Phase 1/2 trial shows promising efficacy of nadunolimab in combination with platinum doublet as 2nd line therapy in patients with NSCLC

#1350P

Astrid Paulus[1]; Marius Zemaitis[2]; Saulius Cicenas[3]; Zanete Zvirbule[4]; Camilla Rydberg Millrud[5]; Susanne Magnusson[5] Nedjad Losic[5]; Dominique Tersago[5] and Luis Paz-Ares[6]

[1]Centre Hospitalier Universitaire de Liège, Liège, Belgium; [2]Department of Pulomonology Medical Academy Lithuania University of Health Science, Kaunas, Lithuania; [3]National Cancer Institute, Vilnius, Lithuania; [4]Riga East Clinical University, Riga, Lativa; [5]Cantargia AB, Lund, Sweden; [6]Hospital Universitario 12 de Octubre, Madrid, Spain

Background

- Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer, stromal and immune cells in most solid tumors including non-small cell lung cancer (NSCLC). IL1RAP is essential for IL-1α and IL-1β signaling, both of which are involved in tumor progression and therapy resistance.
- Resistance to PD1/PDL1 inhibitors can be caused by myeloid cell mediated immunosuppression in the tumor microenvironment (TME). IL-1 is important for the establishment of an immunosuppressive TME by the generation and recruitment of immunosuppressive cells such as myeloid derived suppressor cells (MDSC) and macrophages.[1-4]
- Nadunolimab is a fully humanized, ADCC-enhanced IgG1 anti-IL1RAP antibody that blocks both IL-1α and IL-1β signaling and targets cells for FcγR-mediated cell killing.
- Previously reported interim results from combination of nadunolimab plus platinum doublets in NSCLC patients from the phase I/IIa CANFOUR trial (NTC03267316) show acceptable safety and promising efficacy with increased PFS and OS compared to historical control.
- Here, we report extended subgroup and biomarker analysis of nadunolimab plus platinum doublets as first-line or second-line post-pembrolizumab treatment (1L/2L) in patients with advanced NSCLC from the CANFOUR trial.

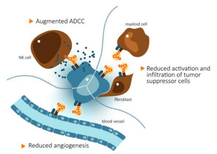

Figure 1: *Mode of action of nadunolimab*

Study design

- Stage III or IV NSCLC
- NCG arm: Squamous/non-squamous
- NCP arm: Non-squamous
- Chemotherapy naïve and previous pembrolizumab allowed
- ECOG PS 0 or 1

NCG arm → 1 mg/kg (n=17); 2.5 mg/kg (n=3); 5 mg/kg (n=13) Nadunolimab[a] + Cisplatin/Gemcitabine[b] FPI: Jul 2019; LPI: Oct 2021

NCP arm → 2.5 mg/kg (n=10) Nadunolimab[c] + Carboplatin/Pemetrexed[d] FPI: Jan 2022; LPI: Mar 2023

→ Treatment until PD → Survival follow-up

Primary endpoints
Incidence of grade ≥3 AE related to nadunolimab

Secondary endpoints
ORR; PFS per RECIST1.1; OS

Exploratory endpoints
Effects on biomarkers in serum and tumor biopsies

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. Nadunolimab given on day 1 and 8 in cycles of 21 days.
d. 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 2: Summary of the study design for the NSCLC cohorts in part II of the CANFOUR trial.

Table 1: Patient demographics and baseline characteristics, mITT*

	mITT (n=40)	1L (n=23)	2L (n=17)
Age; years			
Median (Range)	65 (39-77)	64 (39-76)	66 (56-77)
Sex; n (%)			
Female/Male	15 (38%) / 25 (63%)	7 (30%) / 16 (70%)	8 (47%) / 9 (53%)
ECOG PS; n (%)			
0/1	16 (40%) / 24 (60%)	9 (39%) / 14 (61%)	7 (41%) / 10 (59%)
Histology; n (%)			
Squamous	13 (33%)	7 (30%)	6 (35%)
Non-squamous	26 (65%)	15 (65%)	11 (65%)
Unknown	1 (3%)	1 (4%)	0
Prior therapies; n (%)			
Adjuvant chemotherapy	2 (5%)	1 (4%)	1 (6%)
Pembrolizumab 1L	17 (43%)	0	17 (100%)
Radiation	6 (15%)	0	6 (35%)
Surgery	4 (10%)	2 (9%)	2 (12%)
Study Treatment; n (%)			
NCG	30 (75%)	16 (70%)	14 (82%)
NCP	10 (25%)	7 (30%)	3 (18%)

