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Liposomal irinotecan and 5-fluorouracil/leucovorin in older patients with metastatic pancreatic cancer – A subgroup analysis of the pivotal NAPOLI-1 trial

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ABSTRACT

Objectives: Pancreatic cancer is a highly lethal disease predominantly affecting older patients. Characterization of outcomes in these patients may help optimise treatment decisions. The global, phase 3 NAPOLI-1 trial (NCT01494506) demonstrated an overall survival (OS) benefit with liposomal irinotecan and 5-flurouracil/leucovorin (nal-IRI + 5-FU/LV) versus 5-FU/LV. This subgroup analysis explored impact of age on outcomes in NAPOLI-1 patients, and nal-IRI + 5-FU/LV efficacy and safety in older patients.

Materials and Methods: This exploratory, post-hoc analysis of the NAPOLI-1 trial included patients aged ≥eighteen years (no upper limit) with metastatic pancreatic adenocarcinoma that had progressed on gemcitabine-based therapy. Patients were stratified by age (cut-offs at 65, 70, and 75 years); OS and progression-free survival (PFS) were estimated by Kaplan-Meier analysis.

Results: Of 417 randomized patients, 192 (46%), 110 (26%) and 43 (10%) were aged ≥65, ≥70 and ≥ 75 years, respectively. Mortality risk and risk of disease progression were similar in older and younger patients independent of treatment (HRs for median [m]OS/mPFS comparisons were 0.88/0.95 [<65 versus ≥65 years], 0.89/0.88 [<70 versus ≥70 years] and 1.04/0.98 [<75 versus ≥75 years]; $P > .25$). Reduced mortality/morbidity risk with nal-IRI + 5-FU/LV in older subgroups was in line with the wider population. No additional toxicities with nal-IRI + 5-FU/LV were observed in older patients: 86% of patients ≥75 years versus 69% <75 years required a dose delay or reduction due to toxicities (43% versus 32% dose reductions).

Discussion: Results suggest that older patients with metastatic pancreatic adenocarcinoma that progressed on prior gemcitabine-based treatment can benefit from second-line therapy, supporting nal-IRI + 5-FU/LV treatment in older patients.

1. Introduction

Pancreatic cancer predominantly affects older patients – the median age at diagnosis is 70 years, and approximately two-thirds of cases are in patients older than 65 years [1,2]. Mortality closely mirrors incidence [3], with almost 70% of related deaths occurring in patients over 65 years old [1,2]. The incidence and mortality of pancreatic cancer has increased alongside a demographic shift towards an aging

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population [3,4]. Meanwhile, five-year survival rates remain in single digits [3,5,6], particularly in older patients (5.8% in the 65–79 age group and 3.3% in patients aged ≥80 years) [7]. Without significant advances in early detection strategies and effective treatments, pancreatic cancer is projected to become the second greatest cause of cancer-related death in the US by 2030 [5].

Despite the predominance of pancreatic cancer in older patients, they are often under-represented in, or excluded from, clinical trials [8–11], and a smaller proportion receive chemotherapy, or other tumour-targeted treatment, in clinical practice compared with younger patients [8,9,12]. Treatment bias towards higher rates of intervention for younger patients has also been observed with surgical resection [13]. Although treatment guidelines state that advanced age is not in itself a contraindication for any major treatment modality (surgery, chemotherapy or radiation) [14], physicians must take account of frailty and comorbidity when determining appropriate treatment. Despite perceptions that older patients are likely to have worse outcomes, several studies have observed similar benefit in younger and older patients undergoing chemotherapy [8,9], surgical resection [13,15,16], or any tumour-targeted treatment [12].

Gemcitabine-based therapy is often the preferred first-line chemotherapy option for older patients with metastatic pancreatic adenocarcinoma because it is generally well tolerated. More intensive regimens, such as FOLFIRINOX or gemcitabine plus *nab*-paclitaxel, have demonstrated superior efficacy to gemcitabine monotherapy [10,17], but with increased toxicity, therefore these regimens are recommended for patients with good performance status (Eastern Cooperative Oncology Group 0–1) [14,18,19], who tend to be younger and fitter. Indeed, patients aged 75 and over were excluded from the pivotal PRODIGE 4/ACCORD 11 trial of FOLFIRINOX [10].

Liposomal irinotecan (nal-IRI) in combination with 5-flurouracil and leucovorin (5-FU and LV) was the first regimen to be approved for use as second-line therapy for metastatic pancreatic adenocarcinoma, based on results of the pivotal NAPOLI-1 trial [20,21]. NAPOLI-1 was a global, phase 3 study of nal-IRI, as monotherapy and in combination with 5-FU/LV, in patients with metastatic pancreatic adenocarcinoma who had progressed following gemcitabine-based therapy [22]. Overall survival (OS) and progression-free survival (PFS) were significantly improved with nal-IRI + 5-FU/LV versus the 5-FU/LV control and quality of life was maintained over time; adverse events were predictable and manageable.

A pre-specified subgroup analysis of the NAPOLI-1 study indicated that improvements in OS with nal-IRI + 5-FU/LV versus 5-FU/LV alone were similar in patients aged ≤65 and > 65 years (hazard ratio [HR] 0.61 and 0.73, respectively) [22]. Here we report a NAPOLI-1 post-hoc analysis to further explore the benefits of nal-IRI + 5-FU/LV in older patients, according to age stratifications of <65/≥65, <70/≥70, and < 75/≥75 years.

2. Methods

2.1. NAPOLI-1 Trial Design and Patients

NAPOLI-1 was an international, open-label, randomized, phase 3 trial, which has been previously described [22]. Briefly, trial participants were adults aged ≥eighteen years (no upper age limit) with confirmed metastatic pancreatic ductal adenocarcinoma and distant metastatic disease who exhibited disease progression after prior gemcitabine-containing therapy (neoadjuvant, adjuvant, locally advanced, or metastatic setting). Patients had adequate haematological, hepatic, and renal function, and Karnofsky performance status ≥70.

The trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization 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. Patients provided written informed consent, and the trial was registered with ClinicalTrials. Gov (NCT01494506). The study protocol was approved by institutional review boards of both the study sponsor and of each participating study centre.

Patients were randomized to nal-IRI monotherapy, nal-IRI + 5-FU/LV (following a protocol amendment), or a 5-FU/LV control [22]. nal-IRI monotherapy was given at 120 mg/m^2 (expressed as irinotecan hydrochloride trihydrate salt, equivalent to 100 mg/m^2 expressed as irinotecan free base) every three weeks, the combination arm comprised nal-IRI 80 mg/m^2 (expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m^2 expressed as irinotecan free

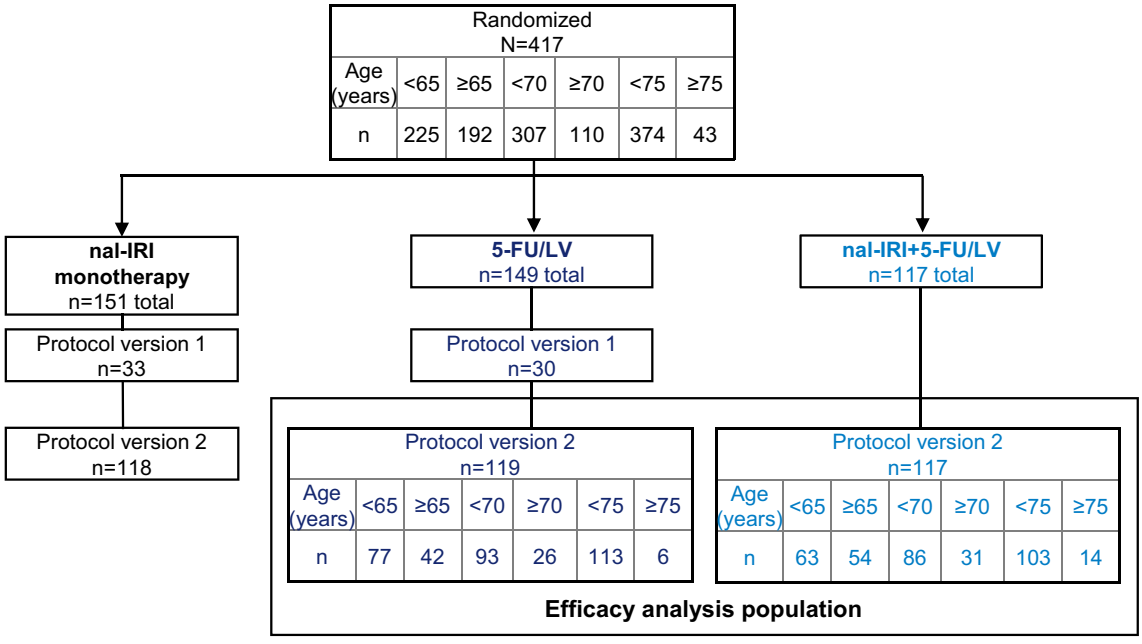

Fig. 1. Patient flow in the phase 3 NAPOLI-1 trial split by age group to highlight the efficacy population and age subgroups in the current analysis. Patients had metastatic pancreatic adenocarcinoma and had previously progressed on gemcitabine-based treatment. The CONSORT diagram for the overall trial has been published previously [22].

base), 5-FU 2, 400 mg/m^2, and LV 400 mg/m^2 every two weeks, and the control included 5-FU 2000 mg/m^2 and LV 200 mg/m^2 once weekly for the first four weeks of a six-week cycle. Dose modifications were permitted in order to help manage toxicities. Modifications included dose delay (≤3 weeks) to allow recovery from toxicity, and dose reduction due to toxicity. Dose re-escalation was not permitted.

2.2. Post-hoc Analysis

Age stratifications were applied with cut-offs at 65 years (</≥65 years), 70 years (</≥70 years) and 75 years (</≥75 years), based on age at screening visit. The impact of age on outcomes, irrespective of treatment allocation, was explored in the overall NAPOLI-1 intention to treat (ITT) population (all patients randomized to any treatment arm). Median OS and PFS were estimated for each age subgroup using Kaplan-Meier analysis. HRs and corresponding 95% confidence intervals (CI) were estimated for each pair of age subgroups (<65 versus ≥65 years; <70 versus ≥70 years; <75 versus ≥75 years) using unstratified Cox proportional hazards regression.

Efficacy of nal-IRI + 5-FU/LV, based on median OS, PFS, objective response rate (ORR), and time to treatment failure (TTF), was analysed in the subset of patients who were randomized to the combination and control arms after addition of the combination arm (protocol version 2). This post-hoc analysis was not powered for formal assessment of treatment differences; however, exploratory pairwise comparisons were performed between study treatments within each age subgroup by unstratified log-rank test. Additional efficacy analyses included measures of tumour response per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, and changes in the biomarker carbohydrate antigen 19-9 (CA19-9); response defined as ≥50% reduction from baseline in CA19-9 levels.

2.3. Safety Evaluation

Safety and treatment exposure were evaluated within age subgroups in the combination arm only. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 in patients who received ≥one dose (including a partial dose) of study treatment; haematological parameters were assessed based on laboratory evaluations. Shifts from baseline to end of treatment or highest post-dose CTCAE grade were summarized by treatment group.

