Randomized, Double-Blind, Placebo-Controlled Phase III Study of Paclitaxel ± Napabucasin in Pretreated Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

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ABSTRACT

Purpose: To compare napabucasin (generator of reactive oxygen species) plus paclitaxel with paclitaxel only in patients with second-line advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Experimental Design: In the double-blind, phase III BRIGHTER study (NCT02178956), patients were randomized (1:1) to napabucasin (480 mg orally twice daily) plus paclitaxel (80 mg/m^2 i.v. weekly for 3 of 4 weeks) or placebo plus paclitaxel. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and safety.

Results: Overall, 714 patients were randomized (napabucasin plus paclitaxel, $n = 357$; placebo plus paclitaxel, $n = 357$). 72.1% were male, 74.6% had gastric adenocarcinoma, and 46.2% had peritoneal metastases. The study was unblinded following an interim analysis at 380 deaths. The final efficacy analysis was performed on 565 deaths (median follow-up, 6.8 months). No significant differences were observed between napabucasin plus paclitaxel and placebo plus paclitaxel for OS (6.93 vs. 7.36 months), PFS (3.55 vs. 3.68 months), ORR (16% vs. 18%), or DCR (55% vs. 58%). Grade ≥3 adverse events occurred in 69.5% and 59.7% of patients administered napabucasin plus paclitaxel and placebo plus paclitaxel, respectively, with grade ≥3 diarrhea reported in 16.2% and 1.4%, respectively.

Conclusions: Adding napabucasin to paclitaxel did not improve survival in patients with pretreated advanced gastric or GEJ adenocarcinoma. Consistent with previous reports, the safety profile of napabucasin was driven by manageable gastrointestinal events; grade ≥3 diarrhea occurred at a higher frequency with napabucasin plus paclitaxel versus placebo plus paclitaxel.

Introduction

Globally, approximately 1.1 million patients were diagnosed with and 769,000 patients succumbed to gastric cancer in 2020 (GLOBOCAN 2020. World; http://globocan.iarc.fr). Surgery is considered the only potentially curative treatment. However, approximately 60% of patients present with locally advanced or metastatic disease at diagnosis (1–3). Nearly all patients with advanced gastric cancer progress on first-line therapy or exhibit primary refractory disease (2–4).

During the planning stages of this study (BRIGHTER), which began in 2012, second-line treatment options for patients with advanced gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma included single-agent paclitaxel (5–10), docetaxel

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Clin Cancer Res 2022;XX:XX–XX

doi: 10.1158/1078-0432.CCR-21-4021

Translational Relevance

Approximately 60% of patients with gastric cancer present with locally advanced or metastatic disease at diagnosis. Following first-line treatment, patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma have a median overall survival of only 4 to 13 months. Levels of reactive oxygen species (ROS) are often elevated in cancer cells. To compensate, tumor cells can upregulate antioxidant proteins, such as NAD(P)H:quinone oxidoreductase 1 (NQO1). Napabucasin, a generator of ROS, can be bioactivated by the antioxidant protein NQO1. Based on the hypothesis that increasing ROS levels beyond a cytotoxic threshold will culminate in cancer cell death, napabucasin was evaluated for its antitumor potential in patients with second-line advanced gastric or GEJ adenocarcinoma in the double-blind, phase III BRIGHTER trial. In this study, the addition of napabucasin to paclitaxel did not improve clinical outcomes relative to paclitaxel monotherapy.

(11, 12), or irinotecan (9, 13, 14). Median overall survival (OS) for second-line chemotherapy ranges from 4.0 to 13.2 months (5–15). The mAb ramucirumab did not receive its first regulatory approval until April 2014 (16). When administered following failure of fluoropyrimidine- or platinum-based chemotherapy, combination treatment with ramucirumab and paclitaxel confers a median OS of only 9.6 months (10). Thus, patients with advanced gastric or GEJ adenocarcinoma remain in need of a second-line treatment regimen that can substantially prolong survival.

Levels of reactive oxygen species (ROS) are often elevated in cancer cells. To compensate, tumor cells upregulate antioxidant proteins, such as NAD(P)H:quinone oxidoreductase 1 (NQO1), that help protect the cell from what might normally be damaging levels of ROS (17). NQO1, the levels of which have been found to be higher in malignant versus healthy cells (18–21), can bioactivate napabucasin, an orally administered agent that generates ROS (22). Based on the hypothesis that increasing ROS levels beyond a cytotoxic threshold will culminate in cancer cell death, napabucasin was evaluated for its antitumor potential (17, 22–24).

NQO1-expressing cancer cells secrete factors that promote the phosphorylation of STAT3 in tumor cells and cells of the tumor microenvironment (TME; ref. 23). The STAT3 pathway, which plays a key role in modifying the TME (25, 26), is dysregulated in approximately 20% to 50% of gastric and GEJ adenocarcinomas (27–29). Elevated levels of phosphorylated STAT3 (pSTAT3) are associated with reduced OS in patients with gastric cancer (27, 28, 30).

pSTAT3 is sensitive to the redox balance in the TME, and because NQO1 can result in STAT3 phosphorylation and bioactivation of napabucasin, high levels of pSTAT3 may reflect tumor cells that are more sensitive to napabucasin due to a combination of NQO1 expression and a favorable redox environment (23, 31, 32). The potential for pSTAT3 to identify patients more likely to respond to napabucasin (23, 32, 33) is supported by results from a prespecified retrospective analysis of a phase III study: median OS was significantly longer in napabucasin-treated versus control (placebo)-treated patients with refractory colorectal cancer who expressed pSTAT3 in both malignant cells and cells of the TME (31).