**Efficacy population, modified intention to treat (mITT; n=40); 3 pts, all in the NCG arm, were excluded from the mITT as they did not receive chemotherapy due to clinical deterioration (n=2) or consent withdrawal (n=1).*

Results

Promising efficacy with nadunolimab plus platinum doublets

Table 2: Efficacy parameters in patients treated with nadunolimab plus cisplatin/gemcitabine or carboplatin/pemetrexed

Efficacy parameter (95% CI)	Total (n=40)	1L (n=23)	2L (n=17)
OS; median, months	13.7 (11.1-18.3)	11.5 (8.9-19.4)	15.7 (11.1-28.8)
PFS; median, months	7.2 (5.6-9.2)	7.2 (4.4-9.2)	7.6 (5.3-10.4)
1-year survival*	54% (37-69)	42% (21-62)	70% (42-86)
ORR	55% (38-71)	44% (23-66)	71% (44-90)
DoR; median, months	6.4 (4.4-9.9)	5.7 (3.4-9.9)	7.5 (3.7-20.3)

*The proportion of patients with 1-year survival is based on Kaplan-Meier estimation.

Longer survival and better response in post-pembrolizumab 2L

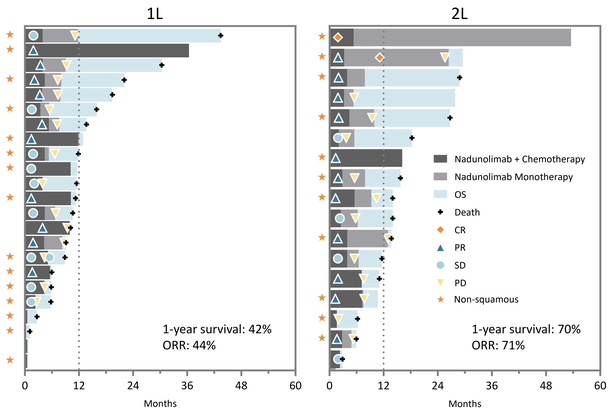

Figure 3: Swimlane with OS, best response, treatment and study duration by patients receiving nadunolimab plus platinum doublets as 1L or post-pembrolizumab 2L. Platinum was given for 4-6 cycles and then patients continued either on nadunolimab monotherapy or in combination with gemcitabine or pemetrexed. At data cut-off 3 patients were still receiving nadunolimab based therapy. All 2L patients received pembrolizumab as 1L treatment.

Patients post-pembrolizumab have an enhanced serum level of T cell related cytokines

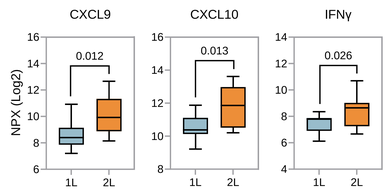

Figure 4: Serum was collected at baseline and analyzed for levels of CXCL9, CXCL10 and IFNγ by Olink using the Immuno-oncology panel. CXCL9 is an IFNγ inducible chemokine important for the recruitment of effector T cells and NK cells, CXCL10 is also an IFNγ inducible chemokine involved in the migration of T cells and NK cells, whereas IFNγ promotes the effector T cell differentiation and activation. These chemokines/cytokines can therefore be involved in facilitating anti-tumor responses.

Higher tumor levels of IL1RAP+ immune cells, CD8+ T cells and NK cells in patients previously receiving pembrolizumab

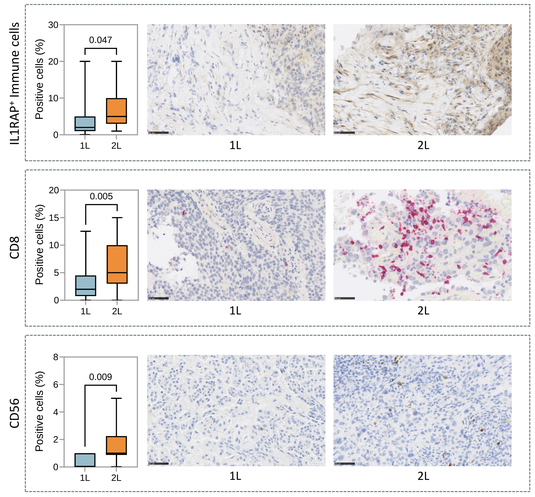

Figure 5: Screening biopsies were stained for the presence of IL1RAP+ immune cells (n=30; upper panels), CD8+ T cells (n=32; middle panels) and NK cells (CD56; n=31; lower panels). IL1RAP+ immune cells was scored as percentage positive cells within the whole tumor biopsy whereas CD8+ T cells and NK cells was scored as percentage positive cells in the tumor nest. Representative pictures are shown for 1L and 2L patients.

