Safety, efficacy and biomarker data in non-small cell lung cancer patients treated with the anti-IL1RAP antibody nadunolimab in combination with platinum doublet

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Introduction

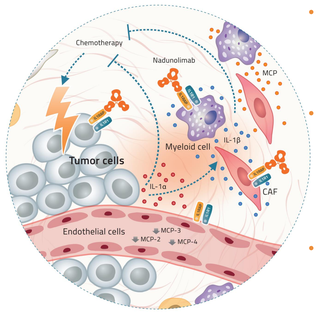


Figure 1: *Nadunolimab blocks IL-1 signaling and induces ADCC in the TME.*

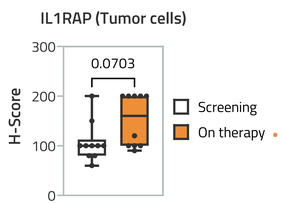
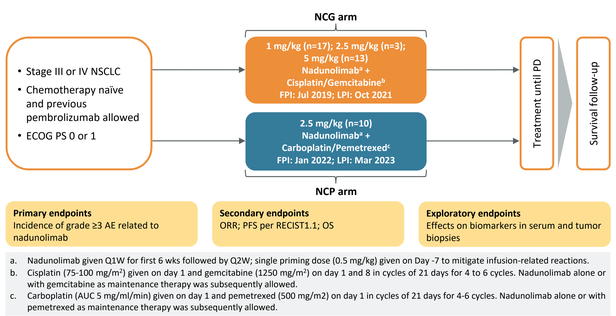


Figure 2: *IHC analyses of IL1RAP on tumor cells in NSCLC biopsies at screening and after 4 wks of NCG.*

- Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer, stromal and infiltrating immune cells of many solid tumors. IL-1α and IL-1β modulate tumor-promoting factors via IL-1 receptor type 1 (IL-1R1), which requires IL1RAP.
- Chemotherapy upregulates IL-1α in non-small cell lung cancer (NSCLC), which stimulates IL-1β release by stromal cells[1-3]. IL-1α/IL-1β contribute to chemoresistance in the tumor microenvironment (TME)[4-5]. Blockade of both IL-1α/IL-1β in combination with chemotherapy thus constitutes an attractive therapeutic approach for cancer.
- Nadunolimab (CAN04) is a fully humanized monoclonal IgG1 antibody targeting IL1RAP. It inhibits tumor-promoting and chemoresistance signals mediated by IL-1α and IL-1β, and induces ADCC of IL1RAP-expressing cells (Fig 1).
- Interim results for combination of nadunolimab and cisplatin/gemcitabine (NCG) in NSCLC pts from the ongoing phase I/IIa trial CANFOUR (NCT03267316) showed acceptable safety and promising efficacy with increased PFS and OS compared to historical controls, with the highest clinical benefit in the non-squamous subtype[6]. NCG also increased the expression of tumor cell IL1RAP in NSCLC (Fig 2).
- Here, we report extended interim efficacy and biomarker data of NCG in first- or second-line (1L/2L) pts with advanced NSCLC in CANFOUR. Also reported is initial efficacy of nadunolimab and carboplatin/pemetrexed (NCP) in CANFOUR, and NCG in late-stage (≥3L) NSCLC pts from the phase I/II CESTAFOUR trial (NCT05116891).

Study design



a. Nadunolimab given Q1W for first 6 wks followed by Q2W; single priming dose (0.5 mg/kg) given on Day -7 to mitigate infusion-related reactions.
b. Cisplatin (75-100 mg/m²) given on day 1 and gemcitabine (1250 mg/m²) on day 1 and 8 in cycles of 21 days for 4 to 6 cycles. Nadunolimab alone or with gemcitabine as maintenance therapy was subsequently allowed.
c. Carboplatin (AUC 5 mg/ml/min) given on day 1 and pemetrexed (500 mg/m2) on day 1 in cycles of 21 days for 4-6 cycles. Nadunolimab alone or with pemetrexed as maintenance therapy was subsequently allowed.

Figure 3: *Summary of the study design for the NSCLC cohorts in part IIa of the CANFOUR trial.*

CANFOUR:

- **NCG arm:** Efficacy population, modified intention to treat (mITT; n=30) is shown. Three pts did not receive chemotherapy due to clinical deterioration (n=2) or consent withdrawal (n=1).
- **NCP arm:** Five of ten pts treated long enough for initial efficacy assessment are shown in Fig 5.

CESTAFOUR:

- The four ≥3L NSCLC pts given 1 (n=3) or 1.75 mg/kg (n=1) nadunolimab with CG are shown in Fig 5.

