Phase 1/2a trial of nadunolimab, a first-in-class fully humanized monoclonal antibody against IL1RAP, in combination with cisplatin and gemcitabine (CG) in patients with non-small cell lung cancer (NSCLC)

A Paulus[1]; S Cicenas[2]; Z Zvirbule[3]; L Paz-Ares[4]; A Awada[5]; I Garcia Ribas[6]; N Losic[6]; M Zemaitis[7]

[1]CHU de Liège, Liege, Belgium; [2]National Cancer Institute, Vilnius, Lithuania; [3]Riga East Clinical University Hospital, Riga, Latvia; [4]Hospital Universitario 12 de Octubre, Madrid, Spain; [5]Institut Jules Bordet, Brussels, Belgium; [6]Cantargia AB, Lund, Sweden; [7]Department of Pulmonology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

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Introduction

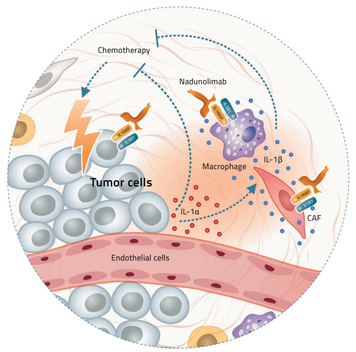

Figure 1: Nadunolimab synergizes with chemotherapy.

Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer and stromal cells of many solid tumors. IL-1α and IL-1β modulate tumor-promoting and other downstream factors (e.g. IL-6, IL-8, CRP) by signaling via IL-1 receptor type 1 (IL-1R1), which requires dimerization of IL-1R1 and IL1RAP.

Chemotherapy may trigger IL-1α release by tumor cells, which stimulates release of IL-1β by stromal cells[1-3]. The presence of both forms of IL-1 in the tumor microenvironment contributes to chemoresistance[4-5]. Blockade of both IL-1α and IL-1β may thus constitute an attractive therapeutic approach for cancer in combination with chemotherapy.

Nadunolimab (CAN04) is a fully humanized monoclonal IgG1 antibody targeting IL1RAP. IL1RAP blockade by nadunolimab offers a unique therapeutic approach compared to other IL-1-targeting concepts; it inhibits the tumor-promoting and chemoresistance signals mediated by both IL-1α and IL-1β, and induces ADCC of IL1RAP-expressing cells.

Preliminary interim results of nadunolimab in combination with cisplatin/gemcitabine (CG) in non-small cell lung cancer (NSCLC) patients from the ongoing CANFOUR phase I/IIa clinical trial (NCT03267316) have been presented showing promising efficacy with increased PFS and OS compared to historical controls[6]. Here, we report extended preliminary interim efficacy, safety and biomarker results of nadunolimab in combination with CG in patients with advanced NSCLC.

Study Design

Study population (n=33):
- Stage III or IV NSCLC
- Chemotherapy naïve and previous pembrolizumab allowed
- ECOG PS 0 or 1

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

Figure 2: Summary of the study design for the NSCLC cohorts in part IIa of the CANFOUR study.

Safety population: n=33; efficacy population: modified intention to treat (mITT): n=30. Three patients did not receive chemotherapy due to clinical deterioration (n=2) or consent withdrawal (n=1).

Patient Characteristics

Table 1: Patient demographics and disease characteristics.

	All (n=33)
Age; years	
Median (Range)	64.0 (39-77)
Sex; n (%)	
Female/Male	10 (30%)/23 (70%)
ECOG PS; n (%)	
0/1	14 (42%)/19 (58%)
Stage; n (%)	
III/IV	3 (9%)/30 (91%)
Histology; n (%)	
Squamous	14 (42%)
Non-squamous	18 (55%)
Unknown	1 (3%)
Prior therapies; n (%)	
Adjuvant chemotherapy	1 (3%)
Pembrolizumab monotherapy	16 (48%)
Radiation	4 (12%)
Surgery	1 (3%)

Enrollment was completed in Oct 2021.

At data cut-off on 15 April 2022, 21% of patients were still on treatment and 64% alive.

Patients were recruited in Lithuania (n=14), Belgium (n=11), Latvia (n=4), Spain (n=2), Austria (n=1) and Estonia (n=1).

Results

Efficacy

Table 2: Response parameters.

