Nimotuzumab Plus Gemcitabine for K-Ras Wild-Type Locally Advanced or Metastatic Pancreatic Cancer

Shukui Qin, MD[1]; Jin Li, MD[2]; Yuxian Bai, MD, PhD[3]; Zishu Wang, MD[4]; Zhendong Chen, MD, PhD[5]; Ruihua Xu, MD, PhD[6]; Jianming Xu, MD[7]; Hongmei Zhang, MD[8]; Jia Chen, MD[9]; Ying Yuan, MD[10]; Tianshu Liu, MD[11]; Lin Yang, MD, PhD[12]; Haijun Zhong, MD[13]; Donghui Chen, MD[14]; Lin Shen, MD, PhD[15]; Chunyi Hao, MD, PhD[15]; Deliang Fu, MD, PhD[16]; Ying Cheng, MD[17]; Jianwei Yang, MD[18]; Qiong Wang, MD[19]; Baoli Qin, MD[20]; Hongming Pan, MD[21]; Jun Zhang, MD, PhD[22]; Xianhong Bai, MD[23]; and Qingshan Zheng, MD, PhD[24]

DOI https://doi.org/10.1200/JCO.22.02630

ABSTRACT

PURPOSE In a phase IIb trial of nimotuzumab plus gemcitabine, substantial clinical benefits were observed in patients with locally advanced or metastatic pancreatic cancer (PC). Therefore, we conducted a phase III clinical study to verify the efficacy and safety of this combination regimen in patients with K-Ras wild-type tumors (ClinicalTrials.gov identifier: NCT02395016).

PATIENTS AND METHODS Eligible patients were randomly assigned to receive nimotuzumab (400 mg once per week) or placebo followed by gemcitabine (1,000 mg/m^2 on days 1, 8, and 15, once every 4 weeks) until disease progression or unacceptable toxicity. The primary end point was overall survival (OS) and the secondary end points were progression-free survival (PFS), response rates, and safety.

RESULTS A total of 480 patients were screened; 92 patients were enrolled and 82 patients with K-Ras wild-type tumors were eligible. In the full analysis set, the median OS was 10.9 versus 8.5 months, while the restricted mean survival time (RMST) was 18.05 versus 11.14 months for the investigational versus control arm (ratio of control *v* investigation = 0.62 [0.40-0.97]; $P = .036$). Median PFS was 4.2 versus 3.6 months in the investigational versus control arm (log-rank $P = .04$; hazard ratio, 0.60 [0.37-0.99]) and the restricted mean PFS time was 8.08 versus 4.76 months (RMST ratio, 0.58 [0.38-0.90]; $P = .036$). Both OS and PFS were longer in the nimotuzumab group than in the placebo group. The objective response rates and disease control rates were 7% versus 10% and 68% versus 63% for the investigational and control groups, respectively. The incidence of adverse events were comparable between the two groups.

CONCLUSION In patients with locally advanced or metastatic K-Ras wild-type PC, nimotuzumab plus gemcitabine significantly improved OS and PFS with a good safety profile.

ACCOMPANYING CONTENT

Protocol

Accepted July 20, 2023
Published August 30, 2023

J Clin Oncol 41:5163-5173

View Online Article

INTRODUCTION

Pancreatic cancer (PC) is a common and fatal malignancy that occurs worldwide. Eighty percent of PC cases are diagnosed as advanced or metastatic stage.[1] Twenty-five percent of patients with advanced PC are at a locally advanced stage, with a median overall survival (mOS) of 6-9 months. Approximately 60%-70% of patients with advanced PC are at the metastatic stage, with mOS of only 3-5 months.[2-9] Unfortunately, the current regimens are unsatisfactory. Encouraging the achievement of new regimens has been developed in many other cancer fields but rarely in PC. Therefore, there is an urgent need for effective therapies to prolong the survival of patients with PC.

Nimotuzumab is a recombinant humanized monoclonal antibody against the epidermal growth factor receptor (EGFR). A phase IIb study (PCS07) done in Germany showed that nimotuzumab plus gemcitabine might significantly improve the mOS (8.6 months *v* 6.0 months) of locally advanced or metastatic PC, especially for the wild-type K-Ras gene subgroup (11.62 months *v* 5.67 months; 1-year survival rates, 53.8% *v* 15.8%, respectively).[10] In 2014, gemcitabine was widely used and was considered the standard of care for first-line treatment regimen for patients with advanced PC in China. Thus, we conducted a phase III trial (NOTABLE study) to verify the efficacy and safety of nimotuzumab plus gemcitabine as first-line treatment for patients with locally advanced or metastatic PC.

CONTEXT

Key Objective

Does nimotuzumab (a humanized epithelial growth factor receptor monoclonal antibody) plus gemcitabine regimen provide an overall survival (OS) benefit for patients with locally advanced or metastatic K-Ras wild-type pancreatic cancer (PC)?

Knowledge Generated

In a multicenter, randomized, double-blinded, phase III clinical trial in China, patients with locally advanced or metastatic K-Ras wild-type PC were enrolled. The results showed that nimotuzumab plus gemcitabine significantly improved OS and progression-free survival with a good safety profile compared with the placebo-gemcitabine group.

Relevance *(E.M. O'Reilly)*

This randomized trial confirms that identification of KRAS wild-type PC is clinically important and therapeutically relevant and can be successfully targeted.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD.

PATIENTS AND METHODS

Study Oversight

The NOTABLE study was approved by each institution's independent ethics committee, the Chinese Drug Regulatory Authority, and the National Medical Products Administration, adhering to the Helsinki Declaration on human medical research.[11]

The investigators and authors designed the Protocol (online only) using a sponsor (Biotech Pharmaceutical Co, Ltd). The principal investigators from each site adhered to the study protocol. In addition, data were collected and analyzed by professional third-party statisticians who certified the accuracy and completeness of the reported data.

Patents

Patients with locally advanced or metastatic PC were screened. Each patient signed an informed consent form before screening. Eligible patients were age 18-75 years with histologically confirmed locally advanced/metastatic PC with the K-Ras wild-type gene (Sanger gene sequence). Other inclusion criteria were a Karnofsky performance status (KPS) score ≥60, ineligibility for radical radiotherapy or surgery, previous adjuvant chemotherapy (if any) for more than 6 months before enrollment, at least one measurable lesion (RECIST 1.1),[12] and an estimated life expectancy of 12 weeks or more, together with normal organ function.

