**1. Mechanism of Action**

Here, we tested the combination of NKG2A and PD-1 blockade in an immune checkpoint receptor NKG2A (Natural Killer Group 2A). NKG2A is expressed as a heterodimer specific for HLA-E (Human Leukocyte Antigen-E) in humans and orthologous Qa-1b in mice. Uptake ligand binding, CD94-NKG2A triggers inhibitory signaling that retains NK and CD8+ T cell responses. HLA-E is frequently up-regulated on cancer cells of many solid tumors or acute myeloid leukemia (AML) cells. Blocking the PD-1 pathway has proven efficient as anti-tumor therapy. Nevertheless many patients remain refractory to these therapeutics. Combination treatment with PD-1 blockers enhances the anti-tumor efficacy of PD-1/PD-L1 inhibition by IFN-α.

**2. Qa-1b and PD-L1 are increased on A20 tumor infiltrating NK and CD8+ T cells in vivo**

NKG2A immune checkpoint blockade enhances the anti-tumor efficacy of PD-1/PD-L1 inhibitors in a preclinical model.

**3. Qa-1b and PD-L1 are increased on A20 tumor infiltrating NK and CD8+ T cells in vivo**

The data show that the combination of both mAbs, CDE684 and anti-asialo-GM1 (100 µL, ip) mAbs.

**4. NKG2A and PD-1 expression on A20 tumor infiltrating NK and CD8+ T cells**

NKG2A-PD-1- NK cells against Qa-1b expressing A20 (Qa-1b) in spleen lymphocytes (n=3-6 experiments).

**5. Anti-NKG2A in vitro and in vivo efficacy**

Qa-1b and PD-L1 expression was measured by flow cytometry.

**6. Increased frequency of NKG2A+PD-1+ CD8+ T cells in tumors of anti-PD-1 resistant mice**

Individual tumor volumes of one experiment.

**7. Combined NKG2A and PD-1 blockade increases complete response rate and survival**

CR: 63%, PR: 10%. NKG2A+ NK cells against Qa-1b expressing A20 tumor cells were not modified by anti-PD-1 treatment (data not shown).

**Conclusion**

- NKG2A is expressed on tumor infiltrating NK cells.
- NKG2A blockade on a subset of CD8 T cells also expressed PD-1 is further increased in PD-1 resistant mice.
- NKG2A blockade delays A20 tumor growth.
- Combination of PD-1 with NKG2A blockade results in significant anti-tumor responses, characterized by an increased frequency of complete tumor cell regressions.

These data support the rationale for the clinical testing of combination with anti-PD-1 or anti-PD-L1.

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**References**

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