Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial

Andrea Wang-Gillam, Chung-Pin Li, György Bodoky, Andrew Dean, Yan-Shen Shan, Gayle Jameson, Teresa Macarulla, Kyung-Hun Lee, David Cunningham, Jean F Blanc, Richard A Hubner, Chang-Fang Chiu, Gilberto Schwartsmann, Jens T Siveke, Fadi Braiteh, Victor Moyo, Bruce Belanger, Navreet Dhindsa, Eliel Bayever, Daniel D Von Hoff*, Li-Tzong Chen*, for the NAPOLI-1 Study Group†*

Summary

Background Nanoliposomal irinotecan showed activity in a phase 2 study in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapies. We assessed the effect of nanoliposomal irinotecan alone or combined with fluorouracil and folinic acid in a phase 3 trial in this population.

Methods We did a global, phase 3, randomised, open-label trial at 76 sites in 14 countries. Eligible patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy were randomly assigned (1:1) using an interactive web response system at a central location to receive either nanoliposomal irinotecan monotherapy (120 mg/m² every 3 weeks, equivalent to 100 mg/m² of irinotecan base) or fluorouracil and folinic acid. A third arm consisting of nanoliposomal irinotecan (80 mg/m², equivalent to 70 mg/m² of irinotecan base) with fluorouracil and folinic acid every 2 weeks was added later (1:1:1), in a protocol amendment. Randomisation was stratified by baseline albumin, Karnofsky performance status, and ethnic origin. Treatment was continued until disease progression or intolerable toxic effects. The primary endpoint was overall survival, assessed in the intention-to-treat population. The primary analysis was planned after 305 events. Safety was assessed in all patients who had received study drug. This trial is registered at ClinicalTrials.gov, number NCT01494506.

Findings Between Jan 11, 2012, and Sept 11, 2013, 417 patients were randomly assigned either nanoliposomal irinotecan plus fluorouracil and folinic acid (n=117), nanoliposomal irinotecan monotherapy (n=151), or fluorouracil and folinic acid (n=149). After 313 events, median overall survival in patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid was 6·1 months (95% CI 4·8–8·9) *vs* 4·2 months (3·3–5·3) with fluorouracil and folinic acid (hazard ratio 0·67, 95% CI 0·49–0·92; p=0·012). Median overall survival did not differ between patients assigned nanoliposomal irinotecan monotherapy and those allocated fluorouracil and folinic acid (4·9 months [4·2–5·6] *vs* 4·2 months [3·6–4·9]; 0·99, 0·77–1·28; p=0·94). The grade 3 or 4 adverse events that occurred most frequently in the 117 patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid were neutropenia (32 [27%]), diarrhoea (15 [13%]), vomiting (13 [11%]), and fatigue (16 [14%]).

Interpretation Nanoliposomal irinotecan in combination with fluorouracil and folinic acid extends survival with a manageable safety profile in patients with metastatic pancreatic ductal adenocarcinoma who previously received gemcitabine-based therapy. This agent represents a new treatment option for this population.

Funding Merrimack Pharmaceuticals.

Introduction

Pancreatic ductal adenocarcinoma is typically diagnosed late, when curative resection is impossible and prognosis is poor, with only 1–2% of patients surviving at 5 years.[1,2] Gemcitabine-based therapies have been the standard of care for patients with locally advanced or metastatic pancreatic ductal adenocarcinoma for the past two decades.[3–5] However, two combination regimens—FOLFIRINOX (a combination of oxaliplatin, folinic acid, irinotecan, and fluorouracil) and albumin-bound paclitaxel in combination with gemcitabine—have gained acceptance as front-line treatments.[6,7] Despite these advances, progression after front-line therapy is inevitable, leaving patients and clinicians with few options and no universally accepted standard treatment—showing the unmet need in this population.[8]

Irinotecan has been investigated in several small monotherapy[9] and combination therapy[10–20] studies. The findings have provided initial evidence of the activity of irinotecan in the second-line setting. 1 mg of irinotecan hydrochloride trihydrate salt is equivalent to 0·86 mg of irinotecan free base. Nanoliposomal irinotecan comprises irinotecan free base encapsulated in liposome nanoparticles. The liposome is designed to keep irinotecan in the circulation—sheltered from conversion

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*Contributed equally

†Additional investigators listed in the appendix (pp 4, 5)

Washington University School of Medicine, St Louis, MO, USA (A Wang-Gillam MD); **Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan** (Prof C-P Li MD); **St László Teaching Hospital, Budapest, Hungary** (Prof G Bodoky MD); **St John of God Hospital, Subiaco, WA, Australia** (A Dean MD); **National Institute of Cancer Research, National Health Research Institutes, Tainan, and Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan** (Prof L-T Chen MD); **National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan** (Prof L-T Chen, Prof Y-S Shan MD); **TGen, Phoenix, and HonorHealth, Scottsdale, AZ, USA** (G Jameson MSN, Prof D D Von Hoff MD); **Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain** (T Macarulla MD); **Seoul National University Hospital, Seoul, South Korea** (K-H Lee MD); **The Royal Marsden Hospital, London, UK** (Prof D Cunningham MD); **Hôpital Saint-André, Bordeaux, France** (Prof J F Blanc MD);

The Christie NHS Foundation Trust, Manchester, UK (R A Hubner PhD); **China Medical University Hospital, Taichung, Taiwan** (Prof C-F Chiu MD); **Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil** (G Schwartsmann MD); **Klinikum rechts der Isar der T U München, Munich, Germany;** (Prof J T Siveke MD); **Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA** (F Braiteh MD); **and Merrimack Pharmaceuticals, Cambridge, MA, USA** (V Moyo MBBCh, B Belanger PhD, N Dhindsa DDS, E Bayever MBBCh)

Correspondence to: Prof Li-Tzong Chen, National Institute of Cancer Research, National Health Research Institutes, Tainan 704, Taiwan **leochen@nhri.org.tw**

See Online for appendix

Research in context

Evidence before this study

There is no consensus on the standard of care in patients with metastatic pancreatic cancer whose disease progressed after gemcitabine-based therapy despite the availability of more effective front-line treatments. At the time this study was designed, guidelines recommended clinical trials in this setting. Nanoliposomal irinotecan has shown activity in phase 2 studies in solid tumours, including metastatic pancreatic cancer, previously treated with gemcitabine-based therapy.

Added value of this study

In patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy, nanoliposomal irinotecan in combination with fluorouracil and folinic acid increased overall survival, progression-free survival, and time to treatment failure, reduced carbohydrate antigen 19-9 (a pancreatic tumour biomarker), and amplified the number of patients achieving an objective response. In a population with few treatment options, this drug combination was tolerable and did not have a negative effect on quality of life, which are important factors for this population.

Implications of all the available evidence

Nanoliposomal irinotecan in combination with fluorouracil and folinic acid represents a potential treatment option for patients with metastatic pancreatic cancer that progressed after a gemcitabine-based regimen. Future research will assess its use in front-line therapy.

to its active metabolite (SN-38)—longer than free (unencapsulated) irinotecan, which would increase and prolong intratumoral levels of both irinotecan and SN-38 compared with free irinotecan.[21–23] The roughly 5·6-fold higher level of SN-38 found in tumours compared with plasma at 72 h suggests local metabolic activation of irinotecan, which was contained in the liposomal nanoparticles, to SN-38.[21] In a phase 2 study of 40 patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy, nanoliposomal irinotecan at 120 mg/m² every 3 weeks resulted in a median overall survival of 5·2 months, 1-year survival of 25%, and a manageable toxicity profile.[24] The aim of this study (NAPOLI-1) was to assess the effect of nanoliposomal irinotecan, alone and in combination with fluorouracil and folinic acid, compared with a common control (fluorouracil and folinic acid), for patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy.

