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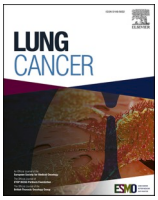

Research Paper

Safety, efficacy, and analysis of biomarkers in patients with advanced non-small cell lung cancer treated with the anti-IL1RAP antibody nadunolimab (CAN04) in combination with platinum doublet

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ABSTRACT

Introduction: Interleukin-1 receptor accessory protein (IL1RAP), expressed in several tumors, is essential for IL-1α and IL-1β signaling which leads to tumor progression and treatment resistance. Nadunolimab, a fully humanized antibody-dependent cellular cytotoxicity-enhanced monoclonal antibody, targets IL1RAP and blocks IL-1α/IL-1β signaling. Efficacy and safety of nadunolimab plus platinum-based doublet chemotherapies were assessed in patients with non-small cell lung cancer (NSCLC) (NCT03267316).

Methods: Patients with advanced NSCLC received nadunolimab plus platinum-based doublet chemotherapies in first-line or second-line post-pembrolizumab. Study objectives included the anti-tumor response, progression-free survival (PFS), overall survival (OS), levels of biomarkers in serum, and immunohistochemistry of baseline and on-treatment tumor biopsies.

Results: 43 patients were enrolled, median age 64 years, 38 % female, and 43 % were treated in second-line post-pembrolizumab. Median PFS was 7.2 months (95 % CI 5.6–9.2), median OS was 13.7 months (95 % CI 11.1–18.3), and 1-year survival was 54 %. The greatest benefits were observed in 11 patients with non-squamous histology treated in second-line post-pembrolizumab: median OS 26.7 months, ORR 91 % including two complete responders (with distinct biomarker profiles), and 1-year survival 82 %. Biomarker analyses showed that patients in second-line post-pembrolizumab had an enhanced level of tumor-infiltrating immune cells compared to treatment naïve patients. Rates of Grade 3+ neutropenia, anemia, and thrombocytopenia were higher than previous reports of platinum-based doublet chemotherapies alone.

Conclusions: Nadunolimab plus platinum-based doublet chemotherapies showed promising efficacy in advanced NSCLC, with the greatest benefit in patients with non-squamous histology treated in second line after relapsing on pembrolizumab treatment.

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CI, confidence interval; CR, complete response; CRP, C-reactive protein; DLT, dose or treatment limiting toxicity; DoR, immune duration of response; DCR, disease control rate; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; IL1RAP, IL-1 receptor accessory protein; IFNγ, interferon gamma; IRR, infusion-related reactions; mITT, modified intention to treat; NK, natural killer cells; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival PD, progressive disease; PD-1/PD-L1, programmed death (ligand) 1; PFS, progression-free survival; PR, partial response; SAE, serious adverse event; SD, stable disease; TME, tumor microenvironment; TNFα, tumor-necrosis factor-alpha.

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1. Introduction

Lung cancer is one of the most common malignances worldwide and a leading cause of cancer-related deaths, with 84 % of cases of the non-small cell lung cancer (NSCLC) type [1]. For individuals without actionable driver mutations, programmed death (ligand) 1 (PD-1/PD-L1) inhibitors form part of the standard of care alongside chemotherapy for patients with advanced/metastatic NSCLC [2]. Treatment of NSCLC with PD-1/PD-L1 inhibitors can markedly improve tumor response rates and prolong survival, but not all patients respond to treatment (primary resistance) and the development of treatment resistance (acquired resistance) is almost inevitable [3,4].

Chronic imbalanced inflammatory responses are a hallmark of cancer and promote tumor initiation, progression and metastasis [5]. Interleukin 1 (IL-1) is a pro-inflammatory cytokine associated with poor prognosis and involved in the development of immunosuppression within the TME, promoting metastases, tumor growth, and treatment resistance [6–10]. The ligands IL-1α and IL-1β bind to IL-1 receptor 1, which dimerizes with the IL-1 receptor accessory protein (IL1RAP) to initiate IL-1 signaling. IL1RAP is overexpressed in many solid tumors and overexpression is associated with a poor prognosis [11,12]. In tumors, IL1RAP is expressed on malignant cells, stromal cells, and immune cells, especially of myeloid lineages. Consequently, blockade of both IL-1α/IL-1β has been heralded as a potential approach for the treatment of cancer [8,11,13–17].

Nadunolimab (CAN04) is a fully humanized, antibody-dependent cellular cytotoxicity (ADCC) enhanced, monoclonal immunoglobulin G1 antibody targeting IL1RAP. It inhibits tumor-promoting and chemoresistance signals mediated by IL-1α and IL-1β and induces ADCC on IL1RAP-expressing cells [18,19]. In mouse models, nadunolimab combined with platinum and non-platinum-based chemotherapy improved anti-tumor effects compared to chemotherapy alone [19]. Platinum-based chemotherapy up-regulates the IL-1 system in human tumor cells, thus promoting chemoresistance [19]. Safety and efficacy of nadunolimab was investigated in a Phase 1/2a multicenter, open-label, dose escalation, dose expansion study (CANFOUR: NCT03267316). Results from Phase 1, in which patients with solid tumors received nadunolimab as monotherapy, showed that nadunolimab was well tolerated [20]. In Phase 2a, nadunolimab combined with standard of care chemotherapy was evaluated in patients with locally advanced/metastatic solid tumors. Promising efficacy was observed in the cohort of patients with advanced/metastatic pancreatic ductal adenocarcinoma where the combination of nadunolimab and gemcitabine/nab-paclitaxel in 76 patients showed an improved overall survival (OS: 13.2 months) compared with historical controls (8.5–9.2 months [21]). Better efficacy outcomes were observed in patients with high baseline IL1RAP expression on tumor cells (IL1RAP high: OS 14.2 months vs IL1RAP low: OS 10.6 months) [22].

Nadunolimab has also been clinically evaluated in combination with the PD-1 inhibitor pembrolizumab in patients with solid tumors who had previously progressed on checkpoint inhibitor treatment (CIRIFOUR: NCT04452214). In this small study, an apparent survival benefit was observed in patients with high levels of effector cells in the tumor microenvironment (TME) at baseline [23].

Here, we present results from the CANFOUR Phase 2a study from patients with advanced/metastatic NSCLC treated with nadunolimab combined with cisplatin/gemcitabine (NCG) or carboplatin/pemetrexed (NCP) in first-line (1L), or in second-line (2L) after relapsing on pembrolizumab.

2. Methods

2.1. Study population

Study participants were at least 18 years of age with histologically or cytologically confirmed, unresectable stage III or stage IV squamous or non-squamous NSCLC, and eligible to receive cisplatin/gemcitabine (squamous or non-squamous NSCLC) or carboplatin/pemetrexed (non-squamous NSCLC only) as 1L chemotherapy for advanced disease, or as 2L after progressing on 1L pembrolizumab monotherapy. The full list of inclusion and exclusion criteria is provided in the supplement.

