The Oncologist, 2023, **28**, e575–e584
https://doi.org/10.1093/oncolo/oyac146
Advance access publication 5 August 2022
Clinical Trial Results

A Phase I Study of Gemcitabine/Nab-Paclitaxel/S-1 Chemotherapy in Patients With Locally Advanced or Metastatic Pancreatic Ductal Adenocarcinoma

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Abstract

Background: Systemic chemotherapy is the primary treatment in patients with locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC). More effective treatment options are highly awaited. The aim of this study was to evaluate the toxicity and feasibility of gemcitabine/nab-paclitaxel/S-1 (GAS) chemotherapy on a 21-day cycle in patients with locally advanced or metastatic PDAC, determine the dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of S-1 in this regimen, and explore preliminary efficacy.

Methods: Eligible patients with locally advanced or metastatic PDAC received GAS chemotherapy on a 21-day cycle. Fixed-dose nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) were given intravenously on days 1 and 8. Different doses of S-1 were given orally twice daily from day 1 to day 14 in a 3+3 dose escalation design. According to patients` body surface area, the dose-escalation design was as follows: patients with a body surface area of 1.25-1.5 m^2 received S-1 40 mg/day initially and the dose was increased to 60 mg or 80 mg. Patients with a body surface area of more than 1.5 m^2 received S-1 60 mg/day initially and the dose was increased to 80 mg or 100 mg. The primary endpoints were to evaluate the toxicity and determine the DLT and MTD of S-1. The secondary endpoint was to evaluate efficacy, including best objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). adverse events (AEs) were evaluated according to the NCI-CTCAE 5.0. Tumor response was assessed using the RECIST 1.1.

Results: A total of 21 eligible patients were included. Due to the infrequence of patients with a body surface area of 1.25-1.5 m^2, only 2 patients were included in cohort of S-1 40 mg. The dose-escalation for patients in this group failed to be enrolled completely. For patients with a body surface area of more than 1.5 m^2, 3 DLTs in 7 patients were detected at cohort of S-1 100 mg (grade 3 thrombocytopenia with hemorrhage, grade 3 rash, and grade 3 mucositis/stomatitis). S-1 80 mg/day (body surface area: >1.5 m^2) was considered to be the MTD in GAS chemotherapy on a 21-day cycle. No grade 4 AEs or treatment-related deaths were observed. The most commonly occurring hematologic AE of any grade was anemia (38.1%). The most frequent nonhematologic AEs of any grade were peripheral neuropathy (38.1%), dyspepsia (23.8%), constipation (23.8%), and alopecia (23.8%). Response assessment showed that the best ORR was 36.8% (7 of 19 patients) and the DCR was 94.7% (18 of 19 patients). The median PFS was 5.3 (95% CI, 4.6 to 6.0) months and the median OS was 10.3 (95% CI, 8.1 to 12.5) months.

Conclusion: GAS chemotherapy (21-day cycle) with nab-paclitaxel 125 mg/m^2, gemcitabine 1000 mg/m^2, and S-1 80 mg/day (body surface area: >1.5 m^2) was found to have acceptable toxicity and significant clinical control in patients with locally advanced or metastatic PDAC. We conclude that further trials with this combination are warranted. (Trial Identifier: ChiCTR1900027833 [chictr.org]).

Key words: gemcitabine; nab-paclitaxel; pancreatic ductal adenocarcinoma; phase I, S-1.

Lessons Learned

- The recommended dose of S-1 in gemcitabine/nab-paclitaxel/S-1 (GAS) chemotherapy on a 21-day cycle was 80 mg/day (body surface area: >1.5 m^2).
- GAS chemotherapy (21-day cycle) with nab-paclitaxel 125 mg/m^2, gemcitabine 1000 mg/m^2, and S-1 80 mg/day (body surface area: >1.5 m^2) was detected with acceptable toxicity and significant clinical control in patients with locally advanced or metastatic pancreatic ductal adenocarcinoma.

Received: 13 March 2022; Accepted: 21 June 2022.

Discussion

Pancreatic cancer is a highly lethal malignancy, accounting for more than 495,000 new cases and 466,000 deaths worldwide in 2020.[1] The majority of pancreatic cancers are pancreatic ductal adenocarcinomas (PDAC), and the 5-year survival of PDAC is less than 10%.[2] For patients with unresectable or metastatic disease, systemic chemotherapy is considered as the primary opinion.[3-5] However, existing regimens of systematic therapy for PDAC are limited and far from ideal. Thus, exploring more effective regimens to improve survival in patients with locally advanced and metastatic PDAC is of great significance.