3. Results

3.1. Patient Characteristics and Disposition

A total of 417 patients were enrolled and randomized in the NAPOLI-1 trial (ITT population): 117 in the nal-IRI + 5-FU/LV arm, 149 in the 5-FU/LV control arm (119 were enrolled following the protocol amendment and were included in treatment comparisons versus nal-IRI + 5-FU/LV), and 151 in the nal-IRI monotherapy arm (Fig. 1). In the overall study population, the median age was 63.0 years (range 31–87) and the mean age was 62.8 years. Almost half of the patient population (46%; n = 192) were aged ≥65 years, 25% (n = 110) were ≥ 70 years, and 10% (n = 43) were ≥ 75 years. In the efficacy analysis population (patients recruited to the combination and control arms following protocol amendment; n = 236) patient demographics and baseline characteristics were generally similar between treatment arms overall and within age subgroups (Table 1). The ≥75 years efficacy population subgroup comprised only 20 patients (fourteen combination and six control). Therefore, although results are presented alongside those for the other age subgroups for completeness, the small sample size limits interpretation of results for this age group.

Table 1
Baseline demographics and characteristics in the efficacy analysis population.

	ITT		<65 years		≥65 years		<70 years		≥70 years		<75 years		≥75 years	
	Comb (n = 117)	Ctrl (n = 119)	Comb (n = 63)	Ctrl (n = 77)	Comb (n = 54)	Ctrl (n = 42)	Comb (n = 86)	Ctrl (n = 93)	Comb (n = 31)	Ctrl (n = 26)	Comb (n = 103)	Ctrl (n = 113)	Comb (n = 14)	Ctrl (n = 6)
Gender, Female/male (%)	41/59	44/56	38/62	44/56	44/56	43/57	40/61	44/56	45/55	42/58	44/56	43/58	21/79	67/33
Age (years)														
Median	63	62	57	58	70	70	60	59	74	72	62	61	78	78
IQR	57–70	55–69	54–61	53–62	67–75	67–73	55–65	54–63	70–78	70–74	55–68	55–66	77–79	77–80
Range	41–81	34–80	41–64	34–64	65–81	65–80	41–69	34–69	70–81	70–80	41–74	34–74	75–81	76–80
Race (%)														
White	62	64	52	56	72	79	58	59	71	81	62	63	57	83
Black	3	3	6	3	0	2	5	2	0	4	4	2	0	17
Asian	29	30	33	38	24	17	31	34	23	15	28	32	36	0
Other	6	3	8	4	4	2	6	4	7	0	6	4	7	0
KPS score (%)														
90–100	59	48	65	47	52	50	63	49	48	42	60	49	50	33
70–80	38	51	33	52	44	50	36	49	45	58	37	50	50	67
50–60	3	0	2	0	4	0	1	0	7	0	3	0	0	0
Baseline CA19–9 (U/μL), median (IQR)	1.28 (0.12, 9.00)	1.29 (0.10, 16.38)	0.58 (0.04, 12.93)	1.81 (0.11, 26.74)	1.50 (0.21, 7.77)	0.52 (0.04, 10.86)	0.68 (0.04, 7.77)	1.55 (0.11, 20.37)	1.51 (0.22, 12.58)	0.34 (0.04, 8.50)	1.28 (0.09, 11.54)	1.06 (0.10, 16.48)	1.70 (0.22, 8.39)	8.21 (0.34, 10.86)
Liver metastases (%)	64	70	65	69	63	71	65	71	61	65	66	70	50	67
Baseline albumin (g/dL), median (IQR)	n = 114 4.1 3.7–4.3	n = 116 4.0 3.6–4.3	n = 61 4.1 3.8–4.4	n = 76 4.0 3.6–4.3	n = 53 3.9 3.6–4.2	n = 40 4.1 3.7–4.3	n = 83 4.1 3.8–4.4	n = 91 4.0 3.6–4.3	n = 31 3.8 3.4–4.1	n = 25 4.1 3.7–4.3	n = 100 4.1 3.7–4.3	n = 110 4.0 3.6–4.3	n = 14 3.8 3.4–4.2	n = 6 4.0 3.7–4.2

Comb, combination (nal-IRI + 5-FU/LV); Ctrl, control (5-FU/LV); IQR, interquartile range; ITT, intent-to-treat efficacy analysis population (all patients randomized to combination or control arms on protocol version 2); KPS, Karnofsky Performance Status; SD, standard deviation.

