A surrogate to the anti-IL1RAP antibody nadunolimab induces tumor microenvironment changes to the metastatic lung and reduces metastatic lesions in mouse models of metastatic cancer

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Introduction

Interleukin-1 Receptor Accessory Protein (IL1RAP) is a co-receptor for the IL1 receptor (IL1R1) and is required for IL1α and IL1β signaling. IL1RAP is expressed in the tumor microenvironment (TME); on cancer cells, stromal cells and on infiltrating immune cells in several types of cancers, including non-small cell lung cancer (NSCLC), pancreatic cancer (PDAC), triple-negative breast cancer (TNBC) and metastatic lesions in these indications.

Nadunolimab (CAND4) is a fully humanized ADCC-enhanced IgG1 antibody targeting IL1RAP and blocking both IL1α and IL1β signaling. Nadunolimab is currently evaluated in combination with chemotherapy in phase I/II clinical trials in NSCLC and PDAC (NCT033267316) and in TNBC (NCT01581462). Interim efficacy data for PDAC and NSCLC show increased OS and PFS compared to that expected from chemotherapy alone based on historical controls. In 73 PDAC patients (modified intention to treat, miITT analysis set) the median IPS was 7.2 months and the median OS was 12.9 months, while in a total of 30 NSCLC patients (miITT analysis set) the overall response rate was 53%, with a median PFS of 6.8 months. Similarly, an initial analysis of the phase IIb part of the TNBC trial (n=12 patients) showed a favorable safety profile and a preliminary response rate of 50%, which compares favorably to the historical response rate of approximately 30% reported for chemotherapy alone.

Objectives

To assess the effects of the murine surrogate antibody to nadunolimab on the metastatic TME using the metastatic 4T1 murine TNBC and B16-F10-luc i.v. models.

Results

Treatment with the nadunolimab surrogate antibody reduces the metastatic burden in the murine 4T1 and B16-F10-luc i.v. models

Metastatic 4T1 TNBC model Metastatic B16 i.v model

Lung metastasis

Number of metastatic lesions

CCL3 ✱

CCL5 ✱

IL1RAP

VEGF ✱

Adhesion Pathway Score

Chemokine and Receptors Pathway Score

Macrophage function Pathway Score

IL1 expression

IL1RAP expression, IHC

IL1RAP expression, flow cytometry

IL1 expression

Conclusions

- Targeting IL1RAP reduces metastatic burden in different mouse models
- Myeloid cells infiltrating the lung metastatic TME express high levels of IL1RAP and targeting of IL1RAP reduces several IL-1 induced cytokines and chemokines both in vitro and in vivo
- Treatment with the nadunolimab surrogate antibody induces strong changes in the metastatic lung microenvironment, including changes in the infiltrating myeloid cells
- Collectively, these data indicate that the IL1RAP-targeting antibody nadunolimab may effectively modulate the TME and counteract the suppressive environment in metastatic tissue, thus reducing the potential for metastatic tumors in cancer patients

References

- *Nkaujpena et al. (2014)*
- *Angluin, Yano, Iritani, Tsubura (2016)*
- *Lucht, Cytokine Nature Immuno (2013)*

*Figure 1.* To assess the effect of the nadunolimab surrogate antibody (nadunolimab) on metastasis, we used the murine lung metastatic 4T1 and B16-F10-luc i.v. models. Balb/c mice were inoculated in the mammary fat pad injection with 4T1 and B16 cells and the number of metastatic lesions were assessed at day 20 by luciferase quantitation in lung and metastatic lesions to the lungs. Results (A) and inset the calculation of metastasis burden (B) shows that nadunolimab reduces the number of metastatic lesions. The bystander effect (C) in the murine model (4T1) shows that nadunolimab reduces the metastatic burden in the 4T1 model.

*Figure 2.* To gain insight into IL1RAP and IL1 expression in metastatic lungs in the 4T1 TNBC model, Balb/c mice were inoculated with 4T1 cells as previously described. On day 16, lung tissues were collected, and single-cell suspension prepared for flow cytometry analysis of infiltrating immune cells and their IL1 expression. A large cluster of myeloid cells was observed (A). Notably, infiltrating salivary and pulp cells had a distinct signature of IL1 compared to other immune cells of murine lung microenvironment, and the number of these cells significantly decreased in the nadunolimab treated mice compared to isotype control (B). Metastasis burden (C) and Metastatic lesion size (D) in experiments performed (n=3) were significantly reduced in mice treated with nadunolimab. For the representative experiment (E) shows that nadunolimab reduced the metastatic burden in the 4T1 model.