FUTURE ONCOLOGY
2025, VOL. 21, NO. 17, 2135–2141
https://doi.org/10.1080/14796694.2025.2514935

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CLINICAL TRIAL PROTOCOL

A multicenter Phase II study of mFOLFOX6 plus nivolumab for gastric cancer with severe peritoneal metastases: WJOG16322G

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ABSTRACT

Advanced gastric cancer (AGC) patients with severe peritoneal metastases (SPM), characterized by massive ascites and/or inadequate oral intake, have a poor prognosis with the median overall survival of around 7 months, even when treated with fluorouracil/l-leucovorin plus oxaliplatin (mFOLFOX6), despite being a treatment options for these patients demonstrated in the WJOG10517G study. However, these patients were excluded from pivotal Phase III trials, including the CheckMate 649 study, which demonstrated the benefit of adding nivolumab to mFOLFOX6, due to tumor-related complications. Given the lack of data on the efficacy and safety of combining nivolumab with mFOLFOX6 for AGC patients with SPM, we initiated a Phase II study to evaluate this combination. The primary endpoint was the 1-year survival rate.

Clinical trial registration: Japan Registry of Clinical Trials (jRCTs) 041220164.

ARTICLE HISTORY
Received 22 December 2024
Accepted 30 May 2025

KEYWORDS
Gastric cancer; severe peritoneal metastases; massive ascites; inadequate oral intake; mFOLFOX6 plus nivolumab

1. Background and rationale

Palliative chemotherapy is the standard treatment for patients with advanced gastric cancer (AGC). The addition of nivolumab to 5-fluorouracil/l-leucovorin (FL) plus oxaliplatin (mFOLFOX6) is one of the standard first-line treatment for patients with human epidermal growth factor receptor 2 (HER2)-negative AGC, as demonstrated in the CheckMate 649 study. This trial showed that chemotherapy combined with nivolumab significantly improved median overall survival (OS) compared to chemotherapy alone (13.8 months vs. 11.6 months; hazard ratio [HR] 0.80; $p < 0.001$) [1].

Peritoneal metastases are the most common metastatic pattern in patients with AGC and often lead to complications such as ascites, bowel obstruction, and paralytic ileus. Among them, AGC patients with severe peritoneal metastases (SPM), defined as massive ascites and/or inadequate oral intake due to peritoneal metastases, account for 3%–10% of AGC patients. These patients have a significantly poorer prognosis than AGC patients without SPM [2,3] and were excluded from pivotal Phase III trials, including CheckMate 649, due to tumor-related complications.

To address this unmet need, alternative treatments for AGC patients with SPM have been investigated in separate clinical trials. The JCOG1108/WJOG7312G study compared FL with FL plus paclitaxel (FLTAX) as first-line treatment in this setting. Although FLTAX did not demonstrate superiority over FL in terms of OS (7.3 months vs. 6.1 months; $p = 0.14$) [2]. However, FLTAX was considered as a preferred regimen because of the longer progression-free survival (PFS) (5.4 months vs 1.9 months; HR 0.64; $p = 0.03$), acceptable toxicity, and a favorable quality of life. The WJOG10517G study evaluated the efficacy and safety of mFOLFOX6 for AGC patients with SPM. The median OS of 7.4 months was comparable to FLTAX, with additional benefits including an oral intake improvement rate of 46% and a 30% reduction in ascites [4,5], suggesting that mFOLFOX6 was one of the treatment options for AGC patients with SPM. A retrospective cohort study reported no ≥grade 3 adverse events in 22 AGC

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Article highlights

Background and rationale
- Advanced gastric cancer (AGC) patients with severe peritoneal metastases (SPM), defined by massive ascites and/or inadequate oral intake, have been excluded from pivotal clinical trials.
- mFOLFOX6 is one of the standard treatments for AGC patients with SPM according to the WJOG10517 study, but their prognosis remains poor.
- Adding nivolumab to mFOLFOX6 as a first-line therapy which is standard treatment for AGC patients without SPM could potentially contribute to improved survival in this setting because the rate of receiving third-line therapy in this setting was only 35%.