Based on the philosophy of using nab-paclitaxel plus gemcitabine (AG) as a platform for combining with other agents proposed recent years,[6,7] a phase I study in Japan proposed a biweekly triple regimen of gemcitabine/nab-paclitaxel/S-1 (GAS) as neoadjuvant chemotherapy in locally advanced PDAC. This study revealed preliminary efficacy with mild toxicity.[8] In order to expand the indication to metastatic PDAC and minimize toxicities, we implemented this phase I study of GAS chemotherapy on a 21-day cycle (Fig. 1).

This study evaluated the toxicity and efficacy of GAS chemotherapy (21-day cycle) in patients with locally advanced or metastatic PDAC. The maximum tolerated dose (MTD) of S-1 in GAS chemotherapy was 80 mg/day (body surface area: >1.5 m^2). Three dose-limiting toxicities (DLTs) were detected at cohort of S-1 100 mg (grade 3 thrombocytopenia with hemorrhage, grade 3 rash, and grade 3 mucositis/stomatitis). The DLTs and the spectrum of adverse events (AEs) reported by this trial were approximately consistent with other clinical trials. The efficacy of this modified GAS chemotherapy showed an improvement on objective response rate (ORR) and overall survival (OS). Three of 9 (33.3%) patients with locally advanced PDAC were successfully converted to be resectable disease, suggesting the regimen of GAS chemotherapy may be effective as neoadjuvant chemotherapy. It would be valuable to conduct further phase II trials.

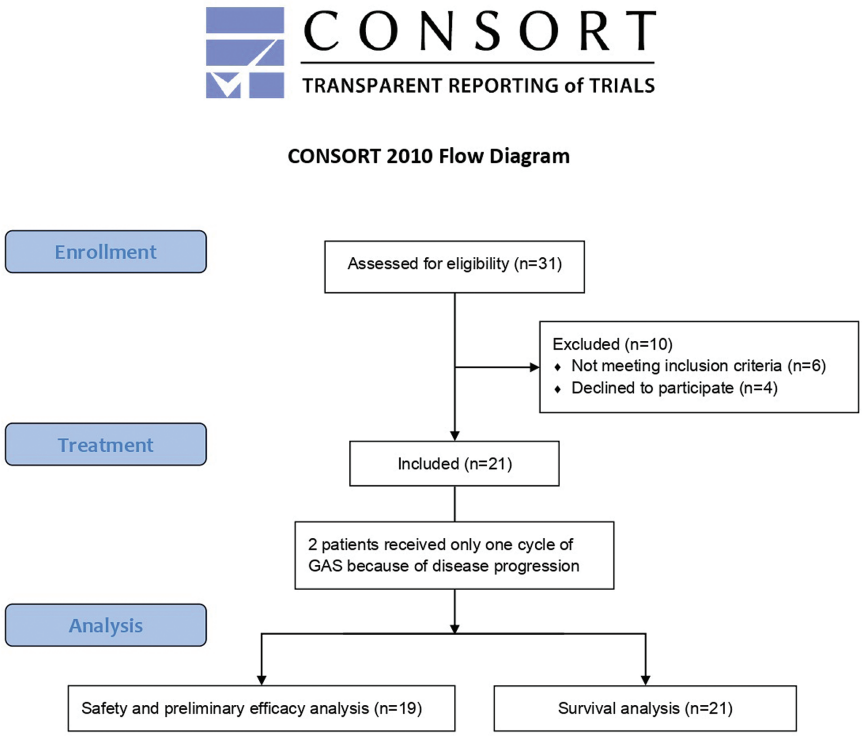

Figure 1. Patient flow diagram. The flow diagram follows the Consolidated Standards of Reporting Trials (CONSORT).

Trial Information	
Disease	Pancreatic ductal adenocarcinoma
Stage of disease/treatment	Locally advanced or metastatic
Prior therapy	None
Type of study	Phase I, 3+3
Primary endpoint	Maximum tolerated dose (MTD) and dose-limiting toxicity (DLT)
Secondary endpoints	Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)
Investigator's analysis	Active and should be pursued further

Additional Details of Endpoints or Study Design

Patients and Eligibility

This was an open-label, single-arm, and single-center phase I trial. Eligible patients were diagnosed with locally advanced or metastatic PDAC pathologically, had not received previous antitumor treatment, were 18-75 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, had an expected survival greater than 3 months, had adequate organ and marrow function, and were detected without active infectious disease or severe comorbidities that would affect survival. Full details of inclusion and exclusion criteria were listed in the protocol.[9]