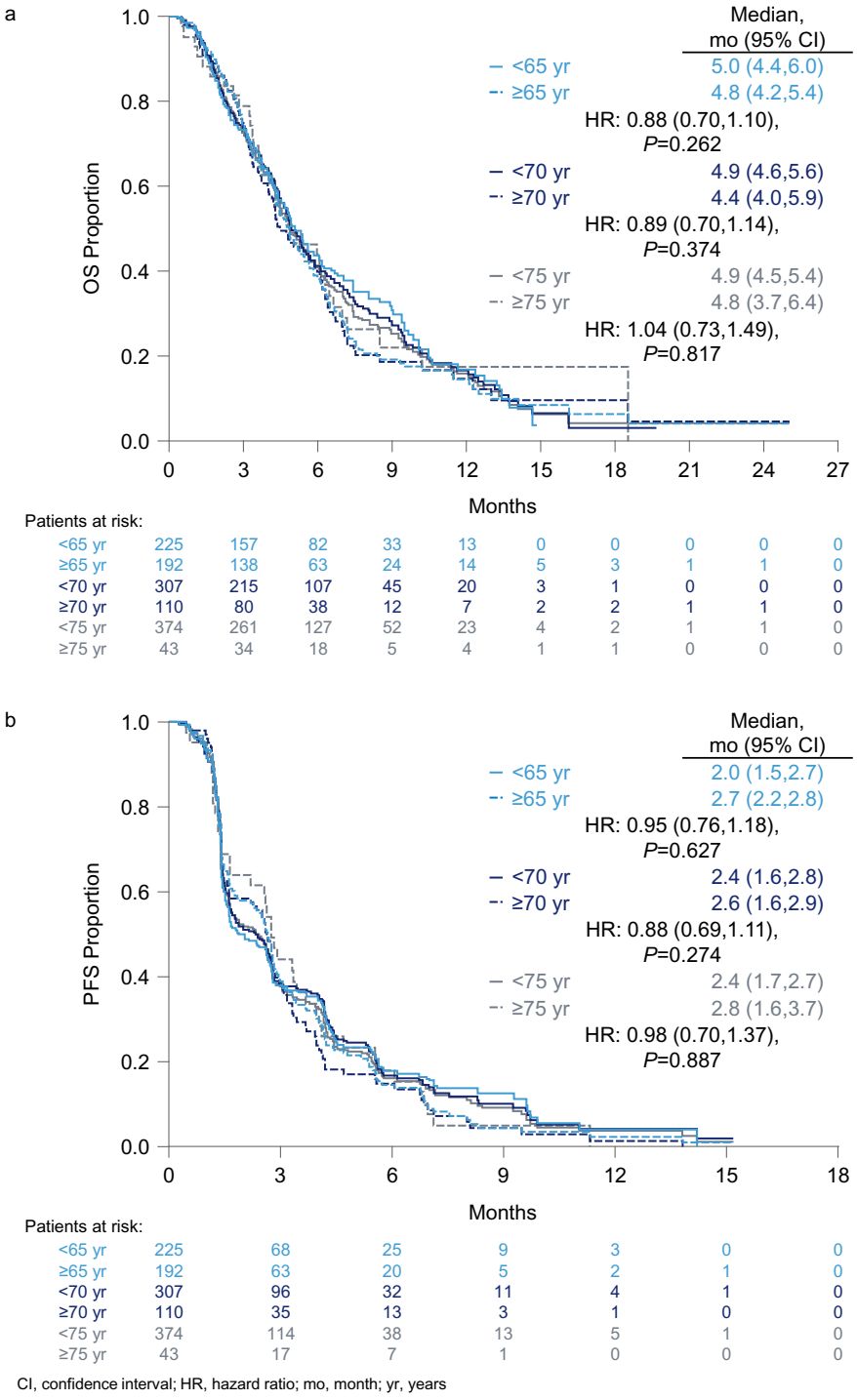

Fig. 2. Overall survival (A) and progression-free survival (B) in the whole ITT population of the NAPOLI-1 trial split according to age subgroups. Patients had metastatic pancreatic adenocarcinoma and had previously progressed on gemcitabine-based treatment.

3.2. Impact of Age on OS and PFS in the Overall NAPOLI-1 Population

Risk of mortality and disease progression were similar in older and younger age subgroups (Fig. 2). Median OS (Fig. 2a) was 5.0 months in the <65 years subgroup (n = 225) versus 4.8 months in the ≥65 years subgroup (n = 192; HR 0.88 [95% CI: 0.70–1.10]; $P = .262$), 4.9 versus 4.4 months in <70/≥70 years subgroups (n = 307/110; HR 0.89 [0.70–1.14]; $P = .374$), and 4.9 versus 4.8 months in <75/≥75 years subgroups (n = 374/43; HR 1.04 [0.73–1.49]; $P = .817$).

In the overall population, median PFS (Fig. 2b) was 2.0 versus 2.7 months in the <65/≥65 years subgroups (HR 0.95 [0.76–1.18]; $P = .627$), 2.4 versus 2.6 months in the <70/≥70 years subgroups (HR 0.88 [0.69–1.11]; $P = .274$), and 2.4 versus 2.8 months in the <75/≥75 years subgroups (HR 0.98 [0.70–1.37]; $P = .887$).

3.3. Treatment Efficacy within Age Subgroups in the ITT Population

Consistent with findings in the overall ITT population [22], median OS was longer with nal-IRI + 5-FU/LV compared with 5-FU/LV alone

Table 2
Efficacy of nal-IRI + 5-FU/LV combination therapy compared with control (5-FU/LV only) by age subgroup.