Design
- This is a multicenter, open-label, single-arm Phase II study to evaluate the efficacy and safety of mFOLFOX6 plus nivolumab in AGC patients with SPM.
- Eligible patients included those with no prior chemotherapy for AGC with SPM, an ECOG PS of 0–2, and adequate organ function.
- Patients with ECOG PS of 2 who have both massive ascites and inadequate oral intake were excluded.
- The primary endpoint was the 1-year survival rate.
- We calculated a sample size of 55, with a 1-year survival rate of 41% deemed promising and 29% deemed unacceptable (one-sided $\alpha = 0.1$; $\beta = 0.3$).
- QOL will be measured using the ePRO, and data on PD-L1 CPS, CLDN 18.2 IHC positive rate, FGFR2b IHC positive rate, MSI-H rate, and NGS-based CGP will be collected.

patients with SPM treated with nivolumab monotherapy as a fifth-line or later treatment [6], suggesting that nivolumab may be safe in this population.

Based on these findings, we initiated a multicenter Phase II study (WJOG16322G) to evaluate the efficacy and safety of mFOLFOX6 combined with nivolumab in AGC patients with SPM. A randomized controlled trial was determined not to be feasible in this setting because AGC with SPM is a rare fraction with 3–10% of AGC patients [2,3], and the presence of a standard treatment arm that did not include nivolumab would further reduce the feasibility of the trial because nivolumab is approved for AGC. WJOG16322G study is the first phase II trial to evaluate the efficacy and safety of mFOLFOX6 plus nivolumab in this setting with exploratory.

2. Methods

2.1. Study design

This multicenter, open-label, single-arm Phase II study evaluates the efficacy and safety of mFOLFOX6 plus nivolumab in patients with AGC and SPM (Figure 1). The study was conducted in compliance with the Clinical Trials Act in Japan and the Declaration of Helsinki. Additionally, it was approved by the Certified Review Board of Aichi Cancer Center Hospital (CRB4200002). Written informed consent was obtained from all participants prior to enrollment. The trial has been registered with the Japan Registry of Clinical Trials (clinical trial identifier: jRCTs041220164).

2.2. Eligibility criteria

Patients with no prior chemotherapy for AGC with SPM, an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0–2, and adequate organ function were eligible for this study. SPM was defined as massive ascites and/or inadequate oral intake due to peritoneal metastases. Patients with an ECOG PS of 2 who presented with both massive ascites and inadequate oral intake simultaneously were excluded. Peritoneal metastasis was defined based on the following criteria: induration detected by digital rectal

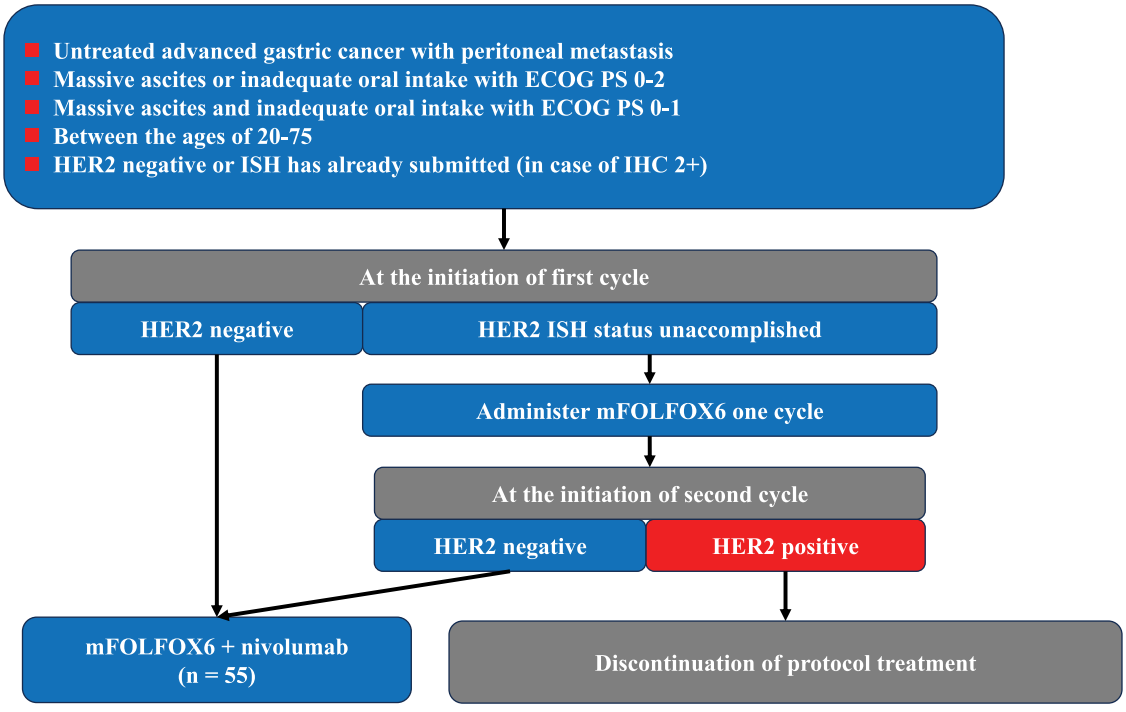

Figure 1. Study design.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, In situ hybridization.

