Efficacy and Safety of the Anti-IL1RAP Antibody Nadunolimab (CAN04) in Combination with Gemcitabine and Nab-Paclitaxel in Patients with Advanced/Metastatic Pancreatic Cancer

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ABSTRACT

Purpose: IL1 pathway upregulation is implicated in pancreatic ductal adenocarcinoma (PDAC) progression, therapy resistance, and survival. Nadunolimab is an IL1 receptor accessory protein (IL1RAP)–targeting antibody with enhanced antibody-dependent cellular cytotoxicity that blocks IL1α/IL1β signaling. We investigated efficacy and safety of nadunolimab in PDAC, in combination with gemcitabine/nab-paclitaxel (GN).

Patients and Methods: Patients with previously untreated locally advanced/metastatic PDAC received nadunolimab (1.0–7.5 mg/kg) every 2 weeks with standard GN. The primary objective was safety; secondary objectives were antitumor response, progression-free survival, and overall survival (OS). Correlations between serum and tumor biomarkers and clinical response were explored.

Results: Seventy-six patients were enrolled; the median age was 63 years (range, 43–89), 42% were female, 97% had metastatic disease, and 9% had received adjuvant chemotherapy. The most frequent grade ≥3 adverse event was neutropenia (66%), typically during cycle 1. Infusion-related reactions occurred in 29% (grade 3, 3%). Only 1 of the 76 patients had grade 3 or above peripheral neuropathy. No marked dose-dependent differences in safety or efficacy were observed among the four dose groups. The median OS was 13.2 months (95% confidence interval, 11.0–15.6), and the 1-year survival rate was 58%. The median immune PFS (immune Response Evaluation Criteria in Solid Tumours) was 7.1 months (95% confidence interval, 5.2–7.4). Treatment efficacy was higher in patients with high versus low tumor baseline IL1RAP expression (OS 14.2 vs. 10.6 months; $P = 0.012$). A reduction in serum IL8 on treatment correlated with prolonged OS.

Conclusions: Nadunolimab combined with GN shows promising efficacy and manageable safety in locally advanced/metastatic PDAC. Higher tumor baseline IL1RAP expression correlated with better outcome.

Introduction

IL1 receptor accessory protein (IL1RAP) is expressed on cancer and stromal cells in several solid tumors, including pancreatic ductal adenocarcinoma (PDAC; refs. 1–5). IL1 receptor dimerization with IL1RAP is required for IL1α and IL1β signaling (5). These proinflammatory cytokines play a critical role in inflammation by inducing production of various cytokines, such as IL8 (6), and also in autoimmunity and malignancy. The IL1 axis has been implicated in tumor-permissive signaling networks in the PDAC tumor microenvironment, including tumor growth, angiogenesis, metastasis, immune suppression, and chemoresistance (4, 7–13). Additionally, high tumor IL1RAP mRNA expression is a prognostic marker for poor outcome in PDAC (4). The IL1 pathway can be upregulated in tumor tissue in response to chemotherapy and thereby contribute to treatment resistance (7). Blockade of both IL1α and IL1β can be achieved by IL1RAP targeting, which could constitute an effective approach for PDAC treatment in combination with chemotherapy.

Nadunolimab is a first-in-class, fully humanized, monoclonal IgG1 anti-IL1RAP antibody with enhanced antibody-dependent cellular cytotoxicity. In preclinical and *in vitro* studies, nadunolimab inhibited tumor-promoting signals mediated by IL1α and IL1β and induced antibody-dependent cellular cytotoxicity of IL1RAP-expressing cells (14, 15). Nadunolimab combined with chemotherapy also resulted in synergistic antitumor effects, indicating a reduction in IL1 pathway–induced chemoresistance (15). IL1RAP blockade by nadunolimab could thus offer a unique approach for the treatment of malignancies compared with other strategies that directly target only IL1α or IL1β (16).

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Clin Cancer Res 2024;30:5293–303

doi: 10.1158/1078-0432.CCR-24-0645

Translational Relevance

This phase II study investigated the safety and efficacy of the novel anti–IL1 receptor accessory protein (IL1RAP) mAb nadunolimab in combination with gemcitabine and nab-paclitaxel in previously untreated patients with metastatic pancreatic ductal adenocarcinoma (PDAC). IL1RAP is upregulated in PDAC, and high tumor IL1RAP mRNA expression is a negative prognostic marker for survival. The most promising effects in this study were observed in patients with high expression of the IL1RAP target on tumor cells, who showed improved survival after treatment with nadunolimab plus chemotherapy compared with patients with low IL1RAP expression—apparently reversing the poorer outcomes expected in these patients. The study results support further development of nadunolimab in combination with standard-of-care chemotherapy for the treatment of patients with PDAC.

The prognosis of metastatic PDAC is poor, and the survival probability is <5% at 5 years with little improvement over the past 20 years (17, 18). More effective treatments for PDAC are urgently needed. CANFOUR was a phase I/IIa multicenter, open-label, dose-escalation, dose-expansion study evaluating nadunolimab as monotherapy (phase I; ref. 19) or combined with standard-of-care chemotherapy in patients with locally advanced/metastatic solid tumors (phase IIa; NCT03267316). Here, we present results from 73 patients with locally advanced/metastatic PDAC treated with nadunolimab combined with gemcitabine/nab-paclitaxel (GN) in the CANFOUR phase IIa study.

Patients and Methods

Study design and patients

Eligible patients were ≥18 years of age with newly diagnosed, histologically or cytologically confirmed, unresectable, locally advanced or metastatic PDAC who had not received previous treatment. Patients were required to have an Eastern Cooperative Oncology Group performance score ≤1 and be eligible to receive GN. Patients who underwent (neo)adjuvant treatments were eligible if the (neo)adjuvant treatment ended at least 6 months prior to inclusion. Inclusion and exclusion criteria are provided in full in the Supplementary Materials.

This phase IIa study had two parts (**Fig. 1**): Part 1 was a phase I dose-escalation stage followed by a maximum tolerated dose (MTD) expansion stage. Dose escalation used a standard 3+3 design that evaluated nadunolimab at 5.0 mg/kg ($N = 6$) and 7.5 mg/kg ($N = 8$) with GN. The starting dose of 5.0 mg/kg in combination was based on monotherapy escalation showing good tolerability up to 10 mg/kg (19). Once the MTD of nadunolimab was defined at 5.0 mg/kg, this cohort was expanded to include a total of 28 patients. When enrollment at MTD was completed, the protocol was amended to add part 2, which included two parallel non-randomized, alternate-assignment expansion cohorts with 1.0 and 2.5 mg/kg nadunolimab ($n = 20$ patients each), to complete safety, efficacy, pharmacokinetic, and pharmacodynamic information from a total of four dosages in preparation for future randomized trials. Enrollment into part 1 ended in September 2020, and enrollment into part 2 commenced in January 2021 (**Fig. 1**). The study ended on April 30, 2024.