In a multicenter, phase Ib/II extension study of 46 patients with pretreated (second-line or higher) advanced gastric or GEJ adenocarcinoma, napabucasin plus paclitaxel was tolerable and resulted in an objective response rate (ORR) of 15% (34). Among a subset of 6 patients who had one prior line of therapy, the partial response rate was 50% and 2 additional patients had stable disease. Based on the activity in minimally treated patients, as well as activity in patients who were more heavily treated, the multicenter, double-blind, randomized, phase III BRIGHTER study was undertaken to compare napabucasin plus paclitaxel with paclitaxel only (standard practice at the time of study initiation) in patients with second-line advanced gastric or GEJ adenocarcinoma.

Materials and Methods

Study design and patients

BRIGHTER was a multicenter, double-blind, randomized, phase III study (ClinicalTrials.gov identifier: NCT02178956) of adults (≥18 years) with advanced (metastatic or locally advanced and unresectable) cytologically or histologically confirmed gastric or GEJ adenocarcinoma. Eligible patients had unresectable or metastatic disease that failed first-line therapy with a regimen containing at least a platinum/fluoropyrimidine doublet; concomitant treatment with an anthracycline or anti-HER2 therapy (trastuzumab) was allowed. Patients who experienced disease progression at any point during neoadjuvant or adjuvant treatment with a platinum/fluoropyrimidine doublet or less than 6 months after the last dose of neoadjuvant or adjuvant treatment were eligible. Patients were required to have evaluable disease (measurable disease was not required), an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤1, hemoglobin ≥9.0 g/dL, platelet count ≥100 × 10^9/L, alanine transaminase level ≤3 × upper limit of normal (ULN; ≤5 × ULN in patients with liver metastases), total bilirubin ≤1.5 × ULN (≤2.0 × ULN in patients with liver metastases), and creatinine ≤1.5 × ULN or creatinine clearance >50 mL per minute. Key exclusion criteria included treatment with anticancer chemotherapy or biologic therapy prior to the first planned dose of napabucasin/placebo within a period of time equivalent to the usual cycle length of the regimen, progression within 6 months of completing prior taxane therapy in the neoadjuvant or adjuvant setting, any taxane therapy in the metastatic setting, and more than one prior systemic regimen in the metastatic setting.

Eligible patients were randomly assigned (1:1) to treatment with either napabucasin plus paclitaxel or placebo plus paclitaxel, with the randomization stratified by geographic region (Asia vs. North America, Europe, or Australia vs. South America), time to progression from start of first-line therapy (<6 vs. ≥6 months), disease measurability per RECIST 1.1 (measurable disease present vs. not present), and prior use of taxane therapy (yes vs. no).

Napabucasin 480 mg (or matched placebo) was administered orally twice daily (total of 960 mg daily). Paclitaxel 80 mg/m^2 was administered as a 1-hour intravenous infusion on days 1, 8, and 15 of each 28-day cycle. Dose modification of napabucasin/placebo and/or paclitaxel was allowed if needed to manage adverse events (AE; Supplementary Tables S1 and S2). If necessary, following a 0.5- to 3-day dose holiday with resolution of symptoms to a tolerable grade 2 napabucasin/placebo could have been resumed at a reduced dose of 240 mg twice daily from a previous dose of 480 mg twice daily. If intolerability recurred at a reduced dose, then following another 0.5- to 3-day dose holiday with resolution of symptoms to a tolerable grade 2, the dose could have been resumed at a further reduced dose to 80 mg twice daily and ultimately to 80 mg once daily following another 0.5- to 3-day dose holiday for patients not tolerating 80-mg twice-daily dosing. If appropriate, dosing could have been reescalated by 80-mg increments every 3 to 7 days (or slower, as tolerated) up to

480 mg twice daily. If a patient did not tolerate once-daily napabucasin 80 mg/placebo, treatment could have been interrupted for 1 to 3 days followed by rechallenge at 80 mg once daily. If necessary, paclitaxel could have been reduced from 80 mg/m^2 to 70 mg/m^2 to 60 mg/m^2 to 40 mg/m^2. If the dose of paclitaxel was reduced because of a potential treatment-related AE, then dose increases were not permitted. Patients continued study treatment until disease progression per RECIST 1.1 or until AEs required permanent discontinuation. If paclitaxel was discontinued due to toxicity, napabucasin or placebo monotherapy was continued until another discontinuation criterion was met. Similarly, if napabucasin or placebo was discontinued due to toxicity, paclitaxel monotherapy was continued until another discontinuation criterion was met.

