Combining CD40 agonist mitazalimab with mFOLFIRINOX in previously untreated metastatic pancreatic ductal adenocarcinoma (OPTIMIZE-1): a single-arm, multicentre, phase 1b/2 study

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Summary

Background Current systemic therapies for metastatic pancreatic ductal adenocarcinoma are associated with poor outcomes with a 5-year overall survival rate under 5%. We aimed to assess the safety and antitumour activity of mitazalimab, a human CD40 agonistic IgG1 antibody, with modified FOLFIRINOX (mFOLFIRINOX; fluorouracil, leucovorin, oxaliplatin, and irinotecan), in chemotherapy-naive patients with metastatic pancreatic ductal adenocarcinoma.

Methods OPTIMIZE-1 was a single-arm, multicentre, phase 1b/2 study which enrolled adults with histologically-confirmed metastatic pancreatic ductal adenocarcinoma and European Cooperative Oncology Group performance status 0 or 1 in 14 university hospitals in Belgium, France, and Spain. The primary endpoint of phase 1b was to determine the recommended phase 2 dose of intravenous mitazalimab (450 µg/kg or 900 µg/kg) when combined with intravenous mFOLFIRINOX (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 150 mg/m², fluorouracil 2400 mg/m²). In the first 21-day treatment cycle, mitazalimab was administered on days 1 and 10, and mFOLFIRINOX on day 8. In subsequent 14-day cycles mitazalimab was administered 2 days after mFOLFIRINOX. The phase 2 primary endpoint was objective response rate. Activity and safety analyses were conducted on the full analysis set (all patients who received the combination of mitazalimab at the recommended phase 2 dose and mFOLFIRINOX for at least two treatment cycles) and safety set (all patients who received any study treatment), respectively. Enrolment is complete, and data represents a primary analysis of the ongoing trial. The trial is registered at Clinicaltrials.gov (NCT04888312).

Findings Between Sept 29, 2021, and March 28, 2023, 88 patients were screened and 70 patients were enrolled (40 [57%] were female and 30 [43%] were male). In phase 1b, 900 µg/kg mitazalimab was determined as the recommended phase 2 dose. Overall, five patients received 450 µg/kg mitazalimab; 65 received 900 µg/kg mitazalimab. No dose-limiting toxicities were observed at 450 µg/kg, and one dose-limiting toxicity was observed at 900 µg/kg. 57 patients were evaluated for activity, and all 70 patients were included in the safety set. At data cutoff on Nov 14, 2023, median follow-up was 12·7 months (95% CI 11·1–15·7). Of the 57 patients, 29 (51%) remained on study and 18 (32%) remained on treatment. The primary endpoint (objective response rate >30%) was met (objective response rates in 23 [40%]; one-sided 90% CI ≥32 of 57 patients). The most common grade 3 or worse adverse events were neutropenia (18 [26%] of 70 patients), hypokalaemia (11 patients [16%]), and anaemia and thrombocytopenia (eight patients [11%]). Serious adverse events were reported in 29 (41%) of 70 patients, the most common being vomiting (five [7%] of 70 patients), decreased appetite (four [6%]), and diarrhoea and cholangitis (three [4%] of 70 patients for each), none considered related to mitazalimab. No treatment-related deaths were reported.

Interpretation Mitazalimab with mFOLFIRINOX demonstrated manageable safety and encouraging activity, warranting continued development in a phase 3, randomised, controlled trial. The results from OPTIMIZE-1 pave the way for further exploration and confirmation of a novel immunotherapy treatment regimen for metastatic pancreatic ductal adenocarcinoma, which is a complex and aggressive cancer with very low survival rates and restricted treatment options.

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Research in context

Evidence before this study

We searched PubMed on Feb 1, 2024, for evidence on CD40 agonists in metastatic pancreatic ductal adenocarcinoma from database inception until the time of search, using the search terms (CD40 AND ["pancreatic cancer" OR "pancreatic ductal adenocarcinoma" OR "PDAC" OR "metastatic pancreatic ductal adenocarcinoma" OR "mPDAC"]), with no language restrictions. This search identified the phase 2 PRINCE trial investigating sotigalimab, with or without nivolumab, with gemcitabine plus nab-paclitaxel in first-line treatments for metastatic pancreatic ductal adenocarcinoma. Sotigalimab with gemcitabine plus nab-paclitaxel led to an overall response rate of 33%, median duration of response of 5·6 months, and a 12-month overall survival rate of 48·1%. Another CD40 agonist, CP-870,893, combined with gemcitabine in patients with chemotherapy-naive, surgically-incurable pancreatic ductal adenocarcinoma in a phase 1 dose-escalation trial resulted in a partial response in four patients, stable disease in 11 patients, and disease progression in four patients. No studies reported mFOLFIRINOX with any CD40 agonist; all studies included administration of chemotherapy before the CD40 agonist. An additional PubMed search ("mitazalimab" OR "ADC-1013" OR "JNJ-64457107") conducted on Feb 1, 2024, again with no date or language restrictions, retrieved two articles reporting antitumour responses in mice bearing bladder tumours with mitazalimab monotherapy, alongside improved survival, via activation of antigen-presenting cells and antigen-specific T cells. A first-in-human study reported that intratumoural administration of mitazalimab in advanced solid malignancies was safe, with evidence of clinical activity. A subsequent phase 1 study of intravenous mitazalimab in 95 patients with advanced solid tumours found mitazalimab to be safe, with 36·8% of patients reporting stable disease. Pharmacodynamic activity identified transient reductions in effector cells and B cells, with remaining immune cells showing transcription profiles consistent with activation.

Added value of this study

To our knowledge, OPTIMIZE-1 is the first study to report on the novel combination of mFOLFIRINOX chemotherapy with mitazalimab, a second generation CD40 agonist, as a first-line treatment for patients with metastatic pancreatic ductal adenocarcinoma. Moreover, to our knowledge, it is the first to employ a priming dose of a CD40 agonist to sensitise the tumour prior to chemotherapy administration. This novel treatment combination and unique dosing schedule resulted in deep responses with an unprecedented duration of response and prolonged overall survival, although these secondary outcomes have not yet been validated against a comparator group and must be interpreted as preliminary. The safety profile of this combination was consistent with mFOLFIRINOX, with no signs of additive toxicity related to the addition of mitazalimab. A correlation between increases in activated T and natural killer cells before the first dose of mFOLFIRINOX and depth of response is suggestive of a mitazalimab-induced immune cell activation contributing to the anti-tumour response. These findings provide evidence on the potential utility of a novel treatment regimen for metastatic pancreatic ductal adenocarcinoma, a cancer with very low survival rates.

Implications of all the available evidence

The findings of this study support the continued development of mitazalimab, in combination with mFOLFIRINOX, in a confirmatory, phase 3, clinical trial in patients with previously untreated metastatic pancreatic ductal adenocarcinoma.

