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Clinical Trial

SAPPHIRE: a randomised phase II study of planned discontinuation or continuous treatment of oxaliplatin after six cycles of modified FOLFOX6 plus panitumumab in patients with colorectal cancer

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Abstract ***Background:*** Fluorouracil (5-FU), leucovorin (LV) and oxaliplatin (FOLFOX) plus panitumumab therapy is a commonly used first-line chemotherapy for metastatic colorectal cancer (mCRC). However, the long-term administration of oxaliplatin is associated with peripheral neuropathy (PN). We investigated whether the planned discontinuation of oxaliplatin after FOLFOX plus panitumumab therapy can maintain efficacy and reduce PN incidence.
Patients and methods: Chemotherapy-naive patients with *RAS* wild-type mCRC, aged ≥20 years, were enrolled and received six cycles of modified FOLFOX6 (mFOLFOX6) plus panitumumab as induction therapy. Patients who completed induction therapy without progression were randomised to mFOLFOX6 plus panitumumab (group A) or to 5-FU/LV plus panitumumab (group B). The primary end-point was the progression-free survival (PFS) rate at 9 months after randomisation. The secondary end-points were PFS, overall survival (OS), time to treatment failure (TTF), response rate (RR) and safety.
Results: In total, 164 patients were enrolled; of whom, 113 patients were then randomised (group A, $n = 56$; group B, $n = 57$). The median follow-up after randomisation was 19.6 months. The PFS rates at 9 months and median PFS were 46.4% (80% confidence interval [CI], 38.1–54.9) and 9.1 months (95% CI, 8.6–11.1) in group A, compared with 47.4% (80% CI, 39.1–55.8) and 9.3 months (95% CI, 6.0–13.0) in group B, respectively. RR, OS and TTF were also similar in both groups. Grade ≥2 PN incidence was lower in group B (9.3%) than in group A (35.7%).
Conclusion: Planned discontinuation of oxaliplatin after six cycles of mFOLFOX6 plus panitumumab is a potential treatment option in patients with mCRC, achieving similar efficacy while reducing oxaliplatin-associated PN compared with mFOLFOX6 plus panitumumab.
Trial registration number: NCT02337946

1. Introduction

Panitumumab is a complete human monoclonal antibody, targeting the epidermal growth factor receptor (EGFR) [1–3]. Its efficacy has been demonstrated as monotherapy or in combined chemotherapy, such as fluorouracil (5-FU), leucovorin (LV) and irinotecan or oxaliplatin (FOLFOX), in patients with metastatic colorectal cancer (mCRC) [1–3].

In the randomised phase III PRIME study, panitumumab plus FOLFOX4 improved progression-free survival (PFS) and overall survival (OS) in patients with wild-type *KRAS* mCRC [1]. However, oxaliplatin administration is often limited because of cumulative peripheral neuropathy (PN) [4,5]. PN persists during and after oxaliplatin treatment, with the estimated incidence of severe PN (grade 2 or 3) reaching 25% after eight and 12 cycles, respectively [4]. In addition, it takes approximately 13 weeks to resolve PN after treatment in most patients owing to deteriorating quality of life. To minimise oxaliplatin-related PN, the OPTIMOX1 trial proposed strategies of stopping or interrupting oxaliplatin [6]. Results showed that a stop-and-go approach, interrupting oxaliplatin administration, reduced PN without affecting the OS of patients who received six cycles (3 months) of FOLFOX7 (cumulative oxaliplatin dose: 780 mg/m^2). Several studies have reported the efficacy of maintenance therapy with first-line treatment for mCRC [7]. These approaches involve intensive first-line therapy, followed by moderate maintenance therapy until progression. For example, intermittent discontinuation of oxaliplatin from FOLFOX plus bevacizumab exhibited superior efficacy and safety, with reduced PN compared with continuous oxaliplatin administration [8]. However, reports of maintenance therapy following oxaliplatin-containing chemotherapy plus an anti-EGFR monoclonal antibody are scarce.

We implemented SAPPHIRE (NCT02337946), a randomised phase II study, to evaluate the planned discontinuation of oxaliplatin treatment after modified FOLFOX6 (mFOLFOX6) plus panitumumab in patients with *RAS* wild-type mCRC. To reduce the incidence of severe PN, six cycles (3 months) of mFOLFOX6 plus panitumumab (cumulative oxaliplatin dose: 510 mg/m^2) was scheduled as induction therapy.

2. Patients and methods

2.1. Patients

Eligible patients had histologically confirmed *RAS* (*KRAS*/*NRAS*) wild-type adenocarcinoma of the colon or rectum with ≥1 measurable lesion according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [9]; were aged ≥20 years; had Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1; had adequate hepatic, haematological and renal function; had estimated life expectancy >6 months and had no previous chemotherapy for mCRC, except adjuvant/neoadjuvant chemotherapy completed >6 months before treatment initiation.

Patients were ineligible if they had received radiotherapy for a measurable or non-measurable lesion 28 days before enrolment, had brain metastasis, synchronous or metachronous cancers other than CRC with a disease-free period of ≤5 years or severe hypersensitivity or were pregnant or lactating. This study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice and all applicable regulations. All patients provided written informed consent. Other details are described in a protocol paper [10].