Methods

Study design and participants

We designed a global, multicentre, open-label, phase 3 study conducted at 76 sites in 14 countries (Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Hungary, Italy, South Korea, Spain, Taiwan, the UK, and USA). We included patients aged 18 years or older with histologically or cytologically confirmed pancreatic ductal adenocarcinoma and documented measurable or non-measurable distant metastatic disease. The disease must have progressed after previous gemcitabine-based therapy given in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting. Other key inclusion criteria were a Karnofsky performance status score of 70 or more and adequate haematological (including absolute neutrophil count >1·5×10⁹ cells per L), hepatic (including normal serum total bilirubin, according to local institutional standards, and albumin levels ≥30 g/L), and renal function. We also enrolled patients who had previously received irinotecan or fluorouracil, or both.

All versions of the protocol and informed consent form were approved by the institutional review board or ethics committees for every site. The study was done according to the principles of the Declaration of Helsinki, the International Conference on Harmonisation Guidance on Good Clinical Practice, and the requirements of the US Food and Drug Administration and local regulatory authorities regarding the conduct of human clinical trials. All patients provided written informed consent.

Randomisation and masking

We initially randomly assigned patients in a 1:1 ratio to receive either nanoliposomal irinotecan monotherapy or a control of fluorouracil and folinic acid (protocol version 1). Following clinical interest in the combination of nanoliposomal irinotecan with other agents, we amended the protocol to add a third arm (1:1:1 ratio) of nanoliposomal irinotecan plus fluorouracil and folinic acid (protocol version 2) after safety data on this combination became available from an ongoing study in metastatic colorectal cancer.[25] Sites continued to enrol patients under protocol version 1 until protocol version 2 was approved at that site.

We randomised patients according to a prespecified scheme generated by an independent statistician within the funder-designated contract research organisation. On confirmation of a patient's eligibility, investigators used a computerised interactive web response system to obtain a patient number, which was associated with a random assignment. We stratified the randomisation by baseline albumin levels (≥40 g/L *vs* <40 g/L), Karnofsky performance status (70 and 80 *vs* ≥90), and ethnic origin (white *vs* east Asian *vs* all others).

Procedures

All patients underwent *UGT1A1* genotype testing. Patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid (combination therapy arm) received an intravenous infusion of nanoliposomal irinotecan over 90 min at a dose of 80 mg/m² (equivalent to 70 mg/m² of irinotecan free base), followed by folinic acid 400 mg/m² over 30 min, then fluorouracil 2400 mg/m² over 46 h, every 2 weeks. For those allocated to the monotherapy arm, nanoliposomal irinotecan was administered at a dose of 120 mg/m² (equivalent to 100 mg/m² of irinotecan free base), every 3 weeks.[24,26] We reduced the initial nanoliposomal irinotecan dose for patients homozygous for the *UGT1A1*28* allele by 20 mg/m² then increased it to the standard dose after the first cycle in the absence of drug-related toxic effects.[27] Patients who were assigned fluorouracil and folinic acid (control arm) received 200 mg/m² of folinic acid as a 30-min infusion followed by an infusion of 2000 mg/m² fluorouracil over 24 h, every week for the first 4 weeks of each 6-week cycle. We based the fluorouracil and folinic acid schedule of the control arm on that used in the CONKO-003 trial[28] and of the combination therapy arm on that used in the PEPCOL study,[25] with expected dose intensities of fluorouracil over a 6-week period of 8000 mg/m² in the control arm and 7200 mg/m² in the combination therapy arm. Treatment continued until disease progression or intolerable toxic effects arose.

We did serial imaging studies and measured amounts of carbohydrate antigen 19-9 (CA19-9) at baseline and every 6 weeks until either disease progression, a new antineoplastic treatment was started, or withdrawal of consent. We did radiographic tumour response assessment according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and we assessed safety by grading adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. We measured quality of life at baseline and every 6 weeks with the European Organization for Research and Treatment of Cancer Quality-of-Life Core Questionnaire (EORTC-QLQ-C30). We assessed clinical benefit response as described elsewhere.[3] We followed up patients every month after treatment termination for survival until death or study completion. An independent data safety monitoring board assessed cumulative safety and other trial-related data at regular intervals.

Outcomes

The primary efficacy endpoint was overall survival. Secondary endpoints included progression-free survival; time to treatment failure; the proportion of patients achieving an objective response; serum CA19-9 response (ie, ≥50% decrease in amount of CA19-9 from baseline at least once during the treatment period); clinical benefit response (ie, either achievement of pronounced and sustained [≥4 weeks contiguous] improvement in pain intensity, analgesic consumption, or performance status, or a combination of these, without any worsening in any of the other factors, or stability in pain intensity, analgesic consumption, and performance status with pronounced and sustained [≥4 weeks contiguous] weight gain); quality of life; and safety. A secondary objective, the pharmacokinetics of nanoliposomal irinotecan as a single agent and in combination with fluorouracil and folinic acid, will be reported separately.

Statistical analysis

We calculated the sample size for the three-arm study through a simulation as part of this study. In the protocol, we planned to enrol 405 patients, for a primary analysis of overall survival after 305 events, to provide at least 98% power to detect a hazard ratio (HR) for death with nanoliposomal irinotecan plus fluorouracil and folinic acid relative to fluorouracil and folinic acid of 0·5, and at least 85% power to detect a HR for death with nanoliposomal irinotecan monotherapy relative to fluorouracil and folinic acid of 0·67.

We did efficacy analyses in the intention-to-treat population (ie, all randomised patients). We analysed safety in patients who received one dose or more (including a partial dose) of study treatment. For the primary efficacy analysis, the null hypotheses tested were: no effect of nanoliposomal irinotecan monotherapy on overall survival relative to control; and no effect of nanoliposomal irinotecan plus fluorouracil and folinic acid on overall survival relative to control. We controlled the family-wise error at a two-sided 0·05 level with the Bonferroni-Holm procedure. For all efficacy and quality-of-life comparisons, the patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid were compared with those allocated the fluorouracil and folinic acid control under the amended protocol (version 2), whereas patients assigned nan] oliposomal irinotecan monotherapy were compared with those allocated the fluorouracil and folinic acid control under either version of the protocol (versions 1 and 2).

We did Kaplan-Meier analyses on each treatment group to obtain non-parametric estimates of median overall survival and progression-free survival and time to treatment failure. We calculated corresponding 95% CIs with the log–log method. We used unstratified Cox proportional hazards regression to estimate HRs and their corresponding 95% CIs. We did two pairwise comparisons of overall survival and progression-free survival between the study treatments by unstratified log-rank test. To assess the robustness of the primary endpoint results, we used a Cox regression model with stepwise selection (p to enter <0·25, p to remain <0·15), with treatment and baseline potential prognostic factors as candidates for inclusion in the model for overall survival. We also did a supportive stratified analysis for overall survival, accounting for randomisation strata.