Introduction

Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide. Pancreatic ductal adenocarcinoma accounts for approximately 80% of all pancreatic cancers. Surgical resection is the only curative treatment option, but more than 75% of patients present with advanced, unresectable, disease.[1] Patients with metastatic pancreatic ductal adenocarcinoma have a 5-year survival rate of under 5%, and an untreated median overall survival of just 3 months.[2,3]

Current first-line treatment options for metastatic pancreatic ductal adenocarcinoma comprise of systemic chemotherapy including the combination regimens gemcitabine plus nab-paclitaxel and FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan).[1] While FOLFIRINOX demonstrates improved outcomes over gemcitabine-based regimens, overall clinical benefits are modest.[4–6] Recently, NALIRIFOX (liposomal irinotecan, oxaliplatin, fluorouracil, and leucovorin) received US Food and Drug Administration approval as first-line therapy for patients with metastatic pancreatic ductal adenocarcinoma, based on results from the NAPOLI-3 trial.[7] While representing the first treatment advance in 10 years for patients with previously untreated metastatic pancreatic ductal adenocarcinoma, given the similar levels of efficacy to FOLFIRINOX, there remains an urgent need for more efficacious and durable therapies.[6]

Pancreatic tumours host an immunosuppressive tumour-promoting microenvironment with limited tumour neoantigen expression, an abundance of immunosuppressive myeloid cells, and reduced expression and function of antigen-presenting dendritic cells.[8,9] Moreover, these tumours are surrounded by a desmoplastic stroma, creating a physical barrier to systemic chemotherapy and cytotoxic T cells and harbouring increased expression of immunosuppressive M2 macrophages over tumoricidal M1 phenotypes. This tumour microenvironment is driven by several oncogenes including the mutated *KRAS* virus oncogene, found in approximately 90% of metastatic pancreatic ductal adenocarcinomas.[9] Glycine 12 (G12) missense

mutations are most common, with G12D and G12V as the most frequent. Each mutation is associated with varying degrees of influence on overall survival in patients with pancreatic cancer.[10]

CD40 is a co-stimulatory receptor expressed on the surface of B cells, monocytes, macrophages, and dendritic cells. CD40 agonist-mediated stimulation re-directs tumour-infiltrating macrophages from M2 to M1 phenotype, promotes fibrotic stromal degradation, and enhances tumour sensitivity to chemotherapy.[11,12] Stimulation of CD40 on dendritic cells that have sequestered antigens released by chemotherapy-induced immunogenic cell death activates effector T cells, resulting in anticancer effects.[13] Combining CD40 agonists with gemcitabine-based chemotherapy shows promise in patients with metastatic pancreatic ductal adenocarcinoma.[14,15]

Structural differences between CD40 agonists influence safety, with reports suggesting that systemic administration might result in dose-limiting, immune-related adverse effects constraining clinical benefit.[16] Mitazalimab (JNJ-64457107, ADC-1013) is a second generation, best-in-class, human IgG1 CD40 antibody which has previously shown clinical activity, and a favourable safety profile in advanced-stage solid tumours.[17–19]

Combining CD40 agonists with modified FOLFIRINOX (mFOLFIRINOX) has not been reported in metastatic pancreatic ductal adenocarcinoma, but is supported by preclinical data.[20] Moreover, exploiting the ability of CD40 agonists to reduce immunosuppression in metastatic pancreatic ductal adenocarcinoma before chemotherapy has not been investigated in a clinical setting. Here, we present the primary analysis of activity, safety, and biomarker data from the novel combination of mitazalimab and mFOLFIRINOX in chemotherapy-naive patients with metastatic pancreatic ductal adenocarcinoma, introducing a unique priming dose of mitazalimab administered 7 days before the initial mFOLFIRINOX dose.

Methods

Study design and participants

OPTIMIZE-1 was single-arm, phase 1b/2 study conducted in 14 university hospitals in Belgium, France, and Spain according to the study protocol and amendments approved by local Institutional Review Boards and independent ethics committees (appendix p 3), and in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonisation.

Eligible patients aged 18 years or older, had a histologically confirmed metastatic pancreatic ductal adenocarcinoma diagnosis, were chemotherapy-naive, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.[21] Key exclusion criteria included other non-ductal pancreatic tumours. Complete eligibility criteria, including laboratory values, and full exclusion criteria are listed in the protocol (appendix). Patients provided written informed consent before enrolment.

Phase 1b followed a Bayesian optimal interval (BOIN) design with three or more patients enrolled at two mitazalimab doses (450 µg/kg or 900 µg/kg). A decision of continuing the enrolment at the same dose, escalation to the next higher dose, or de-escalation to the next lower dose was to be based on a target dose-limiting toxicity rate of 30%. Detailed escalation rules can be found in the protocol (appendix). At least six patients were required to be treated at the dose level before declaring it as the recommended phase 2 dose.

Procedures

In phase 1b, mitazalimab (450 µg/kg or 900 µg/kg) was administered intravenously during a 2-hour, rate-controlled infusion combined with intravenous mFOLFIRINOX (85 mg/m² oxaliplatin over 2 h, 400 mg/m² leucovorin over 2 h, and 150 mg/m² irinotecan over 90 min [starting 30 min after the start of the leucovorin infusion], followed by 2400 mg/m² fluorouracil over 46–48 h) for recommended phase 2 dose determination. During the first 21 day treatment cycle, mitazalimab was administered on day 1 (priming dose) and on day 10, and mFOLFIRINOX on day 8. During subsequent 14-day treatment cycles, mFOLFIRINOX was administered on day 1 and mitazalimab on day 3.

Phase 1b dose escalation required at least three patients to be evaluable for a dose-limiting toxicity at each mitazalimab dose from priming dose until day 21 (cycle 1). Detailed dose-limiting toxicity criteria are in the protocol (appendix). Data from each dose level was reviewed by the data review committee (comprising participating investigators and the Funder's medical representatives, centrally and at each site) before continuation to the subsequent dose or into phase 2.

In phase 2, mitazalimab at the recommended phase 2 dose was administered to all patients, combined with mFOLFIRINOX, with a planned treatment duration up to 12 cycles. A major protocol amendment (protocol version 6.0, approved amendment 5, made on Oct 5, 2022) allowed continued treatment beyond 12 cycles until disease progression, or any other treatment discontinuation or study withdrawal criteria were met. Antitumour activity was evaluated by CT, according to RECIST version 1.1, at screening and every four cycles thereafter. Response endpoints were locally reviewed. Depth of response was characterised as percentage decrease from baseline in the sum of the longest diameters of target lesions over time, and the maximal percent change by best overall response.

See Online for appendix

Adverse events were continuously recorded and coded using Medical Dictionary for Regulatory Activities

version 24.0, with severity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Adverse events of special interest are described in detail in the protocol (appendix). Adverse events considered related to mFOLFIRINOX by investigators permitted a dose adjustment according to standard practice. Mitazalimab dose was reduced by 50% where a mitazalimab-related adverse event resulted in treatment delay by over 2 weeks, with only one dose reduction allowed. Any mitazalimab-related serious adverse event or adverse event worse than grade 2 resulted in mitazalimab being withheld until adverse event resolution. Mitazalimab could be resumed at the previous dose or, if not already dose-reduced, with a 50% dose reduction at the investigator's discretion. After study treatment completion, patients were required to continue to a survival follow-up period.

For laboratory tests, biomarker pharmacodynamic, pharmacokinetic, and anti-drug antibody analysis, samples (whole blood or urine, as applicable) were collected at baseline and throughout treatment, as detailed in the schedule of assessments in the study protocol (appendix).