2.2. Treatment

Patients in the NCG group received nadunolimab at 1.0, 2.5 or 5.0 mg/kg once a week for the first five infusions, and then every other week thereafter. Cisplatin (75–100 mg/m^2) was to be administered on Day 1 and gemcitabine 1250 mg/m^2 on Days 1 and 8 in cycles of 21 days for 4–6 cycles in the absence of progression or toxicity. After completion, subjects could continue treatment with nadunolimab monotherapy or together with gemcitabine.

Patients in the NCP group received 2.5 mg/kg nadunolimab in combination with 4–6 cycles of carboplatin (area under the curve 5 mg/mL/min) and pemetrexed (500 mg/m^2) on Day 1, with nadunolimab alone on Day 8 in cycles of 21 days. Patients were allowed to continue on nadunolimab monotherapy or together with pemetrexed if considered safe and beneficial. During the course of the study, granulocyte colony-stimulating factor (G-CSF) was recommended as prophylaxis.

The NCG group received a priming dose of 0.5 mg/kg nadunolimab given after pre-medication (antihistamines, paracetamol, and corticosteroids) 1 week before commencing Cycle 1. The NCP group did not receive a priming dose but received the first nadunolimab dose in full on Day 1 Cycle 1 as a 4-hour ramping infusion with premedication. Both strategies were used to reduce the risk of infusion-related reactions.

2.3. 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 all applicable ethical and regulatory requirements. Patients provided written informed consent prior to enrollment. The study protocol and associated documents were approved by appropriate ethics committees. Decisions related to treatment modifications were made by a Safety Review Committee comprised of study investigators and the sponsor.

2.4. Clinical outcomes and assessments

Patients underwent periodic disease assessment (every 8 weeks for the NGC group and every 6 weeks for the NCP group) using RECIST 1.1 and iRECIST criteria.

The treatment efficacy was described in terms of overall response rate (ORR), disease control rate (DCR), defined as the best of complete response (CR), partial response (PR) or stable disease (SD), PFS, OS, and duration of response (DoR).

Treatment-emergent adverse events (AEs) were graded using the NCI Common Terminology Criteria for Adverse Events v4.03.

2.5. Translational analysis: Immunohistochemistry analysis and analysis of serum biomarkers

Tumor biopsies collected at screening and after approximately 4 weeks of treatment were stained for the expression of IL1RAP, IL-1α and PDL1, and the presence of CD8+ T cells, NK cells (CD56) and M2 macrophages (CD163). IL1RAP expression was quantified on tumor cells using an H score ([1 × % weakly stained cells] + [2 × % moderate stained cells] + [3 × % strongly stained cells]). IL1RAP expression in stroma was scored as none (0), low (1), medium (2), or high (3) levels, and expression on infiltrating immune cells was scored as the percentage of positive cells.

Serum was collected at baseline and on treatment and analyzed for levels of C-reactive protein (CRP), IL-6, and the T cell related cytokines

chemokine ligands 9 and 10 (CXCL9, CXCL10), and interferon gamma (IFNγ). CRP was measured at study sites, IL-6 levels were analyzed with MSD at central laboratory, and the other cytokines were measured centrally using Olink (Immuno-oncology panel). Detailed methods for the translational analysis are provided in the supplement.

2.6. Statistical analysis

No hypotheses were pre-specified and results were presented using descriptive statistics.

The safety population included all patients who received at least one dose of nadunolimab. Efficacy analyses were performed on the modified Intention To Treat (mITT) population that excluded patients who discontinued after receiving a single dose of nadunolimab without chemotherapy. PFS, OS and DoR were analyzed using Kaplan-Meier estimates. Efficacy was assessed overall, by line of therapy and by histological type. Median relative dose intensity (RDI = Actual/Planned × 100 %] was reported.

An exploratory analysis of the effect of nadunolimab dose on Grade 3–4 AEs and efficacy endpoints was performed using regression models (Supplementary methods).

Changes in serum cytokines from baseline while on treatment were analyzed using Wilcoxon matched-pairs signed rank test, and differences in baseline markers between patients treated in 1L and 2L were compared using Mann-Whitney test.

3. Results

3.1. Patient population

Enrolment of patients with NSCLC occurred in nine sites in Europe, from July 2019 until October 2021 in the NCG group, and from February 2022 until March 2023 in the NCP group. There were 43 patients with advanced/metastatic NSCLC who received nadunolimab; 33 in the NCG group (17 received 1.0 mg/kg nadunolimab, three received 2.5 mg/kg, and 13 received 5.0 mg/kg) and 10 in the NCP group (2.5 mg/kg) (Fig. S1).

At study end, 31 patients had died, four had withdrawn consent, four were still on treatment of whom three continued treatment in a compassionate use setting, three were in OS-follow-up, and one was discontinued by the sponsor during OS-follow-up because of early closure of the study in that country.

Of the 43 patients, three patients (one in the 1.0 mg/kg and two in the 5.0 mg/kg groups) did not receive chemotherapy due to clinical deterioration (n = 2) or consent withdrawal (n = 1) in the interval between nadunolimab priming dose and the first full dose and were excluded from the mITT cohort.

For the mITT cohort, the median age was 64.5 years (range 39–77)

Table 1
Demographic and baseline disease characteristics of the study population (mITT population).

Nadunolimab dose	1L (N = 23)	2L post-pembrolizumab (N = 17)	Non-squamous 1L (N = 15)	Non-squamous 2L post-pembrolizumab (N = 11)	All NSCLC (N = 40)
Study arm NCG/NCP, n (%)	16 (70)/7 (30)	14 (82)/3 (18)	8 (53)/7 (47)	8 (73)/3 (27)	30 (75)/10 (25)
Age (years)					
Mean (SD)	63.0 (8.7)	65.9 (6.3)	62.6 (10)	65.5 (7.2)	64.2 (7.8)
Median (range)	64 (39–76)	66 (56–77)	65 (39–76)	63 (56–77)	64.5 (39–77)
Sex, n (%)					
Male	16 (70)	9 (53)	9 (60)	5 (45)	25 (63)
Female	7 (30)	8 (47)	6 (40)	6 (55)	15 (38)
ECOG Performance Status, n (%)					
0	9 (39)	7 (41)	4 (27)	6 (55)	16 (40)
1	14 (61)	10 (59)	11 (73)	5 (45)	24 (60)
Stage IV at initial diagnosis, n (%)	20 (87)	16 (94)	13 (87)	10 (91)	36 (90)
Histology, n (%)					
Squamous	7 (30)	6 (35)	0	0	13 (33)
Non-squamous	15 (65)	11 (65)	15 (100)	11 (100)	26 (65)
Unknown	1 (4)	0	0	0	1 (3)
Tumor localization at study entry, n (%)					
Bone	4 (17)	5 (29)	1 (7)	4 (36)	9 (23)
Liver	3 (13)	5 (29)	2 (13)	4 (36)	8 (20)
Lung	23 (100)	17 (100)	15 (100)	11 (100)	100 (100)
Lymph Nodes	20 (87)	15 (88)	13 (87)	9 (82)	35 (88)
Other	12 (52)	7 (41)	9 (60)	5 (45)	19 (48)
Prior therapies, n (%)					
Pembrolizumab monotherapy	0	17 (100)	0	11 (100)	17 (43)
Adjuvant chemotherapy	1 (4)	1 (6)	1 (7)	1 (9)	1 (3)
Radiation	0	6 (35)	0	5 (45)	6 (15)
Surgery	2 (9)	2 (12)	2 (13)	1 (9)	4 (10)
Biopsy received for biomarker analysis, n (%)					
Baseline	21 (91)	13 (76)	11 (73)	8 (73)	34 (85)
On treatment	12 (52)	5 (29)	8 (53)	4 (36)	17 (43)