Study Design and Treatment

This was a prospective, multicenter, randomized, double-blinded, phase III clinical study (NOTABLE study), in which eligible patients were randomly assigned (1:1) to receive intravenous nimotuzumab (400 mg) or a placebo once a week. Gemcitabine (1,000 mg/m^2) was administered intravenously once per week (on days 1, 8, and 15) for 3 weeks, rest for 1 week, then once per week for 4 weeks for one treatment cycle. Treatment was continued until disease progression, unmanageable toxicity, or withdrawal of consent was observed. The patients were followed up until death or study completion.

Patients were stratified by tumor localization (head, body, or tail of the pancreas) according to previous surgery, history of biliary obstruction treatment, and adjuvant chemotherapy.

Assessments

The investigators evaluated the tumor response via computed tomography or magnetic resonance imaging scan every 8 weeks, according to RECIST version 1.1. The clinical benefit response (CBR) was evaluated every 8 weeks on the basis of the Burris criteria.[13] Adverse events (AEs) and serious adverse events were monitored by the investigators from the beginning of the treatment and up to 30 days after treatment completion. The detected events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03,[14] and coded and summarized according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 24.0.

Study End Points

The primary end point was overall survival (OS), defined as the time from random assignment to death due to any cause. Subgroup analyses of OS were based on prespecified stratification factors. The secondary end points were progression-free survival (PFS), defined as the time from random assignment until objective tumor progression or death; time to progression (TTP, defined as the time from random assignment until objective tumor progression); objective response rate (ORR), including complete response

(CR) and partial response (PR); disease control rate (DCR), including CR, PR, and stable disease; and CBR on the basis of changes in pain, KPS, and weight. Treatment-related adverse events (TRAEs) were defined as adverse drug reactions (ADRs).

Statistical Analysis

The primary end point was evaluated in the full analysis set (FAS; all eligible patients who received at least one dose of nimotuzumab and had one evaluation of efficacy). Secondary end points were analyzed only in the FAS. A prespecified subgroup analysis of OS and PFS was performed using the FAS. Safety analysis was performed using the safety analysis set (SS; patients received at least one antibody dose).

Statistical analyses were performed using the SAS version 9.4 (SAS Institute, Cary, NC). OS was the primary efficacy end point and was analyzed using the Kaplan-Meier method and stratified log-rank test. If the proportional hazards assumption was unsatisfactory (eg, survival curve crossover), the restricted mean survival time (RMST) model[15] was used to analyze the survival benefit difference. RMST is suggested as a novel alternative measure in survival analyses and may be useful when the proportional hazards assumption cannot be made. A right-censored pattern was used for the OS data. The time point of the RMST model was the closest to the end of the trial.

We calculated that, with a sample of 276 patients, the study would have 80% power to detect a hazard ratio (HR) for death with nimotuzumab plus gemcitabine (investigational arm, or nimotuzumab-gemcitabine) versus placebo plus gemcitabine (control arm, or placebo-gemcitabine) of 0.69. This estimation was based on the results of the full population in the PCS07 study, where the median OS of the gemcitabine monotherapy group was 6 months and the median OS of the investigational arm was 8.7 months. Since patients with K-Ras wild-type PC were rare and recruitment was difficult, we calculated that with a sample of 79 patients and 64 events, the study would have 80% power to detect a HR for death with nimotuzumab-gemcitabine versus placebo-gemcitabine. This assumption was made on the basis of the result of patients with K-Ras wild-type PC in PCS07 study, where the median OS of gemcitabine monotherapy group was 5.67 months, and the median survival of the investigational group was 11.62 months. The sample size re-estimation was approved by the Chinese regulatory authorities. At the time of approval, 92 patients were enrolled and the study was terminated.

Multivariate analysis of survival data was conducted using the Cox proportional hazard model according to prespecified stratification factors to evaluate the treatment effect. In addition to the HR as a measurement of the relative risk of an event, the RMST ratio between arms (control *v* investigation) was estimated after adjusting for covariates. For this analysis, a ratio of <1 indicated survival improvement in the investigational arm. Unlike the HR, the RMST ratio does not rely on any model assumption.[16]

The ORR was analyzed using the Fisher test, while the DCR and CBR were evaluated using the chi-squared test. AEs were classified according to the system organ class, preferred term, or severity grade.

RESULTS

Patients and Treatment Groups

A total of 480 patients from 25 study sites in China were screened between April 2015 and March 2021. Then, 92 patients with the K-Ras wild-type gene were eligible for random assignment, and 90 patients were allocated for treatment. Eight patients who did not have K-Ras wild-type tumors according to a gene confirmatory procedure (seven cases) or PC (one gallbladder carcinoma case), detected during monitoring, were excluded. Finally, 82 patients were analyzed as part of the FAS, and 41 were included in each group. The FAS group was the modified intent-to-treat group (Fig 1).

The demographic and clinical characteristics at baseline were well balanced between the two groups (Table 1).

Efficacy

OS

The OS analysis was based on 76 deaths, including 36 deaths in the nimotuzumab-gemcitabine group and 40 deaths in the placebo-gemcitabine group. The mean follow-up time was 57.6 months and 16.6 months, respectively, for the two groups. The data cutoff was January 27, 2022. The median OS was 10.9 months (95% CI, 5.6 to 16.3) in the nimotuzumab-gemcitabine group and 8.5 months (95% CI, 5.7 to 10.0) in the placebo-gemcitabine group (Cox proportional HR, 0.66; 95% CI, 0.42 to 1.05; log-rank $P = .08$; Fig 2A). When using RMST model, the RMST was 18.05 months (95% CI, 11.71 to 24.38) in the nimotuzumab-gemcitabine group and 11.14 months (95% CI, 8.07 to 14.20) in the placebo-gemcitabine group (RMST ratio of control *v* treatment, 0.62; 95% CI, 0.40 to 0.97; $P = .036$; Table 2). OS was significantly longer in the nimotuzumab-gemcitabine group (Fig 2C).