examination; gastrointestinal stenosis or obstruction confirmed by gastrointestinal series; peritoneal nodules, ascites, hydronephrosis, or obstruction of the extrahepatic bile duct (not attributable to other causes) identified on computed tomography (CT) and pathologically confirmed peritoneal metastases by exploratory surgery.

Massive ascites was defined as continuous ascites spreading throughout the abdominal cavity, as detected on CT. Inadequate oral intake was defined as the requirement for daily intravenous infusion to maintain hydration and nutrition due to symptoms such as nausea or vomiting caused by peritoneal metastases (not pyloric stenosis). These definitions aligned with those used in the JCOG1108/WJOG7312G [2] and WJOG10517G studies [4]. Additional inclusion and exclusion criteria are provided in Table 1.

2.3. Study period

Patient enrollment began in March 2023 and is ongoing. Enrollment will continue until March 2025, covering a 24-month enrollment period. A 12-month follow-up period will be conducted after the last patient is enrolled.

2.4. Study procedures

The mFOLFOX6 plus nivolumab regimen consisted of 240 mg/body of nivolumab followed by 85 mg/m^2 of oxaliplatin and 200 mg/m^2 of l-leucovorin (l-LV) administered simultaneously as a 2-hours intravenous infusion. Subsequently, a 400 mg/m^2 bolus of 5-FU and a 2400 mg/m^2 continuous infusion of 5-FU over 46 h were administered, repeated every 2 weeks. No other anticancer agents were allowed as protocol treatment even if the clinical benefit of drugs such as intraperitoneal chemotherapy, was reported. Adverse events will be graded according to CTCAE version 5.0. The criteria for initiating, reducing the dose or discontinuing mFOLFOX6 are listed in Tables 2 and 3. The criteria for initiating, reintroducing, or discontinuing of nivolumab is listed in Table 4. Protocol treatment will continue until any of the following courses: disease progression, death, patient withdrawal of consent, or unacceptable toxicity.

2.5. Outcome measures/endpoints

The primary endpoint was the 1-year survival rate. The secondary endpoints include PFS, OS, response rate (RR), disease

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	
1)	Written informed consent
2)	Age: between 20 and 75 years
3)	Histologically confirmed adenocarcinoma
4)	HER2-negative or HER2 IHC 2+ with incomplete or unaccomplished ISH results*
5)	Unresectable or recurrent gastric cancer with peritoneal metastasis
6)	Patients without symptomatic brain or spinal cord metastasis or meningeal dissemination
7)	No pleural effusion needed to be removed
8)	No fistula between the tumor and other organs
9)	Measurable or nonmeasurable disease
10)	No previous chemotherapy for gastric cancer
11)	No prior use of oxaliplatin
12)	No prior use of anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibodies
13)	i) Patients with a performance status (PS) of 0–2 who have massive ascites or inadequate oral intake ii) Patients with PS 0–1 who have massive ascites and inadequate oral intake
14)	Adequate organ function i) Neutrophil count ≥ 1,500/mm^3 ii) Hemoglobin ≥8.0 g/dl iii) Platelet count ≥ 100,000/mm^3 iV) Total bilirubin ≤1.5 mg/dl V) AST and ALT ≤ 100 or ≤ 200 IU/l in the case of liver metastasis Vi) Serum creatinine ≤1.5 mg/dl or calculated or measured creatinine clearance ≥20 mL/min
Exclusion criteria	
1)	HER2-positive*
2)	Patients with synchronous or metachronous multiple primary cancer with a disease-free period of ≤2 years at registration
3)	Patients who require systemic therapy including corticosteroids >10 mg/day or other immunosuppressants within 14 days before registration.
4)	Patients with infection that should be treated
5)	Psychiatric disease that is inappropriate for study enrollment
6)	History of any medical condition such as; • Renal insufficiency • Liver insufficiency/Liver cirrhosis • Interstitial pneumonitis • Autoimmune disease requiring treatment • Myocardial infarction within the last 6 months or unstable angina pectoris within the last 3 weeks • Hepatitis B Surface antigen (HBs-Ag): positive • Grade 2 or more peripheral sensory neuropathy • Severe complications that investigators judge
7)	Severe hypersensitivity
8)	Pregnant or lactating female
9)	Patients whom the investigators deem inappropriate for study participation