BRIGHTER was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization-Good Clinical Practice guidelines. The study protocol was approved by the independent ethics committee or institutional review board at each participating site, and all patients provided written informed consent prior to enrollment.

Endpoints

The primary endpoint was OS, which was defined as the time from randomization until death from any cause. Secondary endpoints included PFS (the time from randomization until the first objective observation of disease progression or death from any cause), ORR [proportion of patients with a documented complete response (CR) or partial response (PR)], disease control rate [DCR; proportion of patients with a documented CR, PR, or stable disease (SD)], and safety. Safety was evaluated throughout the study by a data safety monitoring board (DSMB). AEs were coded per the NCI Common Toxicity Criteria for Adverse Events version 4.0. In prespecified, correlative biomarker analyses, OS and PFS were compared in the subgroups of patients with pSTAT3-positivity and pSTAT3-negativity. pSTAT3 status was determined centrally using a laboratory developed test that employed IHC staining of formalin-fixed, paraffin-embedded archival tissue using the D3A7 antibody clone for detection of pSTAT3 at tyrosine 705 (Cell Signaling Technologies). For a patient to be considered pSTAT3-positive, pSTAT3 had to be present both within malignant cells (≥5% of tumor cells stain positively at any intensity) and the associated TME (a score of 2, indicating ≥20% of positive TME is stained to at least a moderate intensity).

Statistics

The primary analysis was performed on the intent-to-treat (ITT) population. Assuming a two-sided alpha of 5%, a total of 566 OS events were needed to detect a 24% reduction in the risk of death with napabucasin plus paclitaxel versus placebo plus paclitaxel (HR = 0.76, corresponding to an increase in median OS from 7.36 to 9.67 months). An interim analysis was planned at two-thirds (n = 380) of all anticipated OS events (two-sided P of 0.012), with the significance level at the final analysis adjusted to preserve overall type-1 error at 5%. OS in the ITT population was summarized using the Kaplan–Meier method and compared primarily by a stratified log–rank test adjusted for the actual stratification variables at randomization (prior taxane therapy was not included as a stratification variable in the statistical analysis due to insufficient sample size; n = 10). The HR for the treatment effect was estimated based on a Cox proportional hazards model, which was stratified in the same manner as in the primary stratified log–rank test.

Secondary outcomes were inferentially assessed using a hierarchical analysis method [i.e., formal statistical analyses were to be undertaken only if the primary outcome (OS) was significantly longer in the napabucasin plus paclitaxel vs. placebo plus paclitaxel treatment arm]. PFS in the ITT population and the correlative endpoints OS and PFS in the pSTAT3-positive and pSTAT3-negative subgroups were analyzed using similar methodology as the primary analysis. ORR and DCR were compared between treatment arms using the Cochran–Mantel–Haenszel test, which was stratified in the same manner as in the primary stratified log–rank test. All patients who received at least one dose of napabucasin/placebo or paclitaxel were included in the safety analysis (safety population). AEs were summarized using descriptive statistics.

Data availability

Data relating to this publication shall remain confidential to the sponsor organization and will not be disclosed, except when disclosure might be required in accordance with pharmacovigilance duties of the parties involved. Individual trial participant data, after deidentification, may be made available in accordance with applicable law to qualified researchers who provide a written request following authorization from the sponsor organization and subject to appropriate data transfer agreements. Data sharing requests should be directed to our corporate website, https://oncology.sumitomo-pharma.com/about/contact/.

Results

Patients

Between October 2, 2014 and December 12, 2016, a total of 714 patients with advanced gastric or GEJ adenocarcinoma were randomized to treatment with either napabucasin plus paclitaxel (n = 357) or placebo plus paclitaxel (n = 357; **Fig. 1**). Baseline characteristics were

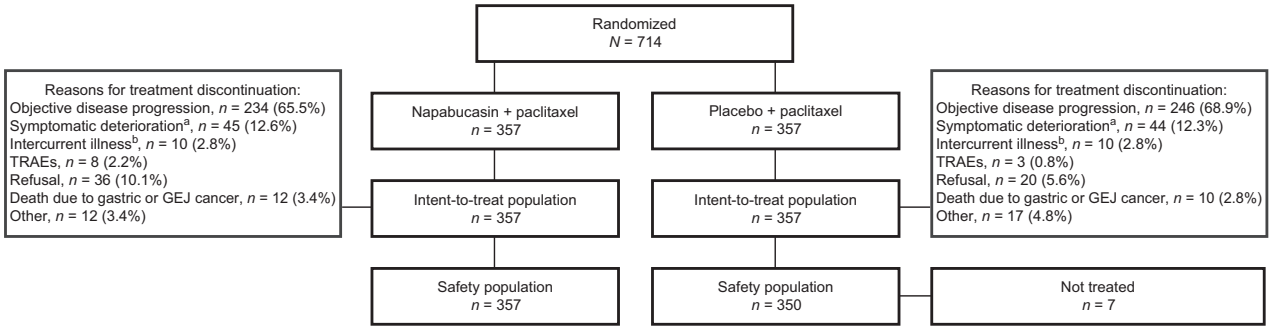


Figure 1.