Treatment and Dose Escalation

Eligible patients received GAS chemotherapy on a 21-day cycle. During each cycle, fixed-dose nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) were given intravenously on days 1 and 8. Different doses of S-1 were given orally twice daily from day 1 to day 14 in a 3+3 dose escalation design.[10] S-1 was provided in 20 mg tablets and the dosage of S-1 was based on the patient`s body surface area. According to previous phase I studies, including S-1monotherapy, S-1 combined with gemcitabine, and S-1 combined with nab-paclitaxel, the recommended dose of S-1 was in the range of 30 to 80 mg/m^2.[11-13] Thus, the dose-escalation design was as follows: patients with a body surface area of 1.25-1.5 m^2 received S-1 40 mg/day initially and the dose was increased to 60 mg or 80 mg. Patients with a body surface area of more than 1.5 m^2 received S-1 60 mg/day initially and the dose was increased to 80 mg or 100 mg. Dose adjustment was permitted when the toxicity was considered to be related to a certain drug. The treatment continued until disease progression (PD), intolerable AEs, or decisions made by patients and researchers.

Endpoints and Assessments

The primary endpoints were to determine the MTD and DLT of S-1 in GAS chemotherapy on a 21-day cycle. The secondary endpoint was to evaluate the efficacy, including ORR, DCR, PFS, and OS. DLT was defined as any grade 4 hematologic toxicity, grade 3 thrombocytopenia with hemorrhage, and any grade 3 or greater nonhematologic toxicity (excluding alopecia and fatigue). MTD was defined as the dose level just below the toxic dose level, at which no more than one patient among 6 patients experienced DLT. DLT, MTD, and AEs were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) 5.0 after the first cycle of GAS chemotherapy. Tumor response was performed by computerized tomography (CT) or magnetic resonance imaging (MRI) using the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 every 2 cycles of GAS chemotherapy. ORR was defined as the proportion of patients with complete response or partial response (PR) as best clinical response. DCR was defined as the sum of ORR and stable disease (SD). PFS was defined as the time from the first cycle of GAS chemotherapy to the presence of PD and treatment discontinuation due to intolerable AEs or decisions made by patients and researchers. OS was defined as the time interval between the first cycle of treatment and patients` death date or the last follow-up date. Kaplan-Meier method was used to evaluate PFS and OS. The 95% confidence intervals (CIs) of PFS and OS were calculated. Microsoft Excel software (version Microsoft Excel 2016, Microsoft Inc.), GraphPad Prism software (version 8, GraphPad Inc.), and IBM SPSS software (version 22.0, SPSS Inc.) were used for statistical analyses.

Drug Information	
Generic/working name—Drug 1	Nab-paclitaxel
Drug type	Small molecule
Drug class	Tubulin/microtubule targeting agent
Dose	125 mg/m^2
Route	Intravenous (i.v.)
Schedule of administration	Days 1 and 8 of a 21-day cycle
Generic/Working name—Drug 2	Gemcitabine
Drug Type	Small molecule
Drug Class	Antimetabolite
Dose	1000 mg/m^2
Route	Intravenous (i.v.)
Schedule of Administration	Days 1 and 8 of a 21-day cycle

Generic/working name—Drug 3	S-1
Drug type	Fluoropyrimidine with antineoplastic activity
Drug class	Antimetabolite
Dose	Patients with a body surface area of 1.25-1.5 m^2: Cohort 1: S-1 40 mg/day; Cohort 2: S-1 60 mg/day; Cohort 3: S-1 80 mg/day Patients with a body surface area of more than 1.5 m^2: Cohort 1: S-1 60 mg/day; Cohort 2: S-1 80 mg/day; Cohort 3: S-1 100 mg/day
Route	Oral (p.o.)
Schedule of administration	Twice daily on days 1-14 of a 21-day cycle

Dose Escalation Table

Dose level	Dose of drug: nab-paclitaxel, mg/m^2	Dose of drug: Gemcitabine, mg/m^2	Dose of drug: S-1, mg/day	Number enrolled
Patients with a body surface area of 1.25-1.5 m^2				
Cohort 1	125	1000	40	2
Cohort 2	125	1000	60	0
Cohort 3	125	1000	80	0
Patients with a body surface area of more than 1.5 m^2				
Cohort 1	125	1000	60	3
Cohort 2	125	1000	80	9
Cohort 3	125	1000	100	7

Patient Characteristics

Number of patients, male	13
Number of patients, female	8
Stage	Local advanced (III), 9; metastatic (IV), 12
Age: median (range)	56 (32-72) years
Number of prior systemic therapies	0
Performance Status: ECOG	0: 5 1: 16 2: 0 3: 0 4: 0
Cancer types or histologic subtypes	Pancreatic ductal adenocarcinoma, 21 Tumor location: Head, 8; Body/tail, 13
Outcome notes	A total of 21 eligible patients were enrolled in this study and received at least 1 cycle of GAS chemotherapy. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is shown in Fig. 1. Treatment details of all patients are shown in Fig. 2. Nine patients were diagnosed with locally advanced PDAC, and 12 were diagnosed with metastatic disease.