*Patients with HER2 immunohistochemistry (IHC) 2+ and unaccomplished HER2 *In situ* hybridization (ISH) could be registered in this study and mFOLFOX6 was administered one cycle. Of these patients, protocol treatment was terminated if the HER2 ISH status turned to be positive.

Table 2. Initiation criteria for mFOLFOX6 and oxaliplatin.

Initiation criteria of mFOLFOX6 (necessary to meet all criteria)	
Neutrophil count	≥1,200/mm^3
Platelet count	≥75,000/mm^3
Total bilirubin	≤2.0 mg/dl
AST (GOT)	≤100 or ≤ 200 IU/l in the case of liver metastasis
ALT (GPT)	≤100 or ≤ 200 IU/l in the case of liver metastasis
Serum creatinine	≤1.5 mg/dl or calculated or measured creatinine clearance ≥20 mL/min
Fever induced by infection, pneumonitis, FN	No evidence of infection causing fever
Diarrhea, mucositis, HFS	≤Grade 1
Initiation criteria for oxaliplatin (necessary to meet all criteria)	
Peripheral sensory or motor neuropathy	≤Grade 1
Allergic reaction	≤Grade 2 (at the prior administer)

Table 3. Dose reduction and discontinuation criteria for mFOLFOX6.

Adverse events (at any time of the previous course)		Fluorouracil (5-FU)	Oxaliplatin
Neutrophil count	<500/mm^3	−1 level	−1 level
	<1000/mm^3 lasting for ≥7 days	−1 level	−1 level
Platelet count	<2.5 × 10^4/mm^3	−1 level	−1 level
	<5 × 10^4/mm^3 lasting for ≥7 days	−1 level	−1 level
FN, diarrhea	Grade 3	−1 level	−1 level
Mucositis, Hand-Foot syndrome	Grade 3	−1 level	–
Allergic reaction	Grade 3	–	Discontinuation
	Grade 1–2	–	Continuation under the reinforcement of prophylaxis for the first time, discontinuation from the second time
Peripheral sensory or motor neuropathy	Grade 2–3	–	Postponement
Pneumonitis	Grade 2	Discontinuation	Discontinuation
Postponement ≥15 days due to ineligibility of the initiation criteria		−1 level	−1 level
Investigator's judgment for dose-reduction or discontinuation necessity		Reduction or discontinuation	Reduction or discontinuation

Table 4. Initiation, reintroduction, and discontinuation criteria for nivolumab.

Immune-related adverse events (including causal relationship with nivolumab)	Initiation criteria (necessary to meet all criteria)	Reintroduction criteria (necessary to meet all criteria)	Discontinuation criteria (necessary to meet any of criteria)
Dermatologic toxicities	≤Grade 2	≤Grade 2	≥Grade 4
Pulmonary toxicities	no evidence	no evidence	≥Grade 1
Hepatitis	≤Grade 1	≤Grade 1	≥Grade 3
Serum amylase/lipase increase	asymptomatic and ≤Grade 3	asymptomatic and ≤Grade 3	symptomatic
Diarrhea or colitis	≤Grade 1	≤Grade 1	≥Grade 3
Serum creatinine increase	≤Grade 1	–	≥Grade 2
Nerve or muscle disorder	≤Grade 1	–	≥Grade 2
Arthritis	≤Grade 1	–	≥Grade 3
Diabetes mellitus	well-controlled blood sugar levels with insulin therapy	improved blood sugar by insulin	–
Hypopituitarism or hypoadrenocorticism	asymptomatic and ≤Grade 2	improvement of symptoms by hormone replacement therapy	≥Grade 4
Thyroid dysfunction	asymptomatic and ≤Grade 2	improvement of symptoms by hormone replacement therapy	–
Eye disorder	≤Grade 1	–	≥Grade 2
Infusion reaction	≤Grade2 (at the prior administration)	-	≥Grade 3
Cardiovascular toxicities (myocarditis, etc)	no evidence	–	≥Grade 1
Other adverse events	≤Grade 2	≤Grade 1	≥Grade 3
Postponement of the administration	–	–	≥6 weeks

