The Oncologist®

Clinical Trial Results

A Phase I Trial of Oxaliplatin, Irinotecan, and S-1 Combination Therapy (OX-IRIS) as Chemotherapy for Unresectable Pancreatic Cancer (HGCSG 1403)

Yasuyuki Kawamoto,[a] Hiroshi Nakatsumi,[b] Kazuaki Harada,[c] Tetsuhito Muranaka,[d] Atsushi Ishiguro,[e] Yoshimitsu Kobayashi,[f] Hideyuki Hayashi,[g] Satoshi Yuki,[c] Kentaro Sawada,[h] Masataka Yagisawa,[i] Shintaro Nakano,[a] Naoya Sakamoto,[c] Yoshito Komatsu[a]

Divisions of [a]Cancer Center and [c]Deparment of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan; [b]Department of Gastroenterology, National Hospital Organization Hokkaido Medical Center, Sapporo, Japan; [d]Department of Internal Medicine, Wakkanai City Hospital, Wakkanai, Japan; [e]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan; [f]Department of Medical Oncology, KKR Sapporo Medical Center, Sapporo, Japan; [g]Genomic Unit, Keio Cancer Center, Keio University School of Medicine, Tokyo, Japan; [h]Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan; [i]Department of Medical Oncology, Japanese Red Cross Kitami Hospital, Kitami, Japan

Key Words. Pancreatic cancer • Combination therapy • Oxaliplatin • Irinotecan • S-1

Trial Information

- **Trial ID**: UMIN000017002
- **Sponsor**: Hokkaido Gastrointestinal Cancer Study Group
- **Principal Investigator**: Yoshito Komatsu
- **IRB Approved**: Yes

Lessons Learned

- Because S-1 is orally administered, OX-IRIS does not necessitate the continuous infusion of 5-FU and is more convenient.
- The recommended dose of OX-IRIS was determined to be level −1 (oxaliplatin, 65 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2), which has manageable safety and promising anticancer activities.

Abstract

Background. OX-IRIS is a new combination therapy of oxaliplatin, irinotecan, and S-1 for unresectable pancreatic ductal adenocarcinoma (PDAC), which may be beneficial because S-1 is administered orally and continuous infusion of 5-fluorouracil (5-FU) is not needed.

Methods. Patients who had not received prior therapy for unresectable PDAC were enrolled. Adenocarcinoma or adenosquamous histology was required. Oxaliplatin and irinotecan were administered on days 1 and 15; S-1 was administered orally twice a day on days 1–14, followed by 14 days of rest (one cycle). Primary endpoints were dose-limiting toxicity (DLT) and maximum tolerated dose (MTD). Secondary endpoints were safety, overall response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results. In level 0 (oxaliplatin, 85 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2), two of five patients experienced DLT. In level −1 (oxaliplatin, 65 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2), DLT could not be evaluated in two of eight patients because one cycle was not completed; one of the remaining six patients experienced DLT. Anemia, thrombocytopenia, fatigue, nausea, anorexia, diarrhea, and peripheral sensory neuropathy were seen frequently in levels 0 and −1. ORR was 30% in levels 0 and −1. Median progression-free survival and median overall survival were 4.1 months (95% confidence interval [CI], 0.0–8.9 months) and 13.7 months (95% CI, 4.8–22.6 months), respectively.

Conclusion. MTD of OX-IRIS therapy was estimated to be level 0, and the recommended dose (RD) for future trial was level −1. ***The Oncologist*** 2021;26:e1675–e1682

Discussion

In this phase I trial, we evaluated the safety and DLT of OX-IRIS therapy. We determined the recommended dose to be level −1 (oxaliplatin, 65 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2) (Fig. 1).