PFS and TTP

PFS was significantly longer in the nimotuzumab-gemcitabine group than in the placebo-gemcitabine group, with median survival time of 4.2 months (95% CI, 2.7 to 7.3) versus 3.6 months (95% CI, 2.0 to 5.0; HR, 0.60; 95% CI, 0.37 to 0.99; log-rank $P = .04$), respectively (Fig 2B). At a follow-up of 31 months, the restricted mean PFS time was 8.08 months (95% CI, 5.20 to 10.94) in the nimotuzumab-gemcitabine group and 4.76 months (95% CI, 3.41 to 6.09) in the placebo-gemcitabine group (RMST ratio, 0.58;

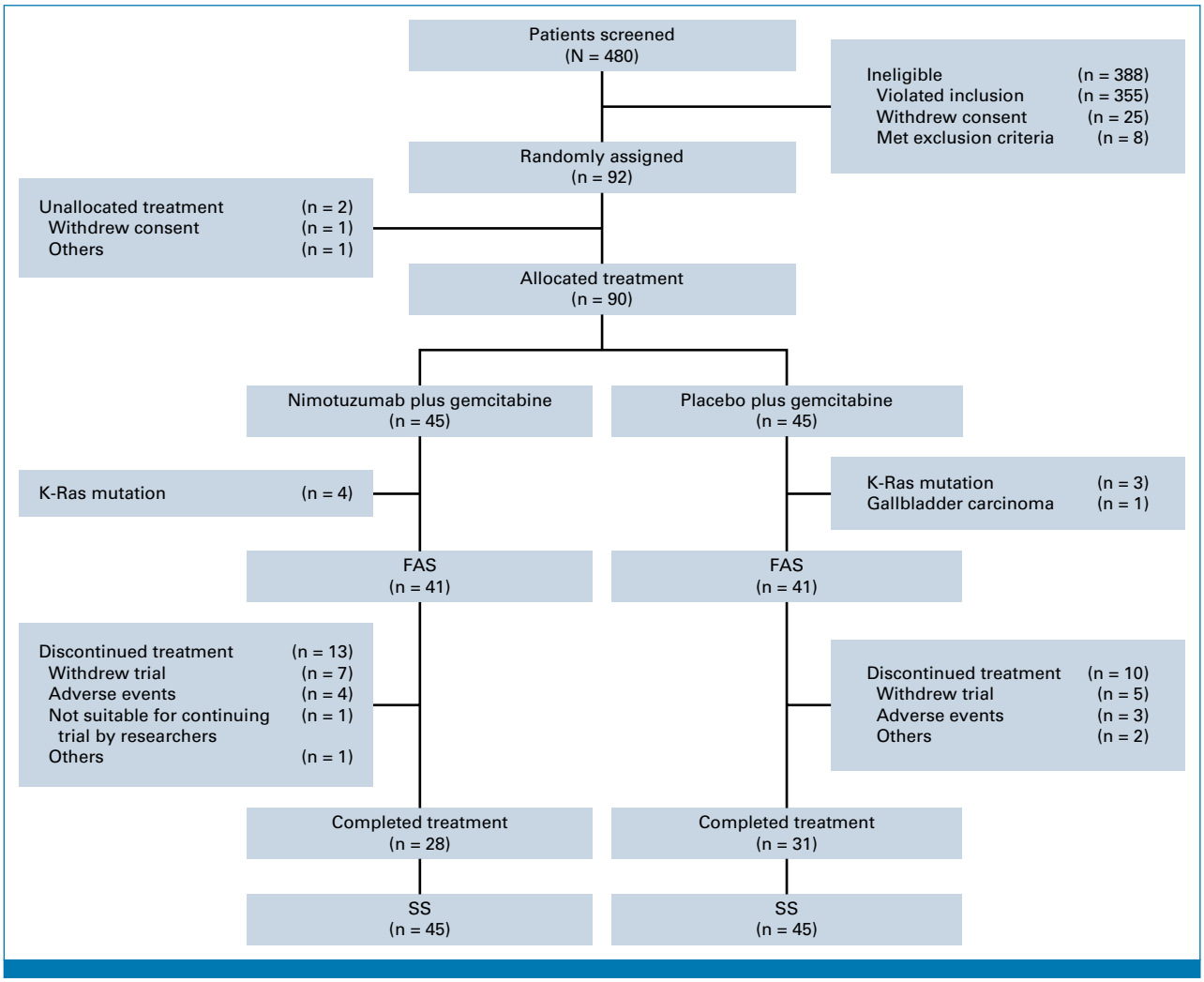

FIG 1. CONSORT diagram. FAS, full analysis set; gem, gemcitabine; SS, safety set.

95% CI, 0.38 to 0.90; P = .036), with a difference of 3.3 months (95% CI, 0.30 to 6.24; adjusted stratification of P = .031; Fig 2D).

The median TTP was 4.7 months (95% CI, 2.7 to 9.0) in the nimotuzumab-gemcitabine group and 3.7 months (95% CI, 2.0 to 5.4) in the placebo-gemcitabine group (HR, 0.67; 95% CI, 0.39 to 1.15; log-rank P = .311) of no significant difference.

ORR and DCR

ORRs were 7.3% (95% CI, 1.5 to 19.9) versus 9.8% (95% CI, 2.7 to 23.1) in the investigational versus control group, and the DCRs were 68.3% (95% CI, 51.9 to 81.9) versus 63.4% (95% CI, 46.9 to 77.9), respectively. The ORR and DCR results were not significantly different between the two groups.

CBR

The CBRs in the nimotuzumab-gemcitabine and placebo-gemcitabine groups were 39.3% (95% CI, 21.2 to 57.4) and 32.2% (95% CI, 15.8 to 48.8), respectively. However, this difference was not statistically significant.

Subgroup Analyses

In the prespecified subgroups, the results were mostly consistent with the pooled results. Compared with the placebo-gemcitabine group, the nimotuzumab-gemcitabine group showed trends of larger survival as well as progression risk reduction in several subgroups, especially for patients without previous biliary obstruction (OS, 11.9 months *v* 8.4 months; HR, 0.54; 95% CI, 0.33 to 0.89; log-rank P = .035; PFS, 5.5 months *v* 3.4 months; HR, 0.5; 95% CI, 0.29 to 0.85; log-rank P = .035; Figs 3A and 3B).