Results

Patient characteristics

Table 1: *Baseline demographics and characteristics for 1L/2L pts treated with NCG by mITT or dose level.*

	mITT (n=30)	1.0 mg/kg (n=16)	2.5 mg/kg (n=3)	5.0 mg/kg (n=11)
Age; years				
Median (Range)	**64 (39-77)**	62 (39-77)	63 (61-75)	66 (61-77)
Sex; n (%)				
Female/Male	**8 (27%)/22 (73%)**	5 (31%)/11 (69%)	0/3 (100%)	4 (36%)/7 (64%)
ECOG PS; n (%)				
0/1	**14 (47%)/16 (53%)**	9 (56%)/7 (44%)	1 (33%)/2 (67%)	4 (36%)/7 (64%)
Histology; n (%)				
Squamous	**13 (43%)**	6 (38%)	2 (67%)	5 (45%)
Non-squamous	**16 (53%)**	10 (63%)	1 (33%)	5 (45%)
Unknown	**1 (3%)**	0	0	1 (9%)
Prior therapies; n (%)				
Adjuvant chemotherapy	**1 (3%)**	1 (6%)	0	0
Pembrolizumab monotherapy	**14 (47%)**	5 (29%)	3 (100%)	6 (46%)
Radiation	**1 (3%)**	0	0	1 (9%)
Surgery	**1 (3%)**	1 (6%)	0	0

- **1L/2L pts treated with NCG** (Table 1; data cut-off Mar 10, 2023): 10% were still on treatment and death had been observed in 70%. Pts were recruited in Lithuania (n=14), Belgium (n=11), Latvia (n=4), Spain (n=2), Austria (n=1) and Estonia (n=1).
- **1L/2L pts treated with NCP** (n=5; data cut-off Mar 10, 2023): Median age 66 years (60-76), 60% male, 80% ECOG PS 1, 100% non-squamous, 40% received previous pembrolizumab monotherapy. 40% were still on treatment and death had been observed in 60%.
- **≥3L pts treated with NCG** (n=4; data cut-off Apr 12, 2023): Median age 66 years (61-77); 50% female; 75% ECOG PS 0; 100% stage IV. 50% were still on treatment and no deaths had been observed.

Efficacy and subgroup analyses

Table 2: *Efficacy parameters for 1L/2L pts treated with NCG by mITT, dose level or non-squamous subtype.*

Efficacy parameter (95% CI)	mITT (n=30)	1.0 mg/kg (n=16)	2.5 mg/kg (n=3)	5.0 mg/kg (n=11)	Non-squamous (n=16)
OS; median, months	**13.7 (10.6-19.4)**	14.0 (6.0-19.4)	NE (11.1-NE)	13.7 (9.1-30.4)	15.9 (6.0-NE)
PFS; median, months	**7.0 (5.5-8.8)**	5.5 (2.7-7.4)	7.6 (3.7-NE)	8.8 (5.6-13.0)	7.3 (2.7-13.0)
1-year survival	**55% (35-72)**	56% (27-78)	50% (1-91)	55% (23-78)	66% (37-84)
ORR	**53% (34-72)**	50% (24-75)	67% (9-99)	55% (23-83)	56% (30-80)
DoR; median, months	**5.8 (3.7-11.2)**	4.6 (3.6-7.5)	NE (5.7-NE)	7.0 (3.4-NE)	11.2 (3.7-NE)

*NE; not estimable

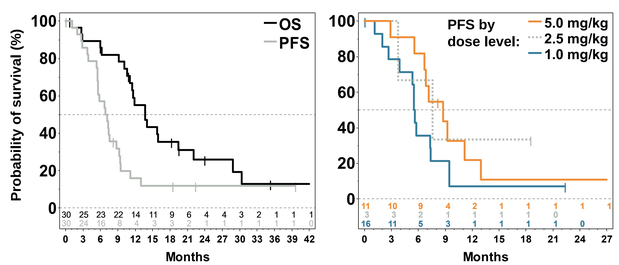


Figure 4: *OS and PFS for 1L/2L pts treated with NCG (mITT; left); PFS by dose level subgroups (right).*

- The 30 1L/2L pts treated with NCG had a median OS of 13.7 months and median PFS of 7.0 months, with a dose-response trend for PFS. Of these, 16 pts with the non-squamous subtype had a more pronounced clinical benefit, including 15.9 months median OS and 11.2 months DoR.
- Confirmed partial responses were observed in the 3 of 5 (60%) 1L/2L pts given NCP, and the 2 of 4 (50%) ≥3L pts given NCG (Fig 5), indicating similar responses as for 1L/2L pts given NCG.