control rate (DCR), ascites response rate, ascites control rate, and ascites drainage-free survival among patients with ascites at enrollment. Additionally, the rate of improvement in oral intake among patients with inadequate oral intake at enrollment, incidence of adverse events, dose intensity, and time to treatment failure (TTF) will also be assessed. Moreover, we will evaluate the efficacy according to the Response Evaluation Criteria in Solid Tumors version 1.1, using CT scans conducted every 8 weeks after the initiation of protocol treatment. The RR will be calculated as the proportion of patients achieving a complete response (CR) or partial response (PR) among those with at least one measurable lesion.

We defined OS as the period from registration to death from any cause, with censoring on the last day the patient is confirmed to be alive. PFS was defined as the period from registration to disease progression or death from any cause,

with censoring on the last day the patient is alive without progression. TTF was defined as the period from registration to treatment discontinuation or death from any cause, with censoring on the last day the patient is alive without treatment discontinuation. Ascites drainage-free survival was defined as the period from registration to the date of drainage, cell-free and concentrated ascites reinfusion, or death from any cause.

Improvement in oral intake was defined as maintaining sufficient oral intake for ≥7 days without the need for daily intravenous drip infusion. Ascites levels were categorized by CT as follows: massive (continuous ascites from the pelvic cavity to the upper abdomen), moderate (not massive or mild ascites), mild (ascites limited to the pelvic cavity or upper abdomen), or no detectable ascites. The ascites response, based on CT scans, was defined as follows: CR (disappearance of ascites), PR (decreased levels of ascites), SD (same level of ascites as before treatment), and progressive disease (increased levels of ascites or drainage frequency). These definitions align with those used in the JCOG1108/WJOG7312G study [2] and the WJOG10517G study [4].

All patient data is collected through electronic data capture from each institution at the West Japan Oncology Group Data Center. Researchers will analyze the clinical data from the database.

We plan to compare the outcomes of mFOLFOX6 in the WJOG10517G study with those of mFOLFOX6 plus nivolumab in this study, using individual patient data to evaluate which regimen would be the better for this setting.

2.6. Quality of Life measurement

In this study, quality of Life (QOL) will be assessed using electronic Patient Reported Outcomes (ePRO) via SmartPRO®, developed by NTT Communications Corporation. The QOL assessment includes a brief questionnaire related to adverse events and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

2.7. Translational research

No study has investigated the programmed cell death ligand 1 (PD-L1) comprehensive positive score (CPS), Claudin 18.2 (CLDN18.2) immunohistochemistry (IHC) positive rate, Fibroblast Growth Factor Receptor 2b (FGFR2b) IHC positive rate, microsatellite instability-high (MSI-H) rate, and gene alterations identified by comprehensive genomic profiling (CGP) in AGC patients with SPM.

We will collect 35 unstained specimens thinly sliced at a thickness of 4 µm from FFPE blocks per one patient after completion of enrollment. We will assess the PD-L1 CPS, CLDN 18.2 IHC positive rate, FGFR2b IHC positive rate, and MSI-H rate using the Dako PD-L1 immunohistochemistry, VENTANA CLDN18 [43-14A] Assay, VENTANA FGFR2b (FPR2-D) mouse monoclonal antibody, and the MSI-IVD Kit (FALCO), respectively. PD-L1 CPS scores have shown association with clinical benefits from the addition of nivolumab to chemotherapy [1]. We will plan subgroup analysis of clinical outcomes including ORR, OS and PFS by those four biomarkers including PD-L1 CPS scores.

NGS-based CGP using the Oncomine Comprehensive Assay v3 (OCAv3, Thermo Fisher Scientific) is planned to identify druggable gene alterations in this context, with the goal of advancing gene-based precision medicine. The OCAv3 can detect 161 cancer-related genes, including 87 genes with hotspot alterations, 43 genes with focal copy number variations, and 51 gene-fusion drivers, by analyzing formalin-fixed paraffin-embedded samples. Through this NGS-based CGP, we will investigate specific genetic abnormalities in AGC with SPM compared to AGC without SPM, aiming to develop advanced treatment strategies for this patient population.