2.2. Study design and treatment

SAPPHIRE was an open-label, multicentre, parallel-group, non-comparative, randomised, controlled, phase II screening trial conducted in academic and primary care centres in Japan. Enrolled patients received induction therapy mFOLFOX6 plus panitumumab (6 mg/kg) once every 2 weeks for six cycles (oxaliplatin 85 mg/m^2, LV 200 mg/m^2, bolus 5-FU 400 mg/m^2, continuous 5-FU infusion at 2400 mg/m^2). Induction therapy was stopped if the patient had experienced PN grade ≥2, ECOG PS ≥ 2, progressive disease (PD), withdrawn informed consent, radiation therapy for a measurable lesion or conversion surgery for curative resection. Patients who completed induction therapy without discontinuation in all cycles, except for bolus 5-FU and panitumumab, were randomised 1:1 to continue mFOLFOX6 plus panitumumab (group A) or to receive 5-FU/LV plus panitumumab (group B) using the minimisation method (Fig. 1A). Randomisation was stratified by the study site, age (≥20 and ≤ 69 years or ≥70 years) and the number of metastasised organs (0, 1 or ≥2) at enrolment and response as per RECIST 1.1 (complete response [CR], partial response [PR] or stable disease) at randomisation. The statistical analysis manager (or designees) prepared the allocation procedures and managed patients' allocation information (accessible only to personnel with independent authorisation from the statistical analysis manager). The patients received the protocol treatment until any of the following occurred: PD, unacceptable toxicity, patient decision or scheduled conversion surgery for curative resection. Dose reduction, interruption and discontinuation of oxaliplatin, 5-FU or panitumumab were allowed in both groups.

2.3. End-points and assessments

The primary end-point was the PFS rate at 9 months after randomisation. The secondary end-points included PFS, OS, response rate (RR), time to treatment failure (TTF) and safety. PFS was defined as time from randomisation to progression or death from any cause, censoring patients without progression on the date of last disease assessment. OS was defined as time from randomisation to death from any cause, censoring patients who had not died on the date last known alive. TTF was defined as time from randomisation to discontinuation of protocol treatment, progression or death from any cause, censoring at the final dosing date of protocol treatment, if patients were on protocol treatment.

Progression was defined as PD based on diagnostic imaging as per RECIST 1.1 or clinical progression that could not be confirmed by diagnostic imaging. RR was defined as the proportion of patients with CR or PR as the best overall response after randomisation as per RECIST 1.1.

Additional end-points were duration of oxaliplatin continuation in group A and duration of panitumumab continuation in both groups. Duration of oxaliplatin treatment (group A only) or panitumumab (both groups) was evaluated from randomisation until oxaliplatin/panitumumab discontinuation, progression or death from any cause, whichever came earliest. Early tumour shrinkage was defined as the percent change in the sum of all target lesion diameters within 8 weeks of cycle 1 to ≤20% of the baseline at enrolment.

Safety was assessed as per the Common Terminology Criteria for Adverse Events (Japanese edition Japan Clinical Oncology Group 4.03). Adverse events (AEs) after enrolment were evaluated, renamed as per MedDRA (20.0) and summarised by System Organ Class and Preferred Term. PN was defined as events classified under the preferred terms of *peripheral neuropathy*,

