Updated safety, efficacy and emerging biomarker data from the Phase Ib part of a Phase Ib/II clinical study of nadunolimab in combination with gemcitabine and carboplatin in patients with advanced triple negative breast cancer (TRIFOUR study)

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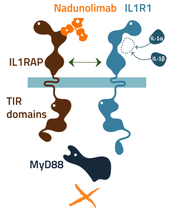
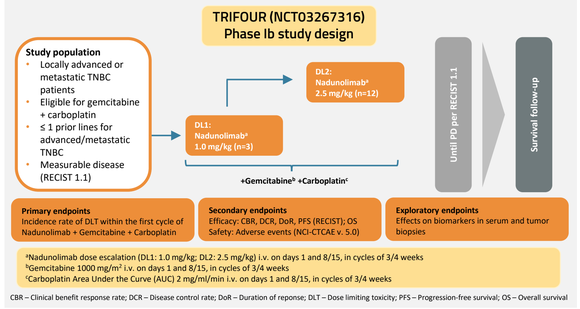
Background

Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer, stromal, and infiltrating immune cells within many solid tumors. Among breast cancer subtypes, triple-negative breast cancer (TNBC) has the highest IL1RAP expression[1]. IL1RAP plays a crucial role in promoting tumor growth via IL1α and IL1β[2].

Chemotherapy leads to upregulation of IL1α and IL1β[3-5] which contribute to tumor growth, chemoresistance, and immune suppression[6]. Thus, blockade of both IL1α/IL1β combined with chemotherapy is a promising approach for cancer treatment.

Nadunolimab, a fully humanized monoclonal IgG1 antibody, inhibits IL1 mediated tumor progression and chemoresistance by targeting IL1RAP to kill tumor cells via antibody-dependent cellular cytotoxicity (ADCC) while simultaneously blocking IL1α/IL1β signaling.



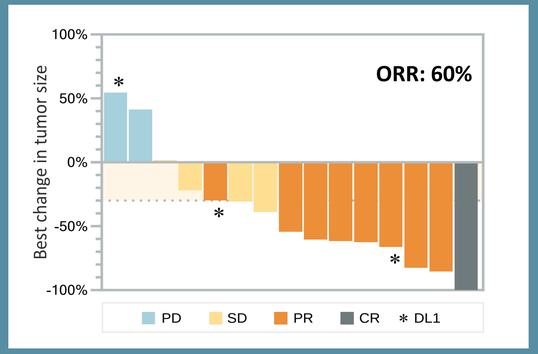


CBR – Clinical benefit response rate; DCR – Disease control rate; DoR – Duration of reponse; DLT – Dose limiting toxicity; PFS – Progression-free survival; OS – Overall survival

Patient Baseline Characteristics

	All patients (n=15)
Patient demographics	
Age (years); median (range)	50 (32-69)
Body mass index; median (range)	25 (17-32)
Menopausal status; Post/Pre; n (%)	10 (67) / 5 (33)
ECOG performance status; 0/1; n (%)	12 (80) / 3 (20)
Disease-free interval (years); median (range); n=14	1.9 (0.2-13.5)
Breast Cancer Characteristics	
Triple-negative; Y/N; n (%)	15 (100) / 0 (0)
Ki67 (%); median (range)	68 (10-90)
BRCA1/2; Positive/Negative/NA; n (%)	0 (0) / 6 (40) / 9 (60)
Tumor Characteristics	
Visceral lesions; Y/N; n(%)	14 (94) / 1 (6)
Metastatic locations; ≤ 3/ >3; n (%)	10 (67) / 5 (33)
Metastasis in liver; Y/N; n (%)	7 (47) / 8 (53)
Prior anti-cancer therapy	
Prior lines of treatment; None/1, n (%)	5 (33) / 10 (67)
Prior ICI in first line therapy; Y/N; n (%)	5 (33) / 10 (67)
Prior platinum agent in (neo)adjuvant treatment; Y/N; n (%)	4 (27) / 9 (73)

Initial results of nadunolimab combined with gemcitabine and carboplatin demonstrates acceptable safety, tolerability, and promising anti-tumor activity in advanced triple-negative breast cancer patients



Waterfall plot representing clinical responses of nadunolimab combined with gemcitabine and carboplatin in terms of best percent change in tumor size (sum of diameters) from baseline (PD – Progressive disease; SD – Stable disease; PR – Partial response; CR – Complete response; DL1 – Dose level 1).