Treatment Exposure

The median duration of treatment was 16 weeks (range, 1-127 weeks) in the nimotuzumab-gemcitabine group and 13 weeks (range, 1-80 weeks) in the placebo-gemcitabine group, in the FAS population. The median exposure dose of nimotuzumab

TABLE 1. Characteristics of the Patients at Baseline

Characteristic	Nimotuzumab-Gemcitabine Group (n = 41)	Placebo-Gemcitabine Group (n = 41)	Total (N = 82)	*P*
Age, years				.265
Median	53	57	55	
Range	19-73	19-73	19-73	
Distribution, years, No. (%)				.600
<65	33 (80)	30 (73)	63 (77)	
≥65	8 (20)	11 (27)	19 (23)	
Sex, No. (%)				.648
Female	14 (34)	17 (41)	31 (46)	
Male	27 (66)	24 (59)	51 (62)	
Race or ethnic group, No. (%)[a]				.494
Han	41 (100)	39 (95)	80 (98)	
Other	0 (0)	2 (5)	2 (2)	
Study site in China, No. (%)				.902
Northern	16 (39)	15 (37)	31 (38)	
Southeast	19 (46)	19 (46)	38 (46)	
Northwest	3 (7)	2 (5)	5 (6)	
Southern	3 (7)	5 (12)	8 (10)	
KPS score, No. (%)[b]				.067
100	0 (0)	1 (2)	1 (1)	
90	25 (61)	16 (39)	41 (50)	
80	11 (27)	21 (51)	32 (39)	
70	4 (10)	3 (7)	7 (9)	
60	0 (0)	1 (2)	1 (1)	
Diagnosis type, No. (%)				1.000
Locally advanced	9 (22)	8 (20)	17 (21)	
Metastatic	32 (78)	33 (80)	65 (79)	
Site of metastatic disease, No. (%)[c]				.648
Liver	24 (59)	24 (59)	48 (59)	
Lymph node	20 (49)	15 (37)	35 (43)	
Lung	5 (12)	9 (22)	14 (17)	
Peritoneum	8 (20)	10 (24)	18 (22)	
Abdominal cavity	12 (29)	9 (22)	21 (26)	
Metastatic sites, No. (%)[c]				.770
1	7 (17)	9 (22)	16 (20)	
2	4 (10)	5 (12)	9 (11)	
3	5 (12)	7 (17)	12 (15)	
>3	23 (56)	18 (44)	41 (50)	
Pancreatic cancer history, year, No. (%)				.519
<1	34 (83)	37 (90)	71 (87)	
≥1	7 (17)	4 (10)	11 (13)	
Pancreatic tumor location, No. (%)				.949
Head	17 (41)	17 (41)	34 (41)	
Body	6 (15)	7 (17)	13 (16)	
Tail	18 (44)	17 (41)	35 (43)	
Previous therapy, No. (%)				1.000
Surgery	23 (56)	23 (56)	46 (56)	
Adjuvant chemotherapy	3 (7)	3 (7)	6 (7)	
Radiation therapy	1 (2)	1 (2)	2 (2)	
Biliary obstruction treatment	4 (10)	4 (10)	8 (10)	

NOTE. There were no significant differences between groups at baseline.
Abbreviation: KPS, Karnofsky performance status.
[a]Race or ethnic group was self-reported.
[b]KPS scores range from 0 to 100, with higher scores indicating better performance status. According to the original protocol, the KPS scores of the screening visit could be applied to the baseline visit.
[c]Metastatic diseases or sites were calculated according to the actual enrolled patients. T test was used to compare age; chi-square test was used to compare the distribution of age/sex/diagnosis type/site of metastatic disease/pancreatic tumor location; race or ethnic group/patients by study sites/KPS/number of metastatic sites/pancreatic cancer history/previous therapy were compared using the Fisher test.

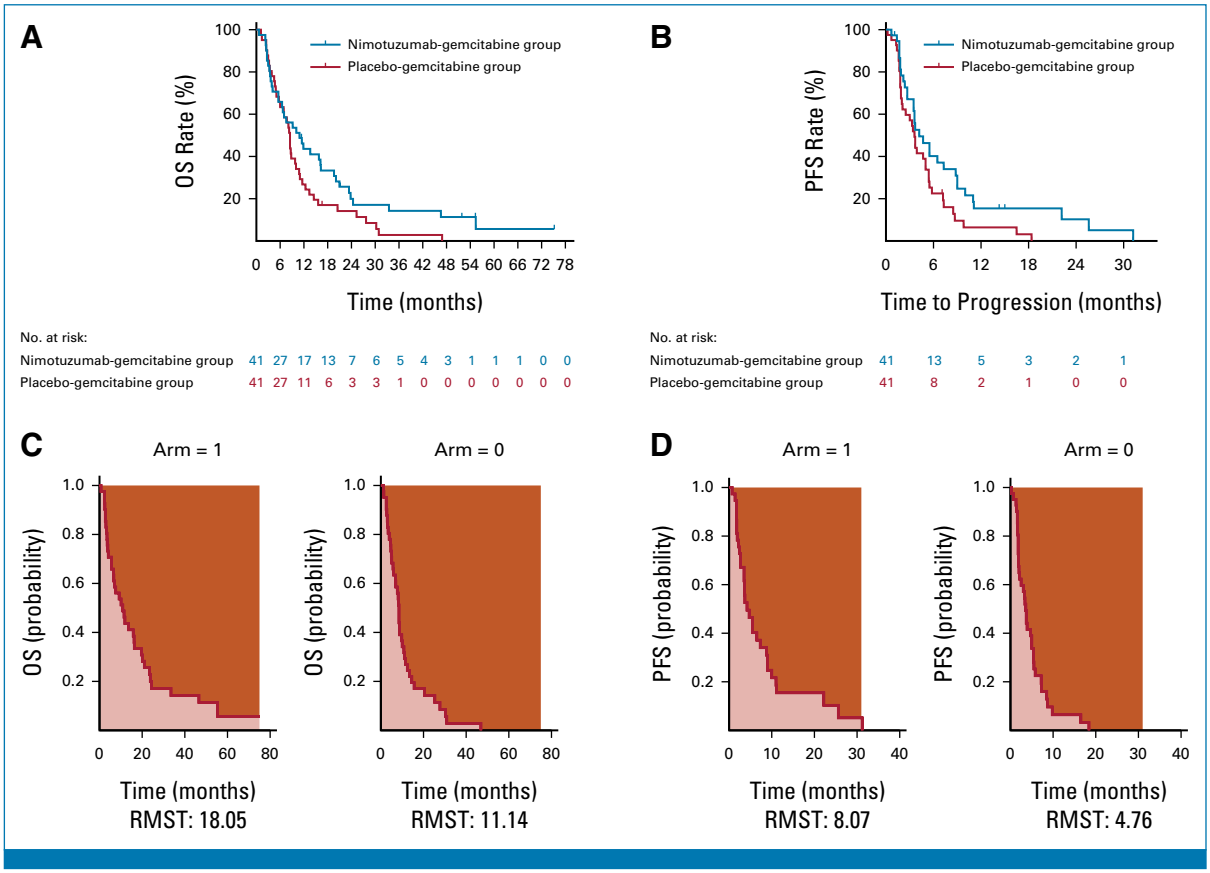

FIG 2. Kaplan-Meier curves for OS and PFS, the RMST test for OS time until the end of trial (75 months). (A) OS. (B) PFS. (C) OS time by the RMST test (arm = 1 is for the nimotuzumab-gemcitabine group, arm = 0 is for the placebo-gemcitabine group; the estimate of RMST is the red area, and the restricted mean lost time is the orange area). (D) PFS time by the RMST test (arm = 1 is for the nimotuzumab-gemcitabine group, arm = 0 is for the placebo-gemcitabine group; estimate of RMST is the red area and the restricted mean lost time is the orange area). OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time.

was 6,400 mg in the nimotuzumab-gemcitabine group (range, 400-50,800 mg; dose frequency, once per week).