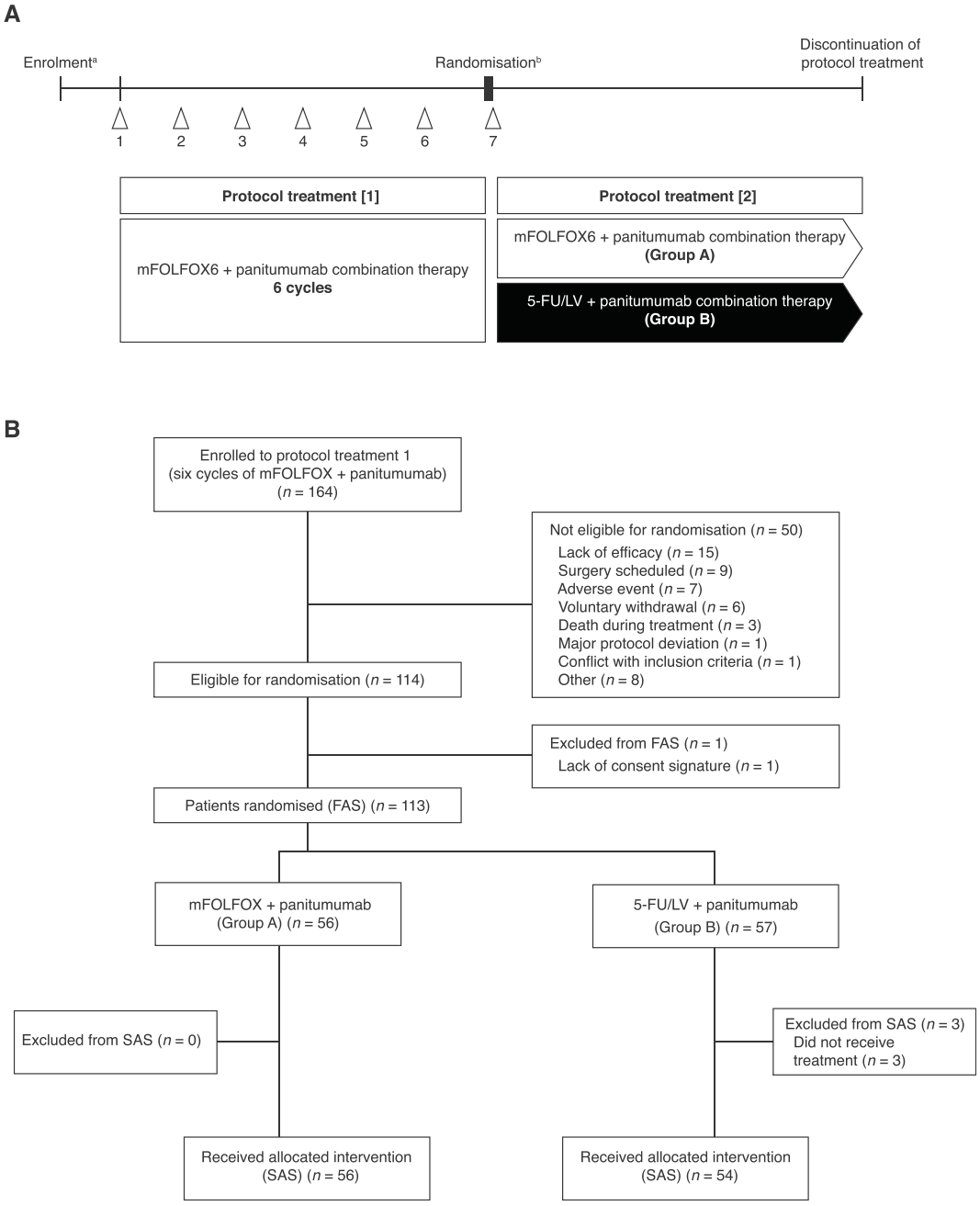

Fig. 1. (A) SAPPHIRE study schema and (B) patient disposition. [a]First administration within 14 days of enrolment. [b]When possible, conducted immediately before administration of cycle 7. 5-FU, fluorouracil; FAS, full analysis set; LV, leucovorin; mFOLFOX6, modified FOLFOX (fluorouracil, leucovorin and oxaliplatin); SAS, safety analysis set.

peripheral motor neuropathy and *peripheral sensory neuropathy* as per MedDRA.

2.4. Statistical analyses

The PFS rate at 9 months was expected to be 50% in group A, with a similar rate in group B [1,10,11]. Using a threshold PFS rate at 9 months for futility of 30%, a true PFS rate at 9 months of 50%, one-sided significance level of 10% and 90% power, 44 patients were required for each group, assuming the one-stage binomial test. Considering ineligible patients and censoring cases, the target patient number for randomisation was 50 per group (total = 100).

The full analysis set (FAS) was defined as all randomised patients, and the safety analysis set as all patients who received at least one dose of protocol treatment after randomisation.

A binomial test was conducted separately for each group under the null hypothesis of 'the true PFS rate at 9 months will be less than the threshold 30% PFS rate at 9 months and the treatment judged as ineffective' at the

one-sided 10% significance level. The PFS rate at 9 months was estimated as the crude proportion of patients alive and without progression at 9 months after randomisation with two-sided 80% confidence intervals (CIs) calculated using the method used by Agresti and Coull [12].

Efficacy analyses of PFS, OS, TTF and oxaliplatin or panitumumab treatment duration were estimated in the FAS using the Kaplan–Meier method, with two-sided 95% CIs calculated for each group. The 95% CI of the quartile was calculated using log-log transformation as per the method used by Brookmeyer and Crowley [13]. For reference, the hazard ratio (HR) for each variable in group B versus group A and its 95% CI (two-sided) were calculated based on a multivariable Cox regression model using stratification factors (except study sites), and a log-rank test was performed for comparison. RR was evaluated for the FAS, and two-sided 95% CIs were calculated for each group as per the method used by Agresti and Coull [12]. For reference, the difference in RR between groups (group B–group A) with associated two-sided 95% CI as per the method used by Agresti and Caffo [14] was calculated.

Exploratory subgroup analyses, including impact of early tumour shrinkage or primary tumour location on PFS, were performed. For sidedness analysis, splenic flexure, descending and sigmoid colon and rectosigmoid junction were defined as left-sided tumours and ascendant colon, hepatic flexure and traverse colon were defined as right-sided tumours.

AEs after enrolment were evaluated using descriptive statistics in the safety analysis set. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

3. Results

3.1. Patients

Between October 2014 and April 2016, 164 patients were enrolled at 53 sites in Japan (Fig. 1B). Data cut-off was 31st August 2017. Of the 114 patients eligible for randomisation, the FAS consisted of 56 patients in group A and 57 in group B. The median follow-up was 19.6 months (95% CI, 18.3–20.9). Twelve patients were ongoing treatment at the time of analysis (group A, 5; group B, 7), and 80 of 113 patients were alive (group A, 40/56; group B, 40/57).

Baseline patient demographics and clinical characteristics are shown in Table 1. No marked differences were observed between groups. In total, 55 patients in group A and 53 in group B had confirmed *RAS* (*KRAS*/*NRAS*) wild-type disease. Three patients (5.3%) in group B, who were enrolled before availability of the expanded *KRAS*/*NRAS* testing, were found to be mutation positive.