Correspondence: Yoshito Komatsu, M.D., Ph.D., Division of Cancer Center, Hokkaido University Hospital, Kita 14, Nishi 5, Kita-ku, Sapporo, Japan 060-8648. Telephone: 8-111-706-5657; e-mail: ykomatsu@ac.cyberhome.ne.jp Received February 11, 2021; accepted for publication May 18, 2021; published Online First on June 21, 2021. http://dx.doi.org/10.1002/onco.13838

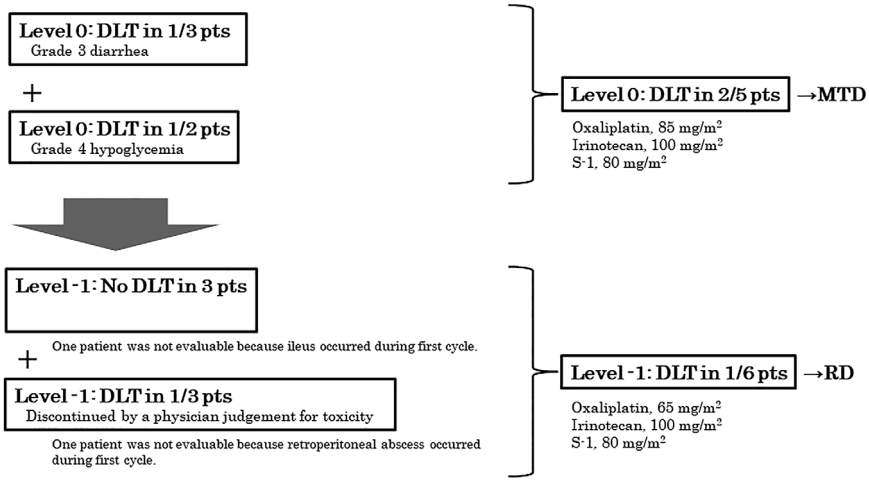


Figure 1. Flow chart of the HGCSG1403 trial. Five patients were treated at level 0 (oxaliplatin, 85 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2), and eight were at level −1 (oxaliplatin, 65 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2). Two of five patients in level 0 experienced DLT. In two of eight patients enrolled in level –1, it was impossible to evaluate DLT because one cycle could not be completed. And one of remaining six patients in level –1 showed DLT.
Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose; pts, patients; RD, recommended dose.

Anemia was common in both level 0 and level −1; however, it did not exceed grade 3. In level 0, anorexia (80%) and thrombocytopenia (60%) were also frequent. One patient experienced grade 3 diarrhea and another grade 3 hypoglycemia caused by anorexia and diarrhea in level 0; hence, we decreased the dose to level −1. At this dose level, the adverse events observed in more than 60% of the patients were nausea, anorexia, and fatigue, all of which were manageable. Although not at higher grades, hematological toxicities were common and were of concern in this therapy. In this small cohort, grade 3 nausea and anorexia were slightly more common, and appropriate supportive care was needed. However, there were no extremely severe adverse events when compared with previous reports of FOLFIRINOX therapy [1–4].

In this phase I trial, the ORR was 30%, and PFS and OS were comparable to the previous data of FOLFIRINOX therapy [1–4].

When the investigator explained the trial therapy, patients considered being pump-free an advantage and agreed to participate in this trial. This regimen would be more convenient not only for the patients but also for the medical staff since, because S-1 is orally administered, it does not necessitate the continuous infusion of 5-FU.

The development of a combination therapy involving oxaliplatin, irinotecan, and S-1 has been previously reported. Including our OX-IRIS regimen, it is not clear which is the most suitable combination. These combinations have manageable safety and promising anticancer activities. The development of an optimal treatment with efficacy and safety is a critical need for patients with PDAC.

The MTD of OX-IRIS therapy was estimated to be level 0 (oxaliplatin, 85 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2), and the RD was determined to be level −1 (oxaliplatin, 65 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2) in the present phase I trial. We are now evaluating the efficacy and safety in a phase II study of the OX-IRIS therapy.

Trial Information	
Disease	Pancreatic cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study	Phase I, 3+3
Primary Endpoints	Maximum tolerated dose, dose-limiting toxicity
Secondary Endpoints	Safety, overall response rate, progression-free survival, overall survival

Additional Details of Endpoints or Study Design

This trial was carried out as a multicenter phase I study at six institutions in Japan and fully complied with the Declaration of Helsinki (2008). HGCSG 1403 trial was reviewed and approved by the Hokkaido University Hospital Research Ethics Committee and by the Ethics Board of each institution (Approval Number: 014-0235). The trial was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000017002; http://www.umin.ac.jp/). Written informed consent was obtained from all the patients before enrollment in the study. Personal identifiable information of any of the participant in any form is not disclosed in this article.