1 L/2 L: first/second line of therapy, mITT: modified intention-to-treat, NCG: nadunolimab plus cisplatin/gemcitabine, NCP: nadunolimab plus carboplatin/pemetrexed, NSCLC: non-small cell lung cancer, SD: standard deviation. Smoking status was not available.

and 63 % were male. There were 26 patients with non-squamous NSCLC, 13 with squamous NSCLC, and one with unknown histology. At diagnosis, 90 % of patients had stage IV disease, and 43 % had received previous treatment with pembrolizumab monotherapy (Table 1). The median time since the last dose of pembrolizumab monotherapy was 35 days (range 28–68), and the median duration of pembrolizumab treatment was 21 weeks (range 6–85).

The median duration of follow-up was 12.7 months (range 0.9–53.8) in the NCG groups and 11.2 months (range 6.2–16.5) in the NCP group. Demographic characteristics were similar in different dose groups (Table S1) and in groups receiving study treatment as 1L or 2L post-pembrolizumab (Table 1).

3.2. Safety

Neutropenia, anemia, and thrombocytopenia were the most frequently reported AEs (Table 2). Neutropenia was reported by 77 % (33/43) of patients, anemia by 67 %, and thrombocytopenia by 65 %. Grade 3/4 AEs were reported by 93 % of patients overall. The most frequently reported Grade 3/4 AEs were neutropenia (65 %) thrombocytopenia (42 %), anemia (30 %), and leukopenia (14 %). The types and severities of AEs were similar across treatment groups (Tables S2 and S3). There were two Grade 5 cases of septic shock in the NCG group: one that was considered unrelated and occurred after discontinuation of study treatment and while on docetaxel; the other occurred during study treatment Cycle 4 and was concomitant with Grade 4 neutropenia. This patient with metastatic squamous cell carcinoma received nadunolimab in 2L and developed febrile neutropenia with *Pseudomonas aeruginosa* grown from blood cultures. Despite normalization of the neutrophil count, the patient died after 5 days due to multi-organ failure. The investigator considered the death unrelated to treatment, but the sponsor assessed that a relationship with the study drug could not be ruled out and deemed the event to be related (Table 2).

After higher-than-expected rates of Grade 3 neutropenia were observed in the 5.0 mg/kg NCG dose group, enrollment at 5.0 mg/kg was stopped and two additional dose groups were included at 1.0 mg/kg and 2.5 mg/kg. G-CSF was initially recommended for all patients experiencing Grade 4 neutropenia and was later implemented as prophylaxis during Cycle 1, start of cycle for NCG arms and mid-cycle for the NCP arm. Exploratory analyses found a dose-dependent relationship with grade 3/4 neutropenia (Supplement). However, this observation may be confounded by the parallel reduction in dose level and implementation of G-CSF during neutropenia. No other dose dependent associations with Grade 3/4 AEs were observed.

Six patients in the NCG group and two in the NCP group experienced IRRs (one Grade 3 in each group), all during the first nadunolimab infusion. Serious adverse events (SAEs) were reported for 24 patients (Table 2). SAEs occurring in more than one patient were thrombocytopenia (n = 4), neutropenia (n = 4), febrile neutropenia (n = 3), pneumonia (n = 3), anemia (n = 2), and septic shock (n = 2). All SAEs due to neutropenia, febrile neutropenia, anemia, and one case of septic shock were considered related to nadunolimab. In addition, three cases of thrombocytopenia, two of pneumonia, and one each of enterocolitis infectious, sepsis, and IRR, were also considered related to nadunolimab.

Mean RDI was 75 % for nadunolimab, 73 % for cisplatin, 78 % for gemcitabine, and 90 % for carboplatin and pemetrexed. The median number of nadunolimab doses, including priming dose, was 15 (range 1–108 doses), and median treatment duration was 6.7 months (range 1 day–53.6 months) (Table S4).

3.3. Overall efficacy

3.3.1. Tumor response rates and survival

Median OS was 13.9 months (95 % CI 11.1–19.4) in the NCG group, 11.3 months (95 % CI 5.8–not reached) in the NCP group, and 13.7 months (95 % CI 11.1–18.3) in all patients (Table 3). Survival at 1 year was 57 %, 48 %, and 54 %, respectively.

Tumor response rates were identical for RECIST 1.1 and iRECIST. ORR was 53 % in the NCG group, 60 % in the NCP group, and 55 % overall (Table 3, Fig. 1A). PR was achieved by 50 % of patients and two patients achieved a CR. All evaluable patients in the mITT had tumor shrinkage of target lesions and 73 % (n = 29) had >30 % decrease in the tumor size (sum of all diameters) (Fig. 1B). Median PFS was 7.0 months in the NCG group, 9.1 months in the NCP group, and 7.2 months overall (Table 3). The median DOR was 5.8 months, 9.5 months, and 6.4 months, respectively. No statistically significant differences in efficacy endpoints were observed between the different dose levels (Table S5), although the lowest dose of 1.0 mg/kg had the numerically shortest PFS and DOR (Supplement and Fig. S2).

Table 2
Summary of safety and grade ≥ 3 treatment-emergent adverse events regardless of causality reported by at least 5 % of patients with NSCLC (Safety population).