CLDN18.2 is the new biomarker strongly recommended to be tested in AGC treatment before initiating first-line therapy according to the SPOTLIGHT study [7] and the GLOW study [8]. The prevalence of CLDN 18.2 positivity was reported as 48.3% among diffuse-type AGC patients based on an integrated analysis of the two studies [9]. If the CLDN18.2 positivity rate in this setting is high, there could be potential for future clinical trials to evaluate the efficacy and safety of mFOLFOX6 plus zolbetuximab for this setting.

3. Statistics

The 1-year survival rate for AGC patients with SPM treated using mFOLFOX6 was 29% [5]. This was considered a treatment benchmark when planning this study, and thus, we set a threshold 1-year survival rate of 29%.

The rate of receiving third-line therapy in this setting was only 35% [5]. However, in a real-world population treated at Aichi Cancer Center Hospital from January 2008 to February 2011, prior to the availability of nivolumab in clinical practice, the rate was 52.2% [10]. This discrepancy can be attributed to the following reasons: first, AGC patients with SPM often experience tumor-related complications, such as ileus and/or inadequate oral intake, leading to poor performance status and clinical challenges in continuing chemotherapy; second, the number of available treatment options is limited due to massive ascites and/or the inability to tolerate oral intake.

Adding nivolumab to mFOLFOX6 at a first-line therapy might improve survival in this setting, as the proportion of patients able to receive nivolumab would increase from 35% or less to 100% in AGC patients with SPM, and from 52.2% or less to 100% in AGC patients without SPM.

Based on the CheckMate 649 study, the HR of mFOLFOX6 plus nivolumab compared to mFOLFOX6 alone at 1 year on the survival curve of the intent-to-treat (ITT) analysis was 0.80. In this study setting, where patients would be expected to benefit from the additive effect of nivolumab, the estimated HR at 1 year was calculated as 0.72. Therefore, the expected 1-year survival rate in this study was 41%.

Accordingly, we calculated a sample size of 55, with a 1-year survival rate of 41% considered promising and 29% deemed unacceptable (one-sided $\alpha = 0.1$; $\beta = 0.3$). Efficacy will be mainly assessed in the full-analysis set (all registered patients, excluding those found to be ineligible after

registration). Safety will be evaluated in the safety population, defined as all patients who received at least one dose of study drugs (nivolumab, oxaliplatin, l-LV, and 5-FU). OS, PFS, TTF, and ascites drainage-free survival will be determined, with their median values estimated using the Kaplan – Meier method. Confidence intervals will be calculated using the Brookmeyer – Crowley method. RR, DCR, rate of improvement in oral intake, ascites response and control rates, and incidence of adverse events with confidence intervals will be calculated based on the underlying binomial distribution.

4. Limitations

This is a single-arm phase II study and the number of planned enrollment patients is limited to only 55 patients. Therefore, rigid conclusions will not be able to be drawn from the results of our study. The rate of prognostic factors cannot be adjusted to those of historical controls, and those unbalanced prognostic factors between this study and historical controls may limit comparability.

5. Ethics and dissemination

The authors state that they have obtained appropriate central review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

6. Conclusion

The WJOG16322G study is the first Phase II trial to evaluate the efficacy and safety of mFOLFOX6 combined with nivolumab in AGC patients with SPM. We expect that our findings will contribute to improving the prognosis for patients in this setting.

Acknowledgments

We wish to thank the member of the West Japan Oncology Group Data Center and Support Office for editing the protocol.