The primary endpoints were the frequency of DLT and the estimation of MTD. This trial used a standard 3 + 3 design, and we evaluated safety and tolerability in 3–6 cases of each level (Table 1). If one of the three patients experienced DLT, three

more were enrolled at the same dose level. The completion of one cycle was considered as the evaluation period of DLT. We defined MTD as the highest dose with more of one-third expression of DLT within the DLT evaluation period. We also defined the level under one stage of MTD (the level at which the expression of DLT was less than one-third) as recommended dose.

Adverse events (Tables 2, 3) were monitored and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The following adverse drug reactions were defined as DLT:

Hematological toxicities	Grade 4 leucopenia or neutropenia Grade ≥3 thrombocytopenia Grade ≥3 anemia Grade ≥3 febrile neutropenia
Nonhematological toxicities	Grade ≥3 nonhematological toxicities

A delay longer than 14 days in starting cycle 2 owing to adverse events

Dose reduction or discontinuation judged by the attending physician according to the toxicities associated with the treatment

The secondary endpoints were the frequency of adverse events, ORR, PFS, and OS. The response was evaluated by the investigator according to RECIST version 1.1 every 6 weeks. PFS and OS were calculated using the Kaplan-Meier method by IBM SPSS Statistics version 20.0 (IBM, Armonk, NY).

The key inclusion criteria were pathologically diagnosed invasive ductal carcinoma (adenocarcinoma or adenosquamous carcinoma), unresectable locally advanced, metastatic, or recurrent disease, 20–75 years of age, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, no prior chemotherapy or radiotherapy for pancreatic cancer, measurable disease or nonmeasurable but evaluable disease, sufficient oral intake, and adequate organ functioning. For patients with recurrence after adjuvant therapy, those who had received the last dose more than 6 months ago were allowed to be enrolled. The key exclusion criteria were active second malignancy, *UGT1A1* *6 or *28 homo variant or *6 and *28 double hetero variant, grade ≥2 peripheral neuropathy, moderate ascites, pleural or pericardial effusion, intestinal pneumonitis or pulmonary fibrosis, uncontrollable diarrhea, uncontrollable diabetes mellitus, and serious complications (organ failure, active infection, ulcer, ileus, mental disorders, or central nervous system disorders).

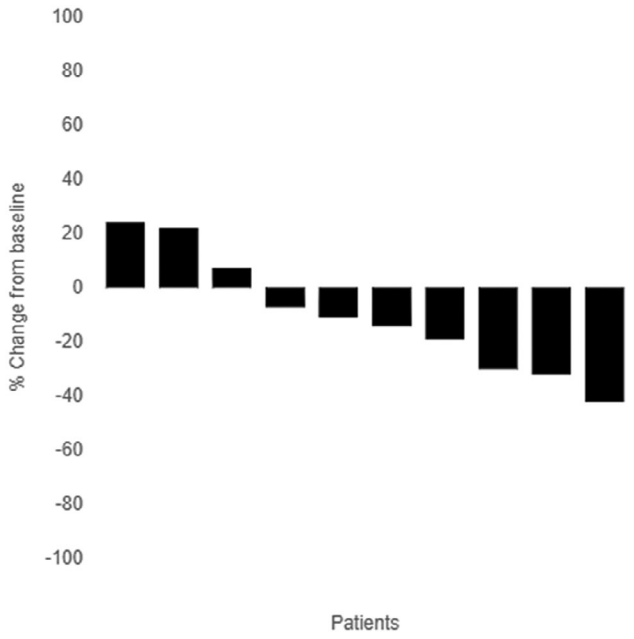
Investigator's Analysis	Active and should be pursued further