Primary Assessment Method : DLT and MTD

Number of patients screened	31
Number of patients enrolled	21
Number of patients evaluable for toxicity	21
Number of patients evaluated for efficacy	19
Evaluation Method	RECIST 1.1

Outcome Notes	Due to the infrequence of patients with a body surface area of 1.25-1.5 m^2, only 2 patients were included in cohort of S-1 40 mg. Thus, the dose escalation for patients in this group failed to be enrolled completely. For patients with a body surface area of more than 1.5 m^2, 3 were included in a cohort of S-1 60 mg, 9 in S-1 80 mg cohort, and 7 in S-1 100 mg cohort. DLT was not observed until the dose of S-1 increased to 100 mg. One DLT was detected among the initial 3 patients at cohort of S-1 100 mg (grade 3 thrombocytopenia with hemorrhage). Four more patients were treated at the same dose level. Two more DLTs (grade 3 rash and grade 3 mucositis/stomatitis) were detected in cohort of S-1 100 mg. Thus, the dose level of S-1 was reduced to 80 mg. Three more patients were enrolled in S-1 80 mg cohort. There were no DLTs observed among 6 patients. Then, 3 more patients were treated with S-1 80 mg to expand the cohort for validation. A total of 9 patients in S-1 80 mg cohort completed the first cycle of GAS chemotherapy without DLTs. Thus, S-1 80 mg/day (body surface area: >1.5 m^2) for 14 days in combination with gemcitabine 1000 mg/m^2 and nap-paclitaxel 125 mg/m^2 given on days 1 and 8 of a 21-day cycle was considered to be the MTD of S-1 in GAS chemotherapy. Adverse events of all the patients are summarized in Table 1. No grade 4 AEs or treatment-related deaths were observed. The most commonly occurring hematologic AE of any grade was anemia (38.1%). The most commonly grade ≥3 hematologic AEs were leukopenia (4.8%), neutropenia (4.8%), and thrombocytopenia (4.8%). The most frequent nonhematologic AEs of any grade were peripheral neuropathy (38.1%), dyspepsia (23.8%), constipation (23.8%), and alopecia (23.8%). The most common grade ≥3 nonhematologic AEs were rash (4.8%) and mucositis/stomatitis (4.8%).

Secondary Assessment Method : Efficacy and Survival

Number of patients screened	31
Number of patients enrolled	21
Number of patients evaluable for toxicity	21
Number of patients evaluated for efficacy	19 for efficacy analysis, 21 for survival analysis
Evaluation Method	RECIST 1.1
Response assessment, CR	0 (0%)
Response assessment, PR	7 (36.8%)
Response assessment, SD	11 (57.9%)
Response assessment, PD	1 (5.3%)
Median duration assessment, PFS	5.3 months (CI: 4.0-6.0)
Median duration assessment, OS	10.3 months (CI: 8.1-12.5)
Outcome Notes	Nineteen patients were included in the response evaluation. The best tumor response was recorded after 2 cycles of treatment. The waterfall plot showed the tumor change from baseline after 2 cycles of GAS chemotherapy in Fig. 3. Response assessment showed that 7 patients achieved PR and 11 patients achieved SD. These patients received 2 cycles of GAS chemotherapy at least and sustained the same response consistently from the first time when the response was assessed as PR or SD until the presence of PD or treatment discontinuation. One patient with liver metastasis at baseline was evaluated as PD because of the development of liver and bone metastases. The ORR was 36.8% (7 of 19 patients) and the DCR was 94.7% (18 of 19 patients). The percent change in CA 19-9 decrease after 2 cycles of GAS chemotherapy from baseline was revealed in Fig. 4. The decrease of CA 19-9 showed the same trend as tumor response.Among 21 patients, the median number of cycles administered was 4 (range 1-8). Three patients received radical pancreatectomy after 3 cycles of GAS chemotherapy with 1 case of PR and 2 cases of SD. The conversion rate of resection in locally advanced group was 33.3% (3 of 9 patients). In all patients the median PFS was 5.3 (95% CI 4.6-6.0) months and the median OS was10.3 (95% CI 8.1-12.5) months. Seven patients were still alive at the last follow-up date. The survival curves were demonstrated in Fig. 5.

Assessment, Analysis, and Discussion

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

This study evaluated the toxicity and efficacy of GAS chemotherapy (21-day cycle) in patients with locally advanced or metastatic PDAC. The recommended dose of S-1 in GAS chemotherapy was 80 mg/day (body surface area: >1.5 m^2). There was an ORR of 36.8%, a DCR of 94.7%, a median PFS of 5.3 months, and a median OS of 10.3 months.