Treatment

During the part 1 escalation and MTD expansion stages, nadunolimab (5.0 or 7.5 mg/kg) was initially given on days 1, 8, 15, and 22 in cycle 1 and on days 1 and 15 from cycle 2 onward. A priming dose of 0.5 mg/kg was administered on day −7 to mitigate infusion-related reactions (IRR) that were identified during the monotherapy escalation (19). Premedication with antihistamines, paracetamol, and corticosteroids was administered with the priming dose. Gemcitabine (1,000 mg/m^2) and nab-paclitaxel (125 mg/m^2) were given on days 1, 8, and 15 in cycles of 28 days.

In part 2 (1.0 and 2.5 mg/kg cohorts), (i) the nadunolimab priming dose was removed, and the first full dose of nadunolimab was given as a 4-hour ramping infusion with premedication; (ii) in cycle 1, the day 22 nadunolimab dose was omitted, and nadunolimab was given on days 1, 8, and 15; and (iii) granulocyte colony–stimulating factor (G-CSF) prophylaxis was recommended in cycle 1. Treatment regimens in part 1 and part 2 were identical from cycle 2 onward.

For all patients enrolled in the trial, the protocol allowed the investigator to continue treatment beyond progression in patients without clinical deterioration until progression was confirmed as per immune Response Evaluation Criteria in Solid Tumours (iRECIST) at the next scan performed at least 4 weeks later. The protocol allowed for the continuation of nadunolimab monotherapy as maintenance therapy once GN was discontinued for reasons other than progressive disease (PD). Details of the administered treatments are provided in the Supplementary Materials.

Study oversight

This study was conducted in accordance with Good Clinical Practice guidelines, ethical principles that have their origin in the Declaration of Helsinki, and other applicable ethical and regulatory requirements. The study protocol was approved by relevant ethical boards at each participating site, and patients provided written informed consent prior to enrollment. Dose escalation and decisions to modify the treatment regimen were taken by a Safety Review Committee made up of study investigators and representatives from the sponsor that met at regular intervals.

Outcomes and assessments

Disease assessment occurred every 8 weeks while on trial following RECIST 1.1 criteria and immune-related response criteria or later, iRECIST criteria (20). As nadunolimab has a mechanism of action that includes potential recruitment of immune cells to the tumor, the protocol allowed patients without clinical deterioration to continue treatment beyond radiologic PD per RECIST 1.1. Both RECIST 1.1 and iRECIST criteria were used to report the results obtained in this study. The disease control rate (DCR) per RECIST 1.1 was defined as the best response of complete response, partial response (PR), or stable disease. The immune DCR (iDCR) per iRECIST was the best response of the immune complete response (iCR), immune partial response (iPR), immune stable disease (iSD), or at least two consecutive immune unconfirmed progressive disease. Response to therapy was based on overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and duration of response (DoR). Safety was graded using the NCI Common Terminology Criteria for Adverse Events v4.03.

Translational analyses

IHC analysis

Screening and on-treatment tumor biopsies were used to assess tumor expression of IL1RAP (polyclonal rbIgG; Cantargia AB), IL1α

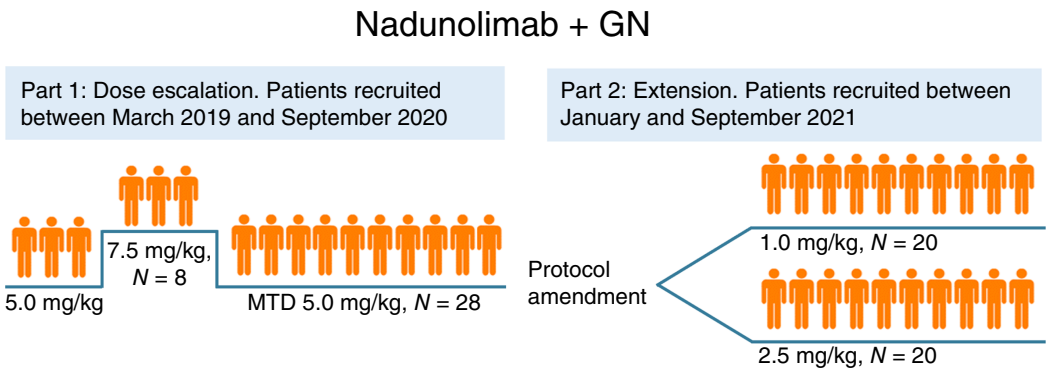

Figure 1.
Study design.

(RRID: AB_306001), PD-L1 (RRID: AB_2819099), neutrophil elastase (clone: SP203; Roche), CD8 (RRID: AB_929437), CD56 (RRID: AB_2941091), CD68 (RRID: AB_307338), and CD163 (RRID: AB_2074540) by IHC. An archival biopsy was accepted as the screening biopsy if the patient had not undergone any systemic treatment after biopsy collection.

Core needle biopsies were available at screening from 49 patients, 13 of whom also provided a biopsy after 4 weeks of treatment. The biopsies were formalin fixed and paraffin embedded. For more details, see the Supplementary Materials. All staining was evaluated and scored by a pathologist. IL1RAP expression was quantified on tumor cells by H-score [(1 × % weakly stained cells) + (2 × % moderate stained cells) + (3 × % strongly stained cells)]; on stroma by evaluating as none, low, medium, or high levels; and on infiltrating immune cells by the percentage of positive cells. IL1α expression on tumor cells was quantified by H-score, on the immune cells by percentage area occupied, and on stroma by evaluating as none, low, medium, and high expression. The expression of PD-L1 was determined by the percentage of positive tumor cells and the percentage of PD-L1–positive immune scores. Percentages of CD56- and CD8-positive immune cells were estimated in the tumor nest, and the level of positive immune cells in the stroma was scored as none, low, medium, or high. CD163- and CD68-positive cells were scored as none, low, medium, and high within the biopsy.

Serum biomarkers

Levels of C-reactive protein (CRP) and a panel of selected inflammation markers related to IL1 signaling (IL1β, IL1α, IL1RA, IL6, IL8, IL33, and TNFα) were measured in patient serum samples at baseline and at repeated time points during treatment (Supplementary Materials). Baseline levels and changes in treatment with nadunolimab and GN were investigated. IL1α, IL1β, and IL33 serum levels were at, or below, the lower limit of quantification and did not yield useful information. To normalize patient samples with study visit and time of treatment, the lowest values for each marker during the first 7 weeks of treatment were identified. These values were divided by the baseline value to obtain a nadir ratio (largest reduction).

Statistical analyses

Efficacy analyses used a modified intention-to-treat population that excluded patients who received a single dose of nadunolimab without chemotherapy. The safety population included all patients receiving at least one dose, even incomplete, of nadunolimab. Patients in escalation and MTD expansion stages were analyzed together because there were no changes in enrollment criteria, treatment, or tumor evaluation between these stages.

The study was descriptive, and no hypotheses were prespecified. Time-to-event estimates used Kaplan–Meier methods, and subgroups were compared using the log-rank test. Biomarker variables were summarized using descriptive statistics. *Post hoc* correlations between biomarkers and OS used Kaplan–Meier methods, and subgroups were compared using the log-rank test. For IL1RAP expression, patient biopsies clustered into two subgroups based on intensity and percent tumor cells stained (H-score) at baseline: one with an H-score of approximately 100 and another with an H-score of approximately 200. The cutoff was set at 150 between the two clusters, and patients were thus divided into IL1RAP-high (H-score ≥150) or IL1RAP-low (H-score <150) subgroups. For the serum biomarkers CRP and IL8, subgroups were divided into high and low by the median value.