Quantification of cytokines and chemokines in serum samples was conducted using a Meso Scale Discovery multiplex electrochemiluminescence-based immunoassay (MSD, Rockville, MD USA); immunophenotyping was conducted in whole blood samples via flow cytometry; *KRAS* mutational status in whole blood was conducted via droplet digital PCR. Pharmacokinetics and anti-drug antibodies were assessed using a validated bioanalytical method (appendix pp 2, 4–5).

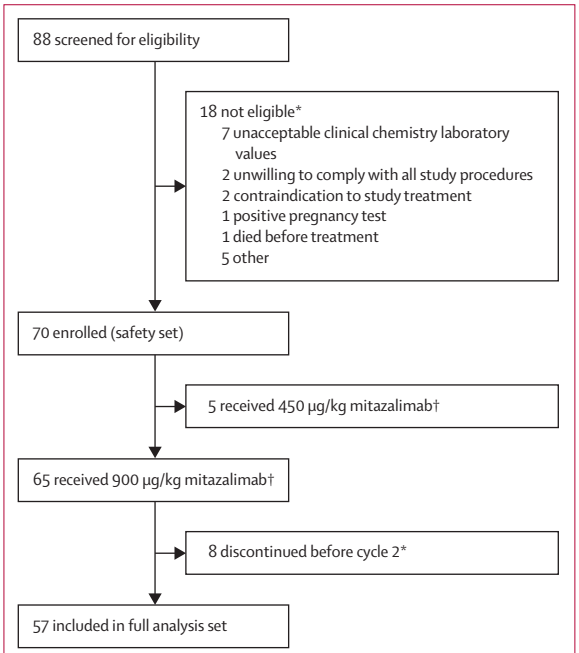

Figure 1: **Trial profile**
*Reasons for ineligibility and study discontinuation can be found in the appendix (pp 7–8). †In combination with modified FOLFIRINOX.

Outcomes

The phase 1b primary endpoint was to determine the recommended phase 2 dose of mitazalimab, assessed by dose-limiting toxicity occurrence. The phase 2 primary endpoint was to assess the clinical activity of mitazalimab in combination with mFOLFIRINOX using objective response rate, defined as the proportion of patients achieving a confirmed complete or partial response (as investigator-assessed via at least consecutive imaging assessments) as per RECIST version 1.1.[21]

Key secondary objectives were best overall response (defined as best response from RECIST version 1.1 categories of complete response, partial response, stable disease, and disease progression, at any time during the study), duration of response (number of days from initial complete response or partial response to disease progression or death due to underlying disease), duration of stable disease (the number of days from the first dose of mitazalimab to progressive disease or death, whichever comes first), disease control rate (either complete response, partial response, or stable disease at each visit as determined by RECIST version 1.1), time to next cancer therapy (number of days from the time from the first dose of mitazalimab to next anticancer treatment initiated), progression-free survival (time from first mitazalimab dose to disease progression or death due to any cause), overall survival (time from first mitazalimab dose to date of death from any cause), and safety (type, frequency, and severity of adverse events). Of note, duration of stable disease was replaced with time-to-progression as a key secondary endpoint as a post hoc change to the statistical analysis plan.

Additional secondary endpoints included assessment of anti-drug antibodies and pharmacokinetic parameters (C_{max}, T_{max}, and area under curve [$AUC_{(0–24h)}$]). Exploratory endpoints included changes in cytokines and chemokines, innate and adaptive immune-cell populations and activation, gene expression, immune signatures, CA19-9 and circulating tumour DNA of differentially expressed genes of interest.

Data presented in this Article are from the primary analysis of OPTIMIZE-1; data collection and analysis for some secondary outcomes (time to next cancer therapy, time to progression) and exploratory outcomes (gene expression analysis and impact on CA19-9 and immune signatures) are ongoing, and not reported here. These will be included in a final analysis of OPTIMIZE-1 study data.

Statistical analysis

Full details of the statistical analyses are described in the study protocol (appendix). No formal statistical hypothesis was defined for phase 1b; patients were pooled with those on the same dose regimen in phase 2 for statistical

	Full analysis set (N=57)	Safety set (N=70)
Age, years		
Median (range)	62 (55–68)	62 (56–68)
Under 65	35 (6%)	40 (57%)
65 or above	22 (39%)	30 (43%)
Sex*		
Female	33 (58%)	40 (57%)
Male	24 (42%)	30 (43%)
Race*		
American Indian or Alaskan Native	0	0
Asian	0	0
Black or African American	3 (5%)	3 (4%)
Native Hawaiian or Other Pacific Islander	0	0
Not reported	16 (28%)	19 (27%)
Other	1 (2%)	1 (1%)
Unknown	0	0
White	37 (65%)	47 (67%)
Ethnicity*		
Unknown	0	0
Hispanic or Latino	3 (5%)	3 (4%)
Not Hispanic or Latino	35 (61%)	41 (59%)
Not reported	19 (33%)	26 (37%)
Time from diagnosis to treatment start in days, median (IQR)	30 (22–35)	29 (21–35)
ECOG performance status		
Grade 0	31 (54%)	38 (54%)
Grade 1	26 (46%)	32 (46%)
Modified Glasgow Prognostic Score		
0	29 (51%)	35 (50%)
1	25 (44%)	31 (44%)
2	3 (5%)	4 (6%)
Previous surgery		
Yes	2† (4%)	3 (4%)‡
No	55 (96%)	67 (96%)
CA19-9 at baseline, U/mL, n	48	61
<100	8 (17%)	9 (15%)
100–1000	13 (27%)	13 (21%)
>1000	27 (56%)	39 (64%)
Neutrophil to lymphocyte ratio, n	56	69
<5	46 (82%)	57 (83%)
>5	10 (18%)	12 (17%)
(Table 1 continues in next column)		
(Continued from previous column)		
Primary tumour location, n	55	67
Head	25 (45%)	29 (43%)
Body	21 (38%)	23 (34%)
Tail	9 (16%)	15 (22%)
Number of target lesions		
1	12 (21%)	12 (17%)
2	19 (33%)	21 (30%)
3 or more	25 (44%)	37 (53%)
Presence of liver metastases		
Yes	42 (74%)	55 (79%)
No	15 (26%)	15 (21%)
Sites of metastatic disease		
Liver	42 (74%)	55 (79%)
Lung	9 (16%)	12 (17%)
Peritoneal	9 (16%)	10 (14%)
Lymph Node	10 (18%)	14 (20%)
Other	16 (28%)	20 (29%)
Number of liver metastasis, n	42	55
1	7 (17%)	8 (15%)
2	14 (33%)	18 (33%)
3 or more	21 (50%)	29 (53%)
Histological subtype		
Adenocarcinoma	56 (98%)	68 (97%)
Adenosquamous carcinoma	0	1 (1%)
Not known	1 (2%)	1 (1%)

Data are n (%) except where specified. CA19–9=carbohydrate antigen 19–9. ECOG=Eastern Cooperative Oncology Group. u/mL=units per mL. *Information on sex, race, and ethnicity was collected via electronic medical records. †Choledoduodenostomy and palliative excision of the primary tumour, respectively. ‡As for the full analysis set, plus one surgery to remove the primary tumour.