MPACT study has proved the efficacy of AG chemotherapy.[14] However, the fact that some patients experienced dose reduction or discontinuation due to AEs remained a cause for concern. Therefore, different combinations of dose and administration were explored. A retrospective study evaluated the efficacy of a dose modification (gemcitabine 1000 mg/m^2 and nab-paclitaxel 125 mg/m^2 on day 1 biweekly), which demonstrated OS was of 10 months and the toxicity was less severe than the AG standard regimen.[15] Another retrospective analysis including elderly patients with

the same modified AG regimen also demonstrated comparable efficacy and acceptable toxicity.[16] A phase I/II study evaluated the MTD of nab-paclitaxel, followed by gemcitabine 1000 mg/m^2 on days 1 and 8, repeated every 21 days. The result recommended nab-paclitaxel 120 mg/m^2 plus gemcitabine as a favorable safety profile with a decent antitumor effect.[17] Therefore, in order to reduce additional healthcare costs, improve the efficacy, and control severe AEs, this trial designed a modified 21-day cycle GAS chemotherapy regimen, which is to add S-1 twice daily from day 1 to day 14 to the modified AG chemotherapy (nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1 and 8). The MTD of S-1 in this regimen was considered as 80 mg/day (body surface area: >1.5 m^2). In the GEST study, the dose of S-1 in GS group for the same body surface area was 100 mg/day.[18] However, the incidence of grade ≥3 neutropenia was 62.2%, significantly higher than that in gemcitabine or S-1 monotherapy group. Considering that this chemotherapy regimen was a combination of 3 agents, the recommended dose of S-1 is acceptable.

Three DLTs were detected in the cohort of S-1 100 mg (grade 3 thrombocytopenia with hemorrhage, grade 3 rash, and grade 3 mucositis/stomatitis). The JASPAC 01 study revealed that the incidence of any grade thrombocytopenia happened more frequently in the gemcitabine group (gemcitabine 70% versus S-1 43%).[19] The MPACT study indicated that AG caused more grade ≥3 thrombocytopenia than gemcitabine alone (13% versus 9%).[14] Therefore, it would be expected that the incidence of thrombocytopenia would rise and an increased risk of hemorrhage would be observed in triple chemotherapy. S-1 is an oral fluoropyrimidine drug, and the toxicities that need to be concerned including myelosuppression, gastrointestinal toxicity and neurological toxicity.[20,21] It can also be observed in this study that as the dose of S-1 increased, the incidence of gastrointestinal toxicity increased. When S-1 was combined with docetaxel, allergic reactions could be detected as DLT.[22] In the GEST study, grade ≥3 rash and mucositis/stomatitis in GS group happened more frequently than in the monotherapy group.[18] The records of grade 3 rash and grade 3 mucositis/stomatitis of this trials were similar to previous studies. Thus, the DLTs and the spectrum of AEs reported by this trial were approximately consistent with other clinical trials.

Compared to the biweekly GAS chemotherapy for locally advanced PDAC in Japan,[8] this study yielded potentially useful results after expanding the indication to metastatic PDAC, with lower dose of S-1, more acceptable toxicities, and more convenient medical experience. What`s more, the efficacy of this modified GAS chemotherapy showed an improvement on ORR (36.8%) compared to MPACT study (23%), LAPACT study (33.6%), and GSET study (29.3%).[14,18,23] An increase in OS was also observed. It may relate to the difference in performance status and disease stage of included patients. Three of 9 (33.3%) patients with locally advanced PDAC were successfully converted to be resectable disease, suggesting the regimen of GAS chemotherapy may be effective as neoadjuvant chemotherapy.

One limitation of this study is this study failed to recommend the MTD in patients with a body surface area less than 1.5 m^2. Based on 2 patients, grade ≥3 AEs were not observed at S-1 40 mg/day in patients with a body surface area of 1.25-1.5 m^2. A more comprehensive dose exploration should be developed in subsequent studies.

Funding

This study was funded by the Sichuan Province Science and Technology Support Program (CN) (Grant No. 2021YFS0047).

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

The data underlying this article are available in the article. Further inquiries can be directed to the corresponding author.