Data availability

The anonymized datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Results

Patients

Seventy-six patients with advanced/metastatic PDAC were enrolled in 76 sites across Europe: Belgium (n = 23), Denmark (n = 14), Germany (n = 11), Lithuania (n = 10), Latvia (n = 8), Sweden (n = 4), Spain (n = 3), Austria (n = 2), and Estonia (n = 1). All patients received at least one dose of nadunolimab, and 73 patients also received a standard dose/schedule of GN (modified intention-to-treat population); three patients in the 5.0 mg/kg cohort discontinued treatment before receiving GN because of consent withdrawal or disease progression and were excluded from the efficacy analysis. All patients but two (3%) were stage IV at study entry. Clinical baseline characteristics were similar across the four dose groups (**Table 1**).

The median duration of follow-up was 12.6 months (range, 0.4–50.5), and the median number of nadunolimab doses was 13 (range, 1–65; Supplementary Table S1). The median relative dose intensity [(actual/planned × 100%) calculated for completed cycles (at least 27 days)] was 76.6% for nadunolimab, 81.6% for nab-paclitaxel, and 81.4% for gemcitabine.

At the study end, three patients (one in the 1.0 mg/kg group and two in the 2.5 mg/kg group) were still on follow-up, of whom one was still on treatment, 59 (78%) had died, and 13 withdrew for other

Table 1. Demographic and baseline disease characteristics[a] (safety population).

Nadunolimab dose	1.0 mg/kg (*N* = 20) *n* (%)	2.5 mg/kg (*N* = 20) *n* (%)	5.0 mg/kg (*N* = 28) *n* (%)	7.5 mg/kg (*N* = 8) *n* (%)	Total (*N* = 76) *n* (%)
Characteristic					
Age (years), mean (SD)	61.5 (9.7)	63.8 (9.5)	64.5 (8.6)	59.9 (12.5)	63.0 (9.5)
Sex					
Male	13 (65)	12 (60)	16 (57)	3 (38)	44 (58)
Female	7 (35)	8 (40)	12 (43)	5 (63)	32 (42)
Stage IV at initial diagnosis	14 (70)	13 (65)	26 (93)	8 (100)	61 (80)
Stage at study entry					
III	1 (5)	1 (5)	—	—	2 (3)
IV	19 (95)	19 (95)	28 (100)	8 (100)	74 (97)
Tumor localization at study entry					
Bone	—	—	1 (4)	1 (13)	2 (3)
Liver	10 (50)	11 (55)	22 (79)	6 (75)	49 (65)
Lung	5 (25)	5 (25)	12 (43)	2 (25)	24 (32)
Lymph nodes	12 (60)	10 (50)	14 (50)	2 (25)	38 (50)
Other	6 (30)	8 (40)	11 (39)	2 (25)	27 (36)
Previous therapy					
Chemotherapy	2 (10)	2 (10)	3 (11)	—	7 (9)
Pancreaticoduodenectomy/ pancreatectomy	2 (10)	3 (15)	4 (14)	—	9 (12)
CA 19-9 (U/mL), median, *n* (range)[b]	1,666, *n* = 20 (1.0–79,200)	137, *n* = 20 (1.2–105,000)	461, *n* = 26 (1.9–100,234)	712, *n* = 4 (8.6–4,490)	550, *n* = 70 (1.0–105,000)
Biopsy available for assessment of biomarkers	12	13	18	6	49
IL1RAP high	8	8	10	3	29
IL1RAP low	4	5	8	3	20

Abbreviation: mITT population, modified intention-to-treat population.
[a]68 participants (89%) were White, 1 was Asian, and 7 were not reported.
[b]CA 19-9 = reported for the mITT population.

reasons. There were 45 patients (59%) who received second-line treatment. The representativeness of study participants is assessed in Supplementary Table S2.

Efficacy analysis part 1

In total, 25 patients received nadunolimab 5.0 mg/kg and 8 patients received the 7.5 mg/kg dose. The median OS was 12.6 months (95% CI, 6.5–24.6) in the 5.0 mg/kg group and 13.0 months (95% CI, 0.7–25.7) in the 7.5 mg/kg group (**Table 2**). The 1-year survival probability was 54% and 63%, respectively. PR was documented in 20% (95% CI, 7–41) of patients in the 5.0 mg/kg group and 38% (95% CI, 9–76) in the 7.5 mg/kg group and was identical using RECIST 1.1 or iRECIST guidelines. PFS rates were 35% at 6 months and 18% at 1 year in the 5.0 mg/kg group and 25% at 6 months and 0% at 1 year in the 7.5 mg/kg group; however, standard RECIST1.1 evaluation did not adequately reflect PFS, as five patients treated with 5.0 mg/kg nadunolimab presented with prolonged benefit of several months beyond radiologic progression at first assessment: two had several consecutive immune unconfirmed progressive disease evaluations (no further PD), and two achieved tumor shrinkage after first PD and compared with baseline that qualified as iSD (Supplementary Fig. S1). Considering the second PD in these five patients as directed by iRECIST, the median immune PFS (iPFS) in the 5.0 mg/kg group was 5.6 months (95% CI, 2.8–9.3) versus 3.7 months (95% CI, 1.9–7.1) for PFS.

Efficacy analysis part 2

In total, 20 patients received nadunolimab 1.0 mg/kg and 20 patients received the 2.5 mg/kg dose. The median OS was 12.9 months (95% CI, 9.9–25.7) in the 1.0 mg/kg group and 14.2 months (95% CI, 6.6–15.6) in the 2.5 mg/kg group (**Table 2**). The 1-year survival probability was 63% and 56%, respectively. PR was the best response in 45% (95% CI, 23–69) of patients in the 1.0 mg/kg group and 30% (95% CI, 12–54) in the 2.5 mg/kg group and was identical using RECIST 1.1 or iRECIST guidelines. The DCR was 75% and 70% using RECIST 1.1 and 80% and 70% using iRECIST, respectively. The PFS was 61% at 6 months and 17% at 1 year in the 1.0 mg/kg group and 56% at 6 months and 19% at 1 year in the 2.5 mg/kg group. The median PFS was 7.2 months (95% CI, 2.7–9.2) and 7.3 months (95% CI, 4.9–9.3), respectively, with minor differences with iPFS.

Overall (parts 1+2) efficacy

The median OS across all dose groups was 13.2 months (95% CI, 10.6–15.5), with a 1-year survival probability of 58% (**Table 2**). Using RECIST 1.1, PR was the best response in 32% (95% CI, 21–43), and the DCR was 71%. Similar results were observed using iRECIST. The median PFS was 5.6 months (95% CI, 3.7–7.4) using RECIST 1.1 and 7.1 months (95% CI, 5.2–7.4) using iRECIST (**Fig. 2**). The DoR was 6.5 months (95% CI, 5.5–10.0). There were no marked differences in efficacy endpoints between the four dose groups. A total of 67% of the patients had a decrease in carbohydrate antigen 19-9 (CA 19-9) of at least 20% from baseline and 25% had a decrease of at least 90%. Eleven patients continued on nadunolimab monotherapy after discontinuation of chemotherapy. The median duration of monotherapy was 3.2 months (range, 0.9–16.8 months).