Nadunolimab dose	All NCG (N = 33)		NCP (N = 10)		All NSCLC (N = 43)	
	n (%)		n (%)		n (%)	
Any AE	31 (94)		10 (100)		41 (95)	
Grade 3/4	31 (94)		9 (90)		40 (93)	
Grade 5	2 (6)		0		2 (5)	
Grade 3/4 AEs related to nadunolimab	24 (73)		9 (90)		33 (77)	
Any SAE	22 (67)		2 (20)		24 (56)	
DLT	4 (12)		0		4 (9)	
AEs leading to study discontinuations	1 (3)		1 (10)		2 (5)	
Preferred Term	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**
Neutropenia	19 (58)	24 (73)	9 (90)	9 (90)	28 (65)	33 (77)
Thrombocytopenia	16 (48)	24 (73)	2 (20)	4 (40)	18 (42)	28 (65)
Anaemia	10 (30)	19 (58)	3 (30)	10 (100)	13 (30)	29 (67)
Leukopenia	3 (9)	3 (9)	3 (30)	4 (40)	6 (14)	7 (16)
Febrile neutropenia	4 (12)	4 (12)	0	0	4 (9)	4 (9)
Pneumonia	3 (9)	5 (15)	0	2 (20)	3 (7)	7 (16)
Weight increased	3 (9)	5 (15)	0	0	3 (7)	5 (12)

AE: adverse event, DLT: dose or treatment limiting toxicity, SAE: serious adverse event, NCG: nadunolimab plus cisplatin/gemcitabine, NCP: nadunolimab plus carboplatin/pemetrexed, NSCLC: non-small cell lung cancer.
Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life-Threatening, Grade 5: Fatal.
Percentages are based on the number (N) of included subjects. n: Number of subjects with an event. When a subject experienced more than 1 event in different preferred terms (PT) or within the same PT all incidences are counted.

Table 3
Efficacy outcomes in patients with NSCLC classified using RECIST (mITT population).

Outcome	1L (N = 23)	2L post-pembrolizumab (N = 17)	Non-squamous 1L (N = 15)	Non-squamous 2L post-pembrolizumab (N = 11)	All NCG (N = 30)	NCP (N = 10)	All NSCLC (N = 40)
Duration of follow-up (months) (95 % CI)	11.4 (6.5–13.4)	15.2 (10.9–27.2)	11.4 (3.4–13.4)	16.5 (6.6–29.2)	14.1 (10.7–19.6)	11.2 (6.2–13.4)	12.4 (10.7–15.2)
Overall survival (months)							
Median (95 % CI)	11.5 (8.9–19.4)	15.7 (11.1–28.8)	11.6 (5.8–22.0)	26.7 (6.2–NE)	13.9 (11.1–19.4)	11.3 (5.8–NE)	13.7 (11.1–18.3)
12 months, % (95 % CI)	42 (21–62)	70 (42–86)	42 (16–65)	82 (45–95)	57 (37–73)	48 (16–74)	54 (37–69)
24 months, % (95 % CI)	18 (5–39)	37 (15–60)	21 (4–48)	51 (19–76)	29 (14–46)	24 (2–62)	26 (13–42)
36 months, % (95 % CI)	12 (2–32)	20 (4–44)	21 (4–48)	26 (4–56)	16 (5–32)	24 (2–62)	14 (5–30)
Response							
ORR, n (%, 95 % CI)	10 (44, 23–66)	12 (71, 44–90)	5 (33, 12–62)	10 (91, 59–100)	16 (53, 34–72)	6 (60, 26–88)	22 (55, 38–71)
CR, n (%)	0	2 (12)	0	2 (18)	2 (7)	0	2 (5)
PR, n (%)	10 (43)	10 (59)	5 (33)	8 (73)	14 (47)	6 (60)	20 (50)
SD, n (%)	9 (39)	4 (24)	7 (47)	0	9 (30)	4 (40)	13 (33)
PD, n (%)	0	1 (6)	0	1 (9)	1 (3)	0	1 (3)
NE, n (%)	4 (17)	0	3 (20)	0	4 (13)	0	4 (10)
DCR, n (%, 95 % CI)	19 (83, 61–95)	16 (94, 71–100)	12 (80, 52–96)	10 (91, 59–100)	25 (83, 65–94)	10 (100, 69–100)	35 (88, 73–96)
Duration of response (months)							
Median (95 % CI)	5.7 (3.4–9.9)	7.5 (3.7–20.3)	9.9 (4.4–NE)	9.1 (3.7–NE)	5.8 (3.7–11.2)	9.5 (4.4–NE)	6.4 (4.4–9.9)
PFS (months)							
Median (95 % CI)	7.2 (4.4–9.2)	7.6 (5.3–10.4)	6.3 (2.7–11.3)	10.4 (5.3–22.2)	7.0 (5.5–8.8)	9.1 (2.6–NR)	7.2 (5.6–9.2)
6 months, % (95 % CI)	62 (38–79)	53 (28–73)	50 (23–72)	73 (37–90)	57 (37–73)	60 (25–83)	58 (41–72)
12 months, % (95 % CI)	12 (2–31)	27 (9–50)	18 (3–43)	42 (14–69)	16 (5–32)	25 (4–55)	19 (8–33)

CI: confidence interval, CR: compete response, DCR: disease control rate, NCG: nadunolimab plus cisplatin/gemcitabine, NCP: nadunolimab plus carboplatin/pemetrexed, NE: not evaluable, NR: not reached, ORR: overall response rate, PD: progressive disease, PR: Partial response, SD: stable disease.

3.3.2. *Biomarker analysis*

Screening biopsies from 30 patients were collected at the start of the study to evaluate the presence of IL1RAP using immunohistochemistry. The IL1RAP protein was expressed on tumor cells and stromal cells, such as cancer-associated fibroblasts, in all evaluated biopsies with a median tumor cell H-score of 100, and predominantly low-to-medium stromal expression. IL1RAP-positive immune cells were detectable in 24 of the 27 tumor biopsies with ≥1 % expression on infiltrating cells (Fig. 1C). Sixteen biopsies were collected after 4 weeks of treatment and the effect on IL1RAP expression was evaluated. There was a trend toward increased IL1RAP expression on tumor cells during treatment. IL-1α was detected in all 10 baseline biopsies that were available for analysis, and 3 out of 6 paired baseline and on-treatment biopsies showed an increased tumor expression of IL-1α (Fig. 1D).

Treatment related effects in serum were investigated by analyzing CRP and IL-6 levels at baseline and after 5 weeks on-treatment. Levels of CRP decreased significantly with treatment in over 90 % of patients, and IL-6 levels showed a decreasing trend, with a decrease observed in 77 % of patients (Fig. 1 E). The patients with a decrease in IL-6 tended to have a higher ORR versus those with stable/increase in IL-6 with treatment (61 % vs 33 %). Further treatment-related effects on systemic inflammation were assessed by analyzing serum samples at baseline and on-treatment using the Olink immuno-oncology panel of 92 analytes. A significant decrease was seen for 36 % of the cytokines analyzed, many of them involved in TME remodeling (for example CXCL1, CXCL5, TWEAK, VEGFA, ANGPT1), and there was an increase in 5 % of the cytokines analyzed (Fig. S3).

3.4. *Efficacy by line of therapy*

Post-hoc analysis of the response to nadunolimab treatment in 1L and 2L post-pembrolizumab revealed that tumor response rates and survival outcomes were consistently higher in patients who had previously received pembrolizumab monotherapy (Table 3, Fig. 2A). Median OS was 15.7 months (95 % CI 11.1–28.8) for nadunolimab and platinum doublets used in 2L to pembrolizumab vs 11.5 months (95 % CI 8.9–19.4) in the 1L setting, and 70 % vs 42 % were alive at 12 months. The ORR was 71 % in 2L post-pembrolizumab, including 2 CRs, vs 43 % in 1L.

