Safety, tolerability, and efficacy of nadunolimab in combination with pembrolizumab in patients with solid tumors

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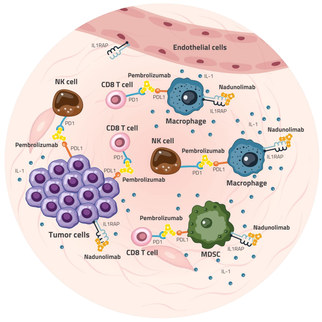
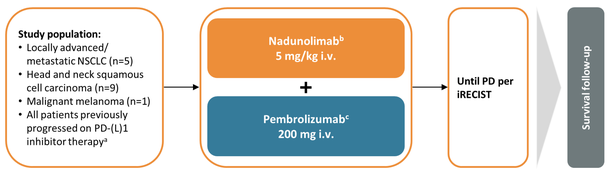
Background

- Treatment resistance to checkpoint inhibitors can be caused by profound immunosuppression from myeloid cells within the tumor microenvironment (TME), which reduces the anti-tumoral effect of CD8 T cell. Infiltration of immune suppressive cells such as M2 macrophages and myeloid-derived suppressor cells (MDSCs) among others are thought to mediate the immuno-suppressive and tumor–promoting environment in the tumor leading to resistance to checkpoint inhibition[1-3].
- Interleukin 1 (IL-1) is important for the generation, expansion and immunosuppressive function of M2 macrophages and MDSCs and is involved in the recruitment of these immunosuppressive cells into the TME[4-6].
- Interleukin-1 Receptor Accessory Protein (IL1RAP) plays a pivotal role in IL-1 signaling and is expressed on tumor cells and infiltrating cells, regulating their activity. Nadunolimab, a fully humanized ADCC-enhanced antibody, targets IL1RAP and blocks IL-1α/β signaling.
- Based on the emerging evidence for the role of IL-1 in resistance to checkpoint inhibitors, we sought to investigate if the addition of nadunolimab could overcome acquired resistance to checkpoint inhibitors in patients who had previously responded to and become resistant to checkpoint inhibitor containing treatment.
- Here, we investigated nadunolimab with pembrolizumab in patients with solid tumors with the primary objective to explore safety, and to additionally describe preliminary efficacy of the combination, including biomarker analysis (NCT04452214).



Study design



[a]Previously having achieved SD or better and stayed on PD-(L)1 inhibitor therapy for ≥12 weeks.
[b]QW in 3-week cycles in Cycle 1 and Cycle 2 and thereafter Day 1 and 8 from Cycle 3 onwards; 0.5 mg/kg priming dose given on Day -7 of Cycle 1 to mitigate infusion-related reactions.
[c]Q3W after nadunolimab on Day 1 of each cycle.

Primary objectives:
- To determine the safety and tolerability of the combination of nadunolimab and pembrolizumab

Secondary objectives:
- To determine preliminary signs of clinical efficacy of nadunolimab in combination with pembrolizumab

Exploratory objectives:
- To evaluate disease-related inflammatory, immune or tumor microenvironment-related para-meters related to the study drugs, in the circulation and in tumor tissue

Baseline Characteristics

Patient characteristics

Table 1: Patient demographics and baseline characteristics

Variable	Total n=15
Age, (years)	
Median (range)	64 (50-79)
Sex, n (%)	
Male	11 (73%)
Female	4 (27%)
Stage IV at study entry	15 (100)
ECOG at screening	
0	1 (7%)
1	14 (93%)
Tumor type	
HNSCC	9(60%)
Melanoma	1 (7%)
NSCLC – adenocarcinoma	4 (27%)
NSCLC – squamous	1 (7%)
Previous therapy	
Radiotherapy	9 (60%)
Surgery	7 (47%)
Systemic therapy	15 (100%)
PD-1 inhibitors	15 (100%)
Platinum compounds	14 (93%)
Tumor burden (mm)*	
Median (range)	50 [16 - 125]

* Sum of all target lesion diameters per RECIST

Previous treatments:
- All patients had received prior treatment with checkpoint inhibitors for 3 - 30 months, with SD or better as best response.
- All but one patient had previously received pembrolizumab; one patient (melanoma) had previously received nivolumab and ipilimumab.
- Additional prior treatments were targeted agents (N=4), immunotherapeutic vaccine or another investigational treatment (N=2).

IL1RAP expression at baseline in patient tumor biopsies

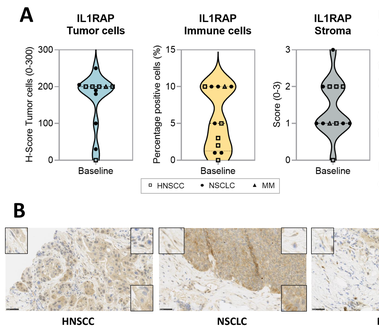


Figure 1: **A)** Screening biopsies were stained for IL1RAP by immunohistochemistry and scored on tumor cells, immune cells and stroma (n=12).

(B) Representative images are shown for each indication. Lower right, upper left and upper right corners show IL1RAP staining of tumor cells, stromal cells, and immune cells, respectively.

PD-L1 expression at baseline in patient tumor biopsies

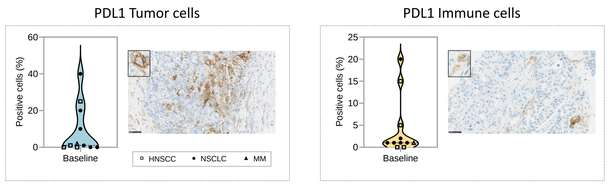


Figure 2: Screening biopsies were stained for PD-L1 by immunohistochemistry (n=11). PDL1 staining was evaluated on tumor cells and immune cells. Representative images shown. Enlarged images are presented in upper left corners.

Results

Combination of nadunolimab with pembrolizumab was safe and well tolerated

Table 2: Treatment-emergent adverse events presented by grade and by preferred term (>2 events)

	Total (n=15)
Any TEAE	15 (100%)
Grade 3/4	7 (47%)
Grade 3/4 related TEAEs	2 (13%)
Grade 5 TEAEs*	1 (7%)
Any SAE	6 (40%)
DLTs**	1 (7%)
TEAEs leading to treatment discontinuation***	1 (7%)

TEAE: treatment-emergent adverse event, SAE: serious adverse event, DLT: dose limiting toxicity
*Grade 5 Pneumocystis jirovecii infection - considered unrelated to treatment by the investigator; **Grade 3 febrile neutropenia in the context of central reservoir infection.
*** Grade 3 pneumonitis

Preferred Term	Grade 3/4	All Grades
Fatigue	1 (7%)	8 (53%)
Pruritus	0	6 (40%)
Hypotension	0	4 (27%)
Arthralgia	0	4 (27%)
Dyspnea	1 (7%)	4 (27%)
Diarrhoea	0	4 (27%)
Weight decreased	0	3 (20%)
Dysphagia	2 (13%)	3 (20%)
Rash	0	3 (20%)
Muscle spasms	0	3 (20%)
Dizziness	0	3 (20%)

Six patients reported 13 treatment-emergent serious adverse events (TESAEs). All TESAEs other than the event of febrile neutropenia (DLT) were assessed by the investigator as unrelated to treatment. One patient discontinued pembrolizumab treatment due to Grade 3 pneumonitis and continued on nadunolimab monotherapy. No important laboratory or vital signs changes occurred during the study.

Promising signs of clinical activity with remarkable benefit in a subset of patients

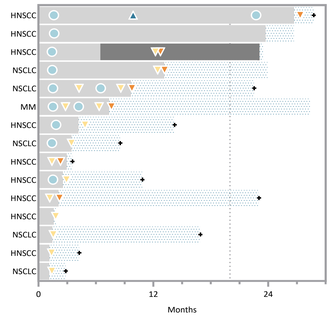


Table 3: Efficacy parameters

Efficacy parameter (95% CI)	Total (n=15)
OS; median, months	19.7 (4.3-28.7)
iPFS; median, months	3.4 (1.4-8.6)
1-year survival	67% (38%-88%)
iORR	7% (0%-32%)
iDoR; median, months	17.4
iDCR	60% (32%-84%)

Figure 3: Patients with clinical benefit were allowed to continue on nadunolimab monotherapy beyond progression. One patient with HNSCC (7%) had confirmed iPR with a duration of response of 17.7 months. Eight subjects (53%) had iSD as best response.

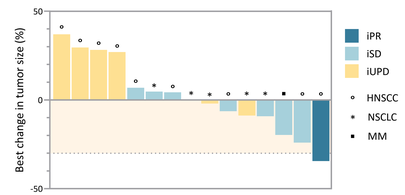


Figure 4: Waterfall plot of maximum percentage change in sum of diameters of target lesions (mm) from baseline.

High baseline levels of NK cells and macrophages and reduced serum level of IL-6 in patients with longest survival

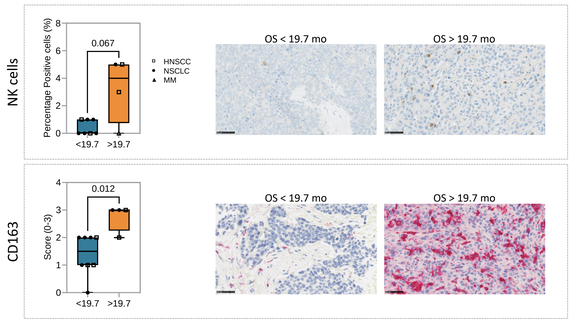


Figure 5: Screening biopsies (n=12) were stained for NK cells (NKp46) and CD163-positive macrophages with immunohistochemistry. Patients were divided according to median OS (</>19.7 months). Positive cells were scored as percentage of NK cells in tumor nests, and the level of CD163-positive macrophages was scored between 0 and 3 within the whole tumor biopsy.

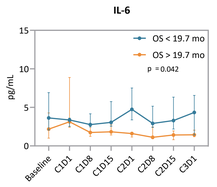


Figure 6: Serum was collected at baseline and after each treatment dose and analyzed for levels of IL-6 using MSD platform. Patients were divided according to median OS (</>19.7 months).

Conclusions

- Combination of nadunolimab with pembrolizumab was safe and well-tolerated.
- Promising signs of efficacy with a disease control rate of 60% and a median OS of 19.7 months. Remarkable clinical benefit was seen in a subset of patients with HNSCC.
- High levels of NK cells and macrophages at baseline appear predictive for beneficial treatment effect of nadunolimab and pembrolizumab. A reduction in IL-6 after combination treatment was also more pronounced in the patients with the best clinical benefit.
- These data strongly support further clinical development.

References

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DOI and contact details

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