Table 2. Efficacy outcomes by nadunolimab dose level classified using RECIST and iRECIST (mITT population).

Outcome	1.0 mg/kg (*N* = 20)	2.5 mg/kg (*N* = 20)	5.0 mg/kg (*N* = 25)	7.5 mg/kg (*N* = 8)	All patients with PDAC (*N* = 73)
OS					
Median—months (95% CI)	12.9 (9.9–25.7)	14.2 (6.9–15.6)	12.6 (6.5–24.6)	13.0 (0.7–25.7)	13.2 (11.0–15.6)
Survival rate:					
12 months, % (95% CI)	63 (38–81)	56 (31–75)	54 (33–71)	63 (23–86)	58 (46–69)
24 months, % (95% CI)	32 (13–52)	22 (7–43)	32 (14–51)	25 (4–56)	28 (18–39)
36 months, % (95% CI)	13 (22–33)	15 (2.9–36)	12 (2.4–30)	0	9 (3–21)
RECIST 1.1					
Response					
ORR % (95% CI)[a]	45 (23–69)	30 (12–54)	20 (7–41)	38 (9–76)	32 (21–43)
PR, *n* (%)	9 (45)	6 (30)	5 (20)	3 (38)	23 (32)
SD, *n* (%)	6 (30)	8 (40)	13 (52)	1 (13)	28 (38)
PD, *n* (%)	2 (10)	—	5 (20)	3 (38)	10 (14)[b]
Not evaluable, *n* (%)	3 (15)	6 (30)	2 (8)	1 (13)	12 (16)
DCR % (95% CI)[c]	75 (51–91)	70 (46–88)	72 (51–88)	50 (16–84)	71 (59–81)
DoR					
Median—months (95% CI)	5.6 (3.6–11.8)	7.4 (3.7–NE)	11.1 (5.5–NE)	3.9 (3.7–NE)	6.5 (5.5–10.0)
PFS					
Median—months (95% CI)	7.2 (2.7–9.2)	7.3 (4.9–9.3)	3.7 (1.9–7.1)	3.7 (0.6–8.5)	5.6 (3.7–7.4)
6 months, % (95% CI)	61 (35–79)	56 (30–76)	35 (17–54)	25 (4–56)	46 (33–58)
12 months, % (95% CI)	17 (4–37)	19 (5–40)	18 (6–35)	0	15 (8–25)
iRECIST					
iResponse					
iORR % (95% CI)[a]	45 (23–69)	30 (12–54)	20 (7–41)	38 (9–76)	31 (21–43)
Benefit beyond initial PD, *n* (%)	—	—	5 (20)	—	5 (7)
iDCR % (95% CI)[b]	80 (56–94)	70 (46–88)	80 (59–93)	75 (35–97)	77 (65–86)
iDoR					
Median—months (95% CI)	5.6 (3.6–11.8)	8.5 (3.7–NE)	11.1 (5.5–NE)	3.9 (3.7–NE)	7.2 (5.5–10.0)
iPFS					
Median—months (95% CI)	7.2 (3.7–9.2)	7.4 (5.1–11.2)	5.6 (2.8–9.3)	3.7 (0.–8.5)	7.1 (5.2–7.4)

Abbreviations: CI, confidence interval; CR, complete response; iDCR, immune disease control rate; iDoR, immune duration of response; iORR, immune overall response rate; iUPD, immune unconfirmed progressive disease; mITT population, modified intention-to-treat population; NE, not estimable; SD, stable disease.
[a]ORR = CR + PR.
[b]5/10 patients had PD/immune confirmed PD.
[c]Disease control = PR + SD + at least two consecutive iUPD per iRECIST.

Correlations between IL1RAP expression in tumor biopsies and outcome

IL1RAP expression in tumor biopsies from a total of 49 patients was measured by IHC: 12 from the 1.0 mg/kg, 13 from the 2.5 mg/kg, 18 from the 5.0 mg/kg, and 6 from the 7.5 mg/kg groups. IL1RAP was expressed on tumor, stromal, and infiltrating immune cells in all evaluated biopsies (**Fig. 3A**). The expression was homogeneous on tumor cells, and all tumor cells within a biopsy expressed similar levels. The stroma showed moderate IL1RAP expression in most biopsies, and in 53% of the biopsies, at least 5% of infiltrating immune cells were IL1RAP positive. For the 13 patients with paired baseline and on-treatment biopsies, IL1RAP expression did not change during treatment in any of the cell populations (Supplementary Fig. S2).

Tumor cell expression was characterized by intensity and percent tumor cells stained (H-score) at baseline. Using the 150 H-score cutoff point for IL1RAP expression, 29 patients (59%) had an H-score ≥150, or IL1RAP-high, and 20 (41%) had an H-score <150, or IL1RAP-low (**Fig. 3B**). IL1RAP-high and -low subgroups were comparable in terms of their clinical baseline characteristics, including serum levels of CRP, IL6, and IL8, as well as frequency and sites of metastases (Supplementary Table S3).

IL1RAP-high patients showed a significantly prolonged survival on nadunolimab plus GN, with a median OS of 14.2 months, as compared with 10.6 months in IL1RAP-low patients ($P = 0.012$). One-year survival was also improved in IL1RAP-high patients (67% vs. 39%; **Fig. 3C**). Prolonged survival was reflected in other efficacy parameters, including improved median PFS (7.4 vs. 5.1 months), a trend for higher ORR (48% vs. 30%), and longer median DoR (8.7 vs. 5.6 months; **Table 3**). The median OS remained longer in the IL1RAP-high subgroup vs. the IL1RAP-low subgroup when the IL1RAP-high threshold was decreased to either >100 or increased to ≥190 ($P = 0.011$ and $P = 0.029$), respectively (Supplementary Table S4), supporting robustness of the results. Individual responses in the IL1RAP-high and IL1RAP-low groups are shown in **Fig. 3D**. Of note, the four evaluable patients with the highest tumor baseline H-score also had the longest survival (50.5, 33.8, 28.8, and 19.4 months). No correlation between the intensity of IL1RAP expression on stromal or immune cells and clinical outcome was observed (Supplementary Fig. S3). In the 11 patients who received nadunolimab monotherapy after discontinuation of chemotherapy, the median duration of monotherapy was longer in the IL1RAP-high group than in the IL1RAP-low group (3.7 months, $n = 7$, vs. 1.8 months, $n = 4$; $P = 0.011$). The median OS was also longer in the IL1RAP-high group treated with monotherapy (28.6 vs. 11.3 months; $P = 0.033$).