Safety

The incidences of AEs in this trial are shown in Table 3. The occurrence of ADRs was similar between the two groups. There was only one case of serious ADR in the nimotuzumab-gemcitabine group. The patient was hospitalized for a CTCAE grade 3 bilirubin increase and anemia, which are listed in the nimotuzumab package insert. Neutropenia, thrombocytopenia, leukopenia, and AST or ALT increased, and rash, fatigue, and fever were comparable between the two groups. No grade 4-5 AEs were observed in this trial.

DISCUSSION

This prospective, randomized, controlled, double-blind, multicenter clinical trial demonstrated that nimotuzumab combined with gemcitabine prolonged the median OS time by 2.4 months and decreased the mortality risk by 34% compared with the placebo group by Cox regression. Once the trial was completed, we observed that the survival curves overlapped until 6 months and gradually separated thereafter. In this situation, the proportional hazard assumption for the Cox regression model does not hold. Consequently, it is not a robust method. Subsequently, we used the RMST model to calculate the survival differences between the two curves using the RMST ratio, which behaves as an analog of the Cox proportional HR. The mortality risk decreased by 38%, which was equivalent to RMST ratio 0.62 (0.40-0.97) calculated at the placebo-gemcitabine versus nimotuzumab-gemcitabine direction, and the differences were statistically significant. The RMST for both OS and PFS was significantly longer in the nimotuzumab-gemcitabine group than in the control group. The 1-year and 3-year OS rates were 43.6% versus 26.8% and 13.9% versus 2.7% in the investigational and control arms, respectively. These results demonstrated that nimotuzumab increased the

TABLE 2. OS, PFS, and Response Rates

Efficacy Variable	Nimotuzumab-Gemcitabine Group (N = 41)	Placebo-Gemcitabine Group (N = 41)	HR/RMST Ratio (95% CI)[a]	*P*[b]
OS, months, median (95% CI)				
OS	10.9 (5.6 to 16.3)	8.5 (5.7 to 10.0)	0.66(0.42 to 1.05)	.08
RMST survival	18.05 (11.71 to 24.38)	11.14 (8.07 to 14.20)	0.62 (0.40 to 0.97)	.036
Survival rate, months, % (95% CI)				
6	66 (49 to 78)	63 (47 to 76)		
12	44 (28 to 58)	27 (15 to 41)		
18	33 (20 to 48)	17 (8 to 30)		
24	20 (9 to 34)	14 (6 to 27)		
36	14 (5 to 27)	3 (0 to 13)		
PFS, months, median (95% CI)				
PFS	4.2 (2.7 to 7.3)	3.6 (2.0 to 5.0)	0.60 (0.37 to 0.99)	.04
RMST survival	8.08 (5.20 to 10.94)	4.76 (3.41 to 6.09)	0.58 (0.38 to 0.90)	.036
PFS rate, months, % (95% CI)				
6	40 (24 to 56)	23 (11 to 37)		
12	16 (6 to 30)	6 (1 to 18)		
18	16 (6 to 30)	3 (0 to 14)		
TTP				
TTP, months, median (95% CI)	4.7 (2.7 to 9.0)	3.7 (2.0 to 5.4)		.137
Progression rate, months, % (95% CI)				
6	59 (43 to 76)	76 (60 to 89)		
12	83 (68 to 94)	85 (69 to 96)		
18	83 (68 to 94)	93 (75 to 99)		
Response				
Objective response rate[c]				
Investigator review				
No. of patients with a response	3	4		>.999
% (95% CI)	7 (2 to 20)	10 (3 to 23)		
Disease control rate[d]				
Investigator review				
No. of patients with a response	28	26		.641
% (95% CI)	68 (52 to 82)	63 (47 to 78)		
Best response according to the investigator review, No. (%)				
CR	0	0		
PR	3 (7)	4 (10)		
SD	26 (63)	22 (54)		
Progressive disease	9 (22)	14 (34)		
Not evaluated	3 (7)	1 (2)		
CBR				
Investigator review				
No. of patients with effective CBR	11	10		.573
% (95% CI)	39 (21 to 57)	32 (16 to 49)		

Abbreviations: CBR, clinical benefit response; CR, complete response; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PR, partial response; RMST, restricted mean survival time; SD, stable disease; TTP, time to progression.

[a]The HR for death is provided for OS, and the HR for progression or death is provided for PFS, with a HR of <1 favoring the nimotuzumab-gemcitabine group. The 95% CI for response-rate ratios was calculated according to the asymptotic 95% CI of the relative risk in the nimotuzumab-gemcitabine group compared with the placebo-gemcitabine group. The RMST ratio was 0.62 (0.40-0.97) calculated at the placebo-gemcitabine versus nimotuzumab-gemcitabine direction.

[b]*P* value was from the log-rank test of four stratified factors according to the tumor lesion site, surgery history, biliary obstruction treatment, and adjuvant chemotherapy.

[c]Objective response included confirmed CR and PR.

[d]Disease control included confirmed CR, confirmed PR, and SD.

median survival time of patients with advanced PC with K-Ras wild-type tumors.

Compared with other studies, the NOTABLE trial showed that nimotuzumab might confer a remarkable survival benefit. In a previous study, the median OS of gemcitabine monotherapy was 5.65 months.[13] However, the median OS was increased to 6.24 months when combined with erlotinib,[17] and 8.5 months and 1-year OS rate of 35% when albumin-paclitaxel was added to gemcitabine.[18] In addition to these regimens, the fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) schedule had the longest median survival time of 11.1 months; its usage is limited owing to side effects.[19] Compared with the current treatment alternatives, the median OS of nimotuzumab-gemcitabine in this study was 10.9 months, and the 1-year OS rate was 43.6%, which was equal to that of the FOLFIRINOX regimen, but with a better safety profile.