Disclosure statement

Munehiro Wakabayashi reports honoraria from Daiichi-Sankyo Co., Ltd, Ono Pharmaceutical Co., Ltd. Toshiki Masuishi reports honoraria from Bayer Yakuhin Co., Ltd, Bristol-Myers Squibb Co., Ltd, Chugai Pharmaceutical Co., Ltd, Daiichi-Sankyo Co., Ltd, Eli Lilly Co., Ltd, Merck Serono Co., Ltd, Ono Pharmaceutical Co., Ltd, Sanofi Co., Ltd, Taiho Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Yakult Honsha Co., Ltd, MSD Co., Ltd, Takata Co., Ltd, Astellas Co., Ltd, Guardant Health Co., Ltd, and Nippon Kayaku Co., Ltd, and research funding from Amgen Co., Ltd, Boehringer Ingelheim Co., Ltd, CMIC Co., Ltd, Daiichi-Sankyo Co., Ltd, Eli Lilly Japan Co., Ltd, MSD Co., Ltd, Novartis Co., Ltd, Ono Pharmaceutical Co., Ltd, Pfizer Co., Ltd, Syneos Health Co., Ltd. Takatsugu Ogata reports honoraria from Ono Pharmaceutical Co., Ltd, Bristol-Myers Squibb Co., Ltd, Taiho Pharmaceutical Co., Ltd, MSD Co., Ltd, Astellas Pharmaceutical Co., Ltd. Fumiyasu Hanamura reports honoraria from Daiichi-Sankyo Co., Ltd, Taiho Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, MSD Co., Ltd, and consulting or advisory role in Daiichi-Sankyo Co., Ltd. Mitsuhiro Furuta reports honoraria from Astellas Pharmaceutical Co., Ltd, Bristol-Myers Squibb Co., Ltd, Eli Lilly Co., Ltd, Merck Bio Pharma Co., Ltd, Ono Pharmaceutical Co., Ltd. Hidekazu Hirano reports honoraria from Novartis Co., Ltd, Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Bristol-Myers Squibb Co., Ltd, and research funding from PPD, Daiichi-Sankyo Co., Ltd, Nippon Boehringer Ingelheim Co., Ltd, ALX Oncology Co., Ltd, BeiGene Co., Ltd, Novartis Co., Ltd, Amgen Co., Ltd, Bristol-Myers Squibb Co., Ltd, Taiho Pharmaceutical Co., Ltd. Yosuke Kito reports honoraria from Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Daiichi-Sankyo Co., Ltd, Chugai Pharmaceutical Co., Ltd. Naoki Izawa reports honoraria from Taiho Pharmaceutical Co., Ltd, Bristol-Myers Squibb Co., Ltd, Daiichi-Sankyo Co., Ltd, MSD Oncology Co., Ltd, Sysmex Co., Ltd, AstraZeneca Co., Ltd, Nippon Kayaku Co., Ltd, Merck Serono Co., Ltd, and research funding from Taiho Pharmaceutical Co., Ltd. Naoki Takahashi reports honoraria from Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Bristol-Myers Squibb Co., Ltd. Toshihiko Matsumoto reports honoraria from Bayer Co., Ltd, Bristol-Myers Squibb Co., Ltd, Chugai Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, Eli Lilly Japan Co., Ltd, Merck Bio Pharma Co., Ltd, MSD Co., Ltd, Ono Pharmaceutical Co., Ltd, Sanofi Co., Ltd, Taiho Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Astellas Pharmaceutical Co., Ltd and Yakult Honsha Co., Ltd, and research funding from Daiichi Sankyo Co., Ltd, Astellas Pharmaceutical Co., Ltd, Sanofi Co., Ltd. Hisato Kawakami reports honoraria from Bristol-Myers Squibb Co., Ltd, Ono Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, MSD Co., Ltd, Taiho Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Novartis Co., Ltd, Astellas Pharmaceutical Co., Ltd and research funding from Daiichi Sankyo Co., Ltd, Astellas Pharmaceutical Co., Ltd, Eisai. Co., Ltd, Bristol-Myers Squibb Co., Ltd, Kobayashi Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd. Takayuki Ando reports honoraria from Daiichi Sankyo Co., Ltd, Eli Lilly Japan Co., Ltd, Bristol-Myers Squibb Co., Ltd, Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, MSD Co., Ltd, Astellas Pharmaceutical Co., Ltd. Keiko Minashi reports research funding from Astellas Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Amgen Co., Ltd, Daiichi Sankyo Co., Ltd, MSD Co., Ltd, PPD-SNBL K.K. Kei Muro reports honoraria from MSD Co., Ltd, Bristol-Myers Squibb Co., Ltd, Ono Pharmaceutical Co., Ltd, Eli Lilly Co., Ltd, Takeda Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, Taiho Pharmaceutical Co., Ltd, and research funding from Astellas Pharmaceutical Co., Ltd, Amgen Co., Ltd, Sanofi Co., Ltd, Novartis Co., Ltd, Parexel International, PRA Health Sciences, Taiho Pharmaceutical Co., MSD Co., Ltd, Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, and consulting or advisory role in Amgen Co., Ltd, Astellas Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, AstraZeneca Co., Ltd, Chugai Pharmaceutical Co., Ltd, and plays advisory role in Astellas Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Amgen Co., Ltd, AstraZeneca Co., Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Funding

This study is funded by Ono Pharmaceutical CO., LTD. in collaboration with the Bristol Myers Squibb. This manuscript was funded by Ono Pharmaceutical CO., LTD. in collaboration with the Bristol Myers Squibb. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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