309

Adding nadunolimab to chemotherapy or antibody drug-conjugates (ADCs) may improve anti-tumor efficacy and counteract peripheral neuropathy

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Introduction

Nadunolimab, a fully humanized ADCC-enhanced monoclonal IgG1 antibody, targets IL-1 receptor accessory protein (IL1RAP) and blocks IL-1 signaling. In clinical studies, nadunolimab has shown good safety and promising efficacy with standard chemotherapies.

In advanced pancreatic ductal carcinoma (PDAC) patients in the CANFOUR trial, combination with nab-paclitaxel and gemcitabine showed 33% ORR, 13.2 months OS, and 28.3% survival rate at 24 months, with best response in the group expressing high levels of IL1RAP protein with 48% ORR, 14.2 months OS, and 35% 24 months survival rate.

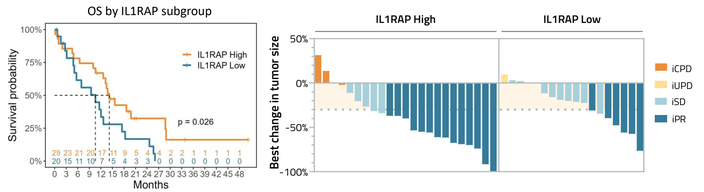


Figure 1. Screening tumor biopsies from 49 patients were grouped based on IL1RAP expression on tumor cells; IL1RAP High and IL1RAP Low. Best response for the IL1RAP high and IL1RAP low subgroups evaluated according to iRECIST criteria.

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious side effect of several chemotherapies like taxanes and oxaliplatin, often seen in over 60% of patients. CIPN can lead to dose reduction or cessation of treatment, impacting on survival. It is a neuroinflammatory condition that limits treatment and severely impairs quality of life, and is driven by nerve damage, immune activation, and cytokine release such as IL-1.

Beyond the anti-tumor efficacy, treatment with nadunolimab significantly delayed onset and reduced incidence of nab-paclitaxel/gemcitabine-related CIPN. CIPN was lower than expected in the total population, only 1 grade 3 neuropathy in 73 patients, and any grade CIPN was reported in 30% of patients receiving higher doses of nadunolimab as compared to 60% of patients who in the lowest dose group.

Gemcitabine/Nab-Paclitaxel

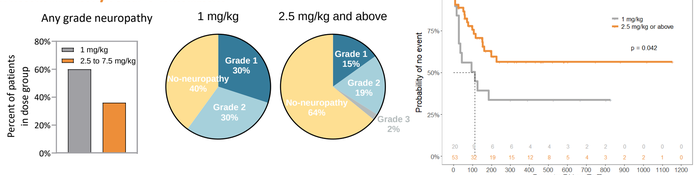
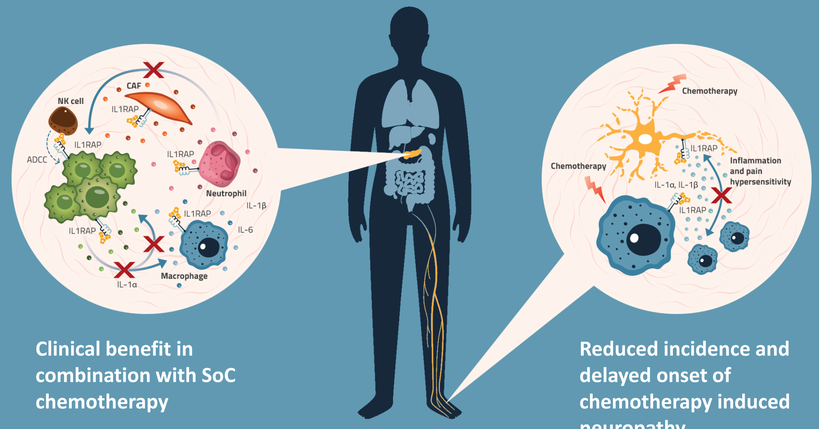


Figure 2. Percentage of patients in each dose group who had a neuropathy of any grade. Dose groups 2.5-7.5 mg/kg nadunolimab were pooled and compared to the 1 mg/kg nadunolimab dose group. Chemotherapy doses given were comparable between the dose groups. Nadunolimab was initially given on days 1, 8, 15, and 22 in cycle 1 and on days 1 and 15 from cycle 2 onward, whereas gemcitabine and nab-paclitaxel were given on days 1, 8, and 15 in cycles of 28 days.