PFS was also significantly higher in the nimotuzumab arm, according to the log-rank *P* value and RMST method. The ORRs of the two treatment groups were similar; however, the DCR and CBR were higher in the nimotuzumab group, although the difference was not statistically significant. These results indicate that nimotuzumab may improve disease control and slow the progression of advanced PC.

In the subgroup analyses, the nimotuzumab-gemcitabine combination showed a greater benefit, which was consistent with the results of the total population analysis. The subgroup analysis should be interpreted with caution because after adjusting the sample size, the subgroups were small. Regarding the safety profile, AEs or ADRs were comparable between the two groups and did not increase after the addition of nimotuzumab. The frequency of total hematologic or nonhematologic AEs (including grade 3 AEs) >10% was similar between the two groups. All TRAEs were grade 1-3, and no grade 4-5 adverse reactions or

A

Subgroup	Nimotuzumab-Gemcitabine (No. of events/patients)	Placebo-Gemcitabine (No. of events/patients)	HR (95% CI)	*P*	*P* for Interaction
All patients	**36/41**	**40/41**	**0.66 (0.42-1.05)**	**.08**	
Tumor site					**.73**
Head	15/17	17/17	0.75 (0.37-1.51)	.42	
Body or tail	21/24	23/24	0.61 (0.33-1.13)	.12	
Surgery					**.1**
Yes	22/23	22/23	0.98 (0.53-1.78)	.94	
No	14/18	18/18	0.4 (0.19-0.84)	.02	
Billiary obstruction					**0**
Yes	4/4	5/5		1	
No	32/37	35/36	0.54 (0.33-0.89)	.02	
Chemotherapy					**.13**
Yes	2/3	2/3	0.33 (0.03-3.98)	.39	
No	34/38	38/38	0.68 (0.43-1.09)	.11	
Type					**.39**
Locally	8/9	8/8	0.74 (0.27-2.07)	.57	
Metastatic	28/32	32/33	0.65 (0.38-1.09)	.1	
KPS score					**.35**
60-80	19/21	19/19	0.53 (0.27-1.04)	.07	
90-100	17/20	21/22	0.82 (0.43-1.57)	.56	
Sex					**.47**
Male	24/27	24/24	0.64 (0.36-1.16)	.14	
Female	12/14	16/17	0.62 (0.28-1.37)	.24	
Age, years					**.4**
<65 years	29/33	29/30	0.7 (0.41-1.19)	.19	
≥65 years	7/8	11/11	0.54 (0.19-1.52)	.24	
Course of disease					**.48**
<1 year	30/34	37/37	0.6 (0.36-0.99)	.04	
≥1 year	6/7	3/4	1.37 (0.32-5.91)	.67	

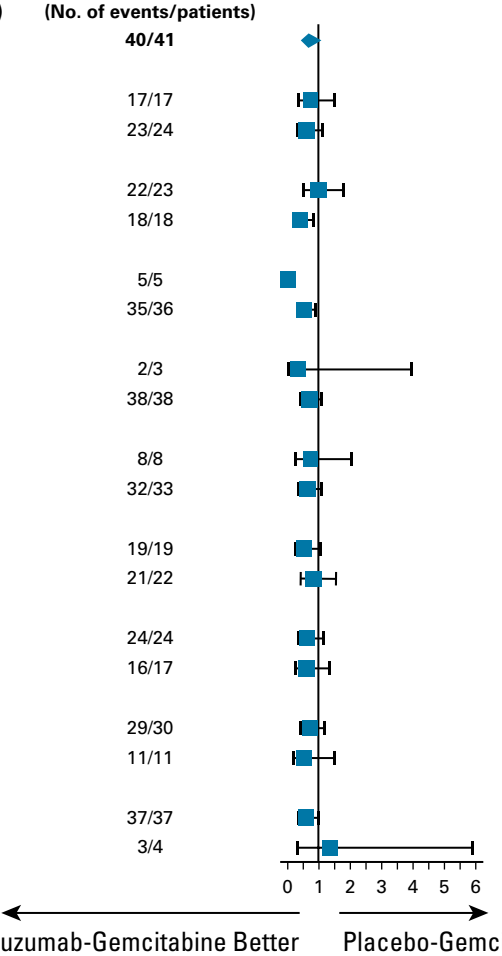

FIG 3. Forest plots of the treatment effect on (A) OS and (B) PFS in prespecified subgroups. The KPS score ranges from 0 to 100, with a higher score indicating better performance status. The HR and *P* value were obtained under the Cox regression model. HR, hazard ratio; KPS, Karnofsky performance status; OS, overall survival; PFS, progression-free survival. (continued on following page)