Table 1
Baseline demographics and clinical information (FAS).

Characteristics	Group A (n = 56)	Group B (n = 57)
Age, median (range), years	69 (25–80)	68 (27–84)
Age ≥70 years, n (%)	25 (44.6)	27 (47.4)
Male, n (%)	41 (73.2)	34 (59.6)
ECOG PS at the start of therapy, n (%)		
0	49 (87.5)	41 (71.9)
1	7 (12.5)	16 (28.1)
ECOG PS at randomisation (cycle 7), n (%)		
0	37 (66.1)	34 (59.6)
1	18 (32.1)	19 (33.3)
2	1 (1.8)	1 (1.8)
Unknown	0 (0)	3 (5.3)
Primary tumour type,[a] n (%)		
Colon	36 (64.3)	37 (64.9)
Rectal	23 (41.1)	27 (47.4)
Primary tumour location, n (%)		
Left[b]	47 (83.9)	42 (73.7)
Right[c]	9 (16.1)	14 (24.6)
Left and right	0 (0)	1 (1.8)
Number of metastatic organs, n (%)		
0	0 (0)	1 (1.8)
1	25 (44.6)	28 (49.1)
≥2	31 (55.4)	28 (49.1)
Site of metastatic disease,[d] n (%)		
Liver	45 (80.4)	38 (66.7)
Lungs	20 (35.7)	19 (33.3)
Peritoneum	7 (12.5)	10 (17.5)
Lymph nodes	18 (32.1)	22 (38.6)
Other	10 (17.8)	7 (12.3)
RAS status,[e] n (%)		
Wild-type	55 (98.2)	53 (93.0)
Mutant	0 (0)	3 (5.3)
Unknown	1 (1.8)	1 (1.8)
Prior adjuvant chemotherapy, n (%)	3 (5.4)	5 (8.8)
Prior surgery, n (%)	42 (75.0)	39 (68.4)
RECIST evaluation at randomisation, n (%)		
CR	1 (1.8)	0 (0)
PR	45 (80.4)	51 (89.5)
SD	10 (17.9)	6 (10.5)
Unknown	0 (0)	0 (0)
ETS during protocol treatment 1 (within 8 weeks of cycle 1), n (%)		
Patients with ETS	35 (62.5)	38 (66.7)
Patients without ETS	18 (32.1)	14 (24.6)
Unknown	3 (5.4)	5 (8.8)

The data shown are for all patients randomised to treatment. Unless otherwise stated, all values are as reported at enrolment.
CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ETS, early tumour shrinkage; FAS, full analysis set; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

[a] Including duplication.

[b] Includes distant one-third of the transverse colon, descending colon, sigmoid colon, rectosigmoid and rectum.

[c] Includes proximal two-thirds of the transverse colon, caecum and ascending colon.

[d] Including patients with multiple metastatic organs.

[e] All patients were confirmed as not having mutations in *KRAS* exon 2. Mutations also include those in *KRAS* exon 3 or 4 or in *NRAS* exon 2, 3 or 4.

3.2. Treatment duration and exposure

The median duration of oxaliplatin treatment after randomisation was 3.8 months (95% CI, 3.1–4.9) in group A. The median duration of panitumumab treatment after randomisation was 7.2 months (95% CI, 5.8–9.0) in group A and 5.8 months (95% CI, 4.5–9.2) in group B (Supplementary Fig. 1).

Relative dose intensity for each agent, including panitumumab, LV, 5-FU and oxaliplatin, after randomisation (cycles 7–12) was maintained from induction therapy (cycles 1–6) (Supplementary Table 1). The median cumulative dose of oxaliplatin was 813 mg/m^2 (range, 390–1020 mg/m^2) in group A and 510 mg/m^2 (range, 345–680 mg/m^2) in group B.

3.3. Efficacy

At final analysis, 28 patients (50.0%) in group A and 29 in group B (50.9%) had PFS events. The PFS rate at 9 months after randomisation was 46.4% (80% CI, 38.1–54.9) in group A and 47.4% (80% CI, 39.1–55.8) in group B, and the null hypothesis of the 9-month PFS rate ≤30% was rejected in both groups ($p = 0.0037$ in group A; $p = 0.0021$ in group B) (Table 2). The median PFS in group A was 9.1 months (95% CI, 8.6–11.1) and in group B was 9.3 months (95% CI, 6.0–13.0) (Fig. 2A). The estimated HR for PFS, based on multiple Cox regression analysis using stratification factors, was 0.93 (95% CI, 0.60–1.43).

The estimated median TTF in group A was 8.1 months (95% CI, 5.9–9.5) and in group B was 6.1 months (95% CI, 4.5–9.3) (Fig. 2B). The estimated HR for TTF was 0.90 (95% CI, 0.60–1.33). The median OS was not reached in both groups, with 16 events in group A and 17 in group B (Fig. 2C). The estimated HR for OS was 1.41 (95% CI, 0.69–2.88). The overall RR after randomisation in group A was 80.4% (95% CI, 68.0–88.8) and in group B was 87.7% (95% CI, 76.4–94.2) (Table 2).

Table 2
Summary of PFS rates and RRs (FAS).