Aim

Building on these promising findings, our aim was to further investigate nadunolimab's potential in mitigating chemotherapy associated neuropathies. Therefore, the incidence and onset of neuropathy in the oxaliplatin-containing chemotherapy arms of the CESTAFOUR (NCT05116891) and CAPAFOUR (NCT04990037) trials were investigated. The primary endpoint of the studies was safety. In addition, using preclinical models, we aimed to generate supportive and mechanistic insights into the role of nadunolimab in counteracting CIPN and its potential for expansion into prevention of ADC payload mediated neuropathies.

Nadunolimab shows promising neuroprotective effect in addition to anti-tumor efficacy in patients with solid tumor indications



Clinical benefit in combination with SoC chemotherapy

Reduced incidence and delayed onset of chemotherapy induced neuropathy

Preclinical data

Chemotherapy induces expression of IL-1 family members

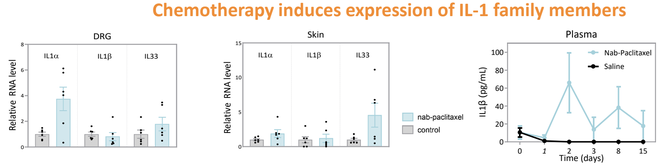


Figure 3. Nab-paclitaxel treatment induces mRNA expression of IL1 and IL33 in dorsal root ganglion (DRG) and skin, and IL1β in plasma, analyzed with qPCR and multiplex immunoassay Legend-Plex.

A nadunolimab surrogate counteracts neuropathy from chemotherapy and ADC payloads

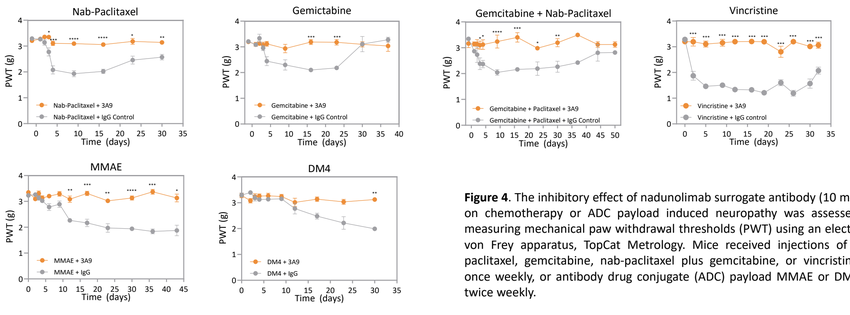


Figure 4. The inhibitory effect of nadunolimab surrogate antibody (10 mg/kg) on chemotherapy or ADC payload induced neuropathy was assessed by measuring mechanical paw withdrawal thresholds (PWT) using an electronic von Frey apparatus, TopCat Metrology. Mice received injections of nab-paclitaxel, gemcitabine, nab-paclitaxel plus gemcitabine, or vincristine i.p once weekly, or antibody drug conjugate (ADC) payload MMAE or DM4 i.p twice weekly.

Clinical data

Association of higher nadunolimab dose with reduced and delayed CIPN in the CESTAFOUR trial

- Patients with locally advanced or metastatic solid tumor indications
- Combination with SoC mFOLFOX
- Maximum of 2 previous systemic treatments with cytotoxic chemotherapy allowed
- ECOG PS 0 or 1

→ nadunolimab + mFOLFOX 0.5 mg/kg (n=7); 1.0 mg/kg (n=7) → Treatment until PD → Survival follow-up

Table 1. Baseline characteristics CESTAFOUR

	0.5 mg/kg nadunolimab (n=7)	1.0 mg/kg nadunolimab (n=7)
Age; years (range)	61 (30-70)	62 (53-68)
Sex; Female/Male; n (%)	4 (57%) / 3 (43%)	2 (29%) / 5 (71%)
BMI	29 (26-30)	24 (17-27)
Diabetes; n (%)	2 (29%)	1 (14%)
Previous neuropathy; n (%)	3 (43%)	4 (57%)