Patient disposition. [a]Symptomatic deterioration without objective disease per RECIST criteria. [b]AEs unrelated to study treatment. GEJ, gastroesophageal junction; RECIST, Response Evaluation Criteria in Solid Tumors; TRAE, treatment-related adverse event.

Table 1. Baseline characteristics.

Parameter	Napabucasin plus paclitaxel (*n* = 357)	Placebo plus paclitaxel (*n* = 357)
Sex, *n* (%)		
Male	261 (73.1)	254 (71.1)
Female	96 (26.9)	103 (28.9)
Age, median (range)	63.1 (254–86.2)	61.7 (24.1–88.0)
Race, *n* (%)		
Caucasian	237 (66.8)	240 (67.6)
Asian	107 (30.1)	102 (28.7)
Other[a]	11 (3.1)	13 (3.6)
Missing	2 (0.5)	2 (0.5)
Body mass index, mean (SD)	23.2 (4.5)	23.6 (4.7)
Histologic type, *n* (%)		
Diffuse	82 (23.0)	88 (24.6)
Intestinal	91 (25.5)	80 (22.4)
Mixed	21 (5.9)	20 (5.6)
Unknown	163 (45.7)	168 (47.1)
Missing	0	1 (0.3)
HER2 status, *n* (%)		
HER2-positive	66 (18.5)	53 (14.8)
HER2-negative	200 (56.0)	199 (55.7)
HER2 unknown	91 (25.5)	105 (29.4)
Prior gastrectomy, *n* (%)	91 (25.5)	102 (28.6)
Prior radiotherapy, *n* (%)	38 (10.6)	36 (10.1)
Prior taxane exposure, *n* (%)	6 (1.7)	4 (1.1)
Progressed on first-line treatment in <6 months, *n* (%)	187 (52.4)	163 (45.7)
Presence of measurable disease per RECIST 1.1, *n* (%)	289 (81.0)	283 (79.3)
ECOG PS, *n* (%)		
0	128 (35.9)	134 (37.5)
1	229 (64.1)	223 (62.5)
Location of primary tumor, *n* (%)		
Gastric adenocarcinoma	258 (72.3)	275 (77.0)
GEJ	99 (27.7)	82 (23.0)
Presence of peritoneal metastases, *n* (%)		
Yes	160 (44.8)	170 (47.6)
No	196 (54.9)	187 (52.4)
Missing	1 (0.3)	0
Number of organ sites involved, *n* (%)		
<2	79 (22.4)	76 (21.3)
≥2	273 (77.6)	281 (78.7)
Missing	5 (1.4)	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; RECIST, Response Evaluation Criteria in Solid Tumors; SD, standard deviation.
[a]Other includes black, American Indian, and "other."

balanced between treatment arms (**Table 1**). The most common reasons for discontinuation of napabucasin or placebo were disease progression (napabucasin plus paclitaxel, 65.5%; placebo plus paclitaxel, 68.9%), symptomatic deterioration (napabucasin plus paclitaxel, 12.6%; placebo plus paclitaxel, 12.3%), and death due to gastric/GEJ cancer (napabucasin plus paclitaxel, 3.4%; placebo plus paclitaxel, 2.8%). The primary reason for stopping the study (i.e., ending follow-up data collection) was death (napabucasin plus paclitaxel, 80.1%; placebo plus paclitaxel, 78.2%).

Treatment

The median (range) total number of treatment cycles was the same for napabucasin plus paclitaxel and placebo plus paclitaxel [4.0 (1–26) and 4.0 (1–22), respectively]. The median (range) duration of exposure to napabucasin was 12.5 (0–105) weeks; the median (range) duration of exposure to placebo was 14.9 (0–88) weeks (Supplementary Table S3). The mean (SD) relative dose intensity of napabucasin and placebo was 72.0% (40.4) and 96.1% (37.4), respectively. The mean (SD) relative dose intensity of paclitaxel was 85.8 (47.2) in the napabucasin treatment arm and 88.7 (33.5) in the control treatment arm (Supplementary Table S4). If the starting dose of 480 mg twice a day (960 mg total) napabucasin was not tolerated, patients could receive a lower dose. For patients in the napabucasin treatment arm, a total dose of 960-mg napabucasin was received a median of 68.9% of all treatment days (97.6% of days for placebo), while a total dose of at least 480-mg napabucasin was received a median of 91.9% of all treatment days (99.4% for placebo). These data indicate that while the majority of patients were able to tolerate the full starting dose of 960 mg daily, nearly all patients tolerated a modified dose of at least 480 mg daily.

Efficacy

The preplanned interim analysis was initially performed on 380 events, with additional analyses performed on survival data accumulated between the interim analysis clinical cutoff and the interim analysis meeting. At interim analysis, 187 (52.4%) patients randomized to napabucasin plus paclitaxel and 193 (54.1%) patients randomized to placebo plus paclitaxel had died. There was no statistically significant difference in OS between napabucasin plus paclitaxel [median OS (95% confidence interval; CI), 6.97 months (6.28–7.79)] and placebo plus paclitaxel [median OS (95% CI), 7.29 months (6.11–8.57); HR = 0.94; 95% CI, 0.77–1.16; $P = 0.5699$]. The DSMB concluded that an OS benefit was unlikely to be demonstrated in the final analysis. The DSMB further stated that although there were no safety risks requiring the trial be stopped, the low probability of OS improvement impacted the overall risk-benefit assessment. The DSMB recommended that patients be informed of their treatment allocation and the interim analysis results so that they, in consultation with the study investigator, may determine whether to continue study treatment. As a result of the interim analysis and DSMB recommendation, the study sponsor terminated the clinical trial on September 15, 2017, with a total of 565 OS events.