Drug Information

Oxaliplatin	
Generic Name	Oxaliplatin
Drug Type	Platinum with antineoplastic activity
Drug Class	Platinum compound
Dose	50–85 milligrams (mg) per squared meter (m^2)
Route	IV
Irinotecan	
Generic Name	Irinotecan
Drug Type	Irinotecan hydrochloride hydrate
Drug Class	Topoisomerase I
Dose	100–180 milligrams (mg) per squared meter (m^2)
Route	IV
S-1	
Generic Name	S-1
Drug Type	Fluoropyrimidine with antineoplastic activity
Drug Class	Antimetabolite
Dose	80 milligrams (mg) per squared meter (m^2)
Route	oral (p.o.)
Schedule of Administration	For OX-IRIS therapy, oxaliplatin and irinotecan were administered on day 1 and day 15. S-1 was administered orally twice a day from day 1 to day 14, which was followed by 14 days of rest, and this regimen constituted one cycle (Fig. 2).

Patient Characteristics	
Number of Patients, Male	8
Number of Patients, Female	5
Stage	Unresectable locally advanced, 4; Unresectable metastatic, 9
Age	Median (range): 62 (49–70) years
Number of Prior Systemic Therapies	Median (range): null
Performance Status: ECOG	0 — 9 1 — 4 2 — 0 3 — 0 Unknown — 0
Other	**Primary tumor site:** Head, 7; Body and tail, 6 **Histology:** Adenocarcinoma, 13 **Metastatic site:** Liver, 7; Lymph node, 2; Lung, 1; Peritoneum, 1 ***UGT1A1*:** Wild type, 10; *6 heterozygous, 1; *28 heterozygous, 2
Cancer Types or Histologic Subtypes	Pancreatic ductal adenocarcinoma, 13; Head of pancreas, 7; Body and tail of pancreas, 6

Primary Assessment Method	
Title	Dose-limiting toxicity
Number of Patients Screened	13
Number of Patients Enrolled	13
Number of Patients Evaluable for Toxicity	11
Number of Patients Evaluated for Efficacy	13
Evaluation Method	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0
Outcome Notes	Five patients were treated at level 0 (oxaliplatin, 85 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2), and the median number of treatment cycles received by them was 4 (range, 1–9). Eight patients were treated at level −1 (oxaliplatin, 65 mg/m^2; irinotecan, 100 mg/m^2; S-1, 80 mg/m^2), and the median number of treatment cycles was 2.5 (range, 1–6). Two of the five patients in level 0 experienced DLT. Among the first three patients, one had grade 3 diarrhea. Hence, two more patients were enrolled in this level. The second patient had grade 4 hypoglycemia caused by anorexia and diarrhea. Because DLT was observed in two of the five patients in level 0, we determined that MTD was reached in level 0, and this trial was shifted to level −1. In two of the eight patients enrolled in level −1, it was impossible to evaluate DLT because one cycle could not be completed. One patient was not evaluable because ileus occurred during the first cycle, and another was not evaluable because retroperitoneal abscess occurred during the first cycle. The first three patients did not exhibit DLT in level −1. Three more patients were enrolled to determine RD in level −1. One of the total six patients in level −1 showed DLT, which was judged by the attending physician and the protocol treatment was discontinued because of grade 2 nausea, anorexia, fatigue, and gastric hemorrhage (Fig. 1). No patients discontinued the protocol treatment owing to adverse events, except for those who experienced DLT.



Waterfall plot: Percentage best response is plotted. Best response of patients 1, 2, and 7 was progressive disease. Patient 7 had a new lesion. Best response of patients 3, 4, 5, and 6 was stable disease, and that of patients 8, 9, and 10 was partial response.

Title	Maximum tolerated dose
Number of Patients Screened	13
Number of Patients Enrolled	13
Number of Patients Evaluable for Toxicity	13
Number of Patients Evaluated for Efficacy	13
Evaluation Method	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Title	Efficacy
Number of Patients Screened	13
Number of Patients Enrolled	13
Number of Patients Evaluable for Toxicity	13
Number of Patients Evaluated for Efficacy	13
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 3$ (30%)
Response Assessment SD	$n = 4$ (40%)
Response Assessment PD	$n = 3$ (30%)
(Median) Duration Assessments PFS	4.1 months, CI: 0.0–8.9
(Median) Duration Assessments OS	13.7 months, CI: 4.8–22.6
Outcome Notes	Overall response rate was calculated in 10 patients who had measurable lesions. The median PFS was 4.1 months (95% CI, 0.0–8.9 months), and the PFS rate at 6 months and 1 year were 38.5% and 15.4%, respectively (Fig. 3A). The median OS was 13.7 months (95% CI, 4.8–22.6 months), and the OS rate at 1 and 2 years were 53.8% and 24.6%, respectively (Fig. 3B).