3.4.1. *Tumor and serum markers in 1L and 2L post-pembrolizumab*

Anti-PD-1 therapies may have profound effects on the tumor microenvironment. Therefore, screening biopsies were evaluated for the presence of IL1RAP-positive immune cells, anti-tumorigenic CD8+ T cells and NK cells (CD56+ immune cells), and M2 macrophages (CD163+ immune cells) using immunohistochemistry. Biopsy analyses showed that patients treated in the 2L post-pembrolizumab setting had significantly higher numbers of IL1RAP+ immune cells (Fig. 2B), CD8+ T cells (Fig. 2C), NK cells (Fig. 2D), and PDL1+ tumor cells (Fig. 2E) present in the tumor biopsies at baseline as compared to patients treated in 1L. A trend towards a higher level of M2 macrophages was also observed in the biopsies from patients previously treated with pembrolizumab (Fig. 2F). There was consistently no correlation between these markers and clinical response across the efficacy endpoints (Fig. S4). Systemic differences in cytokine profile at baseline assessed using Olink revealed a T cell inflammatory profile with increased IFNγ and the T cell attracting chemokines CXCL9 and CXCL10 in patients treated in 2L post-pembrolizumab compared to 1L patients (Fig. 2G). By contrast, there were no significant differences at baseline in CRP or IL-6 levels between patients treated as 1L or 2L post-pembrolizumab.

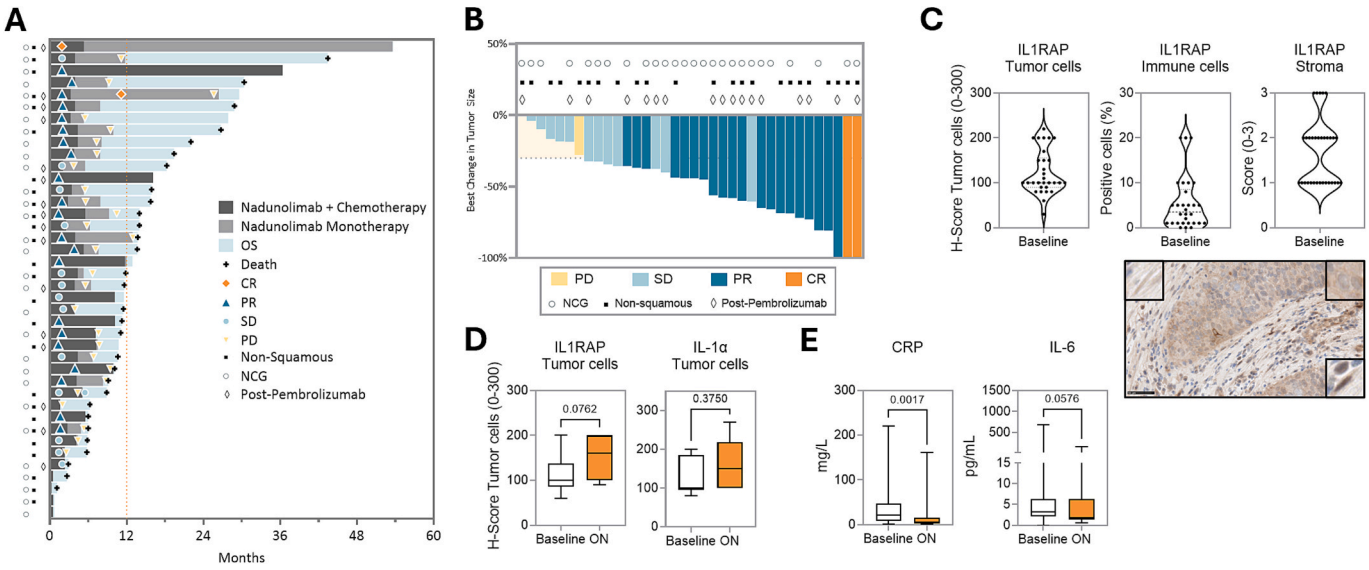

Fig. 1. Efficacy and biomarker analysis of nadunolimab plus platinum doublet chemotherapy treatments in advanced NSCLC. A) Best response, survival, time on treatment and time on study for all patients. Patients received nadunolimab plus platinum doublets as first-line (1L) or as second-line post-pembrolizumab (2L). Platinum was given for 4–6 cycles and then patients continued either on nadunolimab monotherapy or in combination with gemcitabine or pemetrexed. At study end four patients were still receiving nadunolimab-based therapy. B) Waterfall plot of maximum percentage change in sum of diameters of target lesions (mm) from baseline. Four patients with non-evaluable tumor responses are not included. C) IL1RAP expression on tumor cells, immune cells, and stroma from 30 biopsy tissues collected at baseline. Biopsies were stained for the expression of IL1RAP with immunohistochemistry and tumor cell expression was quantified by H-score. IL1RAP expression on infiltrating immune cells was scored as the percentage of positive cells and expression on stroma was scored as none, low, medium, or high levels. Representative images show IL1RAP+ tumor cells (upper right corner), immune cells (lower right corner) and stromal cells (upper left corner). D) IL1RAP (n = 12) and IL-1α (n = 6) expression (H-score) on tumor cells from patients with a baseline and on-treatment biopsy (after approximately 4 weeks of treatment). E) CRP and IL-6 levels in serum samples collected from all patients at baseline and after 5 weeks of treatment (ON). Abbreviations: CR: complete response, CRP: C-reactive protein; IL-6: interleukin 6, IL1RAP: IL-1 receptor accessory protein, OS: overall survival, PD: progressive disease, PR: partial response, SD: stable disease, ON: On-treatment.

3.5. *Efficacy in non-squamous NSCLC by line of therapy*

Post-hoc analysis of response rates in patients with squamous vs non-squamous histology, and by line of treatment, showed that tumor response rates and survival outcomes were consistently higher in patients with non-squamous histology than those with squamous (Table 3). The best outcomes were observed in the 11 patients (eight treated with NCG and three with NCP) with non-squamous NSCLC treated as 2L post-pembrolizumab (Fig. 3A). In these patients, median OS was 26.7 months (95 % CI 6.2-not estimable) vs 11.6 months (95 % CI 5.8–22.0) in 15 patients with non-squamous NSCLC treated in 1L. PFS in 2L non-squamous was 10.4 months (95 % CI 5.3–22.2) vs 6.3 months (95 % CI 2.7–11.3) in 1L non-squamous and 82 % vs 42 % were alive at 1 year, respectively. The ORR was 91 % in patients with non-squamous NSCLC treated in 2L post-pembrolizumab vs 33 % in 1L, and median DoR was 9.1 months (95 % CI 3.7–not estimable) vs 9.9 months (4.4–not estimable) (Table 3). No difference was observed between the NCG and the NCP-treated patient groups.