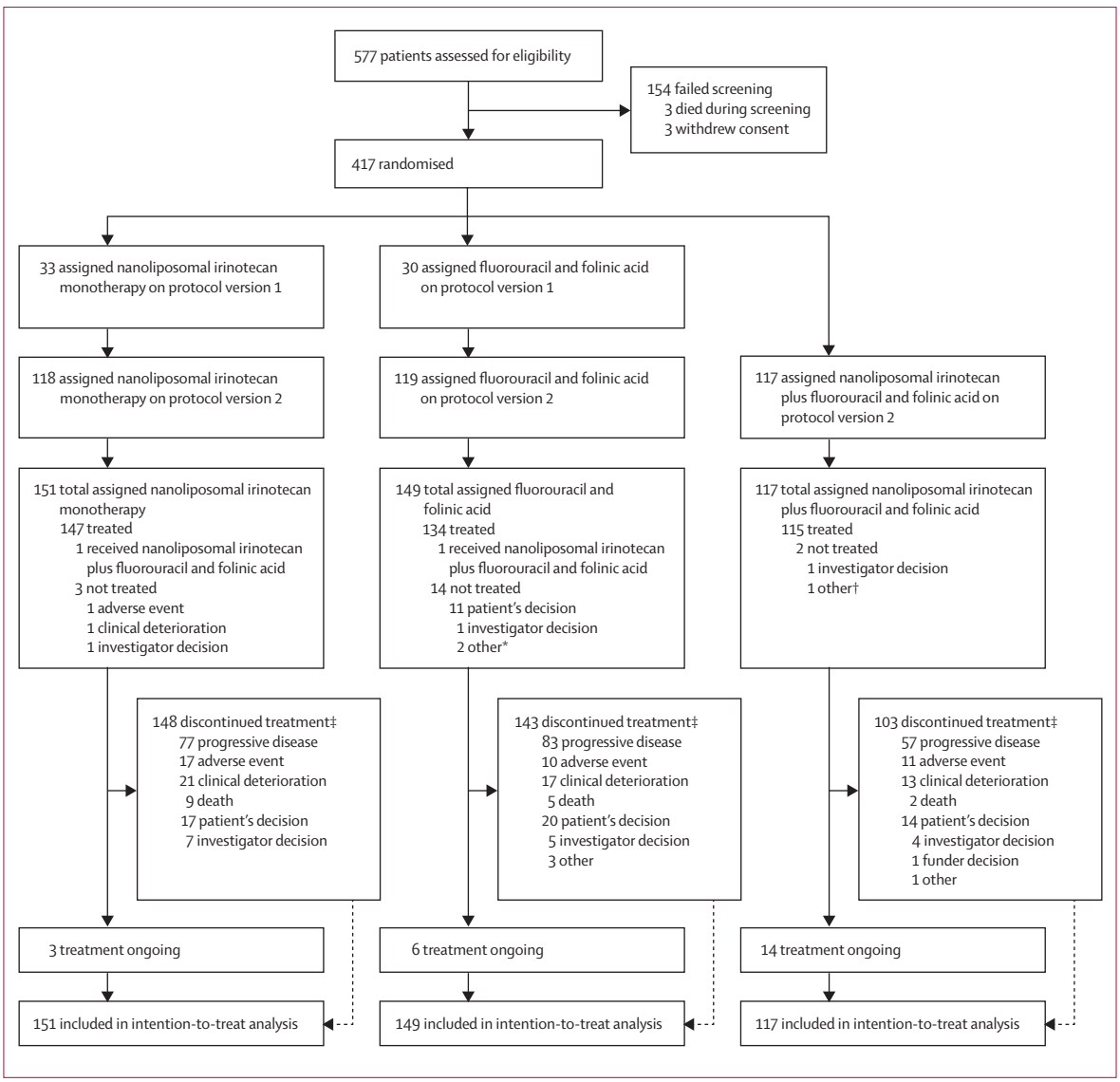

Figure 1: **Trial profile**
*One patient became ineligible after randomisation; one patient had an adverse event that delayed dosing more than 7 days from randomisation. †One patient became ineligible after randomisation. ‡The primary reason for discontinuation was at the discretion of the investigator.

We used Fisher's exact test for pairwise comparisons of objective response, clinical benefit response (we only included treated patients with a baseline pain intensity ≥20/100, baseline opioid pain medication consumption ≥10 mg/day of oral morphine equivalents, and a baseline Karnofsky performance status score of 70–90), and CA19-9 response (we only included treated patients with a baseline CA19-9 value >30 U/mL). We based analyses of progression-free survival and response on tumour and disease progression assessments per the investigator. We did pairwise treatment group comparisons for response classification for each quality-of-life subscale with the Cochran-Mantel-Haenszel test, and we used the Benjamini-Hochberg method to control type I error for comparisons on multiple subscales. We did all analyses and summaries with SAS, version 9.2 (or higher).

This study is registered with ClinicalTrials.gov, number NCT01494506.

Role of the funding source

This study was funded by Merrimack Pharmaceuticals. The study protocol was designed by the funder and external consultants, and data were analysed by a statistician employed by the funder (BB). All authors gathered data and were assisted in writing of the report by a medical writer employed by the funder. L-TC, AW-G, and DDVH had full access to all data in the study, participated in data interpretation, and had final responsibility for the

	Nanoliposomal irinotecan plus fluorouracil and folinic acid combination therapy (n=117)	Fluorouracil and folinic acid combination therapy control (n=119*)	Nanoliposomal irinotecan monotherapy (n=151)	Fluorouracil and folinic acid monotherapy control (n=149)
Men	69 (59%)	67 (56%)	87 (58%)	81 (54%)
Women	48 (41%)	52 (44%)	64 (42%)	68 (46%)
Age (years)	63 (57–70)	62 (55–69)	65 (58–70)	63 (55–69)
Ethnic origin				
East Asian	34 (29%)	36 (30%)	52 (34%)	50 (34%)
Black or African American	4 (3%)	3 (3%)	3 (2%)	3 (2%)
White	72 (62%)	76 (64%)	89 (59%)	92 (62%)
Other	7 (6%)	4 (3%)	7 (5%)	4 (3%)
Region				
Asia	34 (29%)	35 (29%)	50 (33%)	48 (32%)
Europe	47 (40%)	49 (41%)	54 (36%)	55 (37%)
North America	19 (16%)	19 (16%)	26 (17%)	25 (17%)
Other	17 (15%)	16 (13%)	21 (14%)	21 (14%)
Karnofsky performance status score†				
100	18 (15%)	17 (14%)	22 (15%)	22 (15%)
90	51 (44%)	40 (34%)	64 (42%)	54 (36%)
80	38 (32%)	51 (43%)	50 (33%)	61 (41%)
70	7 (6%)	10 (8%)	15 (10%)	11 (7%)
50–60	3 (3%)	0	0	0
Pancreatic tumour location				
Head	76 (65%)	69 (58%)	99 (66%)	81 (54%)
Other	41 (35%)	50 (42%)	52 (34%)	68 (46%)
Amount of CA19-9‡				
≥40 U/mL	92/114 (81%)	91/114 (80%)	125/146 (86%)	116/144 (81%)
<40 U/mL	22/114 (19%)	23/114 (20%)	21/146 (14%)	28/144 (39%)
Site of metastatic lesions§				
Liver	75 (64%)	83 (70%)	101 (67%)	108 (72%)
Lung	36 (31%)	36 (30%)	49 (32%)	44 (30%)
Lymph node, distant	32 (27%)	31 (26%)	44 (29%)	40 (27%)
Lymph node, regional	13 (11%)	14 (12%)	19 (13%)	20 (13%)
Pancreas	75 (64%)	72 (61%)	99 (66%)	97 (65%)
Peritoneum	28 (24%)	32 (27%)	48 (32%)	39 (26%)
Other	27 (23%)	39 (33%)	38 (25%)	48 (32%)

(Table 1 continues on next page)

decision to submit for publication. All authors agreed to submit the report.