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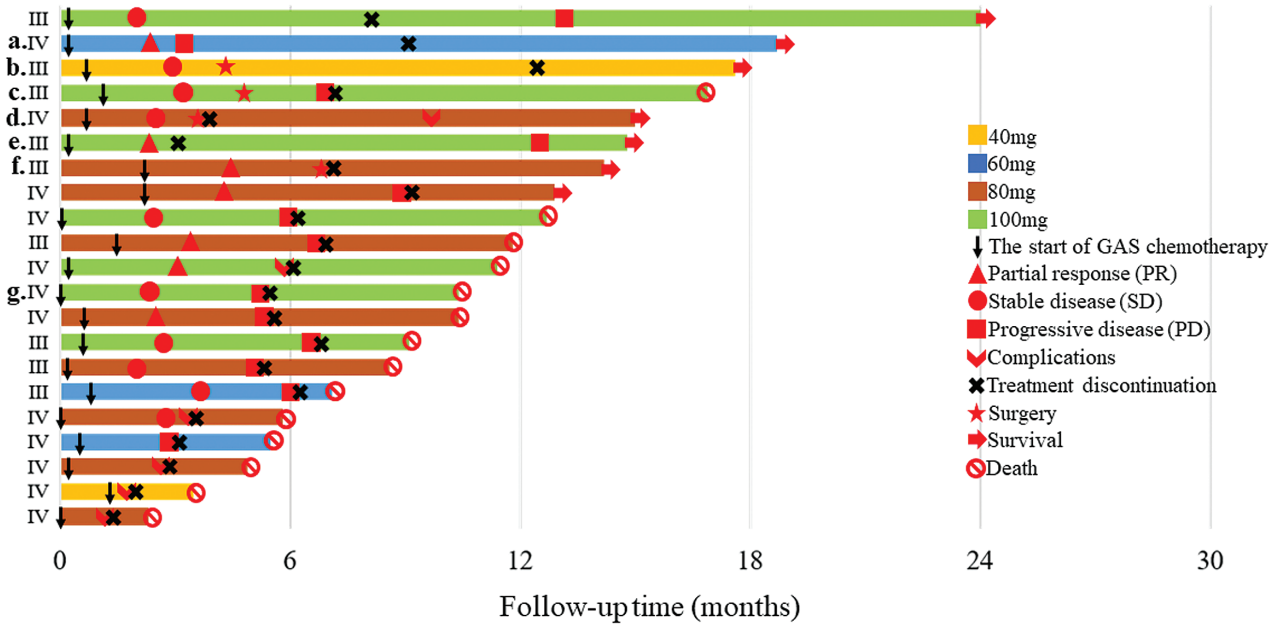
Figures and Tables

Table 1. Reported adverse events

Event	S-1 40 mg			S-1 60 mg			S-1 80 mg			S-1 100 mg			Grades ≥3 (%)	All (%)
Grade	1	2	3	1	2	3	1	2	3	1	2	3		
Hematologic														
Anemia	1	0	0	0	0	0	2	2	0	2	1	0	0 (0)	8 (38.1)
Leukopenia	0	0	0	0	0	1	1	2	0	0	1	0	1 (4.8)	5 (23.8)
Neutropenia	1	0	0	0	0	1	0	2	0	0	0	0	1 (4.8)	4 (19.0)
Thrombocytopenia	0	0	0	1	0	0	1	0	0	1	0	1[a]	1 (4.8)	4 (19.0)
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	0	0	0 (0)	0 (0)
Nonhematologic														
Fever	0	0	0	0	0	0	0	0	0	0	0	0	0 (0)	0 (0)
Fatigue	1	0	0	1	0	0	1	0	0	0	0	0	0 (0)	3 (14.3)
Anorexia	0	0	0	0	0	0	1	1	0	1	0	0	0 (0)	3 (14.3)
Dyspepsia	0	0	0	0	0	0	0	3	0	0	2	0	0 (0)	5 (23.8)
Nausea/vomiting	0	2	0	0	2	0	0	0	0	0	0	0	0 (0)	4 (19.0)
Constipation	1	0	0	0	0	0	1	0	0	3	0	0	0 (0)	5 (23.8)
Diarrhea	0	0	0	0	0	0	0	0	0	2	0	0	0 (0)	2 (9.5)
Alopecia	0	0	0	0	0	0	2	0	0	3	0	0	0 (0)	5 (23.8)
Peripheral neuropathy	0	0	0	0	0	0	0	4	0	0	4	0	0 (0)	8 (38.1)
Rash	0	0	0	0	0	0	0	0	0	0	0	1	1 (4.8)	1 (4.8)
Mucositis/stomatitis	0	0	0	0	0	0	0	0	0	0	0	1	1 (4.8)	1 (4.8)
AST/ALT elevation	0	0	0	0	0	0	1	0	0	1	0	0	0 (0)	2 (9.5)
Creatinine elevation	0	0	0	0	0	0	0	0	0	1	0	0	0 (0)	1 (4.8)
Hyperbilirubinemia	0	0	0	0	0	0	2	0	0	0	0	0	0 (0)	2 (9.5)
Hypoproteinemia	0	0	0	0	0	0	0	1	0	0	0	0	0 (0)	1 (4.8)
Cholestatic jaundice	0	1	0	0	0	0	0	2	0	0	1	0	0 (0)	4 (19.0)