Table 1: **Patient baseline characteristics**

analyses and data summaries. As defined by the BOIN 3+3 design, at least nine patients were required, with three patients at 450 µg/kg and 3+3 at 900 µg/kg.

For phase 2, a Simon's two-stage design was employed, testing the null hypothesis of 30% objective response rates against the alternative historical control of over 30% objective response rates,[4] with a one-sided type 1 error of 10% and 80% power. 23 patients were assessed for activity in stage 1. The cut off limit for stopping for futility was seven or fewer responders ie, if there were at least eight responders (complete or partial) the study would continue to stage 2 and enrol up to 57 activity evaluable patients (ie, having received two or more cycles of mitazalimab and mFOLFIRINOX). The primary endpoint was considered met if 22 or more responses were observed among evaluable patients.

Objective response rate is accompanied by one-sided 90% CIs. For time-to-event endpoints, Kaplan–Meier analysis estimated median values and 95% CIs. There was no informative censoring in the Kaplan–Meier analysis; censoring rules for all time-to-event endpoints can be found in the appendix (p 6). Pharmacokinetic parameters were calculated from the serum concentration-time data using non-compartmental methods.

Post hoc exploratory subgroup analysis of objective response rates and best overall response were summarised using descriptive statistics including two-sided exact binomial 90% CIs or 95% CIs. Analyses of an association between change in $CD38^{+}$ natural killer

T (NKT) cell expression with depth of response, and between longitudinal changes from baseline in *KRAS* mutational status with change in sum of longest diameter of target lesions per patient were also done post hoc.

The full analysis set (all patients who received the combination of mitazalimab at the recommended phase 2 dose and mFOLFIRINOX for at least two treatment cycles) was used for all activity and exploratory endpoints, including all post hoc analyses. The safety set comprised all patients receiving any study treatment.

Statistical analyses were performed using SAS version 9.4. This study is registered with ClinicalTrials.gov (NCT04888312).

Role of the funding source

The funder of the study contributed to the study design, data collection, data analysis, interpretation of data, and writing of the report.

Results

Between Sept 29, 2021, and March 28, 2023, 88 patients were screened for eligibility. 70 patients with chemotherapy-naive metastatic pancreatic ductal adenocarcinoma were included and received study treatment (figure 1; appendix pp 7–8). The cohort included 40 (57%) female patients and 30 (43%) male patients, and median age was 62 years (IQR 56–68). Five patients received 450 µg/kg mitazalimab and 65 patients received one or more doses of 900 µg/kg mitazalimab, both combined with mFOLFIRINOX. No dose-limiting toxicities were observed at 450 µg/kg, and one dose-limiting toxicity was observed at 900 µg/kg. As per the dose-escalation procedure, 900 µg/kg mitazalimab was the recommended phase 2 dose determined by the data review committee of participating investigators and sponsor representatives. In stage 1 of phase 2, 12 patients were responders—either a complete or partial response—allowing the study to pass futility and enrol 57 evaluable patients who all received two or more cycles of 900 µg/kg mitazalimab combined with mFOLFIRINOX. Baseline demographics and clinical characteristics of patients in the full analysis set (n=57) and the safety set (n=70) are in table 1.

In phase 2, the primary endpoint was met (confirmed complete or partial objective response seen in 23 [40%]; one-sided 90% CI ≥32 of 57 patients; table 2). At data cutoff on Nov 14, 2023, median follow-up was 12·7 months (95% CI 11·1–15·7) with 29 (51%) of 57 patients remaining on-study, 18 (32%) on-treatment, and 11 (19%) in survival follow-up.

39 patients discontinued treatment. 32 (56%) of 57 patients had disease progression. Of these, 18 (32%) of 57 received second-line systemic therapies (appendix p 9). One patient opted to undergo radical surgery with curative intent after a deep partial response amounting to a 50% reduction in target lesions, durable for four months.

The median number of treatment cycles was 12 (IQR 7–19). Median mitazalimab exposure was 206 days (IQR 107–345). Details of mFOLFIRINOX exposure is shown in the appendix (pp 10–11). 30 (53%) of 57 patients remained on treatment for more than 6 months. Ten patients (18%) remained on treatment for more than 12 months, with one patient on treatment for 23 months, ongoing as of data cutoff. Five (9%) of 57 patients were late responders with a first documented partial response at their third CT scan and nine (16%) demonstrated long-term (longer than 6 months) stable disease. In all 57 activity-evaluable patients, one patient (2%) demonstrated a complete response; partial response and stable disease were seen in 22 patients (39%) each (figure 2A). The maximal percentage change in tumour size from baseline for each patient and over time can be seen in figure 2B and 2C, respectively; two partial responders demonstrated a complete response in target lesions, with persistent disease evident in non-target lesions. The results for duration of response, progression-free survival and overall survival are shown in table 2 and figure 3.

Post hoc subgroup analyses of objective response rates and best overall response are reported in the appendix (pp 14–15).

Safety data are presented in table 3 and in the appendix (p 12). Grade 3 or worse treatment emergent adverse events were reported in 55 (79%) of the 70 patients in the safety set, the most common being neutropenia (18 [26%] of 70 patients), hypokalaemia (11 [16%] of 70 patients),

	Full analysis set (N=57)
Best overall response	
Complete response	1 (2%)
Partial response	22 (39%)
Stable disease	22 (39%)
Progressive disease	12 (21%)
Disease control rate	45 (79%)
Overall response	
Number of patients with overall response (unconfirmed)	29
Overall response rate: unconfirmed*, % (90% CI)	51% (≥42)†
Number of patients with overall response: confirmed†	23
Overall response rate: confirmed*, % (90% CI)	40% (≥32)‡
Median duration of response, months (95% CI)	12·5 (7·5–NE)
Time to progression, months (95% CI)	7·7 (5·8–NE)
Progression-free survival	
Median progression-free survival, months (95% CI)	7·7 (5·8–11·3)
6-month progression-free survival rate§, (%) (95% CI)	62% (48·3–73·6)
12-month progression-free survival rate§, % (95% CI)	34% (20·8–47·7)
Overall survival	
Median overall survival, months (95% CI)	14·3 (10·0–21·6)
6-month overall survival, % (95% CI)	90% (81·9–97·8)
12-month overall survival, % (95% CI)	59% (44·2–71·7)

NE=not evaluable. RECIST=Response Evaluation Criteria in Solid Tumours. *Complete or partial responses can only be claimed if the criteria for each are confirmed by a repeat assessment at least 4 weeks later. †Two-sided 90% CI 39·3–62·4. ‡Two-sided 90% CI 29·4–52·1.

Table 2: **Activity responses for primary analysis in the full analysis set by investigator assessment per RECIST version 1.1**

anaemia and thrombocytopenia (eight [11%] of 70 patients each). In the safety population, 56 serious adverse events were reported in 29 (41%) patients, the most common being vomiting (five [7%] of 70 patients), decreased appetite (four [6%] of 70 patients), and diarrhoea and cholangitis (three [4%] of 70 patients each), none considered mitazalimab-related. 28 patients died during the study, all as a result of disease progression. No treatment-related deaths were reported.

Adverse events of special interest included infusion-related reaction (14 [20%] of 70 patients), elevated aspartate aminotransferase, alanine aminotransferase, or both (five [7%] of 70 patients), and elevated bilirubin (three [4%] of 70 patients).