Results

Between Jan 11, 2012, and Sept 11, 2013, 417 patients at 76 sites from 14 countries worldwide were randomly assigned to nanoliposomal irinotecan plus fluorouracil and folinic acid (n=117), nanoliposomal irinotecan monotherapy (n=151), or fluorouracil and folinic acid (n=149). 63 patients were enrolled under protocol version 1 before all sites switched to version 2 (figure 1). Patients' demographics and baseline clinical characteristics were similar among the three treatment groups (table 1). 51 (12%) patients received gemcitabine-based therapy in the adjuvant, neoadjuvant, or locally advanced setting but had not had previous treatment for metastatic disease, 234 (56%) had received one previous line of metastatic treatment, and 132 (32%) patients had previously received two or more lines of metastatic treatment.

Seven patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid and seven individuals allocated nanoliposomal irinotecan as monotherapy were homozygous for the *UGT1A1*28* allele. Three patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid were able to escalate to the standard starting dose of 80 mg/m² without need for subsequent dose reduction. One additional patient needed a dose reduction to 40 mg/m², and one discontinued because of an adverse event (grade 3 vomiting). Two of seven patients allocated nanoliposomal irinotecan were able to increase the dose, to 100 mg/m² and 120 mg/m². One patient needed a dose

	Nanoliposomal irinotecan plus fluorouracil and folinic acid combination therapy (n=117)	Fluorouracil and folinic acid combination therapy control (n=119*)	Nanoliposomal irinotecan monotherapy (n=151)	Fluorouracil and folinic acid monotherapy control (n=149)
(Continued from previous page)				
Measurable metastatic sites (n)				
1	19 (16%)	22 (18%)	36 (24%)	26 (17%)
2	49 (42%)	58 (49%)	63 (42%)	72 (48%)
3	22 (19%)	15 (13%)	22 (15%)	21 (14%)
≥4	7 (6%)	8 (7%)	7 (5%)	10 (7%)
Previous therapies or procedures				
Radiotherapy	24 (21%)	27 (23%)	40 (26%)	33 (22%)
Whipple procedure	30 (26%)	33 (28%)	47 (31%)	36 (24%)
Biliary stent	15 (13%)	8 (7%)	13 (9%)	9 (6%)
Previous lines of metastatic therapy				
0¶	15 (13%)	15 (13%)	17 (11%)	19 (13%)
1	62 (53%)	67 (56%)	86 (57%)	86 (58%)
≥2	40 (34%)	37 (31%)	48 (32%)	44 (30%)
Previous anticancer therapy‖				
Gemcitabine alone	53 (45%)	55 (46%)	67 (44%)	66 (44%)
Gemcitabine combination	64 (55%)	64 (54%)	84 (56%)	83 (56%)
Fluorouracil based	50 (43%)	52 (44%)	70 (46%)	63 (42%)
Irinotecan based	12 (10%)	17 (14%)	17 (11%)	17 (11%)
Platinum based	38 (32%)	41 (34%)	54 (36%)	45 (30%)

Data are number of patients (%) or median (IQR). CA19-9=carbohydrate antigen 19-9. *Fluorouracil and folinic acid combination control group based on protocol version 2. †Baseline Karnofsky performance status score was missing for one patient in the fluorouracil and folinic acid group (enrolled under protocol 2) who was subsequently stratified as having a score ≥90. ‡Data were missing for three patients in the nanoliposomal irinotecan plus fluorouracil and folinic acid group and in five patients each in the nanoliposomal irinotecan monotherapy and fluorouracil and folinic acid groups (enrolled under protocol 2). §Investigator-reported with review by the funder's medical team. Some patients had multiple metastatic sites and are listed in more than one group. ¶Patients received neoadjuvant, adjuvant, or locally advanced treatment, but no previous therapy for metastatic disease. ‖Columns add up to greater than 100% because some patients received more than one line of therapy and are listed in more than one group, and regimens might include multiple drug classes, but at least one gemcitabine based.

Table 1: **Baseline characteristics**

reduction to 40 mg/m², but none discontinued because of an adverse event.

The survival analysis was based on 313 deaths, with a cutoff date of Feb 14, 2014. Deaths were recorded in 75 (64%) of 117 patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid, 80 (67%) of 119 individuals allocated the fluorouracil and folinic acid combination control, 129 (85%) of 151 patients assigned nanoliposomal irinotecan monotherapy, and 109 (73%) of 149 individuals allocated the fluorouracil and folinic acid monotherapy control. Median overall survival was 6·1 months (95% CI 4·8–8·9) in patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid and 4·2 months (3·3–5·3) in those allocated fluorouracil and folinic acid (unstratified HR 0·67, 95% CI 0·49–0·92; p=0·012; figure 2A). Median overall survival was 4·9 months (95% CI 4·2–5·6) for patients allocated nanoliposomal irinotecan monotherapy compared with 4·2 months (3·6–4·9) for those assigned fluorouracil and folinic acid (unstratified HR 0·99, 95% CI 0·77–1·28; p=0·94; figure 2B).

Preplanned subgroup analyses showed that the survival benefit of nanoliposomal irinotecan plus fluorouracil and folinic acid was homogeneous across most subgroups (figure 3). In the stepwise Cox regression analysis of nanoliposomal irinotecan plus fluorouracil and folinic acid versus fluorouracil and folinic acid, an association of overall survival was identified between treatment and the following prognostic factors: baseline Karnofsky performance status, albumin, time since receiving most recent anticancer therapy, tumour stage at diagnosis, status of liver metastases, and baseline CA19-9. Adjusting for these prognostic factors, the combination of nanoliposomal irinotecan plus fluorouracil and folinic acid maintained a strong treatment effect on overall survival (HR 0·58, 95% CI 0·42–0·81).

In patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid, median progression-free survival was 3·1 months (95% CI 2·7–4·2) compared with 1·5 months (1·4–1·8) in those allocated fluorouracil and folinic acid (unstratified HR 0·56, 95% CI 0·41–0·75; p=0·0001; figure 2C). In patients allocated nanoliposomal irinotecan monotherapy, median progression-free survival was 2·7 months (95% CI 2·1–2·9) versus 1·6 months (1·4–1·8) for those assigned fluorouracil and