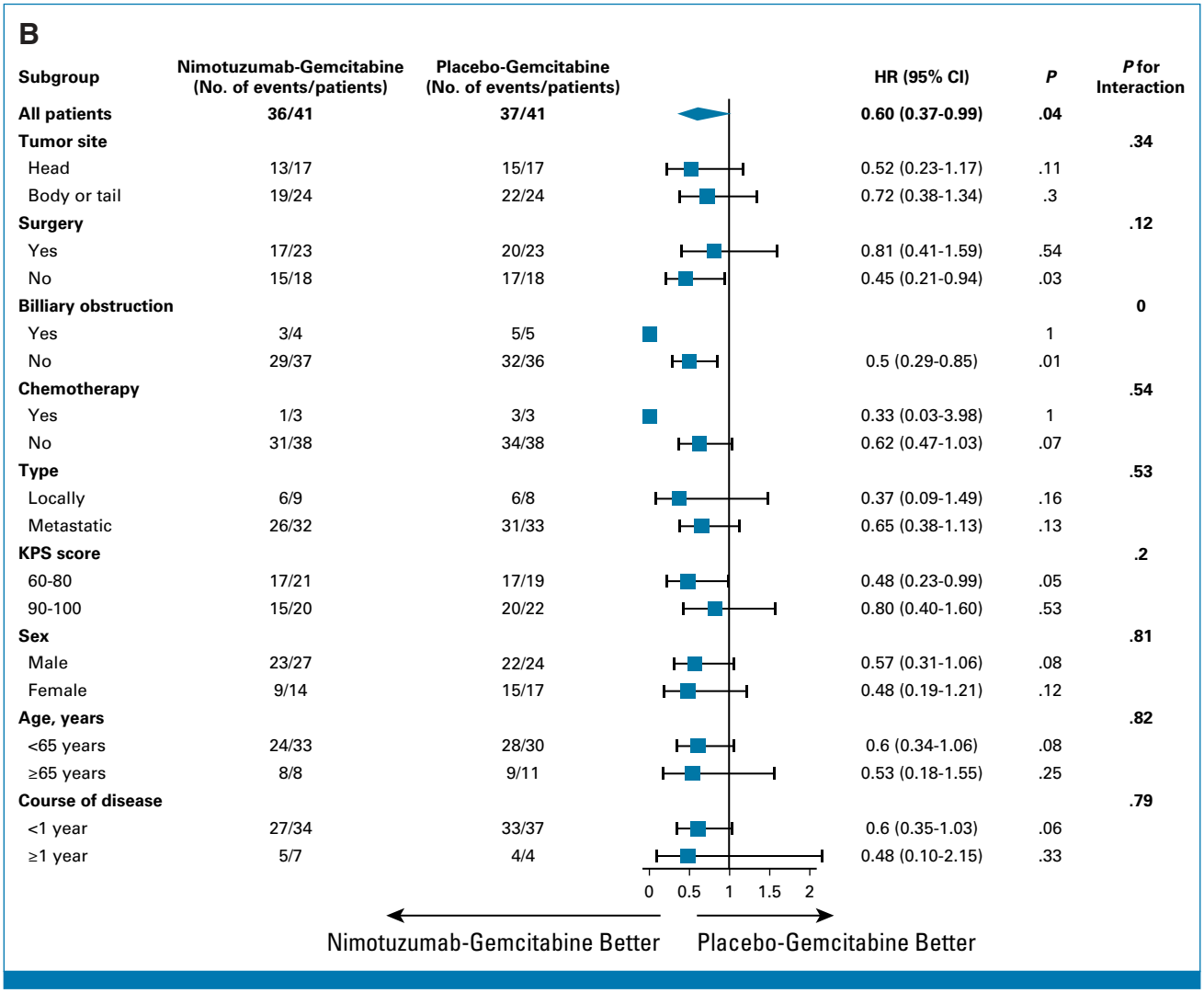

FIG 3. (Continued).

events occurred. Only grade 1-2 rash reactions were observed. This trial confirmed that nimotuzumab has a good safety profile.

The proportion of K-Ras wild-type tumors in our study was 17.1%. This percentage was higher than the internationally reported data, but similar to a previous nationwide study in China (16.8%).[20]

One limitation of this study is that EGFR expression and other genetic mutation types were not evaluated. It is unknown whether patients with activation of the mitogen-activated protein kinase pathway because of *BRAF* mutations would benefit from nimotuzumab treatment. Alternatively, other kinase fusion genes might confer sensitivity to nimotuzumab. Delineating the molecular subtypes of K-Ras wild-type tumors could improve patient selection for nimotuzumab treatment.

Information on subsequent treatments after disease progression was not collected, which is another limitation of this study. Third, although there were no statistically significant differences in baseline characteristics between the two arms, nimotuzumab-treated patients were slightly younger and had a better performance status. These features may have led to the improved treatment compliance. Finally, the study protocol was formulated in 2014, when the standard of care of first-line treatment regimens in China was gemcitabine monotherapy. At that time, FOLFIRINOX was rarely used in China because of its high

TABLE 3. The Overall Incidence of AEs in This Trial

AE	Nimotuzumab-Gemcitabine Group (N = 45), No. (%)	Placebo-Gemcitabine Group (N = 45), No. (%)
ADR	31 (69)	29 (65)
Serious ADR	1 (2)	2 (4)
Drug reduction or discontinued for ADR	4 (9)	6 (13)
Death for ADR	0 (0)	1 (2)
Withdrawal for ADR	2 (4)	1 (2)
Total hematologic AEs (including grade 3) constituting >10% of AEs[a]		
Neutropenia	12 (27)	11 (24)
Thrombocytopenia	10 (22)	9 (20)
Leukopenia	12 (27)	12 (27)
Anemia	7 (16)	10 (22)
AST increased	9 (20)	9 (20)
ALT increased	6 (13)	10 (22)
Total nonhematologic AEs (including grade 3) occurring in >10% of AEs[b]		
Rash	0 (0)	4 (9)
Fatigue	2 (4)	6 (13)
Fever	1 (2)	2 (4)

Abbreviations: ADR, adverse drug reaction; AE, adverse event.
[a]Assessment of the event was made on the basis of laboratory values.
[b]Assessment of the event was made on the basis of investigator assessment of treatment-related AEs.

toxicity (some populations cannot tolerate combination chemotherapy), and gemcitabine/nab-paclitaxel was not the standard practice.

In conclusion, the combination of nimotuzumab and gemcitabine was safe and increased the OS and PFS of patients with locally advanced or metastatic PC with wild-type KRAS.

AFFILIATIONS

[1]Cancer Center of Jinling Hospital, Nanjing, China
[2]Shanghai East Hospital, Shanghai, China
[3]Harbin Medical University Cancer Hospital, Harbin, China
[4]The First Affiliated Hospital of Bengbu Medical College, Bengbu, China
[5]The Second Hospital of Anhui Medical University, Hefei, China
[6]Cancer Center of Sun Yat-sen University, Guangzhou, China
[7]The Fifth Medical Center, General Hospital of People's Liberation Army, Beijing, China
[8]Xijing Hospital, Air Force Medical University of PLA, Xi'an, China
[9]Jiangsu Cancer Hospital, Nanjing, China
[10]The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[11]Zhongshan Hospital, Fudan University, Shanghai, China
[12]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[13]Zhejiang Cancer Hospital, Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Cancer Hospital of the University of Chinese Academy of Sciences, Hangzhou, China
[14]The First People's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[15]Peking University Cancer Hospital & Institute, Beijing, China
[16]Huashan Hospital, Fudan University, Shanghai, China
[17]Jilin Cancer Hospital, Changchun, China
[18]Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, China
[19]Jiangyin People's Hospital, Jiangyin, China
[20]Liaoning Cancer Hospital & Institute, Shenyang, China
[21]Sir Run Run Shaw Hospital Zhejiang University School of Medicine, Hangzhou, China
[22]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[23]Biotech Pharmaceutical Ltd, Corp, Beijing, China
[24]Shanghai University of Traditional Chinese Medicine, Shanghai, China

CORRESPONDING AUTHOR

Shukui Qin, MD, Cancer Center of Nanjing Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing 210002, China; e-mail: qinsk@csco.org.cn.