[a]Thrombocytopenia with hemorrhage
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.



a. The patient received radiotherapy after 3 cycles of GAS, thus we stopped following up on the PFS.

b. After 3 cycles of GAS, the patient received surgery and following with 5 cycles of chemotherapy.

c. The patient had the radical surgery after 3 cycles of GAS, however, because of the intolerable adverse events, the patient received AG as postoperative adjuvant chemotherapy instead of GAS.

d. The patient underwent palliative surgery after 2 cycles of GAS.

e. After 3 cycles of GAS, the patient chose traditional Chinese medicine treatment as maintenance therapy.

f. After 3 cycles of GAS, the patient received radical surgery.

g. The patient was treated with iodine-125 seed implantation after completing 6 cycles of GAS. Thus, we stopped following up on the PFS.

Figure 2. Included patients` course of treatment. The bar plot shows entire treatment during the follow-up and the preliminary efficacy after 2 cycles of gemcitabine/nab-paclitaxel/S-1 (GAS) for locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC).

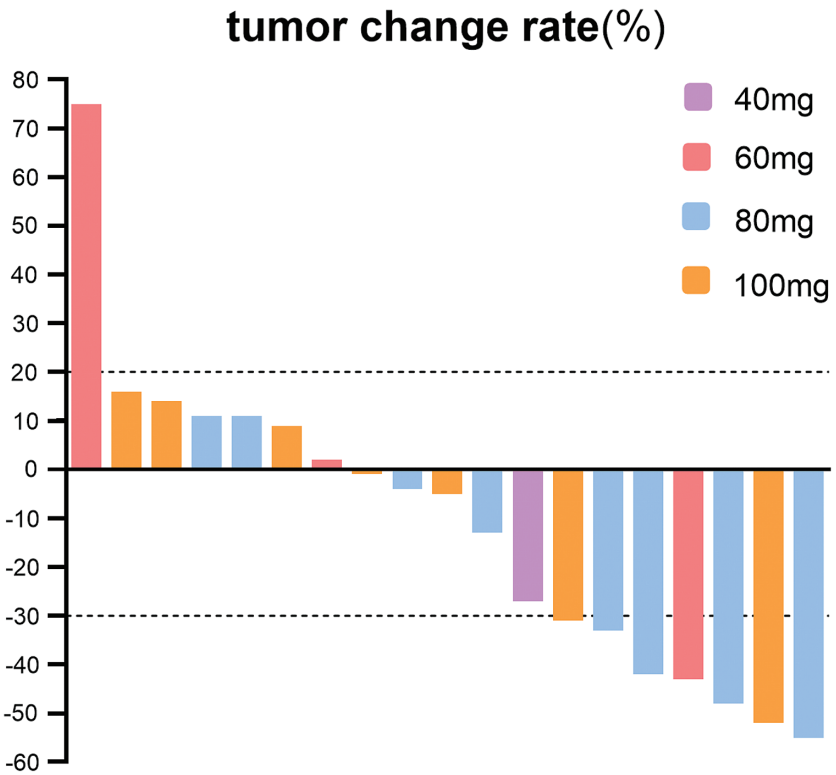


Figure 3. Tumor change rate from baseline after 2 cycles of treatment. Waterfall plot shows overall change in sum of diameter of tumor lesions among evaluable patients (n = 19). The dashed line at 20% indicates the tumor change rate is up to progressive disease (PD). The dashed line at −30% indicates the tumor change rate is considered to be partial response.