Four (6%) of 70 patients discontinued study treatment due to treatment-emergent adverse events: one with fatigue, chest pain, and headache; one with general deterioration in physical health; one with pneumonia; and one with an infusion-related reaction (pruritus; appendix p 12). Three (4%) of 70 patients had one or more dose delays of mitazalimab due to adverse events; dose reduction was required in one patient (1%) of 70. At least one dose reduction of any mFOLFIRINOX component was required for 48 (72%) of 70 patients.

Pharmacokinetic parameters of mitazalimab can be found in the appendix (p 13). Mitazalimab serum concentrations were as expected, with no difference in drug exposure levels between the mitazalimab priming dose and the dose following mFOLFIRINOX (appendix p 16). Three of 66 patients evaluable for immunogenicity developed anti-mitazalimab antibodies during the study, resulting in an immunogenicity incidence of 5%.

The results for the changes in cytokines, chemokines, and innate and adaptive immune-cell populations are shown in the appendix (pp 17–18, 20).

A post-hoc analysis demonstrated that increased CD38^{+} NKT cells at cycle 1, day 8 versus baseline correlated significantly with best depth of response (appendix p 19).

Whole blood samples were available from 49 patients for *KRAS* mutational status evaluation. 46 [94%] of 49 patients expressed a *KRAS* mutation (G12V in 21 [43%] of 49 patients; G12D in 20 [41%] of 49 patients; G12R in five [10%] of 49 patients); and wild type in three (6%) of 49 patients. Patients harbouring G12V and G12R mutations demonstrated improved objective response rates (G12V 13 [62%] of 21 patients [90% CI 41·7–79·4]; G12R three [60%] of five patients [18·9–92·4]) compared with the overall population (appendix p 21; post hoc analysis). Decrease in circulating mutant *KRAS* DNA was observed along with a reduction of target tumour lesion size in most patients in a post-hoc analysis (appendix p 22).

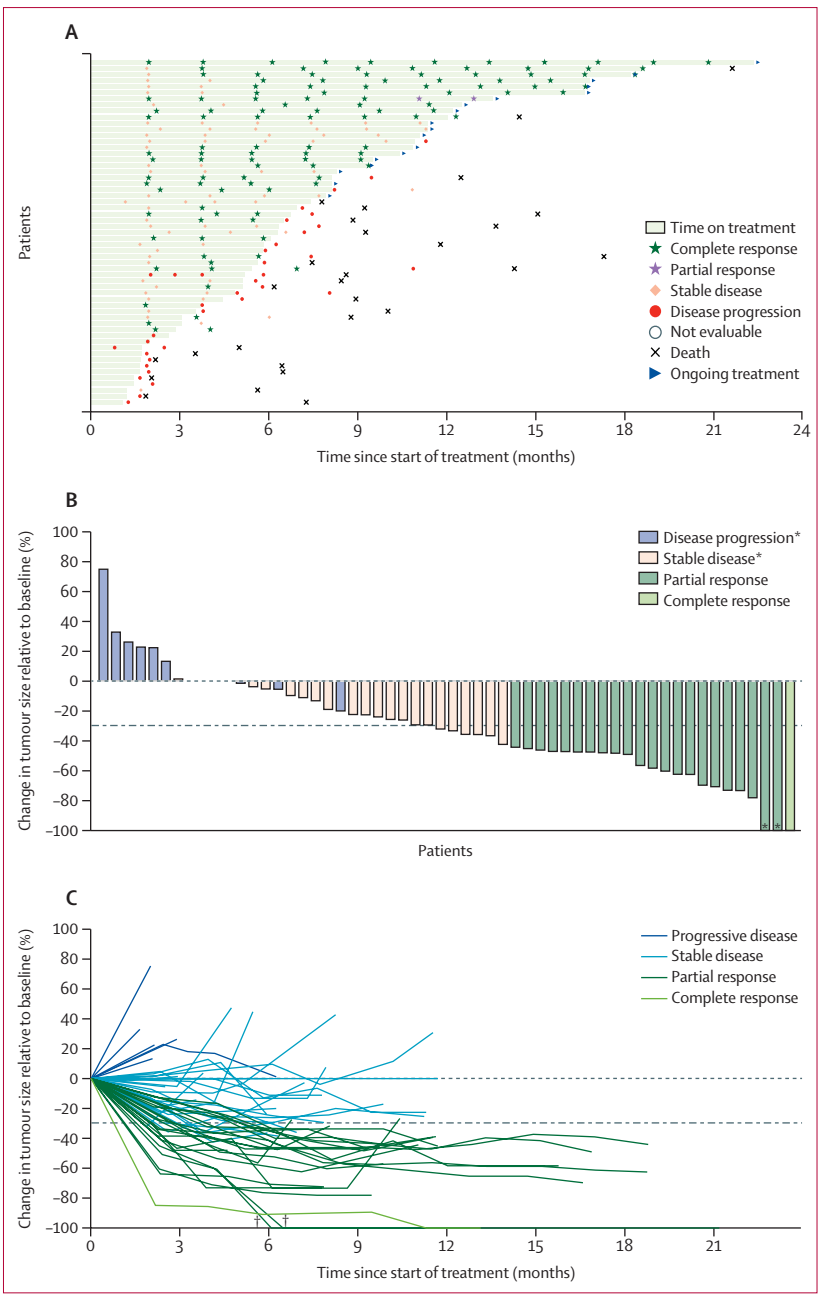

Figure 2: **Depth and duration of response in the full analysis set**
Swimmer plot showing the treatment durations for all 57 activity-evaluable patients (A); waterfall plot showing the maximum percentage change in the tumour size relative to baseline target lesions of individual patients by best overall response (B); spider plot showing the percentage change from baseline in tumour target lesions over time (C). Dashed reference lines refer to values 0 and –30. *Some patients had a small reduction in tumour lesion size at the start of treatment that did not meet the 7-week duration threshold for stable disease classification. †Two partial responders demonstrated a complete response in target lesions, with persistent disease evident in non-target lesions.

Discussion

OPTIMIZE-1 met its primary endpoint with a confirmed objective response rates of 40% in chemotherapy-naive patients with metastatic pancreatic ductal adenocarcinoma treated with mitazalimab and mFOLFIRINOX. This therapeutic combination was associated with a manageable safety profile.