At the time of the final analysis, median OS was 6.93 (95% CI, 6.28–7.69) months for napabucasin plus paclitaxel and 7.36 (95% CI, 6.64–8.15) months for placebo plus paclitaxel (HR = 1.01; 95% CI, 0.86–1.20; $P = 0.8596$; **Fig. 2**). Median PFS was 3.55 (95% CI, 3.22–3.68) and 3.68 (95% CI, 3.48–3.71) months for napabucasin plus paclitaxel and placebo plus paclitaxel, respectively (HR = 1.01; 95% CI, 0.85–1.19; $P = 0.9028$; Supplementary Fig. S1). Among patients with measurable disease ($n = 527$, 80.1%), ORR was 16% for napabucasin plus paclitaxel and 18% for placebo plus paclitaxel, a difference of −2% (95% CI, −8 to 4; $P = 0.7358$). DCR was 55% and 58%, respectively, corresponding to a difference of −3% (95% CI, −11 to 5; $P = 0.6555$).

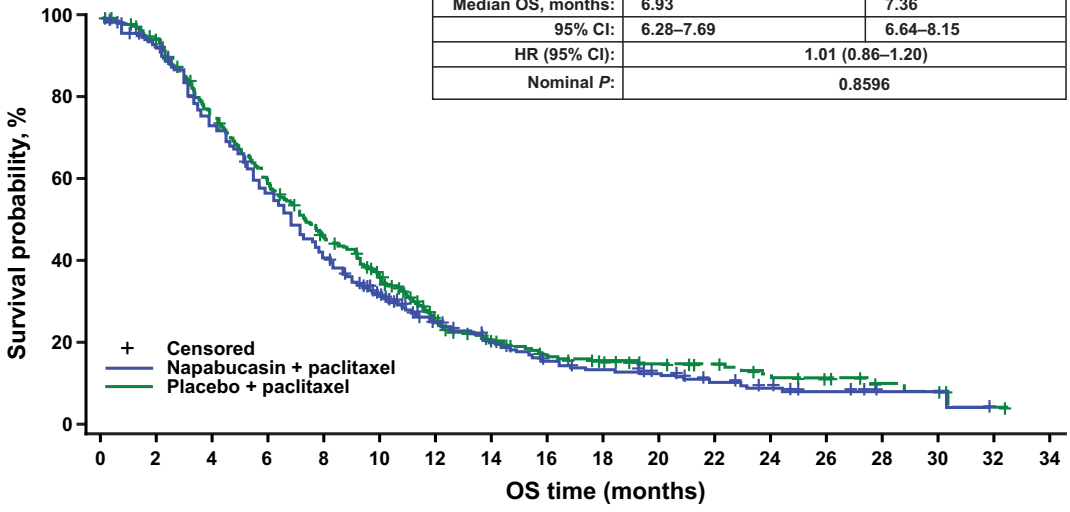
Biomarker analyses

Prospectively-collected tumor tissue samples were retrospectively evaluated for pSTAT3 status in an exploratory analysis. pSTAT3 biomarker data were available for 66.4% (237/357) of patients randomized to napabucasin plus paclitaxel and 69.5% (248/357) of patients randomized to placebo plus paclitaxel. Among the 485 patients with available biomarker data, 260 were pSTAT3-positive (napabucasin plus paclitaxel, $n = 134$; placebo plus paclitaxel, $n = 126$), and 225 were pSTAT3-negative (napabucasin plus paclitaxel, $n = 103$; placebo plus paclitaxel, $n = 122$). Among patients with pSTAT3-positive tumors, OS was not increased by the addition of napabucasin to paclitaxel. Median OS was similar for napabucasin plus paclitaxel (7.39 months) and placebo plus paclitaxel (7.13 months). Similarly, OS rates at 6 and 12 months were similar for napabucasin plus paclitaxel and placebo plus paclitaxel, and there was no significant difference in PFS, ORR, or DCR between treatment arms in the pSTAT3-positive subgroup (Supplementary Table S5; Supplementary Fig. S2).

Among patients administered placebo plus paclitaxel, median OS was numerically shorter in a prespecified subgroup analysis of patients with pSTAT3-positive versus pSTAT3-negative tumors (7.13 vs. 8.02 months; HR = 1.32; 95% CI, 1.00–1.74; Supplementary Table S5; Supplementary Fig. S3). Similarly, PFS was shorter in patients with pSTAT3-positive tumors compared with pSTAT3-negative tumors (3.35 vs. 3.88 months; HR = 1.37; 95% CI, 1.05–1.78; Supplementary Fig. S3), and both ORR and DCR were lower in patients whose tumors were pSTAT3-positive versus pSTAT3-negative (ORR 16% vs. 19%; DCR 50% vs. 66%, respectively; Supplementary Table S5).

