#B091

Interleukin-1 Receptor Accessory Protein (IL1RAP) Overexpression is Associated with Worse Outcome in PDAC and can be Reversed by Nadunolimab Treatment

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Background

- **Interleukin-1 Receptor Accessory Protein (IL1RAP)** is a co-receptor for IL-1 receptor mediated signaling, shown to be involved in tumor growth, chemoresistance and immune suppression. IL1RAP has a strong connection to pancreatic ductal adenocarcinoma (PDAC) where it is expressed on tumor cells, myeloid cells and fibroblasts of the tumor microenvironment. High IL1RAP mRNA expression strongly correlates to shorter overall survival[1-2]. IL-1 related inflammation and high IL1RAP mRNA levels have been shown to correlate with oncogenic KRAS driver mutations, in particular KRAS G12D.[3]

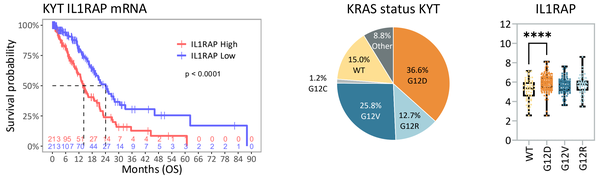


Figure 1: RNAseq data from the Know Your Tumor™ (KYT) database show that high IL1RAP mRNA expression correlates with shorter survival in PDAC[2] (left) and that presence of KRAS mutations, particular G12D, correlate with higher mRNA levels of IL1RAP (right).[3]

- **Nadunolimab** is a fully humanized, ADCC-enhanced, IgG1 anti-IL1RAP antibody that targets IL1RAP and disrupts IL-1 signaling. Nadunolimab was investigated for treatment of locally advanced/metastatic PDAC in combination with gemcitabine/nab-paclitaxel (GN) in the phase I/IIa CANFOUR trial (NCT03267316). Although IL1RAP mRNA correlates to worse prognosis in PDAC, patients with high tumor cell protein expression of IL1RAP at baseline showed the best responses and longest OS (14.2 vs 10.6 months), indicating that IL1RAP is targetable by nadunolimab.[4]

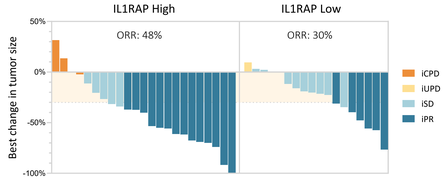


Figure 2: High baseline tumor cell expression of IL1RAP correlates with higher response rate and deeper responses in PDAC patients treated with nadunolimab + GN (IL1RAP High: H-score ≥ 150).[4]

- The Danish **BIOPAC** biobank (NCT03311776) is a multicentered biomarker study with prospective collection of biological material and clinical data from patients with pancreatic cancer to enable basic, clinical and translational research. All patients included are >18 years with a verified pancreatic cancer.

Study objectives

Patients with high tumor cell expression of IL1RAP had the longest survival in the CANFOUR study, where first line metastatic PDAC patients were treated with nadunolimab + GN. The aim of the present study was to investigate if tumor cell expression of IL1RAP affected response to treatment with only GN in a matching cohort of PDAC patients. KRAS mutation status were also investigated to study a possible link between KRAS and IL1RAP.

References

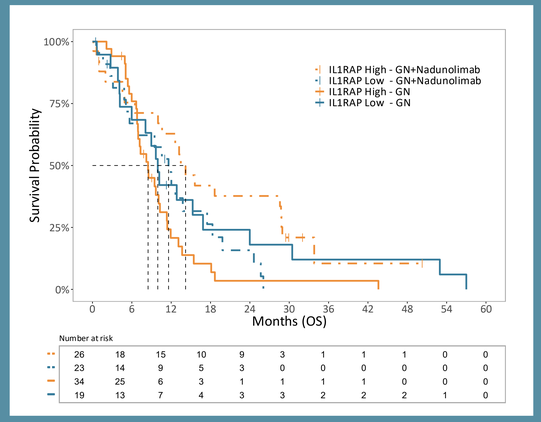
[1] Zhang et al, J Hematol Oncol (2022)
[2] Hansen et al, JITC (2024)
[3] Van Cutsem et al, AACR special conference (2023)
[4] Van Cutsem, Clin Cancer Res (2024)

Acknowledgements

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

High IL1RAP levels on tumor cells predicts poor survival in PDAC

IL1RAP is targetable – nadunolimab reverses the poor prognosis of high IL1RAP expression



Patients with high IL1RAP expression have longer OS compared to patients with low expression when treated with nadunolimab/GN (CANFOUR, 14.2 vs 11.6 months) in contrast to patients treated with GN alone (BIOPAC, 8.5 vs 10.0 months)

Results

Tabel 1: Efficacy and patient demographics of PDAC patients treated with GN (BIOPAC) or nadunolimab/GN (CANFOUR)