All baseline biopsies examined showed tumor cell expression of IL1α and most showed expression of IL1α-positive immune cells,

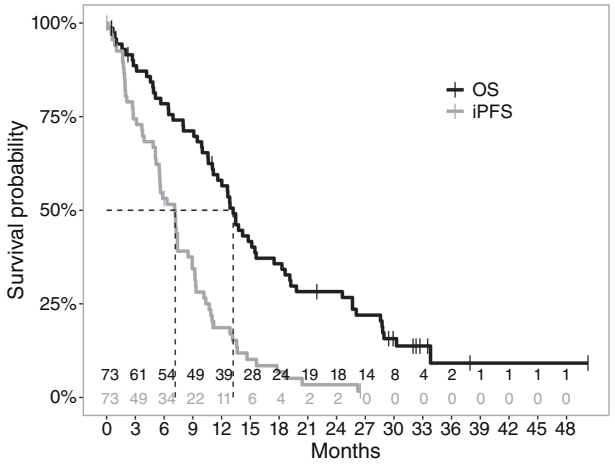

Figure 2.
OS and iPFS (months; mITT population). mITT population, modified intention-to-treat population.

whereas IL1α was sparser in the stroma. With a cutoff set to ≥5%, around one fifth of the biopsies showed PD-L1 expression on tumor cells or immune cells. Slightly more than half of the biopsies showed the presence of CD8 T cells in the tumor nest, with higher cell levels detected in the stroma. Very few NK cells were detected, whereas a mixture of CD68 and CD163 macrophages were present in almost all biopsies. Most biopsies showed no or low levels of neutrophils. No consistent treatment effects were observed in the 13 paired biopsies, and the markers did not show a correlation with clinical outcome with nadunolimab plus GN treatment.

Correlation of soluble serum biomarker levels with survival

None of the measured soluble serum markers at baseline correlated significantly with response, with the exception of low baseline CRP that was prognostic for OS. A longer median OS was observed in patients with baseline CRP levels below the median (11.0 mg/L, $P < 0.001$; **Fig. 4A**). IL6 baseline levels below the median (1.8 pg/mL) showed a trend for a favorable OS ($P = 0.061$) (Supplementary Fig. S4). Baseline IL8 did not impact OS (Supplementary Fig. S4).

CRP levels were reduced significantly during the first 7 weeks of treatment, and there was a trend for a reduction in IL6 (Supplementary Fig. S5). There were no consistent changes at a group level in IL8, TNFα, or IL1RAP levels over the first 7 weeks of treatment (TNFα and IL1RA measured on the first 33 patients only). For IL8, patients ($n = 69$) could be separated into those that experienced reductions and those that showed increases in serum levels over time. The patients who had a reduction in IL8 from baseline while on treatment had significantly improved OS compared with patients with an increase in IL8 (18.3 vs. 9.9 months; $P = 0.015$; **Fig. 4B**).

CA 19-9 levels correlated with response as expected, and a reduction of CA 19-9 from baseline of at least 90% was associated with a favorable prognosis and longer OS (25.7 vs. 11.6 months; $P = 0.006$; **Fig. 4C**).

Safety

The most frequently reported all-grade treatment-emergent adverse event (TEAE) was neutropenia, both overall (76%) and in each dose group. Other common TEAEs (any grade) reported by more than 30% of patients were nausea, fatigue, anemia, diarrhea, peripheral edema, alopecia, decreased appetite, thrombocytopenia, vomiting, pyrexia, and constipation (Supplementary Table S5).

IRRs were reported in 22 patients (29%); 60% experienced the reaction during the first infusion. Grade 3 IRRs were reported in two patients (3%), and no grade 4/5 IRRs were reported. IRRs were mitigated by standard premedication prophylaxis and ramping infusion.

Grade 3/4 TEAEs reported by at least 10% of patients were neutropenia (66%), leukopenia (24%), γ-glutamyltransferase increase (17%), anemia (14%), and febrile neutropenia and thrombocytopenia (each 13%; **Table 4**). There were 31 subjects with grade 3/4 neutropenia or febrile neutropenia in cycle 1 only, 19 subjects had grade 3/4 neutropenia or febrile neutropenia in cycle 1 and in subsequent cycles, and five subjects had at least one grade 3/4 neutropenia only in cycle 2 or beyond. Of the 76 patients in cycle 1, 60 patients continued to cycle 2 (Supplementary Fig. S6A). G-CSF use was at the investigator's discretion, and there was no clear correlation between its use and incidence of neutropenia. Primary G-CSF prophylaxis was recommended later in the enrollment of part 2 and given to six patients dosed with 1.0 and 2.5 mg/kg nadunolimab and was effective in preventing all grades of neutropenia in these patients (Supplementary Fig. S6B). There were no consistently observed differences in safety among the four dose groups. Notably, there were no grade 3/4 cases of peripheral neuropathy, and one case of grade 3 polyneuropathy was reported. Among the 73 patients, when combining the 2.5, 5.0, and 7.5 mg/kg dose groups and compared with the 1.0 mg/kg dose group, the patients who received higher doses of nadunolimab had a lower incidence of any-grade, chemotherapy-induced peripheral neuropathy (36% vs. 60%; χ^2 test $P = 0.06$) and a longer time to the onset of symptoms (log-rank $P = 0.04$).

Nadunolimab at 7.5 mg/kg was above MTD because of neutropenia and febrile neutropenia dose-limiting toxicities occurring during cycle 1. The types and severities of TEAEs were otherwise similar across each dosing group (Supplementary Table S5).

Five patients discontinued the study because of TEAEs [pancytopenia, gastrointestinal hemorrhage, ileus, death (not specified), and *Escherichia coli* sepsis]. Only the case of pancytopenia was considered related to nadunolimab by the investigator. Furthermore, three patients had a grade 5 TEAE: one case of cholangitis at 7.5 mg/kg (this patient had concurrent related grade 4 neutropenia), one case of *Escherichia coli* sepsis at 5.0 mg/kg, and one death (cause not specified) at 2.5 mg/kg. None were assessed by the investigator as related to nadunolimab (**Table 4**). There were no treatment-related deaths.

Treatment-emergent serious adverse events (TESAE) were reported for 58% of patients. A total of 22% of patients had TESAEs considered by the investigator to be related to nadunolimab, with febrile neutropenia (13%), IRR (8%), and pneumonia (3%) reported most frequently. All other nadunolimab-related TESAEs were reported by one patient at most.

Discussion

The CANFOUR trial was an open-label study investigating efficacy and safety of several doses of the anti-IL1RAP antibody nadunolimab in combination with GN as first-line treatment in locally advanced/metastatic PDAC. Efficacy results in this study suggest a benefit from the addition of nadunolimab to GN. The