The two patients who achieved CR were both diagnosed with non-squamous NSCLC and were treated with NCG as 2L post-pembrolizumab (Fig. 3B). All scans were verified and evaluated by an independent central scan assessment. The first patient was a 63-year-old male with lung metastases (stage IV; T2N3M1 at diagnosis; 5.0 mg/kg NCG group) who had previously received pembrolizumab for 19 months (PR as best response). CR was achieved after 56 days of NCG treatment. The DoR was 51.6 months (study completion). This patient continues to receive nadunolimab monotherapy outside of the study (currently 11 months) (Fig. 3C). The second CR was observed in a 63-year-old female with metastases in lymph nodes and lung (stage IV; T3N2M1 at diagnosis; 2.5 mg/kg dose group) who had previously received pembrolizumab for 1.5 months and progressed. CR was achieved on nadunolimab monotherapy 8 months post-NCG. The DoR was 20.3 months after which PD was observed. Representative CT scan images of target lesions are provided (Fig. 3D). The TME profile of these two patients showed no PDL-1 expression on tumor cells, high levels of PDL1+ immune cells, CD8+ T cells, NK cells and IL-1α+ immune cells, and high to median levels of IL1RAP+ immune cells (Fig. S5).

In total, 20 patients continued treatment with nadunolimab monotherapy after completing or stopping the chemotherapy components, with maintenance (n = 12) or improvement (n = 4) in the clinical benefit they obtained. The median duration of nadunolimab monotherapy was 3.3 months (range 1.4–47.3 months). The four patients who experienced clinical improvement while receiving nadunolimab monotherapy were treated between 3.2 and 22.9 months. Median time to progression for the 20 patients who continued on nadunolimab monotherapy was 3.0 months.

4. Discussion

This open-label Phase 2a study investigated the efficacy and safety of nadunolimab plus platinum-based doublet chemotherapy in a cohort of patients with advanced NSCLC. The results suggest a benefit of including nadunolimab in the treatment regimen. OS across the entire study population was 13.7 months, which is observed to be better than historical references from randomized clinical trials of cisplatin/gemcitabine or platinum/pemetrexed in advanced NSCLC (median OS 10.3 and 11.3 months) [24,25].

The rates of ≥Grade 3 neutropenia were higher in patients receiving NCG and NCP than previously reported for cisplatin/gemcitabine or carboplatin/pemetrexed without nadunolimab [24,26,27]. This is likely a result of the combination of nadunolimab with chemotherapy as nadunolimab monotherapy did not give rise to increased levels of neutropenia [20]. Lowering the dose and/or implementing G-CSF treatment reduced the impact of neutropenia and needs further evaluation and

