioration to ECOG PS ≥2, in the ITT population and 3L and 4L+ subgroups of the TAGS study.

3L, third-line treatment; 4L+, fourth or more lines of treatment; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio.

an impact on efficacy, which was previously shown for the whole population of the TAGS study.[14]

QoL was maintained similarly in both subgroup populations analysed, and this is consistent with the population as a whole, in which any QoL deterioration that was observed was associated with deterioration of ECOG PS.[12]

The safety profile of FTD/TPI was generally consistent in the two subgroups assessed in this analysis. Neutropenia and leukopenia were numerically more frequent in the 3L

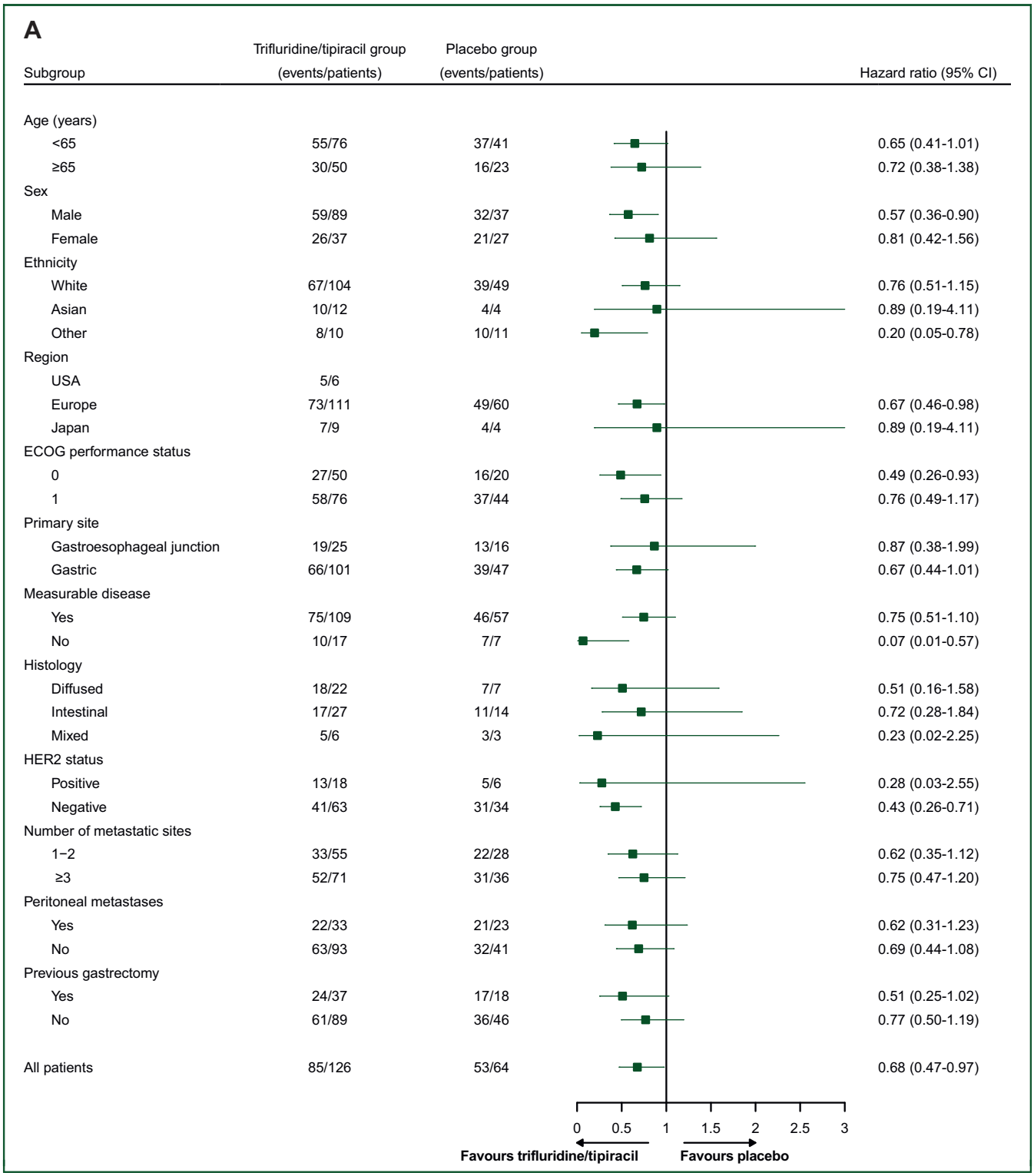

Figure 3. Overall survival by patient subgroups in (A) the 3L treatment subgroup and (B) the 4L+ treatment subgroup, of the TAGS study.
3L, third-line treatment; 4L+, fourth or more lines of treatment; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FTD/TPI, trifluridine/tipiracil; HER2, human epidermal growth factor receptor 2.

