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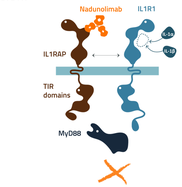
# Nadunolimab, a first in class monoclonal antibody against IL1RAP, in advanced pancreatic cancer

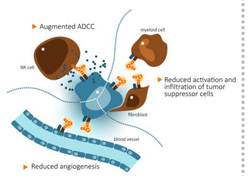
Eric Van Cutsem[1]; Sebastian Ochsenreither[2]; Joelle Collignon[3]; Rikke Eefsen[4]; Audrius Ivanauskas[5]; Camilla Rydberg Millrud[6]; Nedjad Losic[6]; Dominique Tresago[6]

[1]University Hospital Gasthuisberg, Leuven and KULeuven, Leuven, Belgium; [2]Charité Comprehensive Cancer Center/Charité, Department of Hematology, Oncology and Tumor Immunology/German Cancer Consortium (DKTK), Berlin, Germany; [3]CHU de Liège, Liège, Belgium; [4]Herlev og Gentofte Hospital, Herlev, Denmark; [5]The Hospital of Lithuania University of Health Science, Kaunas, Lithuania; [6]Cantargia AB, Lund, Sweden

## Background

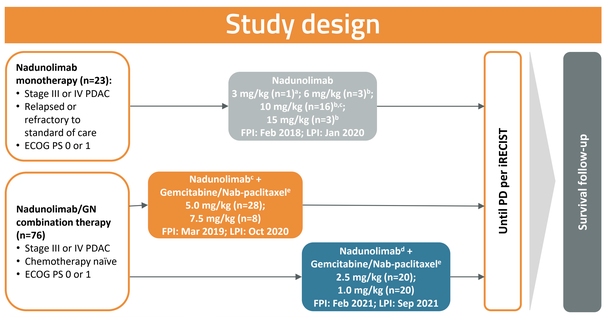
- Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer cells and stromal cells in pancreatic ductal adenocarcinoma (PDAC), where high tumor IL1RAP mRNA expression is a negative prognostic marker[1].
- IL-1 receptor 1 (IL1R1) dimerization with IL1RAP is required for IL-1α/IL-1β signaling. 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.
- KRAS mutations are key drivers of PDAC. They initiate and maintain an inflammatory loop in the pancreatic TME, involving IL-1 signaling[2-3].
- IL-1 cytokines are also involved in chemotherapy induced peripheral neuropathy (CIPN), one of the major nonhematological adverse events arising from chemotherapies. CIPN is a neuroinflammatory condition, with nerve cell damage, immune cell activation and IL-1 release as significant drivers[4-7].
- 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 was investigated for treatment of locally advanced/metastatic PDAC in combination with gemcitabine/nab-paclitaxel (GN) in the phase I/IIa CANFOUR trial (NCT03267316).




**The present analyses investigate the relevance of targeting IL1RAP in PDAC for both therapeutic efficacy of nadunolimab and for potential effects on chemotherapy induced periphery neuropathy.**

## Study design




[a]Q1W; single priming dose (1 mg/kg) given on Day -7 to mitigate infusion-related reactions
[b]Q1W; single priming dose (0.5 mg/kg) given on Day -7 to mitigate infusion-related reactions
[c]Q1W for first 6 wks followed by Q2W; single priming dose (0.5 mg/kg) given on Day -7 to mitigate infusion-related reactions
[d]Given on Day 1 and 15 in cycles of 28 days and on Day 8 in Cycle 1 only; no priming dose
[e]Gemcitabine (1000 mg/m²)/Nab-paclitaxel (125 mg/m²) given in cycles of 28 days on Day 1, 8 and 15 of each cycle

**Table 1:** Patient demographics and disease characteristics at study start.

| | mITT* (n=73) | IL1RAP High (n=29) | IL1RAP Low (n=20) |
|---|---|---|---|
| **Age (years);** mean (range) | 63 (43-89) | 63 (43-87) | 66 (46-89) |
| **Sex (female/male);** n (%) | 30 (41%) / 43 (59%) | 14 (48%)/15 (52%) | 6 (30%)/14 (70%) |
| **ECOG 0/1;** n (%) | 32 (44%) / 41 (56%) | 11 (38%)/18 (62%) | 9 (45%)/11 (55%) |
| **Location of metastases at study start;** n (%) | | | |
| Liver | 47 (64%) | 20 (69%) | 12 (60%) |
| Lymph node | 38 (52%) | 15 (52%) | 8 (40%) |
| Other sites | 44 (60%) | 17 (59%) | 12 (60%) |

**76 patients were included in the study, three did not receive chemotherapy due to consent withdrawal (n=2) or clinical deterioration (n=1) and therefore not included in the modified intention-to-treat (mITT) population (n=73)*