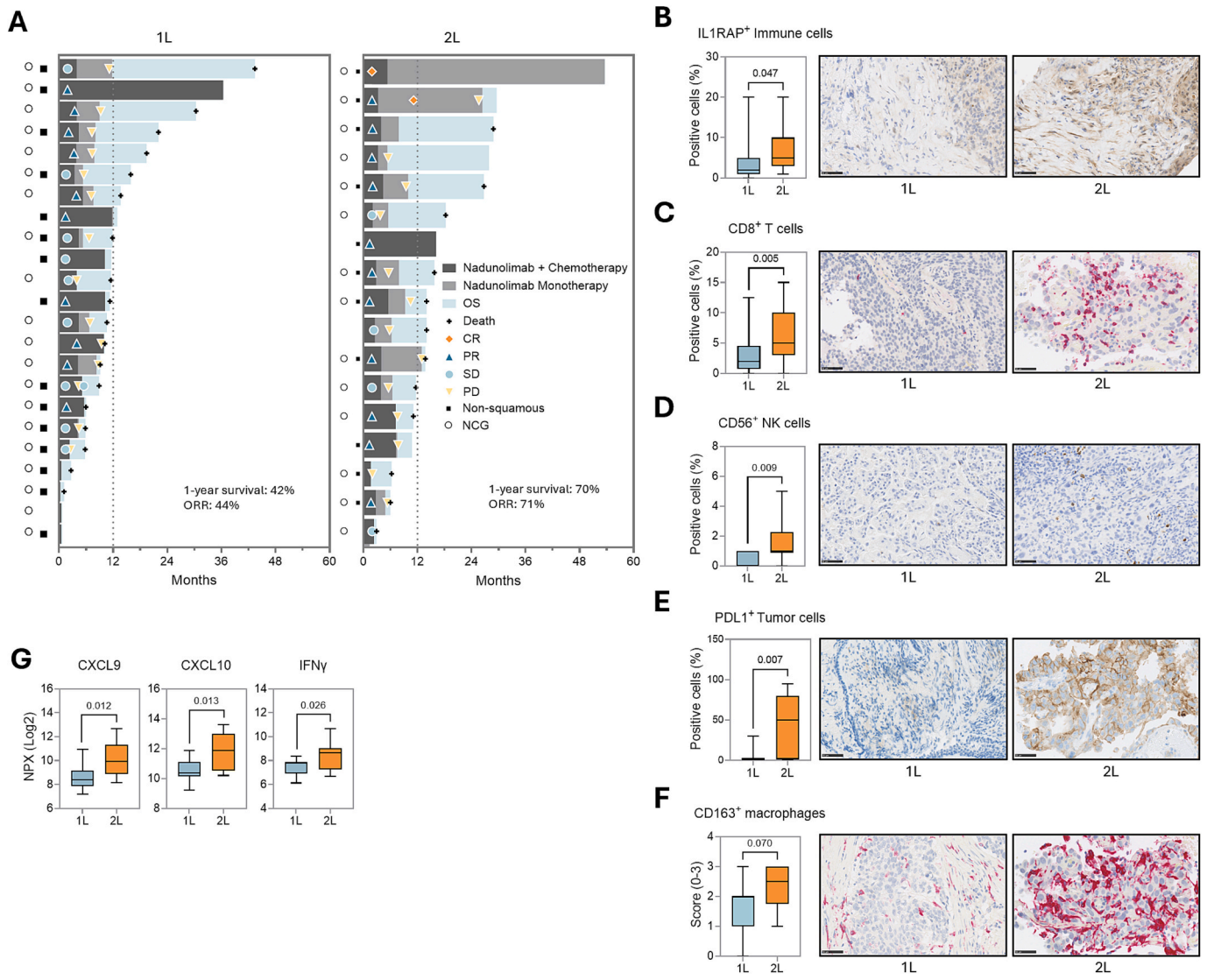

Fig. 2. Efficacy and biomarker analysis in nadunolimab plus platinum doublet chemotherapy treatment as first-line (1L) or second-line post-pembrolizumab (2L). A) Waterfall plot of best response, survival, time on treatment and time on study by line of therapy. Patients received nadunolimab plus platinum-based doublet chemotherapies as 1L or as 2L post-pembrolizumab. Platinum was given for 4–6 cycles and then patients continued either on nadunolimab monotherapy or in combination with gemcitabine or pemetrexed. At study end, four patients were still receiving nadunolimab-based therapy. B) Screening biopsies were stained for the presence of IL1RAP+ immune cells (n = 30), C) CD8+ T cells (n = 32), D) CD56+ NK cells (n = 31), E) PD-L1+ tumor cells (n = 29) and F) CD163+ immune cells (n = 30). IL1RAP+ immune cells were scored as percentage positive cells within the whole tumor biopsy. CD8+ and CD56+ NK cells were scored as percentage positive cells in the tumor nest, and PD-L1 as percentage of positive tumor cells, whereas CD163+ immune cells were scored as 0–3 within the whole biopsy. Representative images are shown for patients treated in 1L or 2L post-pembrolizumab. G) Baseline levels of CXCL9, CXCL10 and IFNγ in patients treated with nadunolimab plus platinum doublets as 1L or 2L post-pembrolizumab. Abbreviations: CR: complete response, IFNγ: interferon-gamma, IL1RAP: IL-1 receptor accessory protein, NK: natural killer, OS: overall survival, PD: progressive disease, PR: partial response, SD: stable disease.

optimization. The use of G-CSF as primary prophylaxis to reduce the incidence of neutropenia has been successfully introduced in another study where nadunolimab was given in combination with chemotherapy [22]. The risk of IRRs during the first administration of nadunolimab has previously been reported [20], and is mitigated with priming dose or ramping infusion together with premedication with corticosteroids, antihistamine and paracetamol.

The treatment effects of nadunolimab plus platinum doublets included decreased serum levels of CRP and IL-6, a cytokine downstream of IL-1 whose decrease is consistent with target engagement. A relationship between treatment and IL-6 is strengthened by the increased response rate in those patients in whom a decrease in IL-6 was observed.

Nadunolimab in combination with platinum doublets tended to increase IL1RAP and IL-1α expression on tumor cells. This is in line with pre-clinical data where platinum-based chemotherapy induced the expression of IL-1 family proteins [19]. The on-treatment effect of the chemotherapy on IL1RAP expression could explain the lack of correlation between baseline IL1RAP expression and improved survival, which we previously observed in patients with advanced pancreatic cancer treated with nadunolimab plus gemcitabine/nab-paclitaxel or as monotherapy [22,28]. The suggested upregulation of IL-1α is consistent with an IL-1 driven environment with increased immunosuppression and chemoresistance resulting from chemotherapy treatment [6,7,9,10,19,29]. This highlights the importance of blocking both IL-1α and IL-1β to reduce IL-1 signaling in the tumor. Indeed, inhibition of only IL-1β in combination with chemotherapy and anti-PD-1 has been tested in metastatic NSCLC without success [30].

In total, 43 % of patients in the study population had previously received pembrolizumab monotherapy, and the most beneficial responses to nadunolimab plus platinum doublets were observed in these

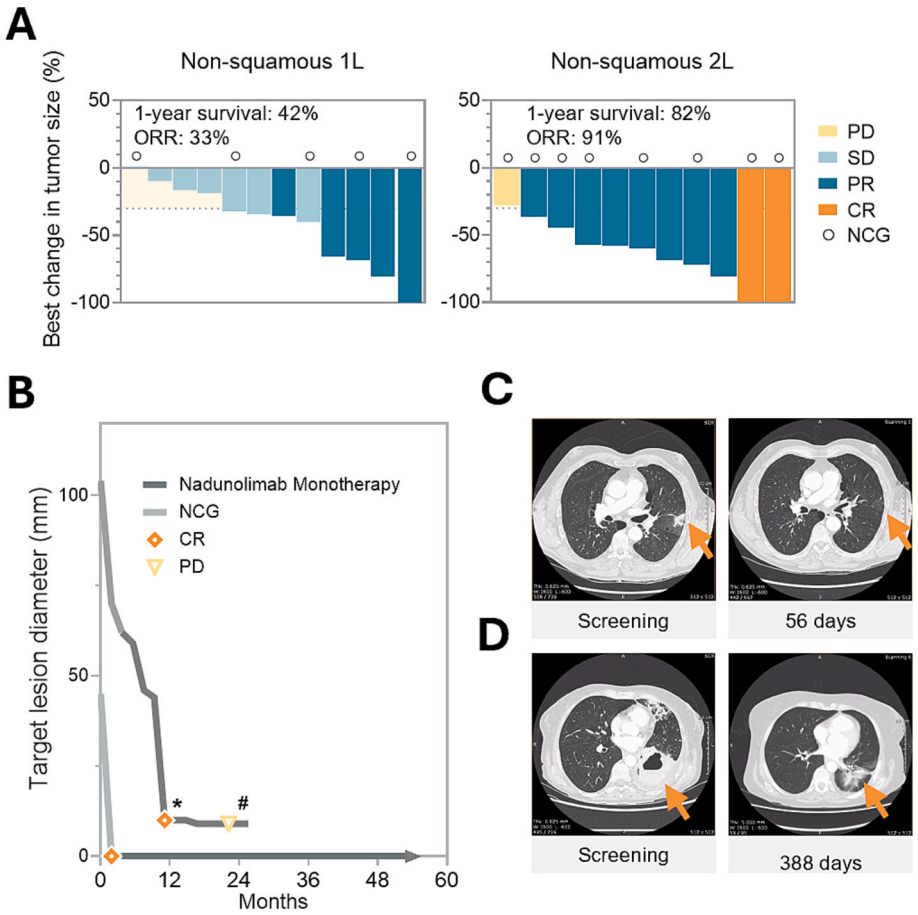

Fig. 3. Responses in patients with non-squamous NSCLC treated with nadunolimab plus platinum doublet chemotherapy as first-line (1L) or second-line post-pembrolizumab (2L). A) Waterfall plot of maximum percentage change in sum of diameters of target lesions (mm) from baseline in patients with non-squamous NSCLC treated with nadunolimab plus platinum-based doublet chemotherapies in 1L or 2L post-pembrolizumab. B) Diameter of target lesions over time in two patients who achieved a complete response. *Two lymph nodes reduced to ≤5 mm. # Nadunolimab treatment continued for 4.2 months after progression due to clinical benefit. C-D) Serial magnetic resonance images of the two patients with complete response. Arrows show tumor location. Remaining scar tissue is visible in the day 388 scan. Abbreviations: CR: complete response, ORR: overall response rate, NCG: nadunolimab combined with cisplatin/gemcitabine, PD: progressive disease, PR: partial response, SD: stable disease.