Efficacy parameter*	All (n=30)**	Non-squamous (n=16)	Squamous (n=13)
ORR [95% CI]	53% [34-72]	56% [30-80]	46% [19-75]
Disease control rate*** (CR+PR+SD) [95% CI]	83% [65-94]	75% [48-93]	92% [64-100]
Median duration of response [95% CI]	5.8 months [3.7-11.2]	11.2 months [NA]	4.1 months [3.4-5.8]
PFS [95% CI]	6.8 months [5.5-8.8]	7.3 months [5.3-13.0]	5.8 months [3.7-7.4]
Median OS [95% CI]	13.7 months**** [NA]	NA	NA
1-year survival [95% CI]	53%**** [26-73%]	NA	NA

*Responses according to RECIST1.1 criteria
**One tumor of unknown histology
***Two patients withdrew early in association with COVID-19
****Based on 37% of events

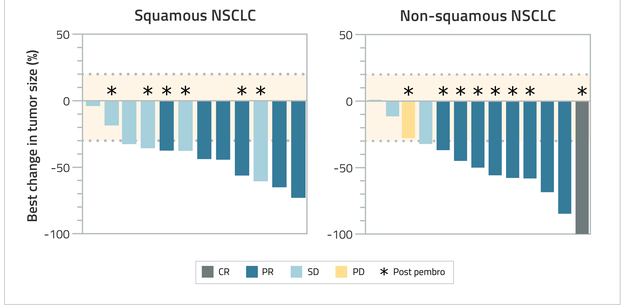

Figure 3: Tumor response evaluated according to RECIST1.1. Responses required confirmation.

One patient (3%) with non-squamous histology had CR as best response, onset after 8.1 weeks, duration of 30 months and still receiving treatment. The patient had previously progressed on pembrolizumab and entered the study with tumors at multiple locations in the lung. Further, 15 patients (50%) showed PR, seven (23%) patients had SD and two (7%) had PD.

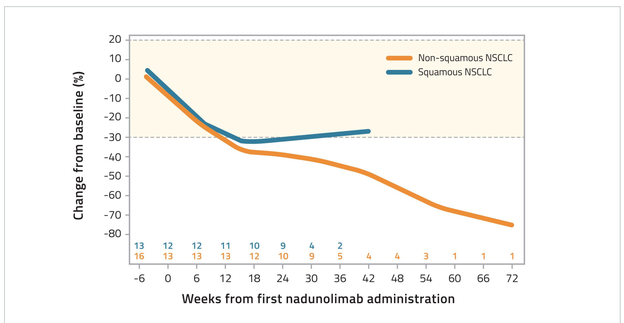

Figure 4: LOESS comparison of tumor size reduction over time by tumor histology.

A more pronounced tumor reduction was observed in patients with non-squamous histology. Nine (56%) patients with non-squamous NSCLC responded compared to six (46%) patients with squamous NSCLC. Of the eight non-squamous NSCLC patients who had previously received treatment with pembrolizumab, seven (88%) achieved response. There were no statistically significant differences between dose groups.

Efficacy

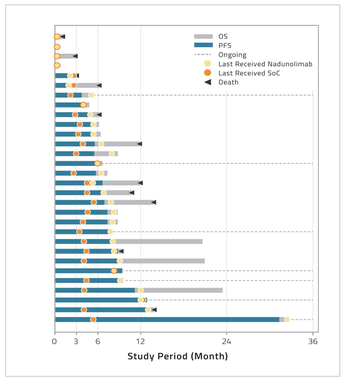

Figure 5: OS, PFS, and treatment/study duration by patient.

At data cut-off, seven patients (23%) were still receiving therapy. Among these, one patient had been on therapy for over 30 months, and another patient for over 12 months.

Twenty-three patients (70%) continued with nadunolimab +/- gemcitabine after 4-6 cycles of scheduled cisplatin. Twelve patients (40%) continued with nadunolimab monotherapy as maintenance ≥3 months (median 4.5 months, range 3.7-27.1).

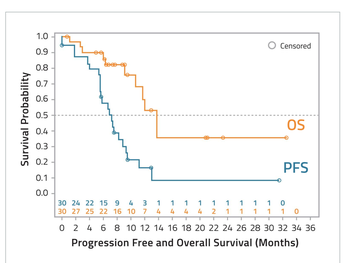

Figure 6: OS and PFS.

With 37% of events observed, median OS is 13.7 months (95% CI not estimable). One-year survival probability is 53% (95% CI 26-73%).

Median PFS is 6.8 months (95% CI 5.5-8.8) with 77% of events at data cut-off. PFS ranges from 0.0 to 31.4 months. Six-month PFS probability is 57% (95% CI 37-73%). Seven (23%) patients were still receiving treatment at data cut-off.

Safety

Table 3: Most common TEAE regardless of relationship (worst grade by patient; grades 3-4 in ≥5%).