	BIOPAC			CANFOUR		
	All (n=53)	IL1RAP High (n=34)	IL1RAP Low (n=19)	All (n=49)	IL1RAP High (n=26)	IL1RAP Low (n=23)
Efficacy parameter (95% CI)						
OS; median, months	9.0 (7.2-11.3)	8.5 (6.8-10.3)	10.0 (4.2-16.9)	12.6 (10.0-18.3)	14.2 (6.6-28.7)	11.6 (5.1-17.5)
PFS; median, months	5.3 (5.0-7.6)	5.3 (4.4-6.2)	7.6 (2.0-9.6)	5.8 (3.8-8.5)	7.4 (3.7-12.9)	5.6 (1.9-7.4)
1-year survival	28.7% (18.4-44.7)	20.8% (10.3-41.8)	42.1% (24.9-71.3)	55.8% (43.0-72.4)	62.8% (46.2-85.4)	47.4% (30.0-74.7)
2-years survival	8.8% (3.5-22.3)	3.5% (0.5-23.6)	18.1% (6.6-49.3)	27.9% (17.3-45.0)	37.7% (22.5-63.1)	15.8% (5.6-44.2)
Baseline characteristics						
Age	66 (46-79)	65 (46-74)	67 (54-79)	65 (43-89)	64 (43-87)	66 (46-89)
Female/Male, n (%)	23 (43) / 30 (57)	19 (56) / 15 (44)	11 (58) / 8 (42)	20 (40) / 29 (58)	13 (50) / 13 (50)	7 (30) / 16 (70)
ECOG PS 0 or 1, n (%)	28 (53) / 25 (47)	16 (47) / 18 (53)	12 (63) / 7 (37)	20 (40) / 29 (58)	9 (35) / 17 (65)	11 (48) / 12 (52)

IL1RAP High: H-score ≥ 190; IL1RAP Low: H-score <190

Results

Tumor cell L1RAP protein is differentially expressed at baseline in PDAC patients

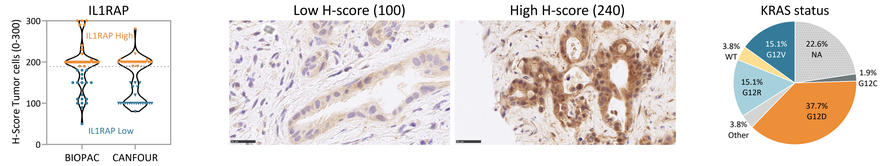


Figure 3: Pre-treatment biopsies from 53 metastatic PDAC patients treated with GN as first line therapy (BIOPAC) were stained for IL1RAP using immunohistochemistry and tumor cell expression of IL1RAP was scored by H-score. The data were compared to a previous analysis of 49 first-line metastatic PDAC patients treated with nadunolimab/GN (CANFOUR). To generate comparable datasets, IL1RAP High was defined as ≥190 and IL1RAP Low as <190 for these analyses (left and middle panels). KRAS mutation status was sequenced from tumor tissue of pre-treatment biopsies from PDAC patients treated with GN (BIOPAC) using Oncomine™ Focus DNA Assay including KRAS gene exon 2, 3, and 4 (codon 1-37, 38-73, and 109-150). KRAS mutation status was obtained from 41 biopsies. Not enough DNA was obtained from 12 of the biopsies and their KRAS status could therefore not be evaluated (NA) (right).

High IL1RAP protein expression at baseline predicts poor survival in PDAC patients treated with GN as first line

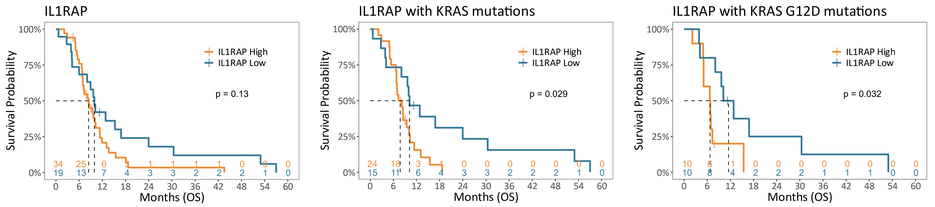


Figure 4: 53 pre-treatment biopsies from metastatic PDAC patients treated with GN as first line therapy (BIOPAC) were stained for IL1RAP using immunohistochemistry and tumor cell expression of IL1RAP was scored by H-score. Shorter OS was observed in patients with a high tumor cell expression of IL1RAP (8.7 months) compared to patients with a low IL1RAP expression (10.0 months). High IL1RAP expression predicts poor survival also in KRAS mutated tumors (IL1RAP High 7.8 vs IL1RAP Low 10.2 months), including G12D mutated tumors (6.7 vs 11.5 months).

Conclusions

- **High tumor cell protein expression of IL1RAP shows a trend towards an association with poor survival in PDAC patients treated with GN.**
- **The elevated expression and prognostic significance of IL1RAP in KRAS mutated tumors underscores the role of IL1RAP as an independent prognostic marker within this subset.**
- **IL1RAP high tumor cell expression correlates with better response to nadunolimab/GN treatment in the CANFOUR study.**
- **These data collectively suggest that IL1RAP is highly relevant in PDAC and can be meaningfully targeted by nadunolimab.**

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