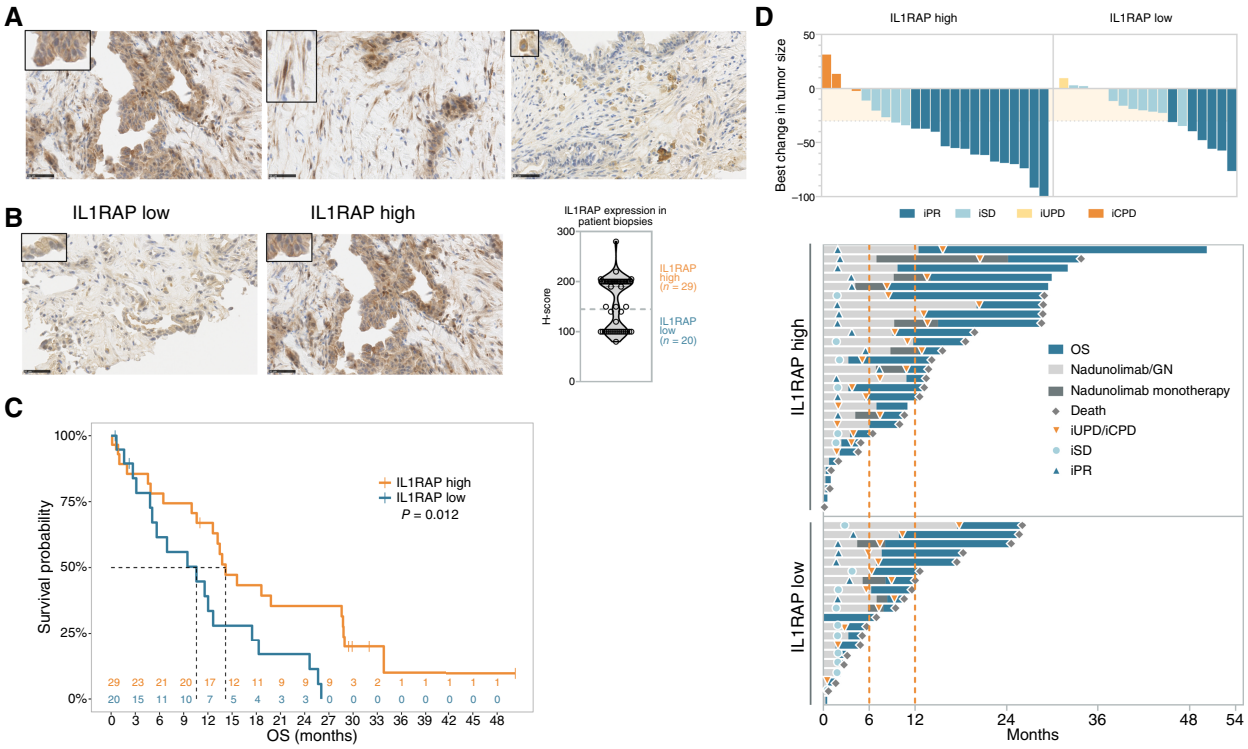

Figure 3.

Baseline tumor IL1RAP expression is associated with deeper and more durable response to nadunolimab and GN. Screening biopsies, archival or study specific, were collected from 49 patients and stained for IL1RAP by IHC. **A,** Representative images are shown of IL1RAP-positive tumor cells (left), cancer-associated fibroblasts (center), and infiltrating immune cells (right). **B,** Tumor cell expression of IL1RAP was quantified by H-score and the distribution plotted; IL1RAP high was defined as ≥150 and IL1RAP low as <150. Representative images of tumor sections with low and high IL1RAP H-score are shown. **C,** The correlation between IL1RAP expression and OS was analyzed with a Kaplan–Meier analysis and IL1RAP-high and IL1RAP-low subgroups compared using the log-rank test. **D,** Clinical responses in the IL1RAP-high and IL1RAP-low groups were visualized in a waterfall (top) and a swimmer plot (bottom). iCPD, immune confirmed progressive disease; iPR, immune partial response; iSD, immune stable disease; iUPD, immune unconfirmed progressive disease.

estimated median OS of 13.2 months for all patients with PDAC receiving nadunolimab and GN and the higher median OS of 14.2 months in IL1RAP-high patients are both longer than the OS reported in phase III trials for GN alone (8.5–9.2 months), FOLFIRINOX (11.1 months), or NALIRIFOX (11.1 months; refs. 21–23). Treatment benefit was also reflected in an ORR of 48% in IL1RAP-high patients (33% overall) versus 23% (29% per investigator review) and 36.2% (per investigator review) using GN alone in previous trials (21, 24). Liver metastases were present in 65% of our patient population, which is somewhat lower than around 80% reported in previously published studies (21, 24).

Notably, high baseline tumor IL1RAP expression was associated with improved survival (OS of 14.2 vs. 10.6 months in IL1RAP-low patients; $P = 0.012$). This was also reflected in the subgroup of patients continuing on monotherapy, with longer treatment benefit in the patients in the IL1RAP-high group versus those in the IL1RAP-low group. This target-based subgroup analysis demonstrates that higher target expression is associated with better

Table 3. Efficacy in patients in the biopsy subgroup ($N = 49$) treated with nadunolimab and GN classified using RECIST and iRECIST.

Efficacy parameter (95% CI)	IL1RAP high ($n = 29$)	IL1RAP low ($n = 20$)	P value (IL1RAP high vs. low)
OS, median, months	14.2 (10.0–28.6)	10.6 (4.8–12.6)	0.012
PFS	7.4 (3.7–11.0)	5.1 (1.9–7.3)	0.012
iPFS, median, months	7.4 (3.7–11.2)	5.8 (2.7–7.4)	0.105
1-year survival	67% (46–81)	39% (18–60)	—
ORR/iORR	48% (29–67)	30% (12–54)	0.205
DoR	8.7 (3.7–11.8)	5.6 (3.9–NE)	0.074
iDoR; median, months	9.5 (3.7–11.8)	5.6 (3.9–NE)	0.044

Abbreviations: iDoR, immune duration of response; iORR, immune overall response rate; NE, not estimable.

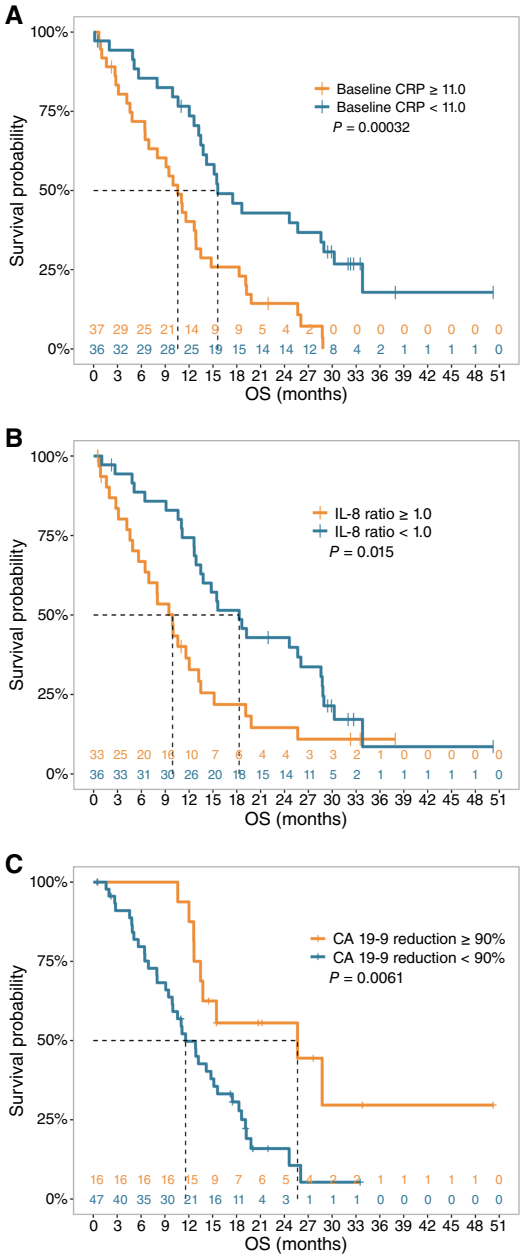

Figure 4.