Figure 5. The mFOLFOX arm of the CESTAFOUR trial included 14 patients treated with nadunolimab at 0.5 mg/kg (n=7) or 1.0 mg/kg (n=7) on day one of each two weeks cycle in combination with mFOLFOX given on day two of every cycle.

mFOLFOX

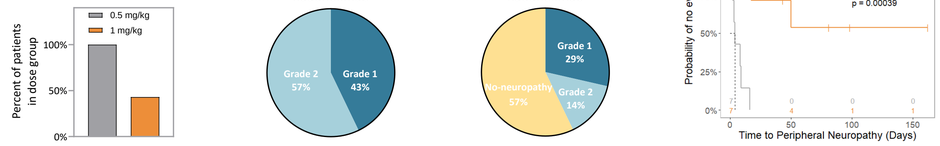


Figure 6. Graphs representing percent of patients with varying grades of neuropathy across both nadunolimab dose groups. Evaluation of time to the first reported neuropathy shows significant reduction in incidence and delayed onset among patients receiving 1.0 mg/kg nadunolimab.

Potential association of higher nadunolimab doses with reduced and delayed CIPN in the CAPAFOUR trial

- Patients with metastatic PDAC
- Combination therapy with SoC mFOLFIRINOX
- No previous treatment for metastatic disease
- ECOG PS 0 or 1

→ nadunolimab + mFOLFIRINOX 0.5 mg/kg (n=8); 1.0 mg/kg (n=3); 1.5 mg/kg (n=4); 2.5 mg/kg (n=3) → Treatment until PD → Survival follow-up

Table 2. Baseline characteristics CAPAFOUR

	0.5 + 1 mg/kg nadunolimab	1.5 + 2.5 mg/kg nadunolimab
Age; years (range)	63 (60-74)	61 (41-77)
Sex; Female/Male; n (%)	7 (64%) / 4 (36%)	5 (71%) / 2 (29%)
BMI	22 (18-28)	23 (18-34)
Diabetes; n (%)	4 (36%)	2 (29%)
Previous Neuropathy; n (%)	1 (9%)	0 (0%)

Figure 7. The CAPAFOUR trial included 18 PDAC patients treated with nadunolimab on day one of every two weeks cycle at doses of 0.5 mg/kg (n=8), 1.0 mg/kg (n=3), 1.5 mg/kg (n=4), and 2.5 mg/kg (n=3) in combination with mFOLFIRINOX administered on day one or two.

mFOLFIRINOX

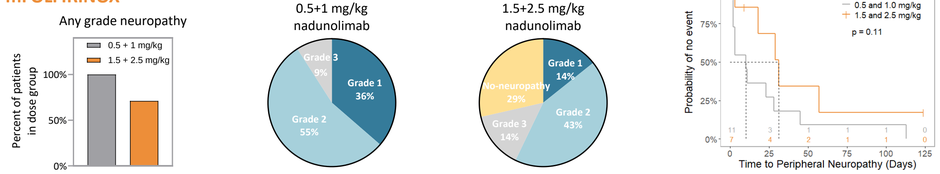


Figure 8. Graphs representing percent of patients with varying grades of neuropathy among nadunolimab low dose groups (0.5 and 1.0 mg/kg) and high dose groups (1.5 and 2.5mg/kg). Evaluation of time to the first reported neuropathy shows a trend towards reduction in incidence and delayed onset among patients receiving higher nadunolimab doses.

Conclusions

- The clinical findings support the association between lower incidence as well as later onset of oxaliplatin and nab-paclitaxel induced CIPN, and higher doses of nadunolimab.
- Nadunolimab mouse surrogate prevents both chemotherapy and payload induced neuropathy in preclinical models, supporting the clinical observations.
- Targeting IL1RAP by nadunolimab may combine antitumor activity with potent reduction of both chemotherapy and ADC payload induced neuropathies.

References:

1. Starobova et al; JEM 218(5), (2021)
2. Brandolini et al; Int. J. Mol. Sci. 20(12) (2019)
3. Klein et al; Toxics 9(10), (2021)
4. Domoto et al; Cells 10(8), (2021)

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