PFS and tumour response	Group A ($n = 56$)	Group B ($n = 57$)
PFS rate, % (80% CI)	46.4 (38.1–54.9)	47.4 (39.1–55.8)
H_0: PFS rate ≤30%	$p = 0.0037$	$p = 0.0021$
Best response, *n* (%)		
CR	8 (14.3)	2 (3.5)
PR	37 (66.1)	48 (84.2)
SD	4 (7.1)	3 (5.3)
PD	6 (10.7)	4 (7.0)
NE	1 (1.8)	0 (0.0)
RR, % (95% CI)	80.4 (68.0–88.8)	87.7 (76.4–94.2)

CI, confidence interval; CR, complete response; FAS, full analysis set; H_0, null hypothesis; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; RR, response rate; SD, stable disease.

Subgroup analysis revealed no clear heterogeneity regarding HR for PFS and OS (Fig. 3). Efficacy by primary tumour location is shown in Supplementary Table 2. The median PFS for patients with right-sided tumours was 3.8 months (95% CI, 0.8–10.5) in group A ($n = 9$) and 8.0 months (95% CI, 4.3–13.0) in group B ($n = 14$), and for those with left-sided tumours, it was 10.5 months (95% CI, 8.8–13.4) in group A ($n = 47$)

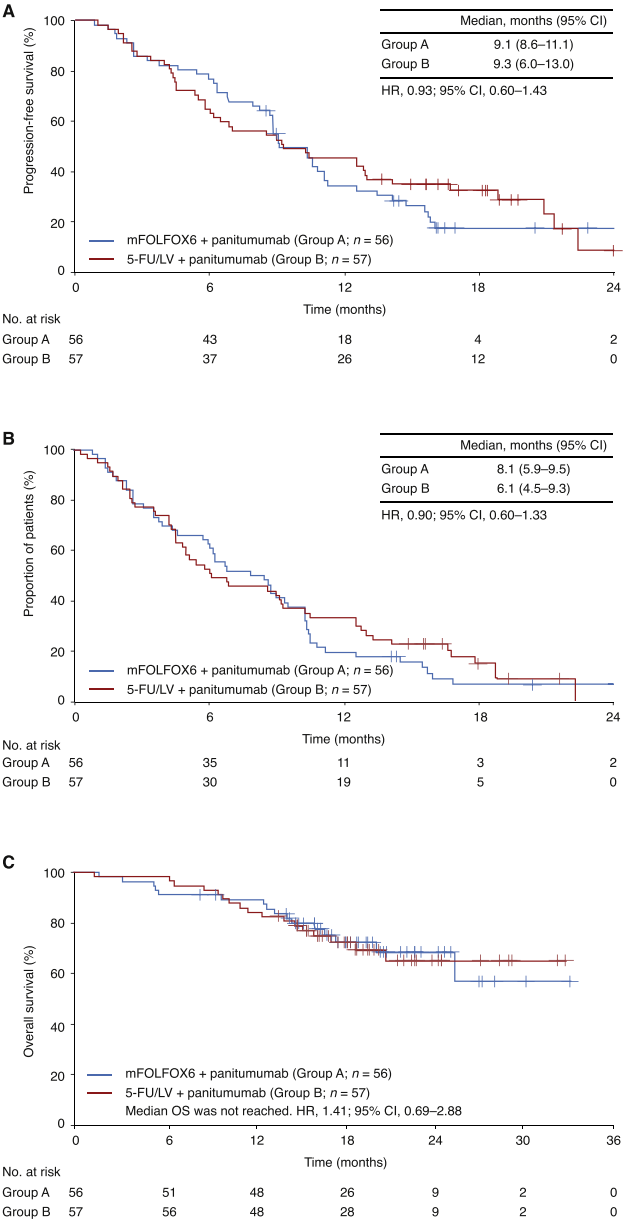

Fig. 2. Kaplan–Meier plots of (A) PFS, (B) TTF and (C) OS in patients receiving mFOLFOX6 plus panitumumab or 5-FU/LV plus panitumumab after six cycles of front-line mFOLFOX6 plus panitumumab therapy (day 0: time of randomisation; FAS). 5-FU, fluorouracil; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; LV, leucovorin; mFOLFOX6, modified FOLFOX (fluorouracil, leucovorin and oxaliplatin); OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