EQUAL CONTRIBUTION

S.Q. is the first author and J.L. is the co-first author.

PRIOR PRESENTATION

Presented at the Clinical Science Symposium at the 2022 ASCO annual meeting, Chicago, IL, June 3-7, 2022.

SUPPORT

Supported by Biotech Pharmaceutical Co, Ltd.

CLINICAL TRIAL INFORMATION

NCT02395016

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.02630.

DATA SHARING STATEMENT

All the authors agree to provide a data-sharing statement for this manuscript. Data-sharing requests should be sent to qinsk@csco.org.cn for deidentified data. Such requests will be considered by the study team after publication, after the review and approval of proposals and with appropriate data-sharing agreements in place.

AUTHOR CONTRIBUTIONS

Conception and design: Shukui Qin, Yuxian Bai, Zishu Wang, Zhendong Chen, Ruihua Xu, Jianming Xu, Jia Chen, Lin Yang, Haijun Zhong, Lin Shen, Chunyi Hao, Deliang Fu, Jianwei Yang, Qiong Wang, Baoli Qin, Hongming Pan, Xianhong Bai, Qingshan Zheng
Administrative support: Lin Shen
Provision of study materials or patients: Jin Li, Ruihua Xu, Lin Yang, Lin Shen, Deliang Fu, Ying Cheng
Collection and assembly of data: Shukui Qin, Jin Li, Yuxian Bai, Zishu Wang, Zhendong Chen, Jia Chen, Ying Yuan, Tianshu Liu, Lin Yang, Haijun Zhong, Donghui Chen, Lin Shen, Chunyi Hao, Deliang Fu, Ying Cheng, Jianwei Yang, Qiong Wang, Baoli Qin, Hongming Pan, Jun Zhang, Qingshan Zheng
Data analysis and interpretation: Shukui Qin, Yuxian Bai, Zishu Wang, Zhendong Chen, Ruihua Xu, Jianming Xu, Hongmei Zhang, Jia Chen, Lin Yang, Haijun Zhong, Donghui Chen, Chunyi Hao, Jianwei Yang, Qiong Wang, Baoli Qin, Hongming Pan, Xianhong Bai, Qingshan Zheng
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. De La Cruz MS, Young AP, Ruffin MT: Diagnosis and management of pancreatic cancer. Am Fam Physician 89:626-632, 2014
2. Xiong HQ, Carr K, Abbruzzese JL: Cytotoxic chemotherapy for pancreatic cancer: Advances to date and future directions. Drugs 66:1059-1072, 2006
3. Li D, Xie K, Wolff R, et al: Pancreatic cancer. Lancet 363:1049-1057, 2004
4. Van Cutsem E, Aerts R, Haustermans K: Systemic treatment of pancreatic cancer. Eur J Gastroenterol Hepatol 16:265-274, 2004
5. Carmichael J: Clinical response benefit in patients with advanced pancreatic cancer. Role of gemcitabine. Digestion 58:503-507, 1997
6. Eckel F, Schneider G, Schmid RM: Pancreatic cancer: A review of recent advances. Expert Opin Investig Drugs 15:1395-1410, 2006
7. Oettle H, Arnold D, Hempel C, et al: The role of gemcitabine alone and in combination in the treatment of pancreatic cancer. Anticancer Drugs 11:771-786, 2000
8. Rocha Lima CM, Flores AM: Gemcitabine doublets in advanced pancreatic cancer: Should we move on? J Clin Oncol 24:327-329, 2006
9. Xiong HQ, Rosenberg A, LoBuglio A: Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, incombination with gemcitabine for advanced pancreatic cancer: A multicenter phase II trial. J Clin Oncol 22:2610-2616, 2004
10. Schultheis B, Reuter D, Ebert MP, et al: Gemcitabine combined with the monoclonal antibody nimotuzumab is an active first-line regimen in KRAS wild-type patients with locally advanced or metastatic pancreatic cancer: A multicenter, randomized phase IIb study. Ann Oncol 28:2429-2435, 2017
11. ASCO Workgroup: Good clinical practice research guidelines reviewed, emphasis given to responsibilities of investigators: Second article in a series. JCO Oncol Pract 4:233-235, 2008
12. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009
13. Burris HA 3rd, Moore MJ, Andersen J, et al: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 15:2403-2413, 1997
14. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, 2010. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
15. Uno H, Claggett B, Tian L, et al: Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol 32:2380-2385, 2014
16. Huang B, Kuan PF: Comparison of the restricted mean survival time with the hazard ratio in superiority trials with a time-to-event end point. Pharm Stat 17:202-213, 2018
17. Moore MJ, Goldstein D, Hamm J, et al: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25:1960-1966, 2007
18. Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369:1691-1703, 2013
19. Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-1825, 2011
20. Zhang X, Mao T, Zhang B, et al: Characterization of the genomic landscape in large-scale Chinese patients with pancreatic cancer. EBioMedicine 77:103897, 2022

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Nimotuzumab Plus Gemcitabine for K-Ras Wild-Type Locally Advanced or Metastatic Pancreatic Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Ruihua Xu
Consulting or Advisory Role: HenRui, BeiGene, AstraZeneca, Junshi Biosciences, Bristol Myers Squibb, Merck Serono, Roche, Astellas Pharma, KYM Biosciences

Lin Shen
Consulting or Advisory Role: MSD, Bristol Myers Squib, AstraZeneca, Daiichi Sankyo, Roche, Mingji Biopharmaceutical, Harbor BioMed, Merck, Boehringer Ingelheim, Sanofi
Research Funding: Nanjing Yaojieankang Biotechnology (Inst), Baiji Shenzhou (Beijing) Biotechnology (Inst), Beijing Xiantong Biomedical Technology (Inst), QiLu Pharmaceutical (Inst), Zaiding Pharmaceutical (Inst), Jacobio (Inst), CANbridge Pharmaceuticals (Inst)

Xianhong Bai
Employment: Biotech Pharmaceutical Co, Ltd
Leadership: Biotech Pharmaceutical Co, Ltd
Stock and Other Ownership Interests: Biotech Pharmaceutical Co, Ltd
Honoraria: Biotech Pharmaceutical Co, Ltd
Travel, Accommodations, Expenses: Biotech Pharmaceutical Co, Ltd

No other potential conflicts of interest were reported.