Adverse Events

See Tables 2 and 3.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Pancreatic adenocarcinoma (PDAC) was the seventh leading cause of cancer death worldwide in 2018 [5]. Surgical resection is the only definitive treatment; however, early detection is difficult, constituting approximately 20% of all curatively resectable cases. Systemic chemotherapy is recommended in patients with locally advanced, distant metastases, and postoperative recurrences that are not amenable to curative resection. Nonetheless, the 5-year overall survival (OS) rate remains under 10%, and median survivals are <1 year.

Combination chemotherapies such as leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine (GEM) plus nab-paclitaxel have improved the outcomes in patients with PDAC [1, 6]. In the ACCORD11 trial, FOLFIRINOX therapy showed substantial survival superiority when compared with GEM monotherapy in patients with untreated distant metastatic pancreatic cancer (PC) [1]. Hence, FOLFIRINOX has become one of the primary standard treatments for unresectable PC. Although FOLFIRINOX is effective, modified regimens have also been developed because of the strong adverse events associated with this therapy [2, 3]. The GEM plus nab-paclitaxel approach demonstrated efficacy against PC in the MPACT trial [6] and serves as another standard treatment option for PC.

In FOLFIRINOX therapy, the continuous intravenous infusion of 5-fluorouracil (5-FU) and the placement of central venous port are inconvenient and burdensome for the patients as well as for the medical staff. This approach can also cause infections and thrombosis related to catheter placement. S-1 is an oral antineoplastic agent developed to enhance the antitumor efficacy and alleviate the gastrointestinal toxicities of the therapy by combining gimeracil and oteracil potassium with tegafur, a prodrug of 5-FU, to increase the serum 5-FU levels [7, 8].

It is important to develop a comparable and more convenient alternative for FOLFIRINOX. OX-IRIS therapy employs a combination of oxaliplatin, irinotecan, and S-1. This strategy is beneficial for patients and medical staff because it does not require the continuous infusion of 5-FU since S-1 is administered orally. We planned this phase I trial to evaluate the potential for OX-IRIS therapy to serve as a new standard treatment for the disease.

Diarrhea has been reported to be more common with IRIS therapy than with FOLFIRI therapy in the FIRIS study with colorectal cancer [9]. In addition, diarrhea of IRIS/therapy has been reported slightly more often in the TRICOLORE study with colorectal cancer [10]. Based on these results, we were concerned that diarrhea with OX-IRIS therapy would increase compared with FOLFIRINOX therapy before the start of this trial. Using the TRICOLORE trial as a reference, the dose of irinotecan in this trial was set at 100 mg/m^2. As a consequence, the incidence of diarrhea was not more than 50% in all grades, and it was 0% in grade ≥3 in the recommended dose (RD).

Efficacy could also be expected in this therapy. In this phase I trial, the overall response rate was 30%, and progression-free survival and overall survival were comparable to the previous data of FOLFIRINOX therapy [1–4].

There are some limitations in this trial. First, the sample size was small because it was a phase I trial. Both safety and efficacy will be evaluated with more cases in phase II trials. Second, the optimal combination of oxaliplatin, irinotecan, and S-1 is not yet known. The development of a combination therapy involving oxaliplatin, irinotecan, and S-1 has been previously reported. In the SOXIRI regimen, patients received S-1 for 2 weeks on alternate days and irinotecan and oxaliplatin on day 1 of a 2-week cycle. The RD was reported to be 80 mg/m^2 of S-1, 85 mg/m^2 of oxaliplatin, and 150 mg/m^2 of irinotecan [11]. Another, S-IROX regimen consisted of S-1 orally from day 1 to day 7 and irinotecan and oxaliplatin on day 1, every 2 weeks for one cycle. The RD was found to be 80 mg/m^2 of S-1, 150 mg/m^2 of irinotecan, and 85 mg/m^2 of oxaliplatin [12]. Including our OX-IRIS regimen, it is not clear which is the most suitable combination.