	ITT		<65 years		≥65 years		<70 years		≥70 years		<75 years		≥75 years	
	Comb (n = 117)	Ctrl (n = 119)	Comb (n = 63)	Ctrl (n = 77)	Comb (n = 54)	Ctrl (n = 42)	Comb (n = 86)	Ctrl (n = 93)	Comb (n = 31)	Ctrl (n = 26)	Comb (n = 103)	Ctrl (n = 113)	Comb (n = 14)	Ctrl (n = 6)
OS (months),														
Median	6.1	4.2	8.9	4.2	5.2	4.3	7.1	3.8	4.7	5.8	6.2	4.2	5.4	4.7
95% CI	4.8–8.9	3.3–5.3	5.3–10.5	3.2–6.1	4.2–6.4	2.7–6.1	5.3–9.3	3.1–5.3	3.6–6.7	2.8–7.0	4.9–8.9	3.2–5.3	3.3–10.2	2.2–NR
HR (95% CI)	0.67 (0.49–0.92)		0.62 (0.40–0.96)		0.69 (0.43–1.11)		0.63 (0.43–0.92)		0.79 (0.43–1.43)		0.66 (0.47–0.91)		0.75 (0.26–2.22)	
p value[c]	**0.012**		**0.030**		0.121		**0.014**		0.437		**0.012**		0.608	
PFS (months),														
Median	3.1	1.5	4.0	1.4	3.1	1.5	3.0	1.4	3.1	2.4	3.1	1.4	3.4	3.0
(95% CI)	2.7–4.2	1.4–1.8	1.5–5.6	1.3–1.9	2.7–4.2	1.4–2.6	2.4–4.3	1.4–1.6	1.5–4.2	1.4–3.0	2.4–4.2	1.4–1.7	1.2–6.1	1.3–5.6
HR (95% CI)	0.56 (0.41–0.75)		0.52 (0.35–0.78)		0.55 (0.35–0.88)		0.53 (0.37–0.75)		0.62 (0.34–1.11)		0.53 (0.38–0.73)		0.70 (0.23–2.09)	
p value[c]	< **0.001**		**0.001**		**0.012**		< **0.001**		0.109		< **0.001**		0.508	
TTF (months),														
Median	2.3	1.4	2.0	1.3	2.3	1.4	2.3	1.3	1.9	1.5	2.1	1.4	2.7	2.7
(95% CI)	1.6–2.8	1.3–1.4	1.5–4.2	1.2–1.4	1.4–2.8	1.3–1.6	1.6–2.9	1.2–1.4	1.4–2.9	1.3–2.6	1.6–2.8	1.3–1.4	1.2–3.4	1.3–5.6
HR (95% CI)	0.60 (0.45–0.78)		0.55 (0.38–0.79)		0.68 (0.45–1.03)		0.56 (0.41–0.77)		0.73 (0.43–1.26)		0.57 (0.43–0.76)		0.84 (0.31–2.28)	
p value[c]	< **0.001**		**0.001**		0.073		< **0.001**		0.266		< **0.001**		0.730	
ORR[a] (%)	16	1	13	1	20	0	15	1	19	0	16	1	21	0
p value[‡]	<**0.001**		**0.011**		**0.002**		<**0.001**		**0.027**		<**0.001**		0.521	
CA19-9 response rate[b]	28/97	7/81	18/51	5/52	10/46	2/29	22/69	5/63	6/28	2/18	25/84	6/76	3/13	1/5
n/N (%)	(29)	(9)	(35)	(10)	(22)	(7)	(32)	(8)	(21)	(11)	(30)	(8)	(23)	(20)
p value[d]	<**0.001**		**0.002**		0.113		<**0.001**		0.453		<**0.001**		1.000	

Descriptive p values <.05 are highlighted in bold text.
CI, confidence interval; Comb, combination (nal-IRI + 5-FU/LV); Ctrl, control (5-FU/LV); HR, hazard ratio; ITT, intent-to-treat efficacy analysis population (all patients randomized to combination or control arms on protocol version 2); KPS, Karnofsky Performance Status; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.
[a] Breakdown of tumour responses is shown in Supplementary Table 1
[b] Response defined as ≥50% reduction in baseline CA19-9 levels, in patients with baseline levels >0.03 U/μl, and at least one post baseline CA19-9 measurement.
[c] Unstratified HR and log-rank P-value.
[d] Two-sided p values from pairwise Fisher's exact test.

in most age subgroups, with comparable magnitudes of mortality-risk reduction (HRs ranging from 0.62 to 0.79, compared with 0.67 in the overall ITT population) (Table 2; Fig. 3).

Of note, patients receiving nal IRI + 5-FU/LV who were < 65 years (n = 63) had a median OS of 8.9 months and those ≥65 years (n = 54) had a median OS of 5.2 months (HR 0.62 [0.39–0.99]; *P* = .043). In comparison, patients in the 5-FU/LV control arm <65 years (n = 77) had a 4.2-month median OS, and those ≥65 years (n = 42) had a 4.3-month median OS (HR 0.76 [0.49–1.19]; *P* = .230).

Median PFS and TTF were longer with nal-IRI + 5-FU/LV than with 5-FU/LV treatment across all age subgroups, with the exception of TTF in the small ≥75 years subgroup (Table 2). Exploratory treatment comparisons between nal-IRI + 5-FU/LV and 5-FU/LV alone showed statistically significant treatment benefits with nal-IRI + 5-FU/LV for OS, PFS and TTF in the younger age subgroups (<65, <70, and < 75 years), which had relatively large sample sizes. In older-age subgroups with smaller populations, HRs favoured combination treatment but did not reach statistical significance, except for PFS in patients ≥65 years (Table 2).

The percentage of patients achieving ORR was considerably higher in the combination therapy arm than the control arm in all age groups (Table 2), as in the overall ITT population [22]. The treatment difference reached statistical significance in all age subgroups except the small ≥75 years group. A trend towards numerically higher ORR was observed with nal-IRI + 5-FU/LV in the older subgroups (19–21%) versus the younger subgroups (13–16%) (Table 2; breakdown of tumour response data in Supplementary Table 1). A CA19–9 response was consistently achieved by a higher proportion of patients receiving nal-IRI + 5-FU/LV (21–35% across age subgroups) compared with 5-FU/LV alone (7–11% in all subgroups except ≥75 years, in which 20% of patients had a CA19-9 response) (Table 2).

3.4. Safety and Tolerability

The safety profile for nal-IRI + 5-FU/LV was similar across patient subgroups, although the overall incidence of drug-related grade ≥ 3 AEs in the combination therapy arm was numerically lower in the ≥65 and ≥ 70 years groups (45–48%) than in the <65 and < 70 years groups (57–59%). In the ≥75 age group the proportion of patients with grade ≥ 3 AEs was similar to that in the <75 subgroup (57% and 53%, respectively) (Table 3). The most common grade 3–4 non-haematological AEs were late-onset diarrhoea (onset >24 h after starting nal-IRI; no grade 3–4 early onset diarrhoea was reported), fatigue, and vomiting (Table 3). However, fewer older (0–7%) than younger (13–14%) patients reported vomiting, and nausea was more common than vomiting in patients aged ≥65 years. Asthenia was also less common in older (0–4%) versus younger (9–11%) age subgroups, as was alopecia (6–7% versus 15–19%) and febrile neutropenia (3% in patients aged <65 years versus 0% in those above) (Table 3).