Efficacy and subgroup analyses

Consistently high response rates with nadunolimab and platinum doublets

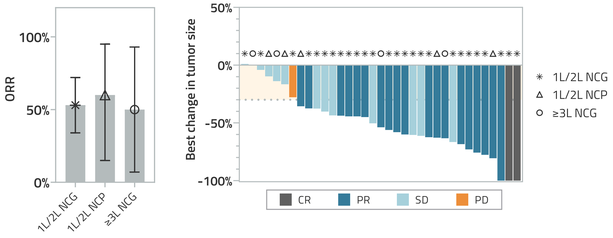


Figure 5: *Overall response rates (left) and best responses (right). ORR above 50% with deep responses.*

NCG therapy results in long-term benefit

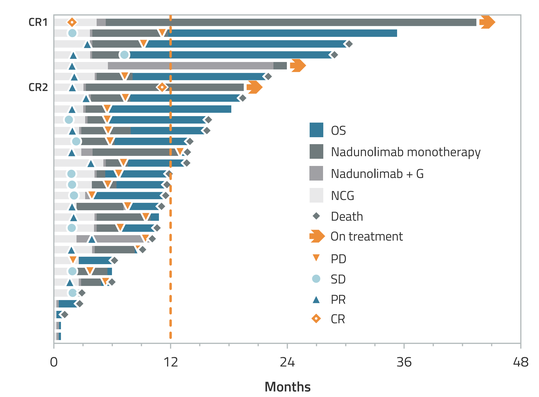
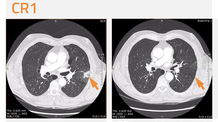


Figure 6: *Treatment course for each individual 1L/2L pt treated with NCG.*

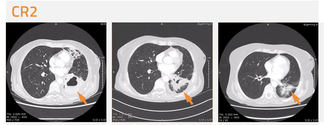
Case stories: Two patients with complete response

CR1



Male, 63 years, non-squamous NSCLC, initial stage IV, 5 mg/kg nadunolimab. Previous pembrolizumab for 19 months (best response PR). Target lesions at baseline: left lung lower lobe (27 mm) and left lung medio-basal segment (18 mm). Larger target lung lesion is shown. CR was achieved after 56 days of NCG treatment. DoR 37.8 months, ongoing.

CR2



Male, 63 years, non-squamous NSCLC, initial stage IV, 2.5 mg/kg nadunolimab. Previous pembrolizumab for 1.5 months (best response PD). Target lesions at baseline: left lung lower lobe (74 mm), lymph node in Barety's space and in aorto-pulmonary window. Target lung lesion is shown. CR was achieved on nadunolimab monotherapy 239 days post-chemotherapy. DoR 16.6 months, ongoing.

Biomarker analyses

Complete responders can be described by IL1RAP/PD-L1⁺ immune cells and PD-L1⁻ tumor cells

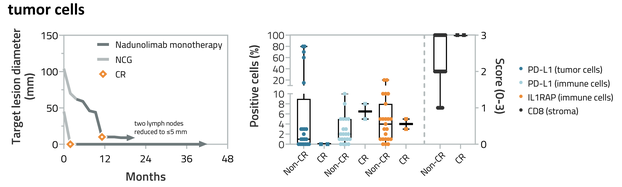


Figure 7: *Target lesion diameter of the two CR pts over time (left). Screening tumor biopsies from 1L/2L pts treated with NCG were analyzed by immunohistochemistry. Per cent PD-L1⁺ and IL1RAP⁺ cells are plotted on the left y-axis and level of CD8⁺ cells on the right y-axis for CR pts (n=2) and non-CR pts (n=26) (right).*

Nadunolimab monotherapy post-chemotherapy maintains low CRP and reduces myeloid chemoattractant proteins

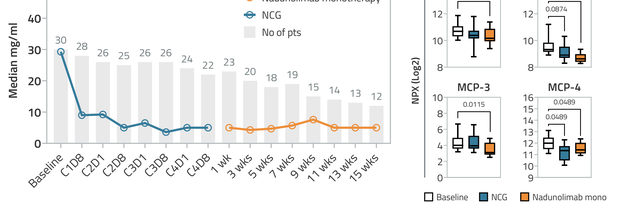


Figure 8: *Serum CRP (left), HGF and MCPs in 1L/2L pts treated with NCG. Samples at baseline, NCG (C1D8) and nadunolimab monotherapy approx. 10 wks post-chemo (n=11) were analyzed by PLA by Olink (right).*

Conclusions

- **Nadunolimab with cisplatin/gemcitabine (NCG) shows promising efficacy in 1L/2L NSCLC: median OS: 13.7 months; median PFS: 7.0 months; 1-year survival: 55%; ORR: 53%**
  - **Strongest clinical benefit was observed in pts with the non-squamous subtype**
  - **A dose-response trend was observed for PFS**
  - **Preliminary data suggest similar ORR in more heavily pretreated pts on NCG, and with nadunolimab in combination with carboplatin and pemetrexed (NCP)**
- **Two pts showed a long-lasting complete response; these could be described by IL1RAP/PD-L1 positive tumor immune cells and PD-L1 negative tumor cells**
- **Several pts retained disease control by nadunolimab monotherapy post-chemo**
  - **Monotherapy maintained reduced serum CRP levels and reduced several biomarkers related to the TME and myeloid cell recruitment**

References

[1] Bruchard et al; Nat Med (2013)
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[5] Zhang et al; Cancer Res (2018)
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