Tumor IL1RAP levels and reduction in serum biomarkers correlate with response in PDAC patients treated with nadunolimab, an anti-IL1RAP monoclonal antibody, in combination with gemcitabine and nab-paclitaxel

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Abstract 2172

Introduction

- Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer and stromal cells in pancreatic ductal adenocarcinoma (PDAC), where high tumor IL1RAP mRNA expression is a negative prognostic marker (Figure 1)[1,2]. IL1RAP dimerization with the IL-1 receptor is required for IL-1α and IL-1β signaling, and the IL-1 axis has been implicated in tumor-permissive signaling networks in the PDAC tumor microenvironment (TME), including tumor growth, chemoresistance and immune suppression.

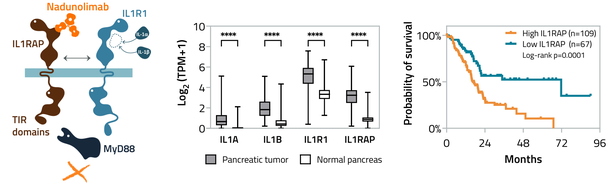
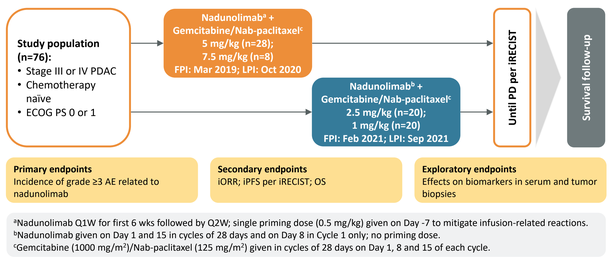


Figure 1: *RNAseq data from stage I-IV pancreatic tumors and normal pancreas from the publicly available databases TCGA and GTEx show upregulation of IL1A, IL1B, IL1R1 and IL1RAP mRNA in pancreatic tumors. Of these, high tumor IL1RAP mRNA expression is a negative prognostic marker for survival.*

- 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 (Figure 1).
- Nadunolimab has potent effects in preclinical models of the PDAC TME with strong effects on tumor cells, cancer-associated fibroblasts and infiltrating myeloid cells.
- Nadunolimab is investigated for treatment of locally advanced/metastatic PDAC in combination with gemcitabine/nab-paclitaxel (GN) in the phase I/IIa CANFOUR trial (NCT03267316).
- Interim results from CANFOUR previously showed acceptable safety and stronger OS, iPFS and 1-year survival compared to reported values for GN alone. Baseline CRP and IL-6 were prognostic for OS[3,4].

Here, we report tumor biopsy and serum biomarker data related to treatment outcomes as well as updated efficacy data for PDAC patients in the CANFOUR trial

Study design



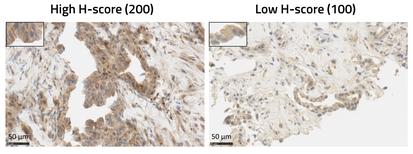
[a]Nadunolimab Q1W for first 6 wks followed by Q2W; single priming dose (0.5 mg/kg) given on Day -7 to mitigate infusion-related reactions.
[b]Nadunolimab given on Day 1 and 15 in cycles of 28 days and on Day 8 in Cycle 1 only; no priming dose.
[c]Gemcitabine (1000 mg/m^2)/Nab-paclitaxel (125 mg/m^2) given in cycles of 28 days on Day 1, 8 and 15 of each cycle.

Figure 2: *Summary of the study design for the PDAC cohorts in part IIa of the CANFOUR trial.*

Results

Target expression

Two patient subgroups can be defined based on IL1RAP expression



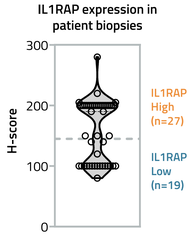


Figure 3: *PDAC screening biopsies stained for IL1RAP. IL1RAP on tumor cells (highlighted in inserts) was quantified by H-score (area stained (0-100%) x intensity of staining (0-3)). Plot shows distribution by H-score: IL1RAP High was defined as ≥150 and IL1RAP Low as <150.*

Patient characteristics

Table 1: *Baseline characteristics.*

	mITT (n=73)	Biopsy subgroup (n=46)	IL1RAP High (n=27)	IL1RAP Low (n=19)
Age; mean (range)				
Years	63 (43-89)	64 (43-87)	63 (43-87)	65 (46-78)
Sex; n (%)				
Female/Male	30 (41%)/43 (59%)	19 (41%)/27 (59%)	13 (48%)/14 (52%)	6 (32%)/13 (68%)
ECOG PS; n (%)				
0/1	33 (45%)/40 (55%)	19 (41%)/27 (59%)	10 (37%)/17 (63%)	9 (47%)/10 (53%)
Tumor location at study entry; n (%)				
Pancreas	68 (93%)	44 (96%)	25 (93%)	19 (100%)
Liver	48 (66%)	30 (65%)	19 (70%)	11 (58%)
Lung	22 (30%)	11 (24%)	5 (19%)	6 (32%)
Lymph node	38 (52%)	21 (46%)	13 (48%)	8 (42%)
Peritoneum	17 (23%)	12 (26%)	6 (22%)	6 (32%)
Serum markers; median (range)				
CA19-9; U/ml	508 (1.0-105000)	508 (1.0-79200)	490 (1.2-79200)	560 (1.0-46500)
Bilirubin; µmol/l	9.8 (3.9-29.2)	9.7 (3.9-29.2)	9.4 (3.9-27.9)	9.8 (4.6-29.2)
Neutrophil to Lymphocyte Ratio; median (range)				
NLR	3.6 (0.9-14.4)	3.5 (0.9-14.4)	3.8 (0.9-14.4)	2.9 (1.4-11.3)

- At data-cut-off (March 10, 2023), 3% of patients were on treatment, death was observed in 71%, and 22% were in follow-up. Patients were recruited in Belgium (n=23), Denmark (n=14), Germany (n=11), Lithuania (n=10), Latvia (n=8), Sweden (n=4), Spain (n=3), Austria (n=2), and Estonia (n=1).
- Efficacy population: Modified intention to treat (mITT), n=73. 76 patients were included in the study, three did not receive chemotherapy due to consent withdrawal (n=2) or clinical deterioration (n=1).
- Biopsy subgroup: 46 patients had screening or archival tumor biopsies that could be analyzed for baseline IL1RAP expression. Patients were further divided based on IL1RAP expression (H-score) into IL1RAP High (H-score ≥150) or IL1RAP Low (H-score <150) subgroups (Figure 3).

Efficacy and subgroup analyses

Nadunolimab/GN show better than expected efficacy; IL1RAP expression is associated with greater response to treatment

Table 2: *Response parameters including 95% confidence intervals.*

Efficacy parameter (95% CI)	mITT (n=73)	Biopsy subgroup (n=46)	IL1RAP High (n=27)	IL1RAP Low (n=19)
OS; median, months	12.9 (10.6-15.5)	13.2 (10.0-18.3)	14.2 (10.6-28.7)	10.6 (3.1-12.6)
iPFS; median, months	7.2 (5.2-8.5)	7.2 (3.9-8.9)	8.0 (3.7-11.2)	5.8 (2.7-7.4)
1-year survival	58% (45%-68%)	58% (42%-71%)	69% (NE*)	40% (17%-62%)
iORR	33% (22%-45%)	43% (29%-59%)	52% (32%-71%)	32% (13%-57%)
iDoR; median, months	7.3 (5.5-11.0)	6.9 (5.5-10.0)	9.5 (3.7-11.8)	5.6 (3.9-NE*)

*NE; not estimable

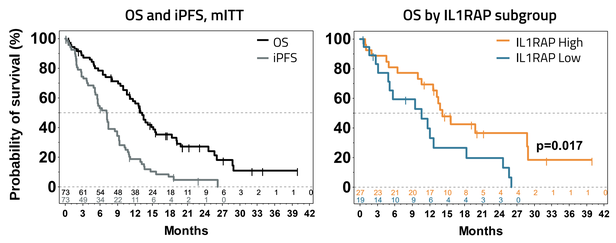


Figure 4: *OS and iPFS for mITT patients (left); OS for the IL1RAP High and IL1RAP Low subgroups (right).*

- Median OS of 12.9 months was observed in mITT patients. This was significantly longer in the IL1RAP High subgroup (14.2 months) compared to the IL1RAP Low subgroup (10.6 months). Trends for benefit were also observed for iPFS, 1-year survival, iORR and iDoR in the IL1RAP High subgroup.
- A robustness analysis where the IL1RAP H-score threshold was set at >100 or ≥190 still showed significantly longer OS in the IL1RAP High subgroup (p=0.014 and p=0.038 respectively).

Results

Efficacy and subgroup analyses

The IL1RAP High subgroup demonstrates deeper and more durable responses to nadunolimab/GN

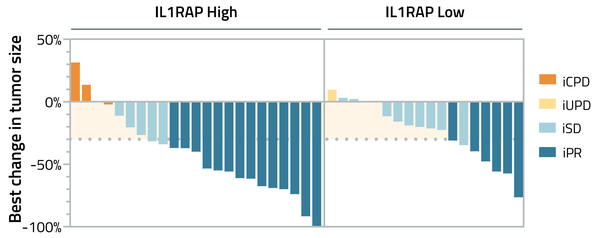


Figure 5: *Best response for the IL1RAP High and IL1RAP Low subgroups evaluated according to iRECIST.*

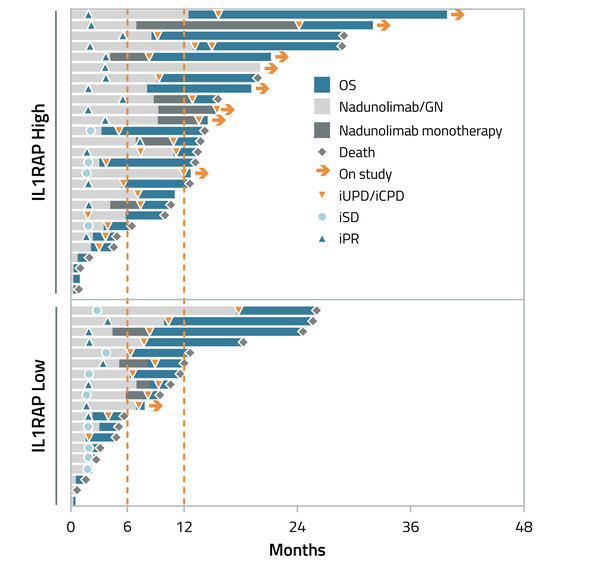


Figure 6: *Treatment course for each individual patient in the IL1RAP High and IL1RAP Low subgroups.*

Serum and biomarker analyses

IL1RAP H-score does not correlate with baseline inflammatory biomarkers

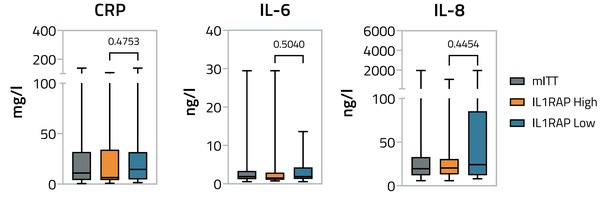


Figure 7: *Baseline levels of CRP, IL-6 and IL-8. Also, Spearman correlation coefficients (r) between H-score and CRP, IL-6 or IL-8 showed no correlation at baseline (-0.09< r <0.04, p >0.55).*

Serum and biomarker analyses

Greater decrease in IL-8 on treatment is beneficial for OS

	Median OS, months			
	Baseline		Nadir/Baseline ratio	
	(lower baseline / higher baseline)	p-value	(lower ratio / higher ratio)	p-value
CRP	15.5 / 10.6	**<0.001**	18.3 / 12.6	0.118
IL-6	15.1 / 11.1	**0.031**	12.8 / 14.8	0.763
IL-8	13.8 / 12.9	0.266	15.6 / 10.0	**0.029**

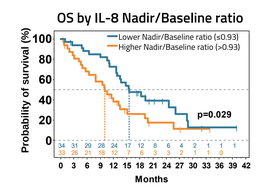


Figure 8: *OS per subgroup of lower/higher baseline and lower/higher nadir/baseline ratio for the indicated biomarkers; nadir refers to lowest post-baseline value within first 50 days. Subgroups were divided per ≤median and >median values. Lower nadir/baseline ratios imply greater reductions of post-baseline values compared to baseline. Includes mITT with data after full dose. OS by IL-8 nadir/baseline ratio is plotted.*

- A greater decrease in IL-8 and a lower baseline of CRP and IL-6 correlated with prolonged OS.

Nadunolimab/GN decrease IL-1-related mediators involved in TME remodeling

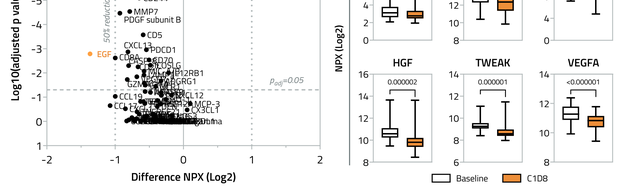


Figure 9: *Serum samples from baseline and 8 days after completion of first combined dose (C1D8) were analyzed by PLA with the Olink 92-protein immuno-oncology panel. Several cytokines and IL-1-related mediators involved in TME remodeling were decreased by treatment (highlighted, shown in box plots).*

Conclusions

- **The anti-IL1RAP antibody nadunolimab combined with gemcitabine/nab-paclitaxel (GN) shows promising overall efficacy in first-line PDAC: median OS: 12.9 months; median iPFS: 7.2 months; 1-year survival: 58%; iORR: 33%**
- **High IL1RAP expression is associated with deeper and more durable responses to nadunolimab/GN; IL1RAP High vs IL1RAP Low patients have:**
  - **median OS: 14.2 vs 10.6 months**
  - **median iPFS: 8 vs 5.8 months**
  - **1-year survival: 69 vs 40%**
  - **iORR: 52 vs 32%**
- **Nadunolimab/GN reduce IL-1-related mediators involved in TME remodeling, and a greater reduction in IL-8 correlates with prolonged OS**

These data strongly suggest that target engagement by nadunolimab is crucial for the efficacy of nadunolimab/GN

Nadunolimab is evaluated in PDAC, TNBC and NSCLC in combination with chemo-therapy; a phase II/III trial of nadunolimab/GN in first-line PDAC is in preparation

References

[1] The Cancer Genome Atlas (TCGA) database
[2] GTEx Portal
[3] Van Cutsem et al, J Clin Oncol (2022)
[4] Paulus et al, J Clin Oncol (2022)

Acknowledgements

We would like to thank the patients and their families for participating in the study, and all study staff at the clinical sites.

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