Immune checkpoint inhibitors have been revolutionary in cancer treatment, but success in metastatic pancreatic

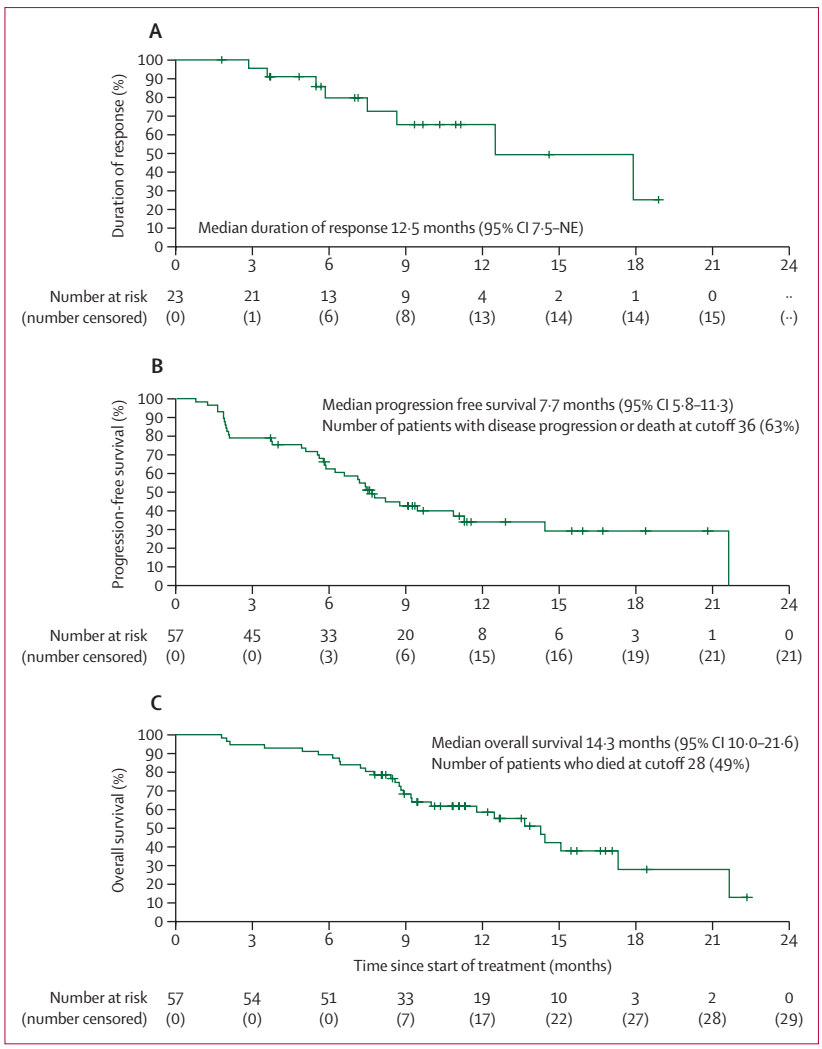

Figure 3: **Kaplan–Meier curve estimates**
Estimates for duration of response (A), progression-free survival (B), and overall survival (C) for all patients in the full analysis set. NE=not evaluable.

ductal adenocarcinoma remains elusive due to the low numbers of effector T cells infiltrating the tumour microenvironment.[22] Patients who are long-term survivors of metastatic pancreatic ductal adenocarcinoma long-term harbour increased neoantigen expression and demonstrate an enhanced immune response. This suggests that combining chemotherapy to increase neoantigen release with an immunostimulant to amplify the antigenic immune response will result in maximal clinical benefits for patients with metastatic pancreatic ductal adenocarcinoma.[23] CD40 antibody agonists show promise in this approach.[16]

The antitumour activity outcomes observed in OPTIMIZE-1, are in line with (and in some cases, even better) than those reported in pivotal studies leading to standard-of-care chemotherapy approval, and in initial studies of other CD40 agonists.[4,5,7,14,24] It is worth highlighting the higher proportion of patients in other studies who had received surgical intervention and chemotherapy in an adjuvant or neoadjuvant setting compared with our study, wherein all patients were chemotherapy-naïve, and only two patients had received previously surgery. Notably, patients receiving adjuvant chemotherapy or surgery report a significantly longer overall survival compared with those not receiving adjuvant chemotherapy or de novo metastatic patients.[25,26] In view of this, the reported outcomes in our study can be regarded as encouraging for this population of patients with poor-prognosis.

The duration of response is more than double that seen with FOLFIRINOX and a 50% increase over that observed with NALIRIFOX.[4,7] Notably, the longest ongoing treatment duration was 23 months, and several patients demonstrated a delayed response, or maintained stable disease for over 6 months, suggesting that addition of mitazalimab to chemotherapy might induce a long-lasting immune response in a sizeable proportion of patients. Importantly, duration of response is considered useful in assessing treatments which may prolong responses, such as immunotherapy, and is considered a clinically important endpoint during regulatory review.[27] It is expected that survival measures and duration of response will continue to improve with ongoing treatment and follow-up, particularly as over half of patients remain on study and approximately a third on treatment, as of data cutoff. The meaningful depth of response is further evidenced by the complete disappearance of target lesions in three patients.

The sequence and timing of mitazalimab administration in relation to chemotherapy is an important, differentiating aspect of OPTIMIZE-1. Introducing a priming dose 7 days before the first dose of chemotherapy was based on preclinical data suggesting this was safe and efficacious, enabling appropriate activation of immune cells before any chemotherapy-induced reduction of myeloid cells, sensitising the tumour to chemotherapy.[28] Subsequent mitazalimab doses given 2 days after mFOLFIRINOX allowed for activation of antigen-presenting cells after induction of immunogenic cell death by mFOLFIRINOX treatment, enabling activation of tumour-specific T cells, promoting long-term antitumour responses. The pharmacodynamic responses and favourable safety data support the sequencing and timing of this treatment regimen, as well as the use of the mitazalimab recommended phase 2 dose in combination with mFOLFIRINOX for further clinical development. The transient reduction in circulating immune cells, probably due to activation-induced migration; the increase in activated B cells, monocytes, and dendritic cells within 24 h; and the increase in activated T and natural killer cells within a week of the mitazalimab priming dose is consistent with previous, proof-of-mechanism studies, suggesting a CD40-driven immunological response.[17,18] Modified FOLFIRINOX induced a reduction in circulating myeloid cells as previously reported, whereas mitazalimab

induced immune activation even when administered after mFOLFIRINOX. The correlation between increases in activated T and NKT cells at day 8 (ie, before the first mFOLFIRINOX dose) and depth of response suggests that mitazalimab-induced immune cell activation contributes to the antitumour response.

The choice of adjunctive chemotherapy is a critical factor. Preclinical studies have demonstrated the ability of CD40 agonists to induce T cell priming, correlating with the potency of the chemotherapy regimen.[13] This rationale was adopted in OPTIMIZE-1 which included mFOLFIRINOX, a chemotherapy regimen associated with increased potency over other regimens.

In comparison with the original full-dose FOLFIRINOX regimen, mFOLFIRINOX (typically reduced-dose irinotecan and absence of bolus fluorouracil) is associated