	Grade 3-4	All grade
Hematological TEAE; n (%)		
Neutropenia	19 (58%)	24 (73%)
Thrombocytopenia	16 (49%)	24 (73%)
Anemia	10 (30%)	18 (55%)
Febrile neutropenia	4 (12%)	4 (12%)
Leukopenia/WBC decreased	3 (9%)	3 (9%)
Non-hematological TEAE; n (%)		
Pneumonia	3 (9%)	5 (15%)

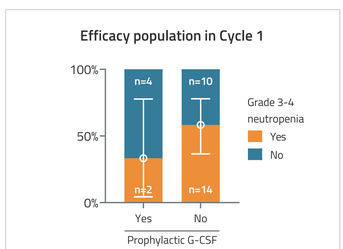

Figure 7: Impact of G-CSF primary prophylaxis on prevention of grade 3-4 neutropenia.

Adverse Events
Treatment-emergent adverse events (TEAE) of grade 3-4 were reported in 61% of the patients. Other TEAE (all grades, regardless of relationship) were hypomagnesemia (36%), diarrhea (24%), fatigue (24%), infusion-related reaction (18%), pain in extremity (15%), and hypokalemia (15%) of which <5% were grade 3-4.

Neutropenia and Febrile Neutropenia
Rates of neutropenia and febrile neutropenia were increased compared to historical data[7]. G-CSF effectively reduced incidence of grade 3-4 neutropenia: In Cycle 1, six patients were treated prophylactically and only two developed grade 3-4 neutropenia (Figure 7). In subsequent cycles, 33% of patients receiving prophylactic G-CSF developed grade 3-4 neutropenia versus 71% if no prophylactic G-CSF was given.

Infusion-Related Reactions (IRR)
IRR (all grades) were observed in 18% of patients (grade 3 only in one patient (3%)) mainly during the first infusion. These could be effectively managed by standard measures.

Biomarker Analyses

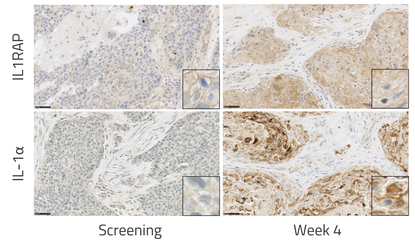

Figure 8: Biopsies from screening and week 4 stained for IL1RAP and IL-1α.

IL1RAP and IL-1α were both detected on the surface and intracellularly in tumor cells and in the stroma by cancer-associated fibroblasts and infiltrating immune cells. Stainings are shown from one representative patient who responded to treatment. In lower right corners, positive tumor cells are presented.

Increased IL1RAP expression was observed after four weeks of treatment in 7 of 7 paired biopsies. Increased expression of the danger signal IL-1α was also observed in 3 of 5 paired biopsies from responding patients, in line with preclinical data. IL-1β was previously shown in infiltrating immune cells in the stroma of NSCLC biopsies.

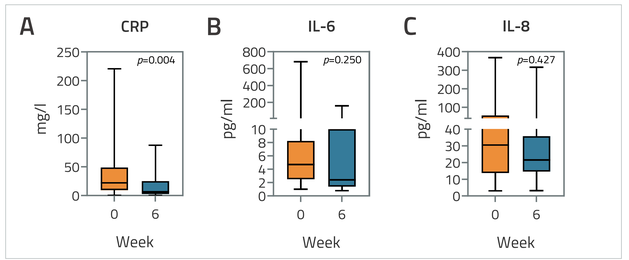

Figure 9: Serum levels of CRP, IL-6 and IL-8 at baseline and at week 6.

Analyses of serum CRP levels were performed at screening and throughout the study, and a persistent decrease was observed by treatment. Difference in serum CRP level between baseline and week 6 is shown in Figure 9A. Serum IL-6 and IL-8 also showed a numerical reduction by treatment (Figure 9B and C).

Conclusions

- Nadunolimab combined with first-line cisplatin/gemcitabine (CG) shows promising efficacy in NSCLC:
  - ORR, median PFS and median OS is higher compared to historical control data for CG alone[7,8,9].
  - The strongest clinical benefit is observed in patients with non-squamous histology.
- The overall safety profile is acceptable; neutropenia, thrombocytopenia and IRR during the first infusion were more common than expected from CG alone.
  - G-CSF treatment reduced the clinical impact of neutropenia during Cycle 1 and subsequent cycles.
  - IRR could be managed by standard measures.
- Treatment resulted in increased IL1RAP and IL-1α expression in tumor tissue and reduced serum levels of CRP, IL-6 and IL-8.
- Nadunolimab is currently evaluated in combination with carboplatin and pemetrexed in non-squamous NSCLC and in various additional indications with chemotherapy or immunotherapy.

References

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Acknowledgements

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