## Results

### The IL1RAP dependent cytokine IL-1α is expressed at higher levels in KRAS mutated PDAC

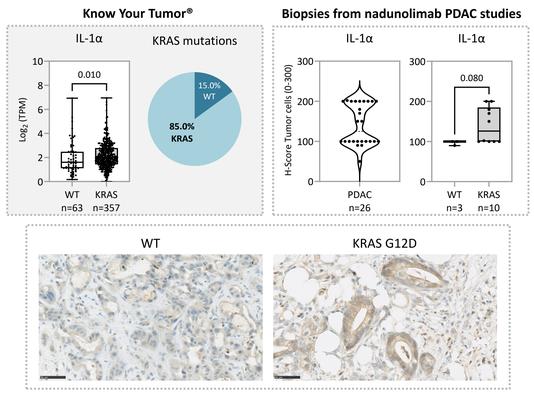



**Figure 1:** KRAS mutation status and IL-1α mRNA expression data from the Know Your Tumor®[8] dataset show that presence of KRAS mutation correlates with high IL-1α mRNA expression (upper left), especially G12D. Screening biopsies from the nadunolimab PDAC studies measuring protein expression of IL-1α show higher levels of IL-1α in KRAS mutated tumors (upper right). Representative images of IL-1α staining in wild type (WT) and KRAS G12D mutated PDAC biopsies (lower).

### Targeting IL1RAP in PDAC shows promising efficacy, and high IL1RAP expression correlates with clinical benefit

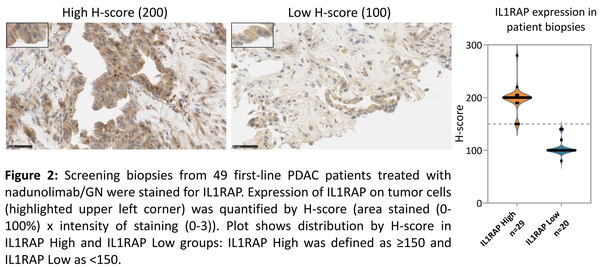



**Figure 2:** Screening biopsies from 49 first-line PDAC patients treated with nadunolimab/GN were stained for IL1RAP. Expression of IL1RAP on tumor cells (highlighted upper left corner) was quantified by H-score (area stained (0-100%) x intensity of staining (0-3)). Plot shows distribution by H-score in IL1RAP High and IL1RAP Low groups: IL1RAP High was defined as ≥150 and IL1RAP Low as <150.

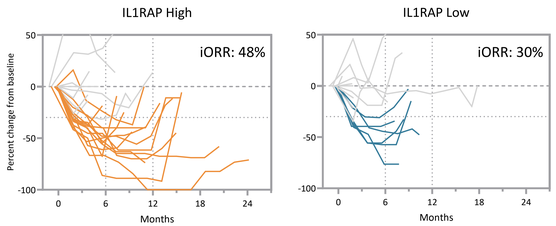



**Figure 3:** Tumor change (%) over time compared to baseline in IL1RAP High (left) and IL1RAP Low (right) subgroups. Orange and blue curves represent confirmed responders, and grey non-responders.

### Longer survival in IL1RAP High patients treated with nadunolimab/GN

**Table 2:** Efficacy parameters in patients treated with nadunolimab/GN.

| Efficacy parameter (95% CI) | mITT (n=73) | IL1RAP High (n=29) | IL1RAP Low (n=20) |
|---|---|---|---|
| **OS;** median, months | 13.2 (10.6-15.5) | 14.2 (10.0-28.7) | 10.6 (4.8-12.6) |
| **iPFS;** median, months | 7.2 (5.2-8.5) | 7.4 (3.7-11.2) | 5.8 (2.7-7.4) |
| **1-year survival** | 58% (45%-69%) | 67% (46%-81%) | 39% (18%-60%) |
| **iORR** | 33% (22%-45%) | 48% (29%-67%) | 30% (12%-54%) |
| **iDoR;** median, months | 7.3 (5.5-11.0 ) | 9.5 (3.7-11.8) | 5.6 (3.9-NE*) |

**NE; not estimable*

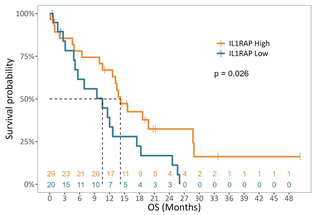



**Figure 4:** Median OS of 13.2 months was observed in mITT patients. Significantly longer OS was observed in the IL1RAP High subgroup (14.2 months) compared to the IL1RAP Low subgroup (10.6 months).