Lower baseline CRP and a decrease in IL8 and CA 19-9 while on treatment with nadunolimab plus GN predict prolonged OS. Serum samples were collected from all patients before start of treatment (baseline) and throughout the study. CRP and CA 19-9 levels were analyzed at local laboratories, IL8 by MSD at a central laboratory, and OS compared using the Kaplan–Meier method. **A,** Baseline CRP ($n = 73$) was divided according to the median. Low baseline CRP is a prognostic biomarker for OS. **B,** Lowest IL8 post-baseline value during the first 50 days (nadir) was divided with the baseline IL8 value (nadir/baseline ratio; $n = 69$). The nadir/baseline ratio was divided on the median into two groups corresponding to those with an increase in IL8 levels and those with a decrease. IL8 reduction by nadunolimab and GN was associated with a significantly prolonged OS. **C,** There were 16 patients (24% of 67 patients with baseline CA 19-9) who had ≥90% decrease in CA 19-9 from baseline over the study period. A ≥90% decrease in CA 19-9 was associated with significantly prolonged survival.

outcomes, as one would expect if the target is relevant for disease evolution. IL1RAP is overexpressed in PDAC, and data from public databases such as The Cancer Genome Atlas (3) suggest that higher expression of IL1RAP in the tumor, e.g., measured as mRNA, is associated with poorer survival outcome (4). This is confirmed by the larger Know Your Tumor database (25), predominantly consisting of metastatic PDAC tumors, in which it is additionally found that IL1RAP expression increases with disease stage [ref. 26; manuscript in preparation]. We observed no change in IL1RAP expression during treatment, suggesting continued high expression of IL1RAP and ongoing effects of nadunolimab. The appropriateness of the assay cutoff used needs further evaluation in future clinical studies with larger data sets and with a control arm included.

These results support the mode of action of nadunolimab and suggest that IL1RAP may constitute a biomarker for patient selection. Based on these preliminary findings, IL1RAP expression on tumor cells should be investigated as a predictive response factor for nadunolimab. As high IL1RAP mRNA expression is associated with poor prognosis in PDAC, the greater treatment benefit we observed in patients with high IL1RAP expression is potentially a significant improvement for this difficult-to-treat patient group. High expression of IL1RAP and other IL1-associated proteins has been described in several solid tumor indications, including PDAC, and tumor-promoting *KRAS* mutations that drive tumor inflammation in PDAC have been implicated in activating the IL1 axis, especially $KRAS^{G12D}$ (11). Fibroblasts and myeloid cells are key drivers in the detrimental proinflammatory environment in PDAC, and IL1 has proven critical for this signaling network in shaping the tolerogenic immune landscape. IL1RAP is expressed on fibroblasts and myeloid cells in the tumor microenvironment, and although IL1RAP on stromal cells was not associated with clinical outcome, it may still be fundamental in relaying signals within the pancreatic tumor to facilitate disease progression.

Elevated circulating inflammatory markers such as IL8 and CRP, which are downstream from IL1 signaling, are associated with worse prognosis in cancer (27, 28). In agreement with previous reports, we found that a low baseline CRP level correlated with prolonged OS. However, baseline CRP could be a prognostic factor independent of nadunolimab and GN, reflecting disease severity. On investigating changes in cytokine levels on treatment, we found that OS was improved in patients with a reduction in IL8, indicating a better efficacy of nadunolimab and GN in these patients, which may be linked to the protumorigenic role of IL8. IL8 has been previously described as a prognostic marker in many malignancies, and its high serum levels are associated with chemoresistance and poor prognosis (29–31).

We observed five patients, all receiving 5.0 mg/kg nadunolimab, who continued treatment beyond initial radiologic PD at first CT scan evaluation and were clinically stable, including stable or decreasing CA 19-9 levels. When evaluated by iRECIST criteria, the median iPFS in the 5.0 mg/kg cohort was similar to PFS estimates in the 1.0 and 2.5 mg/kg groups. None of the patients in part 2 presented with this benefit beyond progression. A possible explanation is the removal of the priming dose on day −7, which resulted in a shorter time span from baseline evaluation until initiation of standard of care and subsequent first on-treatment assessment in the latter (data not shown).

The combination of nadunolimab with GN showed a greater incidence of grade 3/4 neutropenia and febrile neutropenia than that expected for GN alone (66% and 13% vs. 38% and 3%, respectively; ref. 21). Increased neutrophil toxicity has been

Table 4. Summary of safety and grade ≥3 TEAEs regardless of causality reported by at least 5% of patients with PDAC (safety population).

Nadunolimab dose	1.0 mg/kg (*N* = 20) *n* (%)		2.5 mg/kg (*N* = 20) *n* (%)		5.0 mg/kg (*N* = 28) *n* (%)		7.5 mg/kg (*N* = 8) *n* (%)		Total (*N* = 76) *n* (%)	
TEAE										
Any TEAE	20 (100)		20 (100)		28 (100)		8 (100)		76 (100)	
Grade 3/4	17 (85)		19 (95)		24 (86)		8 (100)		68 (89)	
Grade 5	—		1 (5)		1 (4)		1 (13)		3 (4)	
Grade 3/4 TEAEs related to nadunolimab	13 (65)		17 (85)		19 (68)		8 (100)		57 (75)	
Any TESAE	9 (45)		11 (55)		22 (79)		2 (25)		44 (58)	
DLT	—		—		—		1 (13)		1 (1)	
TEAEs leading to study discontinuations	2 (10)		2 (10)		1 (4)		—		5 (7)	
Preferred term	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**
Neutropenia	11 (55)	14 (70)	14 (70)	16 (80)	18 (64)	21 (75)	7 (88)	7 (88)	50 (66)	58 (76)
Leukopenia	4 (20)	6 (30)	2 (10)	3 (15)	10 (36)	11 (39)	2 (25)	2 (25)	18 (24)	22 (29)
γ-GT increased	3 (15)	4 (20)	7 (35)	8 (40)	3 (11)	4 (14)	—	—	13 (17)	16 (21)
Anemia	1 (5)	13 (65)	4 (20)	11 (55)	6 (21)	13 (46)	—	2 (25)	11 (15)	39 (51)
Thrombocytopenia	2 (10)	8 (40)	2 (10)	8 (40)	4 (14)	9 (32)	2 (25)	5 (63)	10 (13)	30 (39)
Febrile neutropenia	3 (15)	3 (15)	1 (5)	1 (5)	5 (18)	5 (18)	1 (13)	1 (13)	10 (13)	10 (13)
Hypertension	2 (10)	3 (15)	2 (10)	2 (10)	2 (7)	3 (11)	1 (13)	2 (25)	7 (9)	10 (13)
Fatigue	1 (5)	9 (45)	3 (15)	11 (55)	2 (7)	16 (57)	—	5 (63)	6 (8)	41 (54)
Alanine aminotransferase increased	3 (15)	6 (30)	1 (5)	5 (25)	—	2 (7)	1 (13)	1 (13)	5 (7)	14 (18)
Vomiting	1 (5)	8 (40)	1 (5)	6 (30)	2 (7)	11 (39)	—	3 (38)	4 (5)	28 (37)
Dyspnea	1 (5)	6 (30)	1 (5)	6 (30)	2 (7)	7 (25)	—	1 (13)	4 (5)	20 (26)
AST increased	3 (15)	4 (20)	1 (5)	4 (20)	—	3 (11)	—	1 (13)	4 (5)	12 (16)
Aspartate aminotransferase increased	3 (15)	4 (20)	1 (5)	4 (20)	—	3 (10)	—	1 (13)	4 (5)	12 (16)
Lymphopenia	1 (5)	2 (10)	1 (5)	2 (10)	2 (7)	2 (7)	—	—	4 (5)	6 (8)
Cholangitis, infective	1 (5)	1 (5)	1 (5)	1 (5)	2 (7)	2 (7)	—	1 (13)	4 (5)	5 (7)