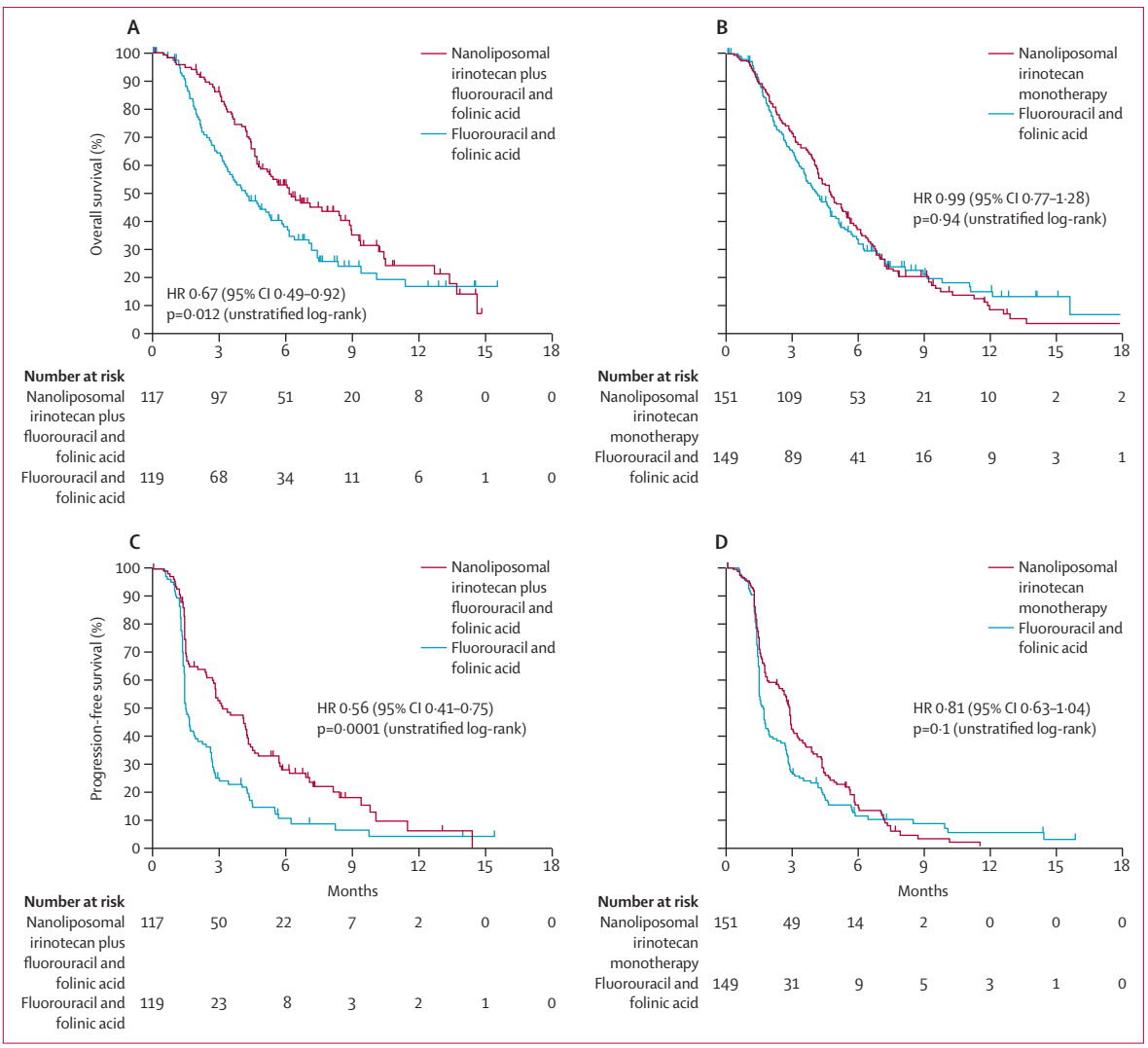

Figure 2: **Kaplan-Meier survival analyses**
HR=hazard ratio. (A) Overall survival with nanoliposomal irinotecan plus fluorouracil and folinic acid versus fluorouracil and folinic acid. (B) Overall survival with nanoliposomal irinotecan monotherapy versus fluorouracil and folinic acid. (C) Progression-free survival with nanoliposomal irinotecan plus fluorouracil and folinic acid versus fluorouracil and folinic acid. (D) Progression-free survival with nanoliposomal irinotecan monotherapy versus fluorouracil and folinic acid.

folinic acid (unstratified HR 0·81, 95% CI 0·63–1·04; p=0·1; figure 2D).

Median time to treatment failure was 2·3 months (95% CI 1·6–2·8) in patients allocated nanoliposomal irinotecan plus fluorouracil and folinic acid compared with 1·4 months (1·3–1·4) in those assigned fluorouracil and folinic acid (HR 0·6, 95% CI 0·45–0·78; p=0·0002). Time to treatment failure did not differ significantly between patients assigned nanoliposomal irinotecan monotherapy and those allocated fluorouracil and folinic acid (1·7 months [95% CI 1·5–2·7] *vs* 1·4 months [1·3–1·4]; HR 0·82, 95% CI 0·65–1·03; p=0·1).

19 (16%) of 117 patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid achieved an objective response compared with one (1%) of 119 individuals allocated fluorouracil and folinic acid (difference 15·4 percentage points, 95% CI 8·5–22·3; p<0·0001). Nine (6%) of 151 patients allocated nanoliposomal irinotecan monotherapy achieved an objective response compared with one (1%) of 149 assigned fluorouracil and folinic acid (difference 5·3 percentage points, 95% CI 1·3–9·3; p=0·02).

28 (29%) of 97 patients allocated nanoliposomal irinotecan plus fluorouracil and folinic acid achieved a CA19-9 response (≥50% decrease from abnormal baseline) versus seven (9%) of 81 assigned fluorouracil and folinic acid (p=0·0006). 29 (24%) of 123 patients allocated nanoliposomal irinotecan monotherapy had a CA19-9 response versus 12 (11%) of 105 assigned fluorouracil and folinic acid (p=0·024).

At baseline, median scores for quality-of-life measures (global health status, functional scale, and symptoms

	Nanoliposomal irinotecan plus fluorouracil and folinic acid	Fluorouracil and folinic acid	Hazard ratio for death (95% CI)
	Events/patients (n/N)	Events/patients (n/N)	
Karnofsky performance status			
90–100	39/66	37/67	0·79 (0·50–1·24)
70–80	36/51	43/52	0·54 (0·35–0·85)
Albumin			
≥40 g/L	30/53	29/54	0·85 (0·51–1·42)
<40 g/L	45/64	51/65	0·52 (0·35–0·79)
Ethnic origin			
White	45/75	53/75	0·62 (0·41–0·92)
East Asian	23/34	25/36	0·49 (0·27–0·90)
Other	7/8	2/8	3·27 (0·67–15·84)
Original tumour location in pancreas			
Head	48/76	45/69	0·80 (0·53–1·20)
Other	27/41	35/50	0·51 (0·31–0·85)
CA19-9			
≥40 U/mL	63/92	66/91	0·62 (0·44–0·88)
<40 U/mL	12/22	13/23	0·83 (0·38–1·83)
Liver metastases			
Yes	54/75	62/84	0·65 (0·45–0·93)
No	21/42	18/35	0·74 (0·39–1·41)
Age (years)			
>65	35/52	31/38	0·73 (0·45–1·19)
≤65	40/65	49/81	0·61 (0·40–0·93)
Sex			
Women	30/48	33/52	0·74 (0·45–1·22)
Men	45/69	47/67	0·60 (0·40–0·91)
BMI			
≥Median	36/58	39/58	0·68 (0·43–1·07)
<Median	39/59	41/61	0·60 (0·38–0·95)
Region			
North America	14/19	11/19	0·79 (0·36–1·75)
Asia	23/34	24/35	0·51 (0·28–0·93)
Europe	28/47	34/49	0·69 (0·42–1·14)
Other	10/17	11/16	0·58 (0·24–1·38)
Stage at diagnosis			
Stage IV	46/61	51/62	0·63 (0·42–0·94)
Other	28/55	28/55	0·72 (0·42–1·21)
Time since diagnosis			
≥Median	38/62	38/60	0·86 (0·55–1·34)
<Median	37/55	42/57	0·46 (0·29–0·73)
Time since metastatic diagnosis			
≥Median	42/61	41/58	0·80 (0·52–1·23)
<Median	32/55	39/60	0·50 (0·31–0·81)
Previous lines of metastatic therapy			
0	10/15	1/15	0·68 (0·28–1·64)
1	40/62	47/67	0·66 (0·43–1·00)
≥2	25/40	23/37	0·68 (0·38–1·20)
Time since last previous therapy			
≥Median	36/64	35/53	0·75 (0·47–1·19)
<Median	39/53	45/66	0·60 (0·39–0·93)
Previous fluorouracil			
Yes	31/50	33/52	0·52 (0·31–0·86)
No	44/67	47/67	0·78 (0·52–1·18)
Previous irinotecan			
Yes	10/12	8/17	1·25 (0·49–3·19)
No	65/105	72/102	0·62 (0·44–0·86)
Previous platinum			
Yes	23/38	26/41	0·68 (0·39–1·19)
No	52/79	54/78	0·66 (0·45–0·97)
Previous radiotherapy			
Yes	13/24	13/27	0·92 (0·42–1·98)
No	62/93	67/92	0·62 (0·44–0·88)
Previous Whipple procedure			
Yes	20/30	18/33	1·23 (0·65–2·33)
No	55/87	62/86	0·50 (0·35–0·73)
Previous biliary stent			
Yes	10/15	5/8	0·44 (0·14–1·43)
No	65/102	75/111	0·68 (0·49–0·95)