group than in the 4L+ group, but this was not considered inconsistent with the overall study population. While the 4L+ group may consist of a more selected population than the 3L group, they will also (by definition) be more heavily pre-treated. It is therefore reassuring that the safety profile of FTD/TPI in 4L+ treatment is consistent with the profile in 3L treatment and in other tumour types.[15]

Although survival benefits in patients receiving FTD/TPI in 4L+ were numerically lower versus 3L, with an mOS of 5.2 versus 3.7 months in the placebo group, the HR was 0.73

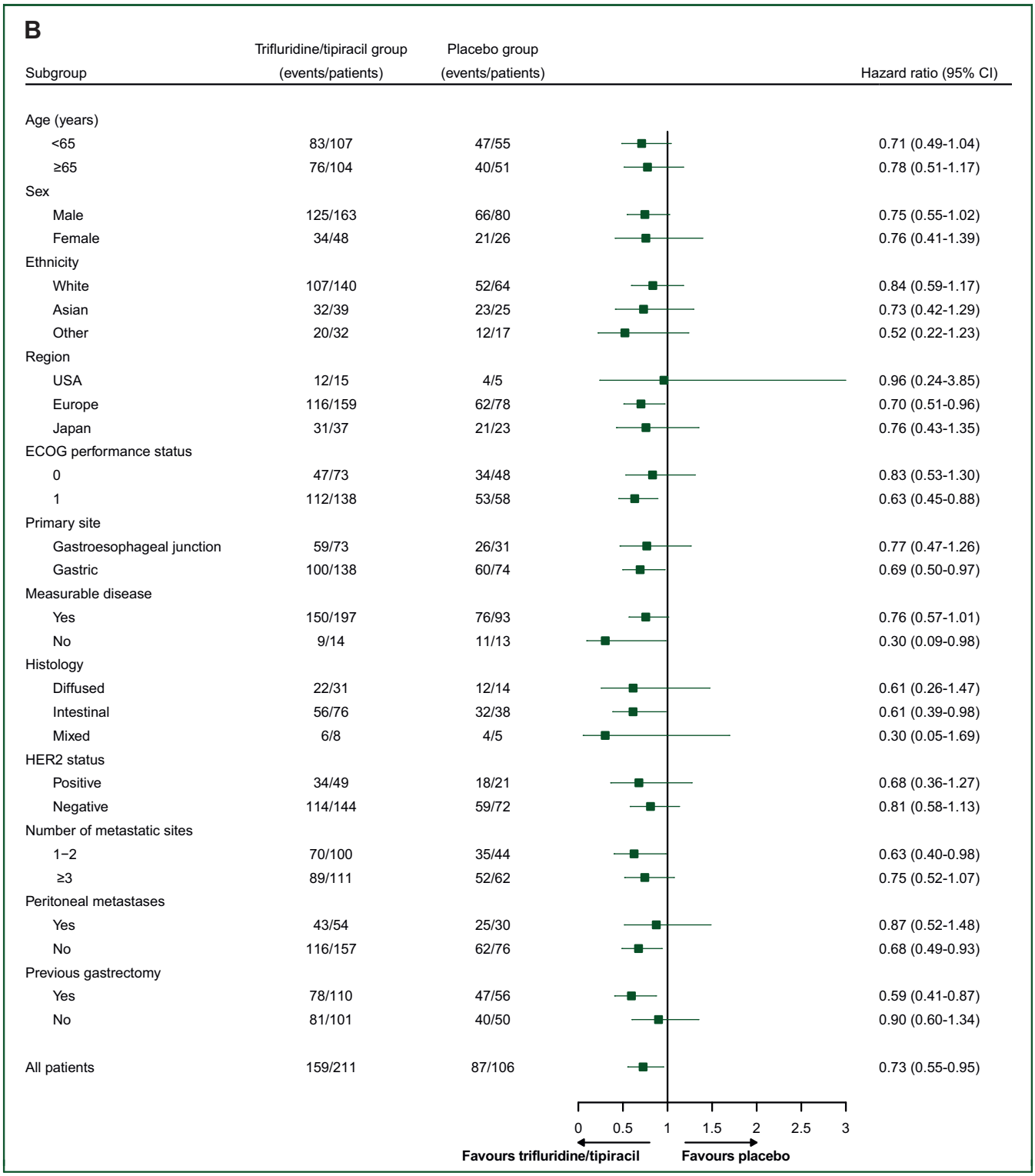

Figure 3. Continued

and the *P* value was 0.0192. Likewise, the potential benefit of FTD/TPI in the 4L+ setting is extended beyond OS, with significant improvements in PFS and maintenance of ECOG PS versus placebo. While these advantages over placebo are numerically smaller in the 4L+ setting than in 3L treatment, the maintenance of PS, QoL (which was generally maintained in this study), and a tolerable safety profile are important benefits for patients moving to 4L treatment.

One interesting observation from this subgroup analysis was that 4L+ use of FTD/TPI was more frequent in Japan and the USA than in Europe. This may be partly due to the approved treatment alternatives in different regions.