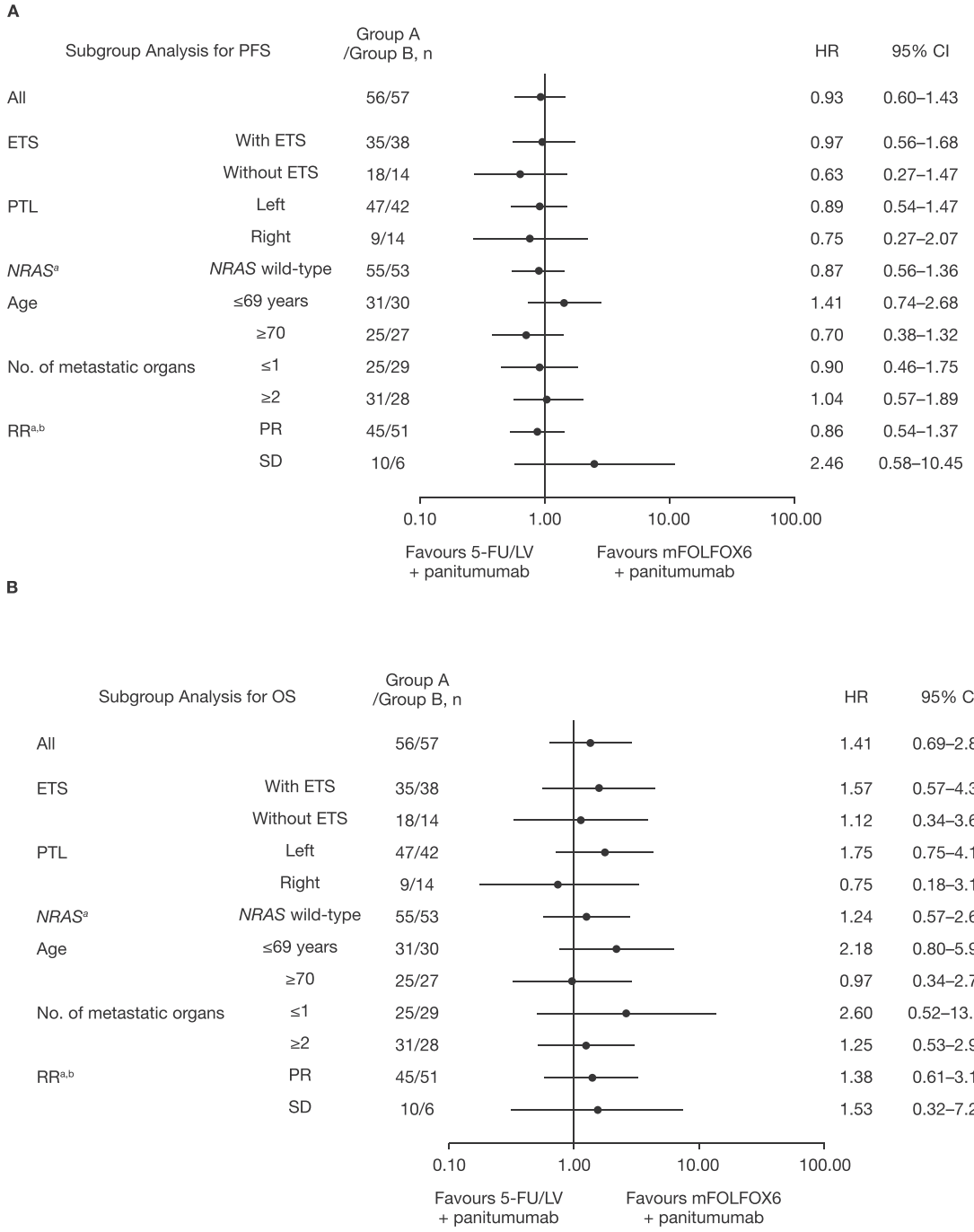

Fig. 3. Subgroup analysis for (A) PFS and (B) OS. One patient with CR was not included. [a]Patients with *NRAS* mutant status not shown owing to low numbers. RECIST evaluation at randomisation. CI, confidence interval; CR, complete response; ETS, early tumour shrinkage; HR, hazard ratio; PFS, progression-free survival; PR, partial response; PTL, primary tumour location; RECIST, Response Evaluation Criteria in Solid Tumours; RR, response rate; SD, stable disease.

and 11.5 months (95% CI, 6.0–20.8) in group B ($n = 42$) (Supplementary Fig. 2).

3.4. Safety

Frequencies of AEs after enrolment are shown in Table 3. There were no appreciable differences between groups without grade ≥2 PN. As patients who experienced grade ≥2 PN during induction therapy were not randomised, the observed incidence of grade ≥2 PN occurred after randomisation. Grade ≥2 PN was reported in 20 patients (35.7%) in group A and 5 patients (9.3%) in group B (Supplementary Fig. 3).

Table 3
AEs after enrolment in >10% of patients in either group (safety analysis set).