Safety

Seven patients randomized to placebo plus paclitaxel did not receive any study treatment and thus were not included in the safety



	Napabucasin + paclitaxel	Placebo + paclitaxel
Median OS, months:	6.93	7.36
95% CI:	6.28–7.69	6.64–8.15
HR (95% CI):	1.01 (0.86–1.20)	
Nominal *P*:	0.8596	

Patients at risk, *n*

Survival time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Napabucasin + paclitaxel	357	321	253	193	140	100	64	48	35	29	24	17	13	6	2	2	0	0
Placebo + paclitaxel	357	327	259	203	156	114	62	45	33	27	22	19	13	10	5	4	1	0

Figure 2.
OS in patients treated with either napabucasin plus paclitaxel or placebo plus paclitaxel. OS, overall survival.

Table 2. Safety summary.

n (%)	Napabucasin plus paclitaxel (*n* = 357)		Placebo plus paclitaxel (*n* = 350)	
TEAEs	**Any grade[a,b]**	**Grade ≥3[c]**	**Any grade[a,b]**	**Grade ≥3[c]**
All TEAEs	352 (98.6)	248 (69.5)	338 (96.6)	209 (59.7)
Diarrhea	304 (85.2)	58 (16.2)	126 (36.0)	5 (1.4)
Nausea	178 (49.9)	15 (4.2)	123 (35.1)	10 (2.9)
Abdominal pain	140 (39.2)	21 (5.9)	93 (26.6)	16 (4.6)
Vomiting	135 (37.8)	17 (4.8)	95 (27.1)	13 (3.7)
Decreased appetite	129 (36.1)	26 (7.3)	103 (29.4)	13 (3.7)
Anemia	126 (35.3)	41 (11.5)	118 (33.7)	39 (11.1)
Fatigue	110 (30.8)	27 (7.6)	92 (26.3)	16 (4.6)
Alopecia	73 (20.4)	2 (0.6)	94 (26.9)	5 (1.4)
Asthenia	73 (20.4)	27 (7.6)	73 (20.9)	11 (3.1)
Constipation	61 (17.1)	0	78 (22.3)	4 (1.1)
Pyrexia	57 (16.0)	1 (0.3)	40 (11.4)	2 (0.6)
Neutrophil count decreased	48 (13.4)	28 (7.8)	53 (15.1)	25 (7.1)
Chromaturia	47 (13.2)	0	3 (0.9)	0
Peripheral neuropathy	46 (12.9)	8 (2.2)	38 (10.9)	4 (1.1)
Weight decreased	41 (11.5)	3 (0.8)	23 (6.6)	1 (0.3)
Peripheral edema	38 (10.6)	2 (0.6)	31 (8.9)	0
Neutropenia	37 (10.4)	17 (4.8)	49 (14.0)	22 (6.3)
Peripheral sensory neuropathy	37 (10.4)	3 (0.8)	47 (13.4)	3 (0.9)
White blood cell count decreased	35 (9.8)	9 (2.5)	43 (12.3)	15 (4.3)
Abdominal pain (upper)	35 (9.8)	3 (0.8)	40 (11.4)	3 (0.9)
Dyspnea	30 (8.4)	2 (0.6)	37 (10.6)	9 (2.6)
TRAEs, grade ≥3[d]	112 (31.4)		37 (10.6)	
Diarrhea	55 (15.4)		3 (0.9)	
Serious TEAEs, any grade	125 (35.0)		101 (28.9)	
Serious TEAEs, grade ≥3	111 (31.1)		90 (25.7)	
TEAE leading to modification of any study treatment	292 (81.8)		211 (60.3)	
TEAE leading to discontinuation of napabucasin or placebo treatment	74 (20.7)		48 (13.7)	
TEAE leading to discontinuation of paclitaxel treatment	74 (20.7)		55 (15.7)	
TEAE leading to death	17 (4.8)		14 (4.0)	

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]TEAEs reported in ≥10% of patients in either treatment arm.
[b]Febrile neutropenia was reported in 1 (0.3%) patient (grade 3) in the napabucasin plus paclitaxel arm and 3 (0.9%) patients ($n = 2$ grade 3, $n = 1$ grade 4) in the placebo plus paclitaxel arm.
[c]TEAEs grade ≥3 reported in ≥5% of patients in either treatment arm.
[d]TRAEs grade ≥3 reported in ≥5% of patients in either treatment arm.