A trend for a lower rate of grade 3–4 decreased neutrophil count was observed in older (10–15%) versus younger (21–25%) patients (Table 3). Other haematological AEs occurred in similar proportions of older and younger patients: 3–7% of patients across all age subgroups had grade 3–4 decreased haemoglobin and only two patients, both aged <65, had grade 3–4 decreased platelet count.

3.5. Treatment Exposure, Dose Modifications, and Dose Intensity

The average duration of treatment exposure in the combination arm was 15 weeks overall. Treatment duration tended to be slightly shorter in older patients (13 versus 17 weeks for ≥65/<65 years; 13 versus 16 weeks for ≥70/<70 years), consistent with somewhat higher rates of discontinuation due to treatment-emergent AEs (TEAEs) in the older subgroups (15–16% in ≥65 and ≥ 70 age groups,

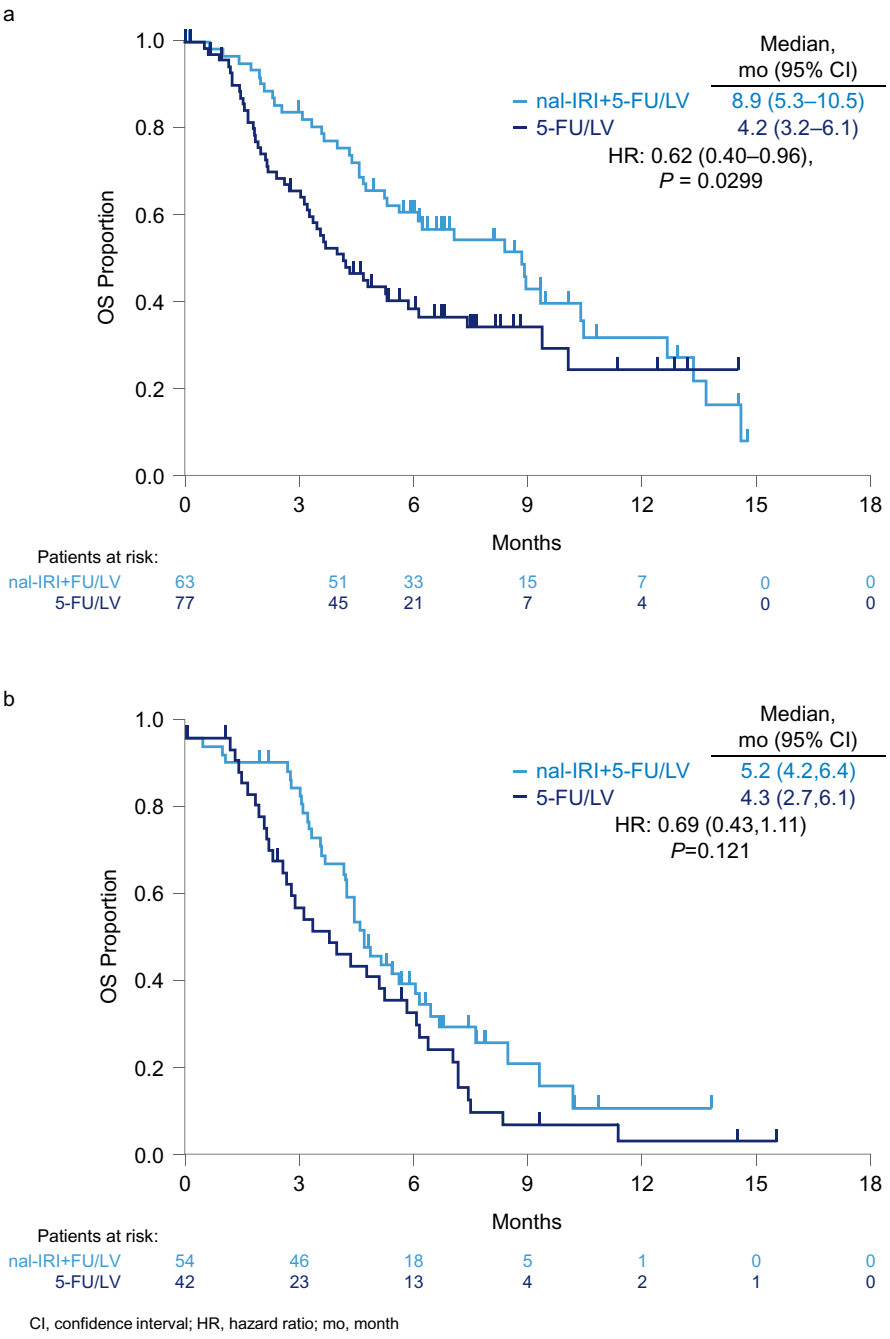

Fig. 3. Overall survival in patients aged <65 (A) or ≥ 65 (B) in the NAPOLI-1 trial receiving nal-IRI + 5-FU/LV versus 5-FU/LV only. Patients had metastatic pancreatic adenocarcinoma and had previously progressed on gemcitabine-based treatment.

compared with 8–9% in <65 and < 70 age groups). When the highest age split (≥75/<75) was applied, treatment duration (14–15 weeks) and discontinuation rates (11–14%) were more similar, suggesting that the 70–74 age group (n = 17) contributed to higher discontinuation rates and shorter treatment durations in their respective subgroups. The proportion of patients requiring dose modifications (dose delay or reduction) due to TEAEs were broadly similar across most age subgroups, but were numerically higher in the small ≥75 years subgroup: 86% (12 of 14 patients) required dose modification compared with 69% (71 of 103 patients) aged <75 years. Dose reductions were required by 6 patients (43%) in the ≥75 years subgroup and 33 patients (32%) aged <75 years (Table 4). Similarly, average relative dose intensity was slightly lower in the ≥75 years age group (76% for nal-IRI and 78% for 5-FU/LV in the combination arm) compared with other subgroups (82–85% for both treatment components) (Table 4).