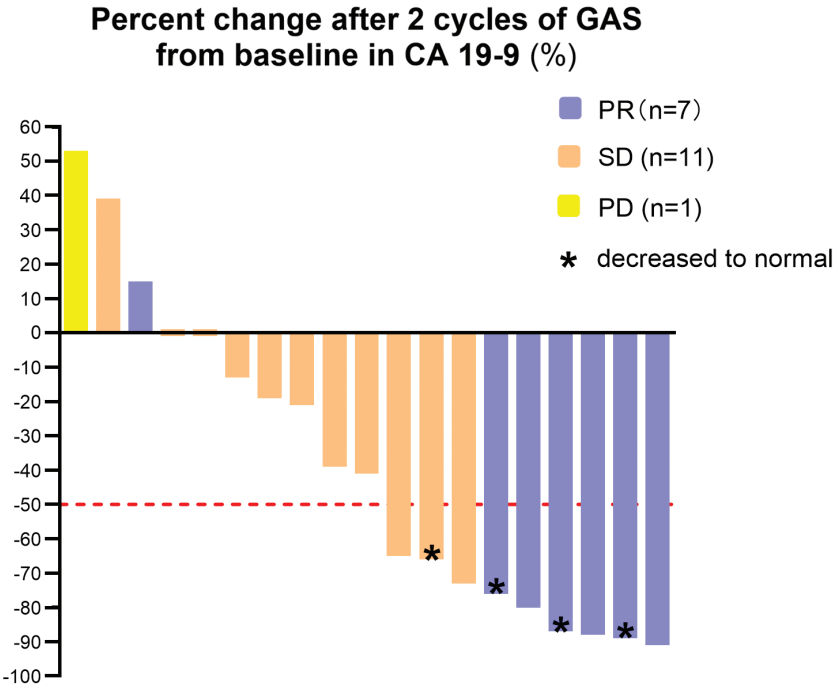


Figure 4. Percent change rate of CA 19-9 from baseline after 2 cycles of treatment. Waterfall plot shows percent change rate of CA 19-9. CA19-9 shows significant decline in patients with partial response after 2 cycles of treatment (n = 19). * denotes that CA 19-9 is reduced to the normal level. The dashed line at −50% indicates a 50% decrease of percent change rate of CA 19-9.

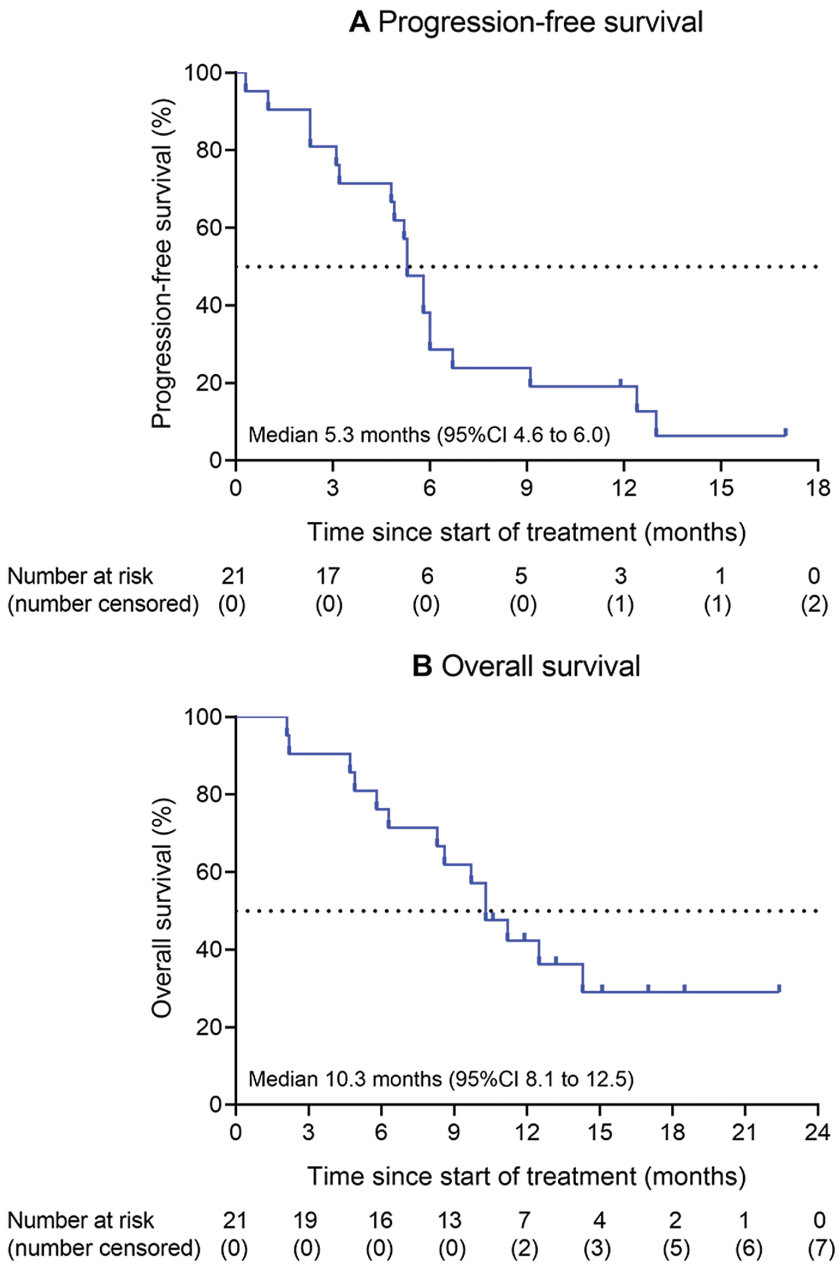


Figure 5. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS) in all treated patients (n = 21). The median PFS was 5.3 months (95% CI 4.6-6.0). The median OS was 10.3 months (95% CI 8.1-12.5).