population analysis. No safety concerns were identified by the DSMB throughout the study. A total of 98.6% of patients treated with napabucasin plus paclitaxel and 96.6% of those treated with placebo plus paclitaxel reported an AE (**Table 2**). Grade ≥3 AEs were observed in 69.5% of patients administered napabucasin plus paclitaxel and 59.7% of those administered placebo plus paclitaxel, with grade ≥3 diarrhea reported in 16.2% and 1.4% of patients, respectively (**Table 2**). In total, 35.0% of patients who received napabucasin plus paclitaxel reported a serious AE, of which 88.8% were grade ≥3 in severity. The corresponding values for patients who received placebo plus paclitaxel were 28.9% and 89.1%. AEs leading to dose modification (reduction, delay, or discontinuation) of any study treatment were reported in 292 (81.8%) patients administered napabucasin plus paclitaxel and 211 (60.3%) patients administered placebo plus paclitaxel. In total, 74 (20.7%) AEs led to discontinuation of treatment with napabucasin, and 48 (13.7%) led to discontinuation of treatment with placebo, with the most common AEs being diarrhea [napabucasin plus paclitaxel, $n = 13$ (3.6%); napabucasin plus placebo, $n = 1$ (0.3%)] and vomiting [napabucasin plus paclitaxel, $n = 10$ (2.8%); placebo plus paclitaxel, $n = 4$ (1.1%)].

Discussion

The primary endpoint of the BRIGHTER study was not met: the addition of napabucasin to paclitaxel did not improve OS compared with paclitaxel monotherapy in patients with second-line advanced gastric or GEJ adenocarcinoma (median, 6.93 vs. 7.36 months). PFS (median, 3.55 vs. 3.68 months), ORR (16% vs. 18%), and DCR (55% vs. 58%) were also similar in the two treatment arms. Outcomes in the control treatment arm were similar to those reported in recent phase III studies of advanced gastric or GEJ adenocarcinoma in which paclitaxel was the comparator (10, 35, 36).

In exploratory biomarker analyses, pSTAT3 positivity was not predictive of clinical benefit from napabucasin. In the literature, STAT3 and pSTAT3 are negative prognostic markers in multiple tumor types (27–29, 37–40). Napabucasin has been shown in the preclinical setting to inhibit phosphorylation (i.e., activation) of pSTAT3 (22, 33). In a prespecified analysis of BRIGHTER, median OS and PFS were numerically shorter and ORR and DCR were proportionally lower in control-treated patients with pSTAT3-positive versus pSTAT3-negative tumors. Although the magnitude of the effect

is small, the results suggest that pSTAT3 positivity is prognostic of poor outcomes in advanced gastric or GEJ adenocarcinoma. The impact of pSTAT3 positivity may vary by cancer type (i.e., gastric cancer vs. colorectal cancer; ref. 32).

The overall AE incidence and dose intensity of paclitaxel was similar in the napabucasin and control treatment arms. However, the rates of some serious AEs and grade ≥3 AEs were higher with napabucasin plus paclitaxel. Grade ≥3 AEs with a higher incidence among patients treated with napabucasin plus paclitaxel were most commonly gastrointestinal in nature (i.e., diarrhea, nausea, abdominal pain, vomiting, decreased appetite), but these rates were similar to those reported in other phase I/II and III clinical studies of napabucasin (41). In addition, data from this trial indicated that a vast majority of patients not tolerating the starting dose of napabucasin was able to tolerate lower doses.

In terms of limitations, BRIGHTER was initiated based on the results of a relatively small, nonrandomized trial of 46 total patients who had received mixed prior treatments. A larger phase II study, or perhaps randomized phase II study, of patients who had received only one prior therapy may have been more informative in designing the BRIGHTER trial. Second, the clinical relevance of BRIGHTER was adversely impacted by the regulatory approval of ramucirumab after the study was underway. Ramucirumab in combination with paclitaxel has since become the standard of care for patients with advanced gastric or GEJ adenocarcinoma following failure of fluoropyrimidine- or platinum-based chemotherapy (42). Thus, ramucirumab plus paclitaxel versus paclitaxel monotherapy would have been a more appropriate comparator. Third, no biomarkers other than pSTAT3 were evaluated, and no pharmacodynamic analyses were performed. Last, due to geographic disparities in patient survival, which itself may be confounded by race and tumor location (among other factors), it may have been preferable to involve fewer regions/countries rather than to undertake a global study (43–52).

To conclude, in the phase III BRIGHTER trial, the addition of napabucasin to paclitaxel did not improve survival in patients with second-line advanced gastric or GEJ adenocarcinoma. In this study pSTAT3 was not a predictive biomarker of clinical activity for napabucasin in GEJ adenocarcinoma. However, results from the control treatment arm of the BRIGHTER study comparing patients with pSTAT3-positive tumors versus patients with pSTAT3-negative tumors support earlier studies (27, 28, 30) that found pSTAT3 expression to be associated with poor prognosis in gastric and GEJ adenocarcinoma.