patients. The post-pembrolizumab population experienced longer survival (OS 15.7 months), a higher ORR (70 %), and greater 1-year survival (70 %) than patients who received nadunolimab plus platinum doublet as 1L (OS 11.7 months, ORR 44 %, and 1-year survival 42 %). The clinical response to platinum doublet chemotherapy after pembrolizumab monotherapy has not been well described. However, several studies of small populations report a better response to chemotherapy in patients previously treated with immune checkpoint inhibitors as compared to treatment naïve patients with NSCLC [31–35]. This suggests that immune checkpoint inhibition induces durable alterations in the anti-tumor immune response that enhances the effect of the next treatment regimen. Consistent with this hypothesis, we observed that the TME was notably different in patients previously treated with pembrolizumab as compared to treatment-naïve patients. Even though patients previously treated with pembrolizumab had lost response to pembrolizumab, they still showed signs of enhanced adaptive immunity both in the TME, with high levels of NK cells and CD8+ T cells, and systemically, with higher concentrations of the T cell and NK cell-recruiting and activating chemokines/cytokines CXCL9, CXCL10 and IFNγ. They also had high levels of PD-L1 on tumor cells as compared to patients treated in 1L. Alteration of adaptive immunity within the TME after treatment with checkpoint inhibitors has previously been reported, together with changes in immune cells from the myeloid lineages [36,37].

Notably, patients in the post-pembrolizumab group also demonstrated an increase in IL1RAP+ immune cells and a trend for an increase in CD163+ macrophages in the TME, potentially indicative of immunosuppression as IL1RAP is highly expressed by myeloid cells, involved in the polarization of macrophages from M1 to M2 phenotype, and in the generation, expansion and recruitment of myeloid-derived suppressor cells [38,39]. CD163 is a marker for M2 macrophages usually associated with immunosuppression, increased tumor aggressiveness, early recurrence, and poor prognosis [40]. The post-pembrolizumab cellular microenvironment may be particularly well-suited for treatment with nadunolimab and chemotherapy, where targeting IL1RAP with nadunolimab can counteract the immunosuppressive TME by blocking IL1RAP on myeloid cells. A TME profile with enhanced levels of both effector cells and myeloid cells was recently reported in patients previously treated with pembrolizumab and this TME signature was found to be beneficial for treatment with nadunolimab in combination with pembrolizumab [41]. Together these findings suggest induction of systemic and localized changes by pembrolizumab treatment, which could be leveraged by nadunolimab-induced IL1RAP blockade to enhance the anti-tumor response of subsequent therapy. Additionally, higher levels of NK cells may directly facilitate nadunolimab efficacy through the ADCC enhanced function.

The 2L post-pembrolizumab group included patients with both squamous and non-squamous histology subtypes. Further evaluation of these groups revealed that the greatest benefits were observed in patients with non-squamous histology treated in 2L post-pembrolizumab,

where OS was 26.7 months, ORR 91 % and the 1-year survival rate 82 %. It is noteworthy that in a 2L treatment setting in advanced non-squamous NSCLC, two patients achieved a CR. One of these patients achieved a CR 8 months after ending chemotherapy and while receiving nadunolimab monotherapy. The second patient with CR remains cancer free and had received 11 months of nadunolimab monotherapy beyond this study at the time of writing. The two CR patients displayed a TME profile in line with other 2L post-pembrolizumab patients and also high levels of PDL1+ and IL-1α+ immune cells.

Interestingly, 20 patients discontinued chemotherapy and continued with nadunolimab monotherapy, including one patient who attained a CR during monotherapy treatment. This may indicate a continued clinical effect of nadunolimab after completion of chemotherapy and may suggest potential for nadunolimab as maintenance treatment.

Strengths of the study include the analysis of biomarkers and tumor samples that shed insights into the mode of action of nadunolimab in NSCLC. Study limitations were the lack of a control group, and the low number of patients in the analyzed sub-groups, of which many were identified post hoc, giving limited value to the biomarker and dose response analyses. Further investigations are warranted to establish the differences between biomarker profiles pre- and post-checkpoint inhibitor treatment and their relevance, such as for patient selection or prediction of outcome. There were no pre-pembrolizumab treatment biopsies available, which would have strengthened the hypothesis that pembrolizumab treatment alters the TME. Additional studies are needed to confirm the optimal nadunolimab dose, to further investigate the potential benefit in patients with non-squamous histology treated in 2L, and to assess the potential benefit of continued nadunolimab monotherapy.

5. Conclusions

Nadunolimab combined with cisplatin/gemcitabine or carboplatin/pemetrexed showed promising efficacy and had an acceptable safety profile in patients with advanced NSCLC. Benefits on OS were observed compared to other published estimates, with the greatest benefit, including two complete responders, observed in patients with non-squamous histology treated in the 2L setting after progressing on pembrolizumab treatment. The effects may potentially involve modulation of an immunosuppressive TME by targeting IL1RAP on myeloid cells. Further evaluation in non-squamous post-pembrolizumab patient populations is warranted.

CRediT authorship contribution statement

Astrid Paulus: Writing – review & editing, Investigation. **Marius Zemaitis:** Writing – review & editing, Investigation. **Saulius Cicenas:** Writing – review & editing, Investigation. **Zanete Zvirbule:** Writing – review & editing, Investigation. **Annika Sanfridson:** Writing – original draft, Visualization. **Camilla Rydberg Millrud:** Writing – original draft, Formal analysis. **Susanne Magnusson:** Writing – review & editing, Project administration, Methodology. **Nedjad Losic:** Writing – review & editing, Validation, Methodology, Formal analysis. **Dominique Tersago:** Writing – review & editing, Supervision. **Ignacio Garcia-Ribas:** Writing – review & editing, Supervision, Methodology. **Lars Thorsson:** Writing – review & editing, Methodology, Conceptualization. **Luis G. Paz-Ares:** Writing – review & editing, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Annika Sanfridson, Camilla Rydberg Millrud, Lars Thorsson, Susanne Magnusson, and Nedjad Losic are employees of Cantargia AB and own stock and/or stock options in Cantargia AB. Zanete Zvirbule reports payment from AstraZeneca for presentations, and support for attending meetings from F. Hoffmann-La Roche Ltd, Merck Sharp & Dohme and AstraZeneca. Dominique Tersago reports consulting fees and reimbursement of travel costs from Cantargia AB. Ignacio Garcia-Ribas reports having been an employee of Cantargia AB and owns stock and/or stock options in Cantargia AB. He reports consulting fees from Cantargia AB and Oncomatryx, has been an external advisor for Oncomatryx. Luis G Paz-Ares reports grants from MSD, AstraZeneca, Pfizer and BMS, consulting fees from Lilly, MSD, Roche, Pharmamar, Merck, Astrazeneca, Novartis, Servier, Amgen, Pfizer, Sanofi, Bayer, BMS, Mirati, GSK, Janssen, Takeda, and Daichii Sankyo, payment for presentations from AstraZeneca, Janssen, Merck, and Mirati. Astrid Paulus, Marius Zemaitis and Saulius Cicenas declare no conflicts of interest.

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Appendix A. Supplementary data

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