4. Discussion

We sought to explore the impact of age on outcomes in the NAPOLI-1 trial, and to evaluate the potential for nal-IRI + 5-FU/LV to improve efficacy in older patients with metastatic pancreatic adenocarcinoma that had progressed on prior gemcitabine-based therapy. Median OS and PFS were similar across all age subgroups when treatment arms were combined, indicating that increasing age is not prognostic of mortality or disease progression in this population and that treatment should not be withheld due to age alone for eligible and sufficiently fit patients. Our results also suggest that the clinical benefit of nal-IRI + 5-FU/LV

Table 3
Adverse events by age subgroup in patients receiving nal-IRI + 5-FU/LV combination therapy.

	Overall (n = 117)	<65 years (n = 63)	≥65 years (n = 54)	<70 years (n = 86)	≥70 years (n = 31)	<75 years (n = 103)	≥75 years (n = 14)
Drug related AE of CTCAE grade ≥ 3 (%)	54	59	48	57	45	53	57
Grade 3–4 non-haematological AEs in >5% of patients (%)							
Diarrhoea (late onset[a])	13	14	11	13	13	13	14
Vomiting	11	14	7	14	3	13	0
Nausea	8	5	11	8	6	8	7
Fatigue	14	13	15	14	13	14	14
Asthenia	8	11	4	9	3	9	0
Abdominal pain	7	8	6	8	3	7	7
AEs of special interest (%)							
Alopecia (grade 1–2)	14	19	7	16	6	15	7
Febrile neutropenia (grade 3–4)	2	3	0	2	0	2	0
Grade 3–4 haematological AEs based on laboratory values (% evaluable patients)							
Neutrophil count decreased	20 (n = 114)	25 (n = 61)	15 (n = 53)	24 (n = 84)	10 (n = 30)	21 (n = 101)	15 (n = 13)
Haemoglobin decreased	6 (n = 115)	7 (n = 61)	6 (n = 54)	7 (n = 84)	3 (n = 31)	6 (n = 101)	7 (n = 14)
Platelet count decreased	2 (n = 115)	3 (n = 61)	0 (n = 54)	2 (n = 84)	0 (n = 31)	2 (n = 101)	0 (n = 14)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events, version 4.0.
[a] >24 h after starting nal-IRI (no grade 3/4 early onset diarrhoea [≤24 h after starting nal-IRI] reported).

observed in the primary analysis of the NAPOLI-1 trial [4] was maintained across age subgroups: HRs for nal-IRI + 5-FU/LV versus 5-FU/LV alone were consistently less than one for multiple outcomes across all ages.

The side-effect profile of nal-IRI + 5-FU/LV in older patients in the NAPOLI-1 trial was manageable and predictable. No additional adverse events were associated with combination treatment in older versus younger patients and the incidence of neutropenia and some of the more common treatment-related grade 3–4 AEs, including vomiting and asthenia, was lower in older patients. This may in part be explained by the slightly higher rate of discontinuation due to TEAEs in older patient subgroups (≥65 years and ≥ 70 years) treated with nal-IRI + 5-FU/LV compared with younger patients, which led to a numerically shorter average treatment duration but similar dose intensities. In addition, dose modifications (delays or reductions) were reported in a higher percentage of patients ≥75 years versus younger patients and it is possible that this also had an impact on the incidence of adverse events in this subgroup. A recent post-hoc analysis suggested that dose modification had no significant impact on survival outcomes in the overall NAPOLI-1 population [23]. In the current subgroup analysis, older age groups had numerically lower median OS versus younger patients but no trend in median PFS was observed.

The lack of additional toxicities in older patients is encouraging and in contrast to other regimens. For example, a retrospective study of FOLFIRINOX (5-FU, LV, irinotecan and oxaliplatin) in older patients (70–79 years) in five centres in France found that, while efficacy was similar to that reported for younger patients in the phase II/III PRODIGE 4/ACCORD 11 trial (which excluded patients aged >75 years) [10], there was an increased incidence of grade 3 neurotoxicity in older patients [24].

nal-IRI represents an improved formulation of irinotecan in various respects. Firstly, nal-IRI is a stable liposomal formulation of irinotecan, which exhibits extended systemic circulation of irinotecan compared with non-liposomal irinotecan; at all time points, 95% of the irinotecan in plasma is contained in the liposome [25]. Furthermore, the liposomal formulation has been shown to increase and prolong intra-tumoural levels of irinotecan and its active metabolite SN-38 [26,27], with increased antitumor activity in vitro at a five-fold lower dose than non-liposomal irinotecan [26].

Our post-hoc analysis with multiple age cut-offs permitted exploration of outcomes in older patients with greater sensitivity than the pre-specified subgroup analysis of a single 65-years cut-off [22] as it revealed variation within the relatively large ≥65 years group [9]. Indeed, some patterns (treatment duration, discontinuation rates, and overall incidence of AEs) observed when the age split was applied at 65 and 70 years, were not apparent with a 75-years split. This suggests a possible transition in the 70–74 age group, although this is difficult to evaluate due to the relatively small sample size of this group in the NAPOLI-1 population. Additionally, limited interpretations can be made with results using the <75/≥75-years split, due to the very small size of the ≥75 years subgroup. The use of multiple age cut-offs also highlights that there is no universally accepted definition of 'elderly' [28], and increased life expectancy and improved therapies have led to shifting perceptions. Other considerations, including frailty and functional status

Table 4
Treatment exposure and dose modifications in the combination therapy treatment arm.