Table 2. Number of patients experiencing adverse events in the 3L and 4L+ groups of the safety analysis population from the TAGS study by treatment arm

Variable	Number of patients (%)			
	3L group (n = 187)		4L+ group (n = 316)	
	FTD/TPI (n = 124)	Placebo (n = 63)	FTD/TPI (n = 211)	Placebo (n = 105)
Any TEAE	122 (98)	60 (95)	204 (97)	97 (92)
Any TEAE of grade ≥3	104 (84)	35 (56)	163 (77)	62 (59)
Any SAE	59 (48)	23 (37)	84 (40)	47 (45)
Any treatment-related TEAE	105 (85)	36 (57)	166 (79)	59 (56)
Any treatment-related SAE	15 (12)	3 (5)	24 (11)	3 (3)
Any TEAE leading to treatment discontinuation	19 (15)	13 (21)	24 (11)	15 (14)
Any TEAE leading to death	21 (17)	5 (8)	24 (11)	14 (13)

3L, third-line treatment; 4L+, fourth or more lines of treatment; FTD/TPI, trifluridine/tipiracil; SAE, serious adverse event; TEAE, treatment-emergent adverse even.

According to the most recent international clinical guidelines, optimal treatment options for patients with GC/EGJ who are fit for chemotherapy could comprise a platinum–fluoropyrimidine doublet, and in the National Comprehensive Cancer Network guidelines the addition of anti-programmed death-ligand 1 (PD-L1; Combined Positive Score ≥5), as 1L therapy in HER2-negative disease; addition of 1L trastuzumab to chemotherapy in HER2-positive disease; and then a taxane alone or in combination with ramucirumab, if available, or irinotecan monotherapy in 2L.[10] Most recent international guidelines propose the use of FTD/TPI as the preferred 3L treatment option for GC/EGJ.[10,16,17] However, unlike the European guidelines from ESMO,[10] the Asian and USA guidelines also suggest other 3L treatment options in specific patient populations.[16,17] Specifically, PD-L1 therapies are recommended as 2L or subsequent therapy, but only in those with microsatellite instability-high tumours or as 3L or subsequent therapy for PD-L1 expression levels by Combined Positive Score ≥1 if no progression with previous immune checkpoint inhibitors.[16,17] The finding of greater OS benefit versus placebo in the 3L setting with FTD/TPI in this sub-analysis lends further validity to guideline recommendations and supports efficacy in a broader patient population than those potentially deriving benefit from immunotherapy. Further study would be useful to also compare these options in the 4L+ setting, to inform future recommendations beyond 3L treatment.

The main limitations of these data are those inherent in exploratory subgroup analyses (especially when they are not pre-planned), such as the fact that the study was not powered to detect statistical significance in these subgroups. In addition, other factors that could have influenced the findings in these subgroups, such as pharmacokinetic differences, were not assessed in the TAGS study and 4L+ treatment was not included in the phase II study of FTD/TPI.[18]

With adherence to the guidelines, patients with inoperable GC/EGJ who maintain a good PS can gain prolonged survival by receiving three or more lines of systemic therapy. In one recent study, an OS from diagnosis of 21.0 months was achieved in patients receiving three or more lines of chemotherapy.[19] This subgroup analysis shows similar OS from diagnosis (1.8 years) in patients receiving FTD/TPI as 3L treatment. The proportion of patients with GC/EGJ who receive 4L+ treatment is low, e.g. 7.9% reported by Hess et al.,[5] which represented ∼44% of patients who had received 3L treatment. In the TAGS study, of the 190 patients receiving 3L treatment, 18.3% in the FTD/TPI arm versus 12.5% in placebo arm went on to receive 4L chemotherapy after the study. Of those in the 4L+ group, 14.2% in the FTD/TPI arm versus 16% in the placebo arm went on to receive fifth-line chemotherapy after the study. Although there is a bias in the selection of patients included in clinical trials, in particular of those included in 3L or later treatment, the mOS data presented in the current analysis suggest that FTD/TPI therapy will provide more benefit if used in 3L than if reserved for later lines.

There is still room to improve treatment options for GC/EGJ across multiple treatment lines. This manuscript responds to this need by clarifying the expectations or outcomes in patients in 3L and 4L+ treatment. However, optimising treatment continues to be an important necessity, and in addition to sequential use of available agents, there is emerging evidence on the use of combination therapy such as FTD/TPI and ramucirumab[20] and FTD/TPI and irinotecan.[21,22] More randomised clinical trial data will be needed to provide guidance on possible 4L+ therapy in GC/EGJ, but this subgroup analysis also provides an insight into the efficacy of FTD/TPI in this setting.

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DATA SHARING

Data not available. The data generated and analysed during this study are on file with Taiho Pharmaceuticals, Co., Ltd. and are not publicly available, according to Taiho's policy on data sharing.

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