Acknowledgments

We thank the patients and their families; the investigators, study coordinators, and nurses at each center; and Hokkaido University Hospital Clinical Research and Medical Innovation Center (Data Center). We also thank Enago (www.enago.jp) for the English language review. This study was supported by the nonprofit organization Hokkaido Gastrointestinal Cancer Study Group (no grant numbers apply).

Disclosures

Yasuyuki Kawamoto: Eli Lilly Japan K.K., Taiho Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Merck Biopharma Co., Ltd. (H); **Hiroshi Nakatsumi:** Taiho Pharmaceutical Co., Ltd. (H); **Satoshi Yuki:** Taiho Pharmaceutical Co., Ltd. (H); **Yoshito Komatsu:** Yakult, Lilly, Nihonkayaku, Daiichi Sankyo, Taiho, Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd. (H, RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–1825.

2. Stein SM, James ES, Deng Y et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer 2016;114:809–812.

3. Ozaka M, Ishii H, Sato T et al. A phase II study of modified FOLFIRINOX for chemotherapy-naive patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol 2018;81:1017–1023.

4. Okusaka T, Ikeda M, Fukutomi A et al. Phase II study of FOLFIRINOX for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. Cancer Sci 2014;105:1321–1326.

5. The Global Cancer Observatory. Available at https://gco.iarc.fr. Accessed November 16, 2020.

6. Von Hoff DD, Ervin T, Arena FP et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013; 369:1691–1703.

7. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. Cancer Res 1993;53:4004–4009.

8. Takechi T, Nakano K, Uchida J et al. Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. Cancer Chemother Pharmacol 1997;39:205–211.

9. Muro K, Boku N, Shimada Y et al. Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: A randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol 2010;11:853–860.

10. Yamada Y, Denda T, Gamoh M, et al. S-1 and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer (TRICOLORE): A randomized, open-label, phase III, noninferiority trial. Ann Oncol 2018;29:624–631.

11. Yanagimoto H, Satoi S, Sho M et al. Phase I study assessing the feasibility of the triple combination chemotherapy of SOXIRI (S-1/oxaliplatin/irinotecan) in patients with unresectable pancreatic ductal adenocarcinoma. Cancer Chemother Pharmacol 2016;77:35–41.

12. Sasaki M, Ueno H, Shiba S et al. Phase I study of S-1, irinotecan plus oxaliplatin combination therapy (S-IROX) for unresectable pancreatic ductal adenocarcinoma. Ann Oncol 2016;27 (suppl 2):ii36.

Figures and Tables

Table 1. Dose modification of this trial

Dose level	Oxaliplatin (mg/m^2)	Irinotecan (mg/m^2)	S-1[a] (mg/day)
Level −2	50	100	80–120
Level −1	65	100	80–120
Level 0 (initial dose)	85	100	80–120
Level +1	85	120	80–120
Level +2	85	150	80–120
Level +3	85	180	80–120

[a]The dose of S-1 is determined according to the body surface area (<1.25 m^2, 80 mg/day; ≥1.25 to <1.5 m^2, 100 mg/day; ≥1.5 m^2, 120 mg/day).

Table 2. Adverse events at level 0 ($n = 5$)

Adverse event	All grades, *n* (%)	Grade ≥ 3, *n* (%)
Leucopenia	2 (40)	0 (0)
Neutropenia	2 (40)	0 (0)
Thrombocytopenia	3 (60)	0 (0)
Anemia	5 (100)	0 (0)
Febrile neutropenia	—	0 (0)
AST increased	3 (6)	0 (0)
ALT increased	3 (6)	1 (20)
Blood bilirubin increased	0 (0)	0 (0)
Creatinine increased	0 (0)	0 (0)
Nausea	2 (40)	0 (0)
Anorexia	4 (80)	0 (0)
Fatigue	5 (100)	0 (0)
Diarrhea	4 (80)	1 (20)
Peripheral sensory neuropathy	4 (80)	0 (0)

Abbreviations: —, not applicable; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Adverse events at level − 1 ($n = 8$)