### Longer disease control on single agent treatment with nadunolimab after nadunolimab/GN in IL1RAP High patients

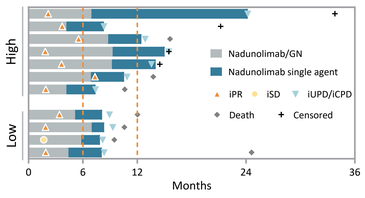



**Figure 5:** 11 patients continued with nadunolimab single-agent use after nadunolimab/GN. Median disease control on single agent treatment was significantly longer for IL1RAP High vs IL1RAP Low patients (3.7 vs 1.8 months; p = 0.011). OS was also longer in IL1RAP High patients (median 15.6 vs. 11.3 months; p=0.09).

### Late-stage IL1RAP High PDAC patients treated with nadunolimab monotherapy show increased benefit (separate cohort)

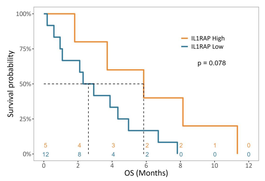



**Figure 6:** Longer OS was observed in the IL1RAP High subgroup (5.8 months) compared to the IL1RAP Low subgroups (2.6 months) (biopsies available for 17 of 23 patients) in the separate monotherapy arm with patients who had relapsed or refractory PDAC without any further treatment options. 8 patients (47%) had received 1 prior line and 9 (53%) 2-5 prior lines of therapy.

### Low incidence of grade 3-4 neuropathy with nadunolimab/GN

**Table 3:** Most common treatment-emergent adverse events, grade 3-4 >10%

| TEAE; n (%) | Grade 3-4 (n=76) | All grade (n=76) |
|---|---|---|
| Neutropenia | 50 (66%) | 58 (76%) |
| Leukopenia/WBC decreased | 18 (24%) | 22 (29%) |
| Thrombocytopenia | 10 (13%) | 30 (40%) |
| Anemia | 10 (13%) | 39 (51%) |
| Febrile neutropenia | 10 (13%) | 10 (13%) |
| GGT increased | 13 (17%) | 17 (22%) |
| **Peripheral neuropathy*** | **1 (1%)** | **31 (42%)** |

**Definition peripheral neuropathy: All AEs that coded to MedDRA high level group term of Peripheral neuropathies plus preferred term Paraesthesia.*

- Only one Grade 3 TEAE of peripheral neuropathy was observed.
- Neutropenia was the most frequently observed TEAE, mainly seen in Cycle 1, which can be controlled with addition of G-CSF.

### Higher nadunolimab doses correlate with lower any-grade chemotherapy induced peripheral neuropathy

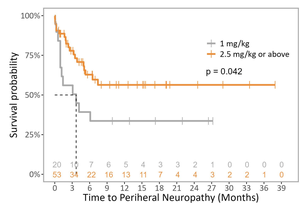



**Figure 7:** Dose groups 2.5-7.5 mg/kg were pooled and compared to the 1 mg/kg dose group. Higher doses of nadunolimab showed a lower incidence of any-grade peripheral neuropathy (36% vs 60%; p=0.06) as well as a longer time to onset (p=0.04). Chemotherapy doses given were comparable between the dose groups. Baseline characteristics for patients in neuropathy subgroups are similar to the overall population.

## Conclusions

- KRAS mutated PDAC tumors have an inflammatory phenotype with upregulation of IL-1α.
- Nadunolimab, an anti-IL1RAP mAb, shows promising efficacy in metastatic PDAC, with strongest effect in patients with high tumor IL1RAP levels at baseline:
  - Patients treated with nadunolimab in combination with GN
  - Patients treated with nadunolimab as single agent after chemotherapy combination
  - Late-stage patients treated with nadunolimab monotherapy
- Peripheral neuropathy with nadunolimab/GN is lower than expected. Higher doses of nadunolimab correlate with a lower incidence of any-grade neuropathy and longer time to onset.
- **Data suggest that nadunolimab provides substantial clinical benefit in PDAC, particularly in patients with high IL1RAP-expressing tumors, and confer a protective effect against chemotherapy induced peripheral neuropathy.**

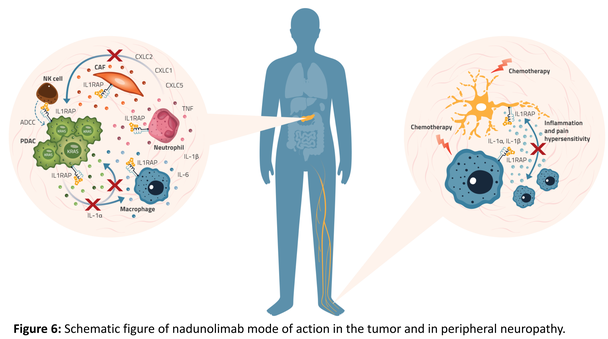



**Figure 6:** Schematic figure of nadunolimab mode of action in the tumor and in peripheral neuropathy.

## References

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