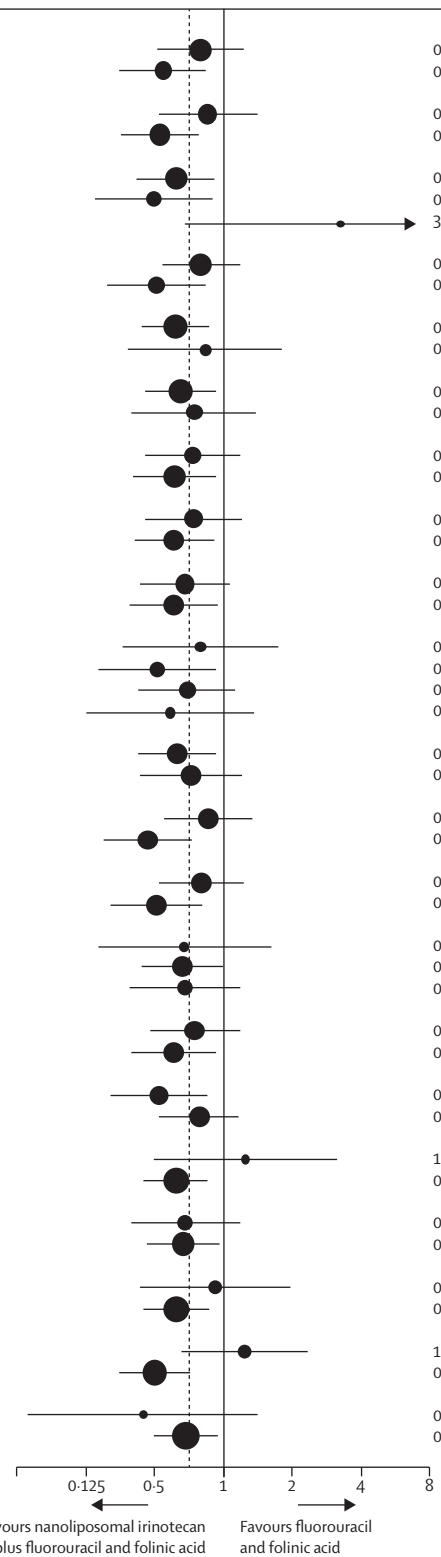

***Figure 3*: Forest plot of treatment effect on survival in prespecified subgroups**
Hazard ratios are depicted by filled circles and 95% CIs by horizontal lines. The size of the circle reflects the size of the subgroup relative to the intention-to-treat population. BMI=body-mass index. CA19-9=carbohydrate antigen 19-9.

scores) were similar between groups. At 6 and 12 weeks, the median functional scale scores did not differ appreciably from baseline, suggesting that the effects of the treatments on functional scale scores were negligible. Clinical benefit response was less than 20% and did not differ significantly between treatment groups (appendix pp 1–3).

In patients allocated nanoliposomal irinotecan plus fluorouracil and folinic acid and nanoliposomal irinotecan monotherapy, median duration of exposure to nanoliposomal irinotecan was 8·7 weeks (IQR 5·4–22·0) and 8·9 weeks (6·0–16·0), respectively, and mean dose intensities were 167·5 mg/m² (SD 44·8) over 6 weeks and 188·0 mg/m² (52·0) over 6 weeks, respectively. Median exposure to fluorouracil was 8·7 weeks (IQR 5·4–22·0) in patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid and 6·0 weeks (5·9–12·1) in those allocated fluorouracil and folinic acid (n=105, protocol version 2); mean dose intensities of fluorouracil were, respectively, 5065·0 mg/m² (SD 1539·1) over 6 weeks and 6710·2 mg/m² (1719·2) over 6 weeks.

Post-progression anticancer therapy was given to 36 (31%) of 117 patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid and 45 (38%) of 119 patients allocated fluorouracil and folinic acid. The use of treatment after progression and the type of therapy used was generally similar between groups. Eight patients assigned the combination therapy and nine patients allocated the control received irinotecan as part of post-progression therapy.

398 (95%) of the 417 patients randomly assigned received at least one dose of study drug and were included in the safety analysis population. The most common treatment-emergent adverse events of all grades in patients whose treatment included nanoliposomal irinotecan were diarrhoea, nausea, and vomiting (table 2). Alopecia occurred in 16 (14%) of 117 patients in the nanoliposomal irinotecan plus fluorouracil and folinic acid group, 32 (22%) of 147 individuals who received nanoliposomal irinotecan as monotherapy, and six (5%) of 134 patients who received fluorouracil and folinic acid. Adverse events that resulted in a dose reduction occurred in 39 (33%) patients in the nanoliposomal irinotecan plus fluorouracil and folinic acid group, 46 (31%) individuals given nanoliposomal irinotecan monotherapy, and five (4%) patients who received fluorouracil and folinic acid. Grade 3 or 4 neutropenic sepsis (including febrile neutropenia) was noted in three (3%) patients in the combination therapy group and six (4%) individuals who had monotherapy, with no events of this type reported in the control group. Granulocyte colony-stimulating factor was administered to 20 (17%) patients receiving nanoliposomal irinotecan plus fluorouracil and folinic acid and 17 (12%) of those treated with nanoliposomal irinotecan monotherapy, compared with one (1%) patient in the fluorouracil and folinic acid group. Grade 4 treatment-emergent adverse events were reported in 12 (10%) patients given nanoliposomal irinotecan plus fluorouracil and folinic acid, 24 (16%) individuals who received nanoliposomal irinotecan monotherapy, and nine (7%) of those in the fluorouracil and folinic acid group. Of these, only three patients in the monotherapy group and one individual receiving control had a gastrointestinal event. 30-day mortality was low in all groups (three [3%] of 117 in the nanoliposomal irinotecan plus fluorouracil and folinic acid group, three [2%] of 151 in the monotherapy group, and four [3%] of 149 with control). Adverse events leading to discontinuation of study drug arose in 13 (11%) patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid, 17 (12%) individuals allocated nanoliposomal irinotecan monotherapy, and ten (7%) patients assigned fluorouracil and folinic acid.