Adverse event	All grades, *n* (%)	Grade ≥ 3, *n* (%)
Leucopenia	4 (50)	1 (12.5)
Neutropenia	2 (25)	1 (12.5)
Thrombocytopenia	3 (37.5)	0 (0)
Anemia	8 (100)	0 (0)
Febrile neutropenia	—	0 (0)
AST increased	3 (37.5)	0 (0)
ALT increased	3 (37.5)	0 (0)
Blood bilirubin increased	0 (0)	0 (0)
Creatinine increased	0 (0)	0 (0)
Nausea	5 (62.5)	1 (12.5)
Anorexia	5 (62.5)	2 (25)
Fatigue	6 (75)	0 (0)
Diarrhea	4 (50)	0 (0)
Peripheral sensory neuropathy	2 (25)	0 (0)

Abbreviations: —, not applicable; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

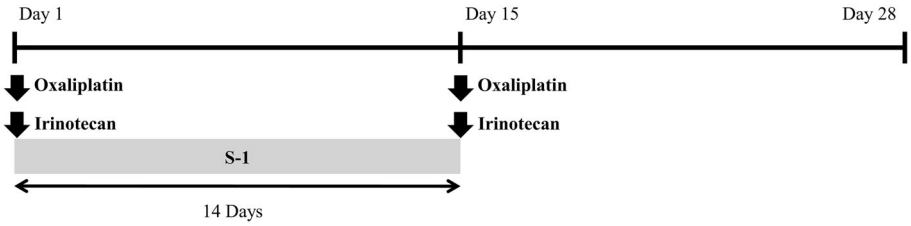


Figure 2. Study treatment. OX-IRIS treatment consists of 28-day cycles with escalated dose of oxaliplatin (50–85 mg/m^2 on day 1 and day 15), irinotecan (100–180 mg/m^2 on day 1 and day 15), and S-1 (80 mg/m^2/day on days 1–14).

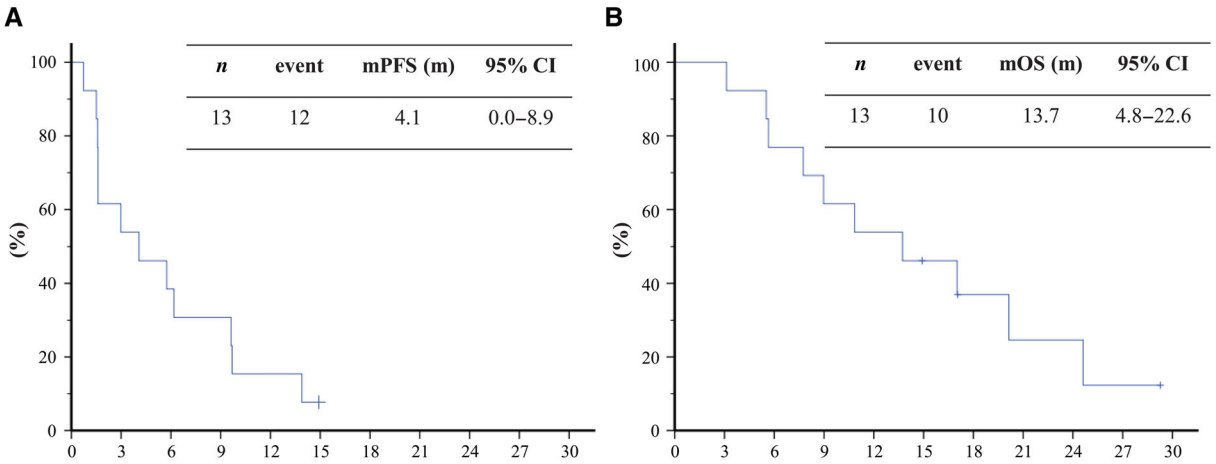


Figure 3. PFS and OS in the HGCSG1403 trial. **(A):** PFS. **(B):** OS. Median PFS was 4.1 months (95% CI, 0.0–8.9 months) and median OS was 13.7 months (95% CI, 4.8–22.6 months) in all 13 patients.
Abbreviations: CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival.