Interleukin-1 Receptor Accessory Protein (IL1RAP) Overexpression is Associated with Worse Prognosis in PDAC and is Targetable by Nadunolimab

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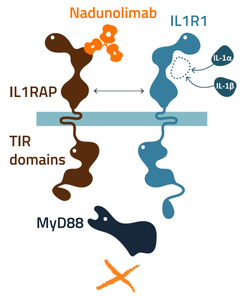
Background

- Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer cells and stromal cells in pancreatic ductal adenocarcinoma (PDAC), where high tumor IL1RAP mRNA expression is a negative prognostic marker[1].
- IL-1 receptor 1 (IL1R1) dimerization with IL1RAP is required for IL-1α/IL-1β signaling. 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.



- 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.
- Nadunolimab has potent effects in preclinical models of the PDAC TME with strong effects on tumor cells, cancer-associated fibroblasts (CAF) 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 efficacy compared to reported values for GN alone, in particular in patients with high tumor baseline expression of IL1RAP[2].

The present analyses investigate the relevance of IL1RAP in PDAC disease severity as well as the therapeutic efficacy of nadunolimab in relation to IL1RAP expression.

CANFOUR study design

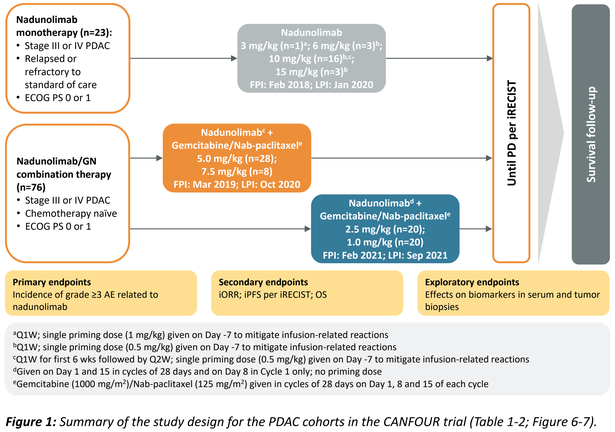
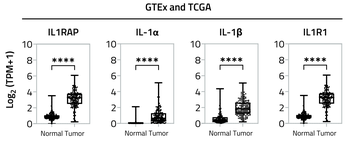


Figure 1: *Summary of the study design for the PDAC cohorts in the CANFOUR trial (Table 1-2; Figure 6-7).*

Results

IL1RAP is upregulated in late-stage pancreatic cancer and its expression correlates with poor survival



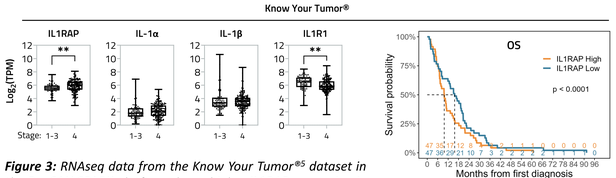


Figure 2: *RNAseq data from normal pancreas and pancreatic cancer samples from the publicly available databases GTEx[3] and TCGA[4] shows upregulation of IL1RAP, IL-1α, IL-1ß and IL1R1 mRNA in pancreatic tumors.*

Figure 3: *RNAseq data from the Know Your Tumor®[5] dataset in the PanCAN SPARK platform shows higher IL1RAP expression in late-stage pancreatic cancer. Survival analyses of pancreatic cancer patients with metastatic disease at first diagnosis show worse outcome with higher tumor IL1RAP mRNA expression.*

High IL1RAP expression correlates with oncogenic KRAS driver mutations

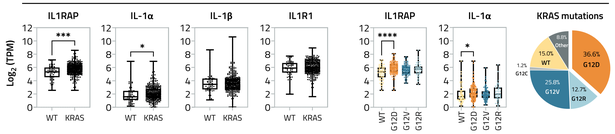


Figure 4: *KRAS mutation status and mRNA expression data from the Know Your Tumor® dataset shows that presence of KRAS mutations, in particular G12D, the most frequent KRAS mutation, correlates with increased expression of IL1RAP and IL-1α.*

IL1RAP is expressed by tumor cells, myeloid cells and fibroblasts

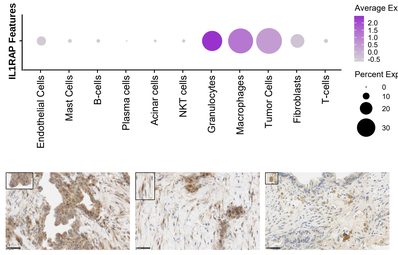
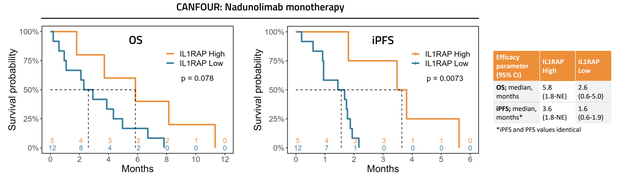


Figure 5: *Single-cell RNA sequencing of tumors from PDAC patients (n=16; upper panel; derived from Steele et al[6]) shows IL1RAP mainly expressed by granulocytes, macrophages, tumor cells and fibroblasts in the TME. Immunohistochemistry (IHC) of PDAC tumor biopsies (lower panel) shows IL1RAP-positive tumor cells (left), CAF (center) and macrophages (right).*

CANFOUR: High tumor baseline IL1RAP level correlates with increased benefit on nadunolimab monotherapy in late-stage PDAC

Table 1: *Baseline characteristics of relapsed/refractory patients treated with nadunolimab monotherapy, or first-line patients with nadunolimab/GN, in the CANFOUR study. Only patients with tumor biopsies available for analysis of baseline IL1RAP expression are shown.*

	CANFOUR: Nadunolimab monotherapy		**CANFOUR:** Nadunolimab/GN	
	IL1RAP High (n=5)	IL1RAP Low (n=12)	IL1RAP High (n=29)	IL1RAP Low (n=20)
Age (years); mean (range)	64 (61-65)	63 (40-81)	63 (43-87)	66 (46-89)
Sex (female/male); n (%)	1 (20)/4 (80)	4 (33)/8 (67)	14 (48)/15 (52)	6 (30)/14 (70)
ECOG 0/1; n (%)	2 (40)/3 (60)	4 (33)/8 (67)	11 (38)/18 (62)	9 (45)/11 (55)
Location of metastases at study entry; n (%)				
Liver	3 (60)	10 (83)	20 (69)	12 (60)
Lymph node	3 (60)	3 (25)	15 (52)	8 (40)
Other sites	2 (40)	7 (58)	17 (59)	12 (60)



Efficacy parameter (95% CI)	IL1RAP High	IL1RAP Low
OS; median, months	5.8 (1.8-NE)	2.6 (0.6-5.0)
iPFS; median, months*	3.6 (1.8-NE)	1.6 (0.6-1.9)

*iPFS and PFS values identical

Figure 6: *Screening biopsies from 17 late-stage PDAC patients treated with nadunolimab monotherapy in the CANFOUR study were stained for IL1RAP by IHC. Tumors with >50% moderate (2+) or strong (3+) staining of tumor cells were classified as IL1RAP high. These patients had a longer OS (left) and iPFS (right).*

CANFOUR: First-line nadunolimab/GN shows promising efficacy in PDAC with the strongest clinical benefit in IL1RAP high patients

Table 2: *Efficacy in patients treated with nadunolimab/GN in the CANFOUR study.*

Efficacy parameter (95% CI)	mITT (n=73)	Biopsy subgroup (n=49)	IL1RAP High (n=29)	IL1RAP Low (n=20)
OS; median, months	13.2 (10.6-15.5)	12.6 (9.5-17.5)	14.2 (10.0-28.7)	10.6 (4.8-12.6)
iPFS; median, months	7.2 (5.2-8.5)	7.2 (3.9-8.9)	7.4 (3.7-11.2)	5.8 (2.7-7.4)
1-year survival	58% (45%-69%)	56% (40%-69%)	67% (46%-81%)	39% (18%-60%)
iORR	33% (22%-45%)	41% (27%-56%)	48% (29%-67%)	30% (12%-54%)
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

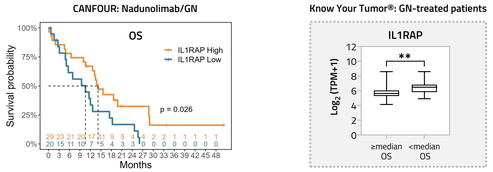


Figure 7: *OS for IL1RAP high and IL1RAP low first-line PDAC patients treated with nadunolimab/GN in CANFOUR (left). In the Know Your Tumor® dataset, GN-treated PDAC patients were divided on median OS and patients with <median OS had higher IL1RAP mRNA compared to patients with ≥median OS (right).*

CANFOUR: Durable benefit of nadunolimab/GN in IL1RAP high PDAC

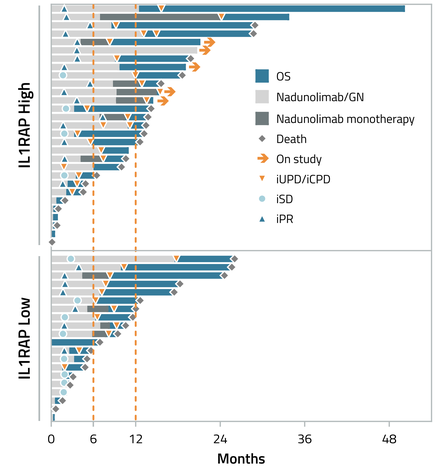


Figure 8: *Treatment course for IL1RAP high and IL1RAP low patients treated with nadunolimab/ GN in CANFOUR. Five patients remain on study; patients are followed until 36 months after end of treatment.*

Conclusions

- **IL1RAP is upregulated in pancreatic cancer, its expression correlates with oncogenic KRAS driver mutations and is strongly associated with poor survival**
- **The anti-IL1RAP antibody nadunolimab combined with gemcitabine/nab-paclitaxel shows promising overall efficacy in first-line PDAC; median OS: 13.2 months; median iPFS: 7.2 months; 1-year survival: 58%; iORR: 33%**
- **High tumor baseline IL1RAP level is associated with clinical benefit from treatment with nadunolimab/GN as well as nadunolimab monotherapy**
- **These data strongly suggest that IL1RAP is a highly relevant protein in PDAC that can be targeted using nadunolimab, a first-in-class anti-IL1RAP antibody**

References

[1] Zhang et al, J Hematol Oncol (2022)
[2] Van Cutsem et al, Cancer Res (2023)
[3] https://gtexportal.org/home/
[4] https://www.cancer.gov/tcga
[5] Pancreatic Cancer Action Network (PanCAN)®
[6] Steele et al, Nat Cancer (2020)

Acknowledgements

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