IL1RAP in TNBC

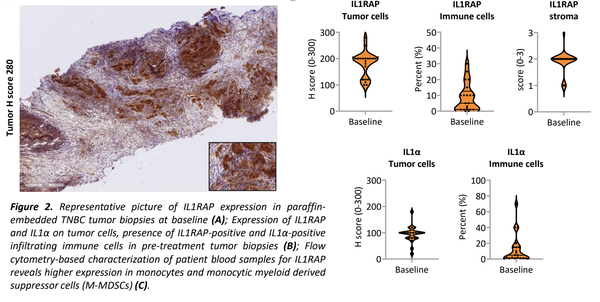


Figure 2. *Representative picture of IL1RAP expression in paraffin-embedded TNBC tumor biopsies at baseline* ***(A)****; Expression of IL1RAP and IL1α on tumor cells, presence of IL1RAP-positive and IL1α-positive infiltrating immune cells in pre-treatment tumor biopsies* ***(B)****; Flow cytometry-based characterization of patient blood samples for IL1RAP reveals higher expression in monocytes and monocytic myeloid derived suppressor cells (M-MDSCs)* ***(C)****.*

Results TRIFOUR Phase Ib

Safety and Efficacy

n (%)	All patients (n=15)	
Adverse event	**Grade ≥3**	**All grades**
Neutropenia	9 (60)	11 (73)
Thrombocytopenia	4 (27)	7 (47)
Anaemia	3 (20)	6 (40)
Febrile neutropenia	2 (13)	2 (13)
Diarrhoea	1 (7)	4 (27)
COVID-19	1 (7)	2 (13)
Hypomagnesaemia	1 (7)	2 (13)
Device-related infection	1 (7)	1 (7)
Hypocalcaemia	1 (7)	1 (7)
Procedural pmneumothorax	1 (7)	1 (7)

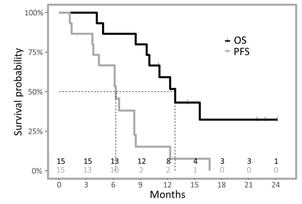


Figure 3. *All grades and grade 3 or higher treatment-emergent adverse events, n(%)* ***(A)****; Kaplan-Meier estimates for progression free survival (PFS) of 6.2 months and overall survival (OS) of 12.8 months* ***(B)***

On treatment biomarker expression and impact of IL8 reduction on overall survival

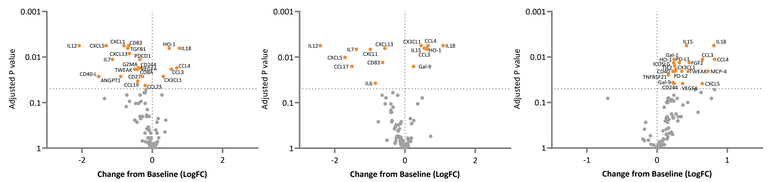


Figure 4. *Volcano plots represent the post-treatment changes in the expression of various biomarkers analyzed from patient serum samples using the Olink Immuno-oncology 92-plex protein panel at time points: cycle 1 day 8 (C1D8), cycle 1 day 15 (C1D15), and cycle 2 day 1 (C2D1).*

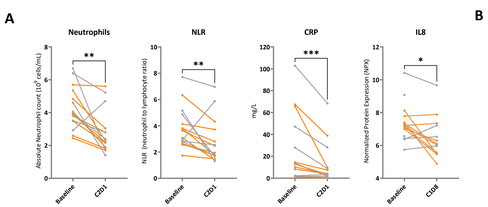
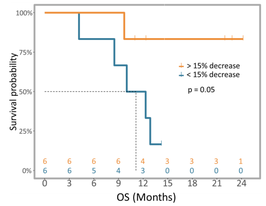


Figure 5. *Graphs show significant decrease in neutrophils, neutrophils to lymphocyte ratio (NLR), and C-reactive protein (CRP) at C2D1 and IL8 at C1D8 compared to baseline; responders in orange, non-responders in gray; * p<0.05, **p<0.01, ***p<0.001* ***(A)****; Kaplan-Meier curve with patients divided equally based on median change (15% decrease) from baseline depicts a trend that a greater decrease in IL8 during treatment is associated with a longer overall survival* ***(B)****.*



Conclusions

Nadunolimab combined with standard gemcitabine and carboplatin demonstrates acceptable safety, tolerability, and promising antitumor activity in advanced TNBC with

- **Overall response rate: 60%**
- **Median PFS: 6.2 months**
- **Median OS: 12.8 months**

Translational analyses of immune cell subsets and biomarkers indicate potential beneficial effects on inflammation and immune response.

The randomized phase II part of the TRIFOUR trial is currently enrolling patients at the 2.5 mg/kg dose of nadunolimab

References

[1] Zheng et al; Biomed Pharmacother (2018)
[2] Liu et al; Cancer Res (2018)
[3] Bruchard et al; Nat Med (2013)
[4] Chung et al; NPJ Breast Cancer (2022)
[5] Tjomsland et al; Neoplasia (2011)
[6] Zhang et al; Cancer Res (2018)

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