NOTE: Percentages are based on the number (*N*) of included subjects. When a subject experienced more than one event in different preferred terms or within the same preferred term, all incidences are counted.
Abbreviations: AST, aspartate aminotransferase; DLT, dose- or treatment-limiting toxicity; GT, glutamyltransferase; *n*, number of subjects with an event.

observed with nadunolimab in other combinations with cytotoxic agents, and significant reductions in some white blood cell populations and a numerical decrease in neutrophils were observed during monotherapy (19). Neutropenia may be mitigated with prophylactic G-CSF during the first cycle, during which the higher-than-expected frequency of events is mainly observed. This will be further evaluated in future studies. Development of grade 3/4 neutropenia is an independent prognostic factor for longer survival in patients with metastatic PDAC treated with GN (32, 33), and several publications have reported that baseline neutrophil to lymphocyte ratio is a prognostic factor in several tumors and specifically in PDAC (34, 35), possibly reflecting a systemic inflammatory state produced by the tumor.

IL1-driven inflammation has been suggested to mediate paclitaxel-induced neuropathy, and the lower-than-expected neuropathy may be connected to IL1 blockade by nadunolimab (36). In our study, only one patient reported grade 3 neuropathy. This is lower than reported for GN (17%; refs. 21, 23). Our data suggest that nadunolimab conferred a protective effect on peripheral neuropathy given that patients in the higher dose groups reported lower incidences of any-grade neuropathy, with a later onset than those in the lowest nadunolimab dose group (1.0 mg/kg). This observation needs to be confirmed in a comparative study, with a more detailed, targeted monitoring and assessment of peripheral neuropathy occurrence.

The 7.5 mg/kg dose of nadunolimab was determined to be above the MTD. Currently available data do not clearly differentiate between doses of 1.0 and 5.0 mg/kg in terms of efficacy or safety. Based on the available clinical, pharmacokinetic, and preclinical data, we expect that doses of 1.0 to 2.5 mg/kg have reached the plateau phase of a dose–response relationship and will be sufficient for therapeutic effect. These doses will be explored further in upcoming studies.

Strengths of the study include the multicenter design across nine countries, led by experts in the field, balanced demographics of patients on each dose level, inclusion of biomarkers and tumor samples, and the intention-to-treat analysis. However, PDAC is a difficult-to-treat disease, and a small improvement in efficacy, while potentially meaningful, can be skewed by confounding factors or interpretation of data, thereby precluding identification of a true versus false efficacy signal. Relative dose intensity in our study was similar to that in other studies in this population (21).

Limitations of the study are the small sample set and the absence of a control group receiving GN alone, which are only partially addressed in the IL1RAP subgroup analysis results and by benchmarking to historical controls for both safety and efficacy. The restricted sample size may have contributed to the apparent lack of a clear dose response in terms of efficacy. The *post hoc* correlation between biomarkers and survival was not corrected for multiple comparisons, and there is a risk of false-positive findings. Larger,

controlled studies are needed to more conclusively evaluate the potential benefit of nadunolimab added to GN and to ascertain if this benefit is primarily realized in a biomarker-selected subgroup.

In summary, nadunolimab combined with GN showed manageable toxicity and promising overall efficacy in first-line treatment for locally advanced/metastatic PDAC. The increased toxicity seems to be restricted to IRRs and neutropenia. The former is managed with standard IRR prophylaxis, and the latter may be addressed by G-CSF prophylaxis in cycle 1. Compared with historical data, the addition of nadunolimab to GN produced clinically relevant improvements in PFS and OS. This was particularly marked in patients whose tumors had high baseline expression of IL1RAP, supporting the mode of action of nadunolimab. A phase IIb randomized controlled trial evaluating two dose levels of nadunolimab in combination with GN as first-line therapy in metastatic PDAC is planned to confirm these observations.

Authors' Disclosures

E. Van Cutsem reports personal fees from Cantargia AB during the conduct of the study, as well as personal fees from AbbVie, Agenus, ALX, Amgen, Arcus Biosciences, Astellas, AstraZeneca, Bayer, BeiGene, Bexon Clinical, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Debiopharm, ElmediX, Eisai, Galapagos, GSK, Hookipa Biotech, Incyte, Ipsen, Eli Lilly and Company, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre, Pfizer, Roche, Seattle Genetics, Servier, Simcere, Takeda, Taiho, and Terumo outside the submitted work. S. Ochsenreither reports other support from Cantargia AB during the conduct of the study, as well as personal fees from MSD, Bristol Myers Squibb, Pfizer, Janssen, Merck, and Immunocore and grants from Bayer outside the submitted work. D. Arnold reports personal fees from Amgen, Bristol Myers Squibb, Merck Sharp and Dohme, Astellas, Arcus Biosciences, Servier, Takeda, Taiho, Janssen, Daiichi Sankyo, Boston Scientific, GSK, and various CME Providers outside the submitted work. E. Baltruskeviciene reports personal fees from Cantargia AB during the conduct of the study, as well as personal fees and other support from Servier and personal fees from Amgen, Roche, Takeda, and MSD outside the submitted work. S. Magnusson reports employment with Cantargia AB and ownership of stock in Cantargia AB. C. Rydberg Millrud reports employment with Cantargia AB and ownership of stock in Cantargia AB. A. Sanfridson reports employment with Cantargia AB and ownership of stock in Cantargia AB. N. Losic reports employment with Cantargia AB and ownership of stock in Cantargia AB. I. Garcia-Ribas reports personal fees and other support from Cantargia AB during the conduct of the study, as well as personal fees from Oncomatryx, Shionogi, and Zumutor Biologics outside the submitted work. D. Tersago reports personal fees and other support from Cantargia AB during the conduct of the study. A. Awada reports personal fees and other support from Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Eisai, Genomic Health, Ipsen, Leo Pharma, Eli Lilly and Company, Merck, MSD, Novartis, Pfizer, and Seattle Genetics, other support from Hengrui, Innate, and Menarini, personal fees from Hikma, and grants from Bristol Myers Squibb and Roche outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

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Acknowledgments

The authors thank the patients and their families for participating in the study and all study staff at the clinical sites. The authors also thank Joanne Wolter (independent) for writing assistance and the pathologist Dr. Pierre Lefesvre for scoring the IL1RAP staining. This study was sponsored by Cantargia AB.

Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received March 2, 2024; revised May 19, 2024; accepted September 26, 2024; published first October 10, 2024.

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