Authors' Disclosures

M.A. Shah reports grants from Sumito Pharma Oncology during the conduct of the study. K. Shitara reports grants from Astellas Pharma, Chugai Pharma, Medi Science, and Eisai; personal fees from Eli Lilly and Company, Bristol-Myers Squibb, Takeda Pharmaceuticals, Pfizer, Novartis, AbbVie, GlaxoSmithKline, Boehringer Ingelheim and Janssen; and grants and personal fees from Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Merck Pharmaceutical, and Amgen; outside the submitted work. F. Lordick reports personal fees from Amgen, Astellas Pharma, Bayer HealthCare, BeiGene, Daiichi Sankyo, Eli Lilly and Company, Elsevier, Incyte, Merck, MSD, Roche, and Servier and grants from BMS outside the submitted work. Y.-J. Bang reports grants from Boston Biomedical (Sumitomo Pharma Oncology Inc. at present) during the conduct of the study; and grants from Genentech/Roche, MSD, Merck Serono, Daiichi Sankyo, Astellas Pharma, BeiGene, and Amgen and personal fees from MSD, Merck Serono, Daiichi Sankyo, Astellas Pharma, BeiGene, Samyang Biopharm, Alexo Oncol, Hanmi, Daewoong, and Amgen outside the submitted work. J.-P. Metges reports personal fees and other support from MSD and Astellas Pharma; other support from Gilead, Sanofi-Aventis, and BeiGene; and personal fees from BMS and Novartis outside the submitted work. K. Muro reports grants from Astellas Pharma, Solasia Pharma, MSD, Parexel Internatinonal, Merck KGaA, Pfizer, and Eisai; grants and other support from Amgen; grants and personal fees from Sanofi-Aventis, Daiichi Snakyo, and Taiho Pharmaceutical; grants, personal fees, and other support from Ono Pharmaceutical and Chugai Pharma; personal fees from Eli Lilly and Company and Bristol-Myers Squibb; other support from AstraZeneca; and nonfinancial support from Takeda outside the submitted work. K.-W. Lee reports grants from Boston Biomedical (Sumitomo Pharma Oncology, Inc at present) (to his institution for conducting clinical trials) during the conduct of the study; grants from Ono Pharmaceutical, Merck Sharp & Dohme, AstraZeneca/MedImmune, Merck KGaA, Pfizer, BeiGene, ALX Oncology, Zymeworks, Macrogenics, Five Prime Therapeutics, Oncologie, Pharmacyclics, Green Cross Corp., ABLBIO, Y-BIOLOGICS, Genexine, LSK BioPharma, Daiichi Sankyo and Taiho Pharmaceutical (to his institution for conducting clinical trials); and personal fees from ISU ABXIS, Bayer HealthCare, and Daiichi Sankyo (consultation) outside the submitted work. L. Shen reports grants from Yaojie Ankang (Nanjing) Technology Co., Ltd., Baiji Shenzhou (Beijing) Biotechnology Co., Ltd., Beijing Xiantong Biomedical Technology Co., Ltd., QiLu Pharmaceutical, and Zaiding Pharmaceutical; other support from Hutchison Whampoa, MSD, Bristol-Myers Squibb, AstraZeneca, Daiichi Sankyo, Roche, Mingji Biopharmaceutical, and Harbour BioMed; and other support from Merck outside the submitted work. S. Tjulandin reports grants and personal fees from Boston Biomedical (Sumitomo Pharma Oncology, Inc at present) during the conduct of the study. N. Starling reports personal fees from Eli Lilly and Company, Pierre Fabre, Servier, GSK, Amgen, Novartis, and Clinical Options; grants, personal fees, and other support from Merck/MSD, and AstraZeneca; grants and other support from BMS; and grants from Pfizer and NIHR EME outside the submitted work. M. Fontaine was a full time employee of Sumitomo Pharma Oncology, Inc during study conduct. C. Oh was a salaried employee of Sumitomo Pharma Oncology Inc. at the time the analyses were undertaken. E.M. Brooks is a salaried employee of Sumitomo Pharma Oncology, Inc. B. Xu is a salaried employee of Sumitomo Pharma Oncology, Inc. C.J. Li reports grants from Boston Biomedical (Sumitomo Pharma Oncology at present) during the conduct of the study; in addition, C.J. Li has napabucasin patents pending, issued, and licensed to Boston Biomedical. L. Borodyansky was a full-time employee of Boston Biomedical (now Sumitomo Pharma Oncology, Inc) during the conduct of the study and data analyses. E. Van Cutsem reports personal fees (advisory boards) from AbbVie, Array, Astellas Pharma, AstraZeneca, Bayer HealthCare, BeiGene, Biocartis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Halozyme, GSK, Helsinn, Incyte, Ipsen, Janssen Research, Eli Lilly and Company, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Pierre Fabre, Roche, Seattle Genetics, Servier, Sirtex, Terumo, Taiho Pharmaceutical, TRIGR, and Zymeworks; and grants from Amgen, Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Ipsen, Eli Lilly and Company, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, and Servier outside the submitted work. No disclosures were reported by the other authors.

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Acknowledgments

This work would not have been possible without the investigators, healthcare professionals, and research staff at each participating institution. The authors would also like to express their gratitude for the patients who participated in this study.

The authors would like to thank Matthew Hitron, MD, for his expertise and critical review of the manuscript.

Medical writing support was provided by Dr. Ian Wright of Adelphi Communications and Tiffany DeSimone, PhD, and Justine Sinnaeve, PhD, of Ashfield MedComms, an Inizio Company. This support was funded by Sumitomo Pharma Oncology, Inc. None of the authors received any compensation for their contributions to this work.

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Received December 15, 2021; revised March 22, 2022; accepted May 24, 2022; published first May 31, 2022.

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