	Overall (n = 117)	<65 years (n = 63)	≥65 years (n = 54)	<70 years (n = 86)	≥70 years (n = 31)	<75 years (n = 103)	≥75 years (n = 14)
Patients with TEAE leading to any dose modification (%)	71	73	69	71	71	69	86
Patients with TEAEs leading to dose reduction (%)	33	37	30	35	29	32	43
Patients with TEAEs leading to dose delay (%)	62	65	57	62	61	58	86
Patients with TEAEs leading to treatment discontinuation (%)	11	8	15	9	16	11	14
Mean relative dose intensity (%)							
nal-IRI	83	82	84	83	84	84	76
5-FU/LV	84	83	85	84	85	85	78
Mean duration of treatment exposure (weeks)	15	17	13	16	13	15	14

5-FU/LV, 5-fluorouracil/leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment emergent adverse event.

may be more relevant than age in determining clinical decisions [19,28]. A retrospective population-based study in the Netherlands found that patients receiving no tumour-targeted treatment were significantly older than patients who did receive tumour targeted treatment (74 years versus 66 years; $P < .001$); furthermore 2.3% of patients with pancreatic cancer received no tumour-targeted treatment due to 'old age', despite 37% of these patients having a stage 1 tumour [12]. Additionally, these patients were less often discussed in a multidisciplinary team consultation. Despite this apparent lack of enthusiasm for treatment of older patients, a recent prospective French study investigating geriatric prognostic factors in the pancreatic adenocarcinoma setting found that Lawton's Instrumental Activities of Daily Living impairment, Cumulative Index Rating Scale-Geriatric ≥2 and weight loss >10%, but not age, were prognostic factors for survival in patients >70 years of age. The investigators concluded that almost 90% of their older patient population could benefit from the same treatment as younger patients [29]. Further research on geriatric assessments and the real-world use of such assessments is warranted.

The NAPOLI-1 trial population was fairly typical of clinical trials in this field in terms of age characteristics [30–32]. It included patients aged up to 87 years, with 46%, 25%, and 10% of patients aged over 65, 70, and 75 years, respectively. This compares with reported age distribution of 64–67% aged ≥65, 50% aged ≥70, and 36–39% aged ≥75 in the general pancreatic cancer population [1,2,9]. NAPOLI-1 was not designed prospectively as a study of older patients, and no geriatric evaluation tests were conducted to describe the older portion of the trial population. Therefore, one limitation of this analysis is that, despite lack of an upper age limit in the enrolment criteria for NAPOLI-1, the trial population contained a lower proportion of older patients than the general metastatic pancreatic adenocarcinoma population. It is not clear to what extent the older patients in this analysis reflect the health or performance status of those in clinical practice. Clinical trial populations are highly selective, and frailer patients may have been excluded on the basis of criteria relating to performance status, comorbidities, or hepatic or renal function, thereby being under-represented. An analysis of the Netherlands Cancer Registry reported worse outcomes in older patients receiving chemotherapy in the 'real-life' setting than those reported in clinical trials [9].

Another limitation of this analysis is that it was not powered to detect statistically significant treatment effects within age subgroups. For most outcomes, statistical significance was reached in the larger, younger age groups but not the smaller, older age groups. However, given the consistent trends in the magnitude and direction of treatment effect, and differences in subgroup sizes, the lack of statistical significance in older age groups may reflect smaller group sizes rather than reduced treatment effect of nal-IRI + 5-FU/LV in older patients.

Nearly half of the NAPOLI-1 population was aged ≥65 years, and outcomes in the older patient subgroups were consistent with those in the wider trial population. Therefore, despite some limitations, this analysis provides valuable insights into treatment response in older patients with metastatic pancreatic adenocarcinoma. In the context of a reported 4.6-month median OS from diagnosis in patients with pancreatic cancer treated in the real-world European setting [33], it is clear that appropriate treatment can improve individual outcomes, irrespective of patient age.

In conclusion, this analysis indicates that older patients with metastatic pancreatic adenocarcinoma who have previously progressed on gemcitabine-based treatment can benefit from second-line treatment. Age was not a prognostic factor for decreased survival in this study population and our observations of clinical benefit with nal-IRI + 5-FU/LV were consistent with those observed in the wider trial population. These results support the use of nal-IRI + 5-FU/LV in older patients with metastatic pancreatic adenocarcinoma following gemcitabine-based therapy.

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Author Contributions

JC was responsible for new statistical analyses reported here.
All authors contributed to data interpretation, drafting, reviewing and approving the manuscript.

Disclosures

JTS has had a consulting or advisory role at Merrimack Pharmaceuticals, Lilly, Amcure, Baxalta (now Shire), and Celgene and has received research funding from BMS, Novartis, Boehringer Ingelheim, and Celgene outside the submitted work. JC is a Shire employee and stockholder. FdJ is an employee of Servier and a Shire stockholder, and was an employee of Shire at the time of the study. LTS has a consultant or advisory role at ONO, BMS, MSD, Eli Lilly, PharmaEngine, Five Prime, Novartis, and Astra Zeneca, received honoraria from: ONO, BMS, MSD, Eli Lilly, PhamaEngine, TTY, SyncoreBio, Five Prime, Novartis, Astra Zeneca, Ipsen, and has received research funding from: Novartis, Pfizer, Merck Serono, Polaris, TTY, SyncoreBio, and Celgene. BM is an Ipsen stockholder. TM has a consultant or advisory role at celgene, servier, shire, amgen, eisai, Incyte. Other authors have nothing to disclose.

Data Sharing Statement

Individual participant data, including data dictionaries, will not be available for this study. The primary study was published in 2015 (Wang-Gillam et al., Lancet 2016, 287[10018: 545-57]) and on clinicaltrials.gov NCT01494506. Ipsen owns the NAPOLI-1 study data and Shire performed this subanalysis.

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