	Grade 1 or 2		Grade 3		Grade 4	
	450 mg/kg mitazalimab (N=5)	900 mg/kg mitazalimab (N=65)	450 mg/kg mitazalimab (N=5)	900 mg/kg mitazalimab (N=65)	450 mg/kg mitazalimab (N=5)	900 mg/kg mitazalimab (N=65)
Any treatment-emergent adverse event*	5 (100%)	63 (97%)	3 (60%)	52 (80%)	0	12 (18%)
Blood and lymphatic system disorders	1 (20%)	25 (38%)	0	26 (40%)	0	8 (12%)
Anaemia	1 (20%)	10 (15%)	0	8 (12%)	0	0
Febrile neutropenia	0	0	0	1 (2%)	0	0
Neutropenia	0	14 (22%)	0	15 (23%)	0	6 (9%)
Thrombocytopenia	1 (20%)	16 (25%)	0	7 (11%)	0	3 (5%)
Cardiac disorders	1 (20%)	1 (2%)	0	2 (3%)	0	0
Pericardial effusions	0	0	0	1 (2%)	0	0
Supraventricular tachycardia	0	0	0	1 (2%)	0	0
Gastrointestinal disorders	4 (80%)	56 (86%)	1 (20%)	17 (26%)	0	0
Abdominal pain	0	11 (17%)	1 (20%)	2 (3%)	0	0
Abdominal pain upper	1 (20%)	4 (6%)	0	1 (2%)	0	0
Ascites	1 (20%)	0	1 (20%)	0	0	0
Constipation	1 (20%)	19 (29%)	0	0	0	0
Diarrhoea	4 (80%)	34 (52%)	0	6 (9%)	0	0
Duodenal obstruction	0	0	0	1 (2%)	0	0
Dysphagia	0	2 (3%)	1 (20%)	0	0	0
Gastrointestinal motility disorder	0	1 (2%)	0	1 (2%)	0	0
Haemorrhoids	0	2 (3%)	0	1 (2%)	0	0
Nausea	3 (60%)	30 (46%)	1 (20%)	3 (5%)	0	0
Gastric obstruction	0	0	0	1 (2%)	0	0
Small intestinal obstruction	0	1 (2%)	0	1 (2%)	0	0
Stomatitis	1 (20%)	8 (12%)	0	1 (2%)	0	0
Vomiting	1 (20%)	19 (29%)	0	3 (5%)	0	0
General disorders and administration site conditions	4 (80%)	44 (68%)	1 (20%)	10 (15%)	0	0
Asthenia	1 (20%)	15 (23%)	1 (20%)	3 (5%)	0	0
Condition aggravated (altered general condition)	0	0	1 (20%)	1 (2%)	0	0
Fatigue	2 (40%)	15 (23%)	0	7 (11%)	0	0
Oedema peripheral	1 (20%)	8 (12%)	0	0	0	0
Pyrexia	2 (40%)	17 (26%)	0	0	0	0
Hepatobiliary disorders	0	5 (8%)	0	3 (5%)	0	0
Biliary obstruction	0	1 (2%)	0	1 (2%)	0	0
Cholangitis	0	1 (2%)	0	3 (5%)	0	0
Infections and Infestations	0	11 (17%)	0	10 (15%)	0	0
Abdominal infection	0	0	0	2 (3%)	0	0
Bronchitis	0	2 (3%)	0	1 (2%)	0	0
COVID-19	0	2 (3%)	0	1 (2%)	0	0
Device-related reaction	0	0	0	2 (3%)	0	0
Oral fungal infection	0	1 (2%)	0	1 (2%)	0	0
Pneumonia	0	1 (2%)	0	2 (3%)	0	0
Urinary tract infection	0	3 (5%)	0	1 (2%)	0	0

(Table 1 continues on next page)

	Grade 1 or 2		Grade 3		Grade 4	
	450 mg/kg mitazalimab (N=5)	900 mg/kg mitazalimab (N=65)	450 mg/kg mitazalimab (N=5)	900 mg/kg mitazalimab (N=65)	450 mg/kg mitazalimab (N=5)	900 mg/kg mitazalimab (N=65)
(Continued from previous page)						
Injury, poisoning, and procedural complications	3 (60%)	23 (35%)	1 (20%)	1 (2%)	0	0
Fall	0	0	1 (20%)	0	0	0
Femoral neck fracture	0	0	0	1 (2%)	0	0
Infusion-related reaction	3 (60%)	23 (35%)	0	0	0	0
Investigations per MedDRA coding	1 (20%)	16 (25%)	0	5 (8%)	0	0
Alanine aminotransferase increased	1 (20%)	12 (18%)	0	2 (3%)	0	0
Aspartate aminotransferase increased	0	8 (12%)	0	2 (3%)	0	0
Gamma-glutamyltransferase increased	0	1 (2%)	0	1 (2%)	0	0
Lipase increased	0	0	0	1 (2%)	0	0
Weight decreased	0	8 (12%)	0	1 (2%)	0	0
Metabolism and nutrition disorders	3 (60%)	30 (46%)	2 (40%)	14 (22%)	0	4 (6%)
Decreased appetite	2 (40%)	14 (22%)	1 (20%)	1 (2%)	0	0
Hypoalbuminaemia	0	2 (3%)	1 (20%)	1 (2%)	0	0
Hypokalaemia	2 (40%)	15 (23%)	1 (20%)	9 (14%)	0	3 (5%)
Hypomagnesaemia	0	9 (13%)	0	1 (2%)	0	1 (2%)
Hyponatraemia	0	2 (3%)	0	1 (2%)	0	0
Malnutrition	0	0	1 (20%)	2 (3%)	0	0
Musculoskeletal and connective tissue disorders	1 (20%)	16 (25%)	0	1 (2%)	0	0
Arthralgia	0	7 (11%)	0	0	0	0
Back pain	0	3 (5%)	0	1 (2%)	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	1 (2%)	1 (20%)	0	0	0
Non-small-cell lung cancer	0	0	1 (20%)	0	0	0
Nervous system disorders	3 (60%)	48 (74%)	1 (20%)	11 (17%)	0	0
Dysarthria	0	8 (12%)	0	0	0	0
Dysgeusia	0	10 (15%)	0	0	0	0
Headache	0	5 (8%)	0	1 (2%)	0	0
Neuropathy peripheral	1 (20%)	18 (28%)	1 (20%)	5 (8%)	0	0
Peripheral sensory neuropathy	0	13 (20%)	0	1 (2%)	0	0
Polyneuropathy	3 (60%)	6 (9%)	0	3 (5%)	0	0
Syncope	0	1 (2%)	0	1 (2%)	0	0
Psychiatric disorders	0	6 (9%)	0	2 (3%)	0	0
Depression	0	0	0	1 (2%)	0	0
Suicide attempt	0	0	0	1 (2%)	0	0
Renal and urinary disorders	1 (20%)	5 (8%)	0	1 (2%)	0	0
Acute kidney injury	0	0	0	1 (2%)	0	0
Respiratory, thoracic, and mediastinal disorders	2 (40%)	5 (8%)	0	2 (3%)	0	0
Cough	1 (20%)	10 (15%)	0	0	0	0
Pleural effusion	0	0	0	1 (2%)	0	0
Pulmonary embolism	1 (20%)	0	0	2 (3%)	0	0
Skin and subcutaneous disorders	1 (20%)	23 (35%)	0	0	0	0
Alopecia	0	14 (22%)	0	0	0	0

Number of patients reflects categorisation by the maximum severity of individual adverse events. All treatment-emergent adverse events of grade 1 or 2 occurring in 10% or more of patients, and all grade 3 and 4 treatment-emergent adverse events are presented. No grade 5 events were reported. Treatment-emergent was defined as occurring or worsening after the priming dose of mitazalimab and up to 28 days after end of treatment. *System organ class and preferred term coded with MedDRA version 24.0 in English.