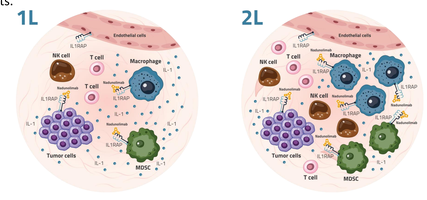

Figure 6: Schematic illustration of the TME of NSCLC patients treated with nadunolimab plus platinum doublet as 1L or post-pembrolizumab 2L.

Best efficacy in non-squamous NSCLC patients receiving nadunolimab plus platinum doublets post-pembrolizumab 2L

Table 3: Efficacy parameters in non-squamous patients treated with nadunolimab plus cisplatin/gemcitabine or carboplatin/pemetrexed.

	Non-squamous	
Efficacy parameter (95% CI)	1L (n=15)	2L (n=11)
OS; median, months	11.6 (5.8-22.0)	26.7 (6.2-NE)
PFS; median, months	6.3 (2.7-11.3)	10.4 (5.3-22.2)
1-year survival*	42% (16-65)	82% (45-95)
ORR	33% (12-62)	91% (59-100)
DoR; median, months	9.9 (4.4-NE)	9.1 (3.7-NE)

*The proportion of patients with 1-year survival is based on Kaplan-Meier estimation
NE; not estimable

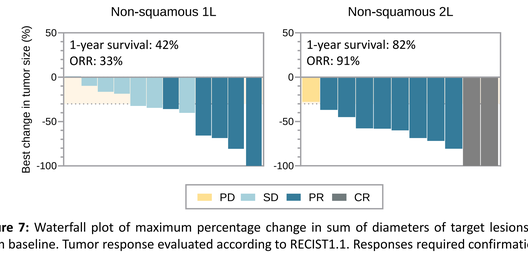

Figure 7: Waterfall plot of maximum percentage change in sum of diameters of target lesions (mm) from baseline. Tumor response evaluated according to RECIST1.1. Responses required confirmation.

Two complete responders in non-squamous NSCLC patients post pembrolizumab

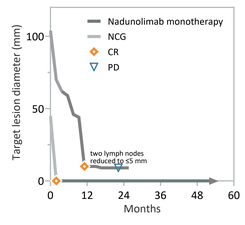

Figure 8: Target lesion diameter of the two CR patients over time.

- **Male, 63 years, non-squamous stage IV NSCLC, 5 mg/kg nadunolimab.** Previous pembrolizumab for 19 months (best response PR). CR was achieved after 56 days of NCG treatment. DoR 51.6 months (study completion). Patient continued nadunolimab monotherapy treatment outside study (currently 8 months).
- **Female, 63 years, non-squamous stage IV NSCLC, 2.5 mg/kg nadunolimab.** Previous pembrolizumab for 1.5 months (best response PD). CR was achieved on nadunolimab monotherapy 7.9 months post-NCG. DoR 20.3 months after which PD was observed. Nadunolimab treatment was continued for 4.2 months after progression due to clinical benefit.

Conclusions

- **Nadunolimab plus platinum doublets show promising efficacy in NSCLC patients. Best response was seen post-pembrolizumab in non-squamous patients with an OS of 26.7 months and ORR of 91% including two CRs.**
  - Despite high levels of intra-tumoral T cells and NK cells, high levels of IL1RAP positive immune cells may suppress adaptive immunity. The potent treatment effects is hypothesized to involve counteraction of the immunosuppressive TME by targeting IL1RAP on myeloid cells.
  - Further evaluation in non-squamous NSCLC post-pembrolizumab patient population is warranted.

References

[1] Weber et al; Front Imunol (2018)
[2] Jenkins et al; Br J Cancer (2018)
[3] Das et al; Cancer Res (2020)
[4] Kaplanov et al; PNAS (2019)

Acknowledgements

We would like to thank the patients and their families for participating in the study, and all study staff at the clinical sites. The study was sponsored by Cantargia AB.

DOI and contact details

DOI Luis Paz-Ares: Financial interest for Cantargia – advisory board; additional other financial interest in various biotechnology and pharmaceutical companies.
Corresponding author: apaulus@chuliege.be