	Group A (n = 56)					Group B (n = 54)				
Adverse event, n (%)	All grades	G1	G2	G3	G4	All grades	G1	G2	G3	G4
Peripheral neuropathy	40 (71.4)	20 (35.7)	19 (33.9)	1 (1.8)	0 (0.0)	36 (66.7)	31 (57.4)	5 (9.3)	0 (0.0)	0 (0.0)
Paronychia	29 (51.8)	13 (23.2)	12 (21.4)	4 (7.1)	0 (0.0)	25 (46.3)	7 (13.0)	13 (24.1)	5 (9.3)	0 (0.0)
Dermatitis acneiform	25 (44.6)	9 (16.1)	14 (25.0)	2 (3.6)	0 (0.0)	19 (35.2)	7 (13.0)	10 (18.5)	2 (3.7)	0 (0.0)
Stomatitis	24 (42.9)	8 (14.3)	11 (19.6)	5 (8.9)	0 (0.0)	29 (53.7)	15 (27.8)	10 (18.5)	4 (7.4)	0 (0.0)
Neutropenia	27 (48.2)	1 (1.8)	8 (14.3)	13 (23.2)	5 (8.9)	27 (50.0)	1 (1.9)	5 (9.3)	17 (31.5)	4 (7.4)
Loss of appetite	21 (37.5)	9 (16.1)	8 (14.3)	4 (7.1)	0 (0.0)	13 (24.1)	6 (11.1)	4 (7.4)	3 (5.6)	0 (0.0)
Malaise	20 (35.7)	8 (14.3)	12 (21.4)	0 (0.0)	0 (0.0)	13 (24.1)	8 (14.8)	5 (9.3)	0 (0.0)	0 (0.0)
Diarrhoea	16 (28.6)	6 (10.7)	6 (10.7)	4 (7.1)	0 (0.0)	7 (13.0)	5 (9.3)	0 (0.0)	2 (3.7)	0 (0.0)
Skin dryness	15 (26.8)	11 (19.6)	4 (7.1)	0 (0.0)	0 (0.0)	16 (29.6)	13 (24.1)	2 (3.7)	1 (1.9)	0 (0.0)
Hypomagnesemia	15 (26.8)	5 (8.9)	1 (1.8)	8 (14.3)	1 (1.8)	19 (35.2)	5 (9.3)	5 (9.3)	7 (13.0)	2 (3.7)
Dysgeusia	14 (25.0)	11 (19.6)	3 (5.4)	0 (0.0)	0 (0.0)	10 (18.5)	8 (14.8)	2 (3.7)	0 (0.0)	0 (0.0)
Nausea	14 (25.0)	10 (17.9)	4 (7.1)	0 (0.0)	0 (0.0)	14 (25.9)	11 (20.4)	3 (5.6)	0 (0.0)	0 (0.0)
Rash	13 (23.2)	8 (14.3)	3 (5.4)	2 (3.6)	0 (0.0)	14 (25.9)	4 (7.4)	6 (11.1)	4 (7.4)	0 (0.0)
Skin toxicity	12 (21.4)	2 (3.6)	4 (7.1)	6 (10.7)	0 (0.0)	9 (16.7)	2 (3.7)	5 (9.3)	2 (3.7)	0 (0.0)
Leukocytopenia	14 (25.0)	0 (0.0)	10 (17.9)	3 (5.4)	1 (1.8)	20 (37.0)	0 (0.0)	11 (20.4)	9 (16.7)	0 (0.0)
Palmar/plantar dysesthesia	8 (14.3)	4 (7.1)	4 (7.1)	0 (0.0)	0 (0.0)	13 (24.1)	3 (5.6)	8 (14.8)	2 (3.7)	0 (0.0)
Vomiting	8 (14.3)	4 (7.1)	3 (5.4)	1 (1.8)	0 (0.0)	4 (7.4)	3 (5.6)	0 (0.0)	1 (1.9)	0 (0.0)
Fatigue	8 (14.3)	5 (8.9)	0 (0.0)	3 (5.4)	0 (0.0)	6 (11.1)	4 (7.4)	2 (3.7)	0 (0.0)	0 (0.0)
Fever	7 (12.5)	5 (8.9)	2 (3.6)	0 (0.0)	0 (0.0)	6 (11.1)	5 (9.3)	1 (1.9)	0 (0.0)	0 (0.0)
Thrombocytopenia	7 (12.5)	2 (3.6)	4 (7.1)	1 (1.8)	0 (0.0)	5 (9.3)	3 (5.6)	2 (3.7)	0 (0.0)	0 (0.0)
Hypersensitivity	6 (10.7)	2 (3.6)	3 (5.4)	1 (1.8)	0 (0.0)	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	6 (11.1)	1 (1.9)	2 (3.7)	3 (5.6)	0 (0.0)

AE, adverse event; G, grade.

4. Discussion

SAPPHIRE is the first randomised trial to evaluate the planned discontinuation of oxaliplatin treatment after mFOLFOX plus anti-EGFR antibody. The results of this study indicate that the planned discontinuation of oxaliplatin treatment reduced PN without any reduction in efficacy.

Several studies have evaluated cetuximab or panitumumab as monotherapy or combined with 5-FU/LV as maintenance therapy after oxaliplatin-based chemotherapy plus anti-EGFR antibody as induction therapy. The MACRO-2 study showed that cetuximab monotherapy as maintenance after induction with eight cycles of mFOLFOX6 plus cetuximab resulted in similar efficacy, yet reduced incidence of neuropathy compared with continued mFOLFOX6 plus cetuximab [15]. However, the VALENTINO study, comparing panitumumab monotherapy or 5-FU/LV plus panitumumab after eight cycles of induction therapy with FOLFOX plus panitumumab, showed that monotherapy was inferior in terms of 10-month PFS rates [16]. Similarly, a recent retrospective analysis of the PEAK and PRIME studies showed that maintenance with panitumumab plus 5-FU/LV after 11–12 cycles of an oxaliplatin-containing regimen was well tolerated and may be associated with better outcomes than strategies not containing panitumumab [17]. Thus, anti-EGFR antibody monotherapy may not be a suitable treatment option after oxaliplatin-based induction chemotherapy regarding efficacy. Our results suggest that maintenance therapy with 5-FU/LV plus panitumumab could be a more useful option regarding efficacy and safety than continued oxaliplatin treatment after six cycles of FOLFOX plus panitumumab, despite a relatively shorter induction duration and lower cumulative oxaliplatin dose than previous studies. The median duration of oxaliplatin treatment in the present study was 6.8 months, including the 3-month induction period, and the median cumulative dose of oxaliplatin was 813 mg/m^2 in group A, which was similar to other studies [1,15].