Of 47 patients who died during the study or within 30 days from the last dose of study drug, 30 deaths were attributed to pancreatic cancer, 16 were due to an adverse event (five related to treatment, according to the investigator), and the cause was unknown for one. The treatment-related adverse events that resulted in death were gastrointestinal toxic effects (n=1, nanoliposomal irinotecan monotherapy), infectious enterocolitis (n=1, nanoliposomal irinotecan monotherapy), septic shock (n=1, nanoliposomal irinotecan monotherapy; n=1, nanoliposomal irinotecan plus fluorouracil and folinic acid), and disseminated intravascular coagulation with pulmonary embolism (n=1, nanoliposomal irinotecan monotherapy). 90 (61%) of 147 patients assigned nanoliposomal irinotecan monotherapy had a treatment-emergent serious adverse event compared with 56 (48%) of 117 individuals allocated nanoliposomal irinotecan plus fluorouracil and folinic acid and 60 (45%) of 134 patients assigned fluorouracil and folinic acid.

	Nanoliposomal irinotecan plus fluorouracil and folinic acid combination therapy (n=117)		Nanoliposomal irinotecan monotherapy (n=147)		Fluorouracil and folinic acid control (n=134)	
	Any grade	Grades 3–4	Any grade	Grades 3–4	Any grade	Grades 3–4
Diarrhoea	69 (59%)	15 (13%)	103 (70%)	31 (21%)	35 (26%)	6 (4%)
Vomiting	61 (52%)	13 (11%)	80 (54%)	20 (14%)	35 (26%)	4 (3%)
Nausea	60 (51%)	9 (8%)	89 (61%)	8 (5%)	46 (34%)	4 (3%)
Decreased appetite	52 (44%)	5 (4%)	72 (49%)	13 (19%)	43 (32%)	3 (2%)
Fatigue	47 (40%)	16 (14%)	54 (37%)	9 (6%)	37 (28%)	5 (4%)
Neutropenia*	46 (39%)	32 (27%)	37 (25%)	22 (15%)	7 (5%)	2 (1%)
Anaemia	44 (38%)	11 (9%)	48 (33%)	16 (11%)	31 (23%)	9 (7%)
Hypokalaemia	14 (12%)	4 (3%)	32 (22%)	17 (12%)	12 (9%)	3 (2%)

Data are number of patients (%). The table shows grade 3 and 4 adverse events reported in ≥5% of patients whose treatment included nanoliposomal irinotecan with ≥2% incidence versus fluorouracil and folinic acid. *Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia.

Table 2: **Adverse events**

Discussion

The results of this international, multicentre, randomised, phase 3 study (NAPOLI-1) showed that nanoliposomal irinotecan plus fluorouracil and folinic acid significantly improved the overall survival of patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy. Progression-free survival, objective tumour response, time to treatment failure, and CA19-9 tumour marker response in patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid were also significantly superior to fluorouracil and folinic acid control. In the preplanned analyses of each subgroup, overall survival was increased in patients with a Karnofsky performance score less than 90, a concentration of albumin less than 40 g/L, CA19-9 greater than 40 IU/mL, and liver metastases who were assigned nanoliposomal irinotecan plus fluorouracil and folinic acid, versus those allocated fluorouracil and folinic acid. Furthermore, patients with unfavourable prognostic factors who were assigned nanoliposomal irinotecan plus fluorouracil and folinic acid achieved lower HRs compared with patients assigned fluorouracil and folinic acid, supporting the possible use of nanoliposomal irinotecan plus fluorouracil and folinic acid in this population. Use of post-progression anticancer therapy was generally similar between treatment groups.

Patients assigned nanoliposomal irinotecan monotherapy achieved a median overall survival of 4·9 months, which was consistent with the 5·2 months recorded in a previous phase 2 study of nanoliposomal irinotecan in 40 patients with similar demographics and baseline disease characteristics.[24] Although patients assigned nanoliposomal irinotecan monotherapy did not show superiority in overall survival or progression-free survival compared with those allocated fluorouracil and folinic acid, they had better objective and CA19-9 responses, suggesting that nanoliposomal irinotecan alone has some activity against pancreatic cancer. However, nanoliposomal irinotecan as monotherapy was administered at a higher dose and a lower frequency, which resulted in patients assigned to this group having a higher incidence of gastrointestinal adverse events compared with those allocated the nanoliposomal irinotecan combination regimen.

The choice of fluorouracil and folinic acid as control was based on several factors. First, there is no universally accepted standard treatment for metastatic pancreatic ductal adenocarcinoma following gemcitabine-based therapy. Second, there is a preference for using approved drugs as controls in registration trials, and fluorouracil is an approved agent for treatment of pancreatic cancer. Third, fluorouracil and folinic acid served as the control in CONKO-003,[28] a controlled study in patients with advanced and metastatic pancreatic ductal adenocarcinoma following gemcitabine therapy, thereby setting a precedent. We did not change the control after adding the third arm of nanoliposomal irinotecan plus fluorouracil and folinic acid to our study because 63 patients had been treated with the original schedule and changing it would render the data not available for inclusion in the final analysis. Fourth, no data existed on use of the fluorouracil and folinic acid dose and schedule (FOLFIRI.3) given without irinotecan for treatment of metastatic pancreatic ductal adenocarcinoma, so although it would have been an ideal control arm it would not have historical precedence. Although we acknowledge that the fluorouracil and folinic acid regimen used in the combination arm was different from the control, which is not a standard design with the study drug being added to the same control regimen, the fluorouracil and folinic acid regimen given with nanoliposomal irinotecan was optimised for the combination. It is highly unlikely that the difference in dosing created bias in favour of the investigational arm, because the planned and recorded fluorouracil dose intensities were lower in the investigational arm compared with the control arm. The significantly improved overall survival in patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid, particularly in view of the lower fluorouracil dose intensity compared with the fluorouracil and folinic acid control, supports the benefit of combining nanoliposomal irinotecan with fluorouracil and folinic acid. Finally, it should be noted that the control arm in NAPOLI-1 performed better than did the historical control (CONKO-003)[28] with respect to overall survival (3·3 months in CONKO-003 *vs* 4·2 months in NAPOLI-1).

The NAPOLI-1 and CONKO-003 studies used the same dose and schedule of fluorouracil and folinic acid as control. Moreover, relatively similar median overall survival was reported in both studies (6·1 months with nanoliposomal irinotecan plus fluorouracil and folinic acid in NAPOLI-1 *vs* 5·9 months with oxaliplatin plus fluorouracil and folinic acid in CONKO-003). However, findings of a more recent study comparing an oxaliplatin plus fluorouracil and folinic acid regimen failed to show superiority of overall survival over fluorouracil and folinic acid (n=54 in each arm; 6·1 months *vs* 9·9 months; p=0·02).[29] The reasons for these contradictory results are not clear, but they show the hazards of cross-study comparisons. Despite the similarities between NAPOLI-1 and CONKO-003, there are many differences. For example, the study population in NAPOLI-1 consisted of patients with metastatic pancreatic ductal adenocarcinoma who had progressed after previous gemcitabine-based therapy in a neoadjuvant, adjuvant, locally advanced, or metastatic setting. Patients in CONKO-003 had advanced cancer, which included a heterogeneous group of both metastatic and locally advanced disease (12%)—those with locally advanced disease having a historically documented better survival.[28] Moreover, patients in CONKO-003 had disease that had progressed with first-line gemcitabine monotherapy, and they had to start on the study within 4 weeks of disease

progression. On the other hand, patients in NAPOLI-1 had received gemcitabine either as monotherapy or in combination, for any stage of disease at any time in the past, in many cases having received multiple lines of different treatments; their disease had to be progressing with distant metastases only, irrespective of the previous line of therapy for inclusion. Patients' enrolment for CONKO-003 (n=168) occurred between 2004 and 2007 at 16 sites in Germany.[28] The larger, global, NAPOLI-1 study (n=117 study arm, n=119 control arm after protocol amendment) was conducted between 2012 and 2013 at 76 sites worldwide: more than a third of patients in NAPOLI-1 were not of white ethnic origin. The consistency of the results of NAPOLI-1 in a diverse population at multiple medical centres supports the robustness of the positive outcome. The biggest difference between CONKO-003 and NAPOLI-1 with respect to safety is that, unlike with the oxaliplatin plus fluorouracil and folinic acid regimen, nanoliposomal irinotecan plus fluorouracil and folinic acid is not associated with neuropathy and should be considered as a treatment option for patients who fail the albumin-bound paclitaxel and gemcitabine combination.