Table 3: **Overview of treatment-emergent adverse events**

with a better safety profile, with comparable efficacy and clinical outcomes.[29] Consistent with clinical practice, mFOLFIRINOX was the chemotherapy combination chosen for our study. The overall safety profile in OPTIMIZE-1 was consistent with mFOLFIRINOX administration, further reflected in the fact that

30 patients remained on combination treatment for over 6 months, and ten patients remained on treatment for over 12 months, supporting long-term administration.[4]

Dose levels and mitazalimab exposure was higher than those reported for other conditional agonistic antibodies.[14,24] Importantly, no cytokine release syndrome, seen with other CD40 agonists, was reported in OPTIMIZE-1, alluding to an improved safety profile of this second generation CD40 agonist.[30] The administration of pre-medications and post-medications (antihistamines and antileukotrienes) for mitazalimab infusions can reduce the incidence and severity of infusion-related reactions, adding to its favourable safety profile.[18] Additionally, signals of additive or synergistic hepatotoxicity were monitored in this study, as aspartate aminotransferase and alanine aminotransferase elevation has been seen independently with mitazalimab and mFOLFIRINOX. Importantly, there were no hepatotoxicity-related treatment discontinuations.

The OPTIMIZE-1 trial population revealed a *KRAS* mutational profile consistent with known literature in pancreatic cancer.[10] Of particular interest was the increased objective response rates, progression-free survival, and overall survival in patients harbouring G12V and G12R mutations, aligning with previous data and outcomes with FOLFIRINOX. Our data also confirm the poorer prognosis associated with patients having *KRAS* G12D-mutant tumours.[10] These findings warrant further studies into the role of mitazalimab and mFOLFIRINOX in subpopulations of patients with different *KRAS* mutations.

We acknowledge that the non-randomised study design and resultant lack of chemotherapy control group are limitations of the OPTIMIZE-1 trial. Additionally, the information on mutational status of patients in OPTIMIZE-1 is restricted to only *KRAS*.

The long-lasting responses and biomarker associations reported in OPTIMIZE-1 are highly encouraging, implying a potential immunomodulatory contribution of mitazalimab. Data are supportive of the continued development of mitazalimab and mFOLFIRINOX in metastatic pancreatic ductal adenocarcinoma in a confirmatory setting. A randomised, controlled international phase 3 study is being prepared to assess the effect of mitazalimab and mFOLFIRINOX on overall survival in patients with metastatic pancreatic ductal adenocarcinoma compared with mFOLFIRINOX alone.

Contributors

J-LVL, SVA, PE, and YPdC conceived and designed the study and protocol, and KES contributed to the protocol. J-LVL was the principal investigator. J-LVL, IB, HP, KPG, AL, EM, PAC, J-FB, LP, JFB, MRG, RAP-C, IG, and TM were study site investigators and contributed to the implementation of the study and data collection. J-LVL, IB, HP, KPG, AL, EM, PAC, J-FB, LP, JFB, MRG, RAP-C, IG, and TM were responsible for the execution of the study. Tommy Schyman (BC Platforms, Lund, Sweden; OPTIMIZE-1 study statistician) was responsible for statistical analysis with additional oversight from YPDC and SVA. J-LVL, TM, YPdC, SVA, KES, and PE contributed to data analysis, interpretation of study results, and preparation of the report. KES, PE, YPdC, and SVA prepared the first draft of the manuscript. JLVL, TM, SVA, and YPdC had access to all of the data from the study, and J-LVL and YPdC verified the raw data. All authors critically reviewed and edited the manuscript and approved the final version for submission. All authors, including corresponding author, had full data access and control over manuscript final approval and submission. The corresponding author had final responsibility to submit the manuscript for publication, on behalf of all authors.

Declarations of interests

J-LVL, IB, HP, AL, EM, JFeB, LP, JFB, IG, and MRG declare no competing interests. KPG has received honoraria from Ipsen, Servier, Merck, Bristol Myers Squibb (BMS), Serb, and Nordic Pharma; support for attending meetings or travel from Ipsen, and Servier, and MSD; has participated on a data safety monitoring board or advisory board for Servier, BMS, MSD, and AstraZeneca; and is Vice President for Belgian Group of Digestive Oncology. PAC has received honoraria from BMS, Boehringer Ingelheim, Brenus Pharma, Scenic Biotech; research funding to institution from AbbVie, Adlai Nortye, Alligator, Amgen, Astex, AstraZeneca, Boehringer Ingelheim, Bleuprint, C4 Therapeutics, Dragonly, Daiichi Sankyo, Exelixis, GSK, Incyte, Iteos, Janssen, Kinnate, Kazia, Lilly/Loxo, Merus, Molecular Partners, MSD, Novartis, OSE Immunotherapeutics, Pierre Fabre, Relay, Roche/Genentech, Sotio, Taiho, Tango, Toray, Turning Point/BMS, and Transgene. RAP-C received support from Alligator Bioscience for the present manuscript and reports consulting fees from Roche, BMS/Celgene, Eisai Europe, AstraZeneca Spain, Astellas Pharma, Servier, and Ipsen; payments for honoraria from BMS, Servier, AstraZeneca Spain, Astellas Pharma; payment for expert testimony from Servier; support for attending meetings or travel from Lilly, Roche, BMS; participation on data safety monitoring board or advisory board from Roche, BMS/Celgene, AstraZeneca Spain, and Servier. KES, PE, SVA, and YPdC are all employees of and have stock or stock options in Alligator Bioscience. PE is an inventor on the patents relating to mitazalimab, and KES is a co-author of patents for mitazalimab (patents owned by Alligator Bioscience). TM reports grants or contracts from MSD, Novocure, QED Therapeutics, Roche Farma, Sanofi-Aventis, Servier, Zymeworks, AbbVie Farmaceútica, Ability Pharmaceuticals, Agios Pharmaceuticals, Amgen, Aslan Pharmaceuticals, AstraZeneca, Basilea Pharmaceutica International, Bayer, BeiGene, BioKeralty Research Institute, BioLineRx, Blueprint Medicines, Boston Biomedical, BMS, Cantargia, Celgene, Eisai, Erytech Pharma, F. Hoffmann-La Roche, FibroGen, Halozyme, Incyte, Ipsen Bioscience, Ipsen Pharma, Lilly, Loxo Oncology, MedImmune, Merck Sharp & Dohme, Nelum, Novartis, Novocure, OncoMed Pharmaceuticals, QED Therapeutics, VCN Biosciences, and Zymeworks; consulting fees from Ability Pharmaceuticals, Arcus Bioscience, AstraZeneca, Basilea Pharma, Baxter, BioLineRX, Celgene, Eisai, Incyte, Ipsen Bioscience; payment for honoraria from Janssen, Lilly, Esteve, Daïchi, Biontech, Novartis, Jazz Pharmaceuticals; payment for attending meetings or travel from Servier, AstraZeneca, Sanofi, Incyte, Lilly, MSD, and Roche; participation on a data safety monitoring board or advisory board for Ability Pharmaceuticals, Arcus Bioscience, AstraZeneca, Basilea Pharma, Baxter, BioLineRX, Celgene, Eisai, Incyte, and Ipsen Bioscience.

Data sharing

De-identified, individual, patient data, together with a data fields dictionary, that underlie the results reported in this Article (text, tables, figures, and appendices), will be made available in a timely manner, upon request to Alligator Bioscience. Requests can be made by email to info@alligatorbioscience.com. Data recipients are required to enter a formal data sharing agreement. Requests will be considered from investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose, for individual patient data meta-analysis. Proposals may be submitted up to 36 months after publication. The study protocol is available in the appendix.

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