In patients receiving chemotherapy plus an EGFR antibody, those with left-sided tumours are reported to have superior OS, PFS and RR than those with right-sided tumours [18,19]. Although a limited number of patients were evaluated in our study, patients with left-sided tumours also had superior PFS and RR. In addition, subgroup analysis in our study suggested that the planned discontinuation of oxaliplatin did not affect efficacy in patients with left- or right-sided tumours.

There are several limitations in the present study that warrant mention. First, the present study was designed to be a non-definitive screening comparison of an experimental treatment regimen against a randomised standard-treatment control arm [20]. It was not designed to show non-inferiority of group B to group A as the primary end-point. For primary end-point analysis, the threshold PFS rate at 9 months for futility of 30% was based on a phase II single-stage design [4,21]. However, both groups A and B exceeded the 30% threshold and exploratory statistical analysis suggested a similar level

of efficacy in both groups A and B, as shown in the equivalent HR for PFS. We therefore consider 5-FU/LV plus panitumumab to be a promising regimen. Second, the follow-up period was not long, and the OS data were immature. In addition, patients with *BRAF* mutations were not examined in this study. However, as the population of patients with mCRC and *BRAF* mutations in Japan has been reported as 5.4% [22], the proportion of these patients was also low in the present study. Given that the present study was randomised, we consider the impact of patients with mCRC and *BRAF* mutations on the outcome of each group to be equivalent.

In conclusion, the SAPPHIRE study showed that the planned discontinuation of oxaliplatin treatment after six cycles of mFOLFOX6 plus panitumumab is a potential treatment option in patients with mCRC. Further investigation should help validate the non-inferiority of oxaliplatin discontinuation after mFOLFOX6 plus anti-EGFR antibody as induction therapy for patients with mCRC. A phase II study of maintenance therapy with 5-FU/LV plus panitumumab versus 5-FU/LV alone after FOLFOX plus panitumumab in patients with mCRC (PanaMa; NCT01991873) is underway, which will help inform the results of the present study.

Author contributions

N.N., J.S., H.M., K.O., S.K. and T.M. were involved in the study concept and study design. N.N., J.S., H.M., Y.M., M.N., M.T., M.K., H.K., T.K., N.M., S.N., M.F., H.K., T.T., T.T., K.M. and H.S. were involved in data acquisition. N.N., J.S., H.M., K.O., S.K. and T.M. were involved in quality control of data and algorithms. K.O. conducted statistical analysis. N.N., J.S., H.M., K.O., Y.M., S.K. and T.M. contributed to manuscript preparation. All authors contributed to data analysis, data interpretation, manuscript editing and manuscript review and approved the final manuscript.

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Conflict of interest statement

M.N. has received honoraria from Takeda Pharmaceutical Co., Ltd., Merck & Co., Inc., Chugai Pharmaceutical Co., Ltd., Bayer AG, Taiho Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Eli Lilly and Company and Sanofi SA. M.T. attended a speakers bureau for Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd. and Eli Lilly and Company. M.T. reports compensation for travel/accommodation/expenses from Takeda Pharmaceutical Co., Ltd. M.K. has received honoraria from Chugai Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Takeda Pharmaceutical Co., Ltd. and Eli Lilly and Company. T.K. has received honoraria from Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Bayer AG, Eli Lilly and Company, Yakult Honsha Co., Ltd. and Sanofi SA. T.K. declares funding from Chugai Pharmaceutical Co., Ltd. T.Ta. has received honoraria from Takeda Pharmaceutical Co., Ltd. H.S. has received honoraria from Bayer AG, Chugai Pharmaceutical Co., Ltd., Eli Lilly and Company, Merck KGaA, Merck Sharp & Dohme Limited, Takeda Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd. and Yakult Honsha Co., Ltd. S.K. and T.M. are employed by Takeda Pharmaceutical Co., Ltd. H.M. has received honoraria from Takeda Pharmaceutical Co., Ltd. and Chugai Pharmaceutical Co., Ltd. H.M. declares funding from Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Daiichi Sankyo Pharmaceutical Co., Ltd. and Ono Pharmaceutical Co., Ltd. J.S. has received honoraria from Chugai Pharmaceutical Co., Ltd., Tsumura Co., Ltd. and Nihon Kayaku Co., Ltd. J.S. has also received a consultancy fee from Takeda Pharmaceutical Co., Ltd. K.O. has received honoraria from Eisai Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Pharmaceutical Co., Ltd. and Asahi Kasei Pharma Corp. K.O. has also received a consultancy fee from Takeda Pharmaceutical Co., Ltd. and Ono Pharmaceutical Co., Ltd. All remaining authors have declared no conflicts of interest.

Data sharing statement

Takeda makes patient-level, de-identified data sets and associated documents available after applicable marketing approvals and commercial availability have been received, an opportunity for the primary publication of the research has been allowed and other criteria have been met as set forth in Takeda's Data Sharing Policy (see https://www.takedaclinicaltrials.com for details). To obtain access, researchers must submit a legitimate academic research proposal for adjudication by an independent review panel, who will review the scientific merit of the research and the requestor's qualifications and conflict of interest that can result in potential bias. Once approved, qualified researchers who sign a data sharing agreement are provided access to these data in a secure research environment.

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Appendix A. Supplementary data

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