With respect to combination therapies containing unencapsulated irinotecan plus fluorouracil and folinic acid in second-line pancreatic cancer, Yoo and colleagues[10] did a randomised phase 2 trial comparing modified versions of FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and FOLFIRI (folinic acid, fluorouracil, and irinotecan) regimens for treatment of gemcitabine-refractory advanced pancreatic cancer. However, in that study, the median overall survival was short (3·5 months with FOLFOX and 3·9 months with FOLFIRI). Various other prospective and retrospective studies of FOLFIRI had small sample sizes and were of single-arm design. Of these, the longest median overall survival—6·6 months—was reported in a small (n=63) non-randomised study that included use of either the FOLFIRI.1 or FOLFIRI.3 regimens.[14] These two regimens differ in that FOLFIRI.3 does not include a fluorouracil bolus and divides the irinotecan dose in two, with the second irinotecan dose being given after fluorouracil and folinic acid administration. The next most effective study was a retrospective analysis of a small population (n=40) of patients with gemcitabine-refractory locally advanced and metastatic cancer, which showed an overall survival of 6·0 months.[11] Although promising, these studies show the need for large randomised, multicentre studies to clearly identify optimum therapy for patients with previously treated metastatic pancreatic cancer. Irinotecan-containing regimens have not been a standard until the advent of the FOLFIRINOX regimen in front-line metastatic pancreatic cancer.

Despite additional toxicity, the quality of life of patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid was not appreciably different from those allocated the fluorouracil and folinic acid control, which is an important measure in patients with metastatic pancreatic ductal adenocarcinoma, who are generally in poor health from the effects of the underlying disease and previous treatments. Little difference between study treatments was reported in clinical benefit response; however, assessment of this outcome is limited because of the burdensome requirements of data collection from these very sick patients. The pain component, based on patient-reported daily diary data, had low compliance (60% [250/417] of intention-to-treat patients eligible). The precision of the clinical benefit response classification rules, which call for 4 consecutive weeks with robust criteria for improvement and less robust criteria for negative clinical benefit, also restricted the assessment.

Adverse events in our study were consistent with those in previous studies of nanoliposomal irinotecan.[22,24,26] Despite a lower delivered dose per cycle and lower observed mean dose intensity of nanoliposomal irinotecan compared with the monotherapy arm, patients in the nanoliposomal irinotecan plus fluorouracil and folinic acid group had a higher incidence of grade 3 or 4 neutropenia than did those receiving nanoliposomal irinotecan monotherapy, which could be attributable to the addition of fluorouracil and folinic acid. However, the incidence of neutropenic sepsis was low in all treatment groups. Conversely, patients in the nanoliposomal irinotecan plus fluorouracil and folinic acid group had less frequent severe diarrhoea than did those receiving nanoliposomal irinotecan monotherapy. The incidence of alopecia was also lower in patients receiving nanoliposomal irinotecan plus fluorouracil and folinic acid than in those in the nanoliposomal irinotecan monotherapy group. The lower nanoliposomal irinotecan dose every 2 weeks—even in combination with fluorouracil and folinic acid—showed a better therapeutic index for severe gastrointestinal events than did nanoliposomal irinotecan at a higher dose every 3 weeks. Most patients tolerated the gastrointestinal adverse events, with around 11% of patients in each nanoliposomal irinotecan-containing treatment group discontinuing treatment because of any adverse event. Of note, there were no reports of hand-foot syndrome, which can be associated with irinotecan and pegylated liposomal doxorubicin therapy, in any study group.

The value of using this nanoliposomal irinotecan-containing regimen immediately after FOLFIRINOX treatment is still not clear, because very few patients received previous irinotecan in this study. Further investigation is needed to answer this question with confidence. Aside from this consideration, nanoliposomal irinotecan plus fluorouracil and folinic acid could potentially become a new standard of care for patients with metastatic pancreatic ductal adenocarcinoma whose disease has progressed following treatment with gemcitabine-based therapy.

In conclusion, the results of this phase 3 study show that nanoliposomal irinotecan in combination with

fluorouracil and folinic acid extends survival and improves other efficacy variables in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based regimens, and has a manageable and mostly reversible safety profile. However, it is not possible to generalise the results of this study to patients with low performance status, as shown by a Karnofsky performance status less than 70 and albumin less than 30 g/L, and those with increased bilirubin, all of which occur in this disease. Future studies will assess the use of nanoliposomal irinotecan in other settings, including first-line therapy and the role of sequencing various regimens for pancreatic cancer.

Contributors

DDVH, L-TC, AW-G, VM, BB, ND, and EB led and coordinated the study design. All authors recruited patients and contributed to data collection. BB and EB analysed data, which was interpreted by all authors. L-TC, AW-G, DDVH, GB, AD, BB, and EB drafted the manuscript with input from all other authors. All authors have seen and approved the final report.

Declaration of interests

GB, C-FC, JFB, RAH, K-HL, C-PL, GS, TM, and Y-SS declare no competing interests. FB and JTS report personal fees from Merrimack Pharmaceuticals advisory boards, outside the submitted work. L-TC reports other funding from Merrimack Pharmaceuticals, during the conduct of the study; and personal fees from PharmaEngine, outside the submitted work. DC reports grants from AstraZeneca, Amgen, Celgene, Merck Serono, Sanofi, Merrimack Pharmaceuticals, and Medimmune, outside the submitted work. AD reports personal fees from AstraZeneca and Specialized Therapeutics, outside the submitted work; grants and personal fees from Roche, outside the submitted work; and grants from Boehringer Ingelheim, outside the submitted work. GJ reports grants from Merrimack Pharmaceuticals, during the conduct of the study. DDVH reports grants from Merrimack Pharmaceuticals, during the conduct of the study; and personal fees from AlphaMed Consulting, outside the submitted work. AW-G reports grants from Newlink, EMD, Pfizer, AstraZeneca, Precision Biological, BioMed Valley, Halozyme, ChemoCentryx, OncoMEd, ADURO, and Millennium, outside the submitted work; other fees from Pfizer and Merrimack Pharmaceuticals, outside the submitted work; and grants from Merrimack Pharmaceuticals, Prometheus, and CTI, outside the submitted work. EB, ND, and VM are employees of Merrimack Pharmaceuticals and have a patent (Methods for treating pancreatic cancer using combination therapies comprising liposomal irinotecan) issued to Merrimack Pharmaceuticals. BB is employed as statistician at Merrimack Pharmaceuticals.

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