Combination of monalizumab and durvalumab as a potent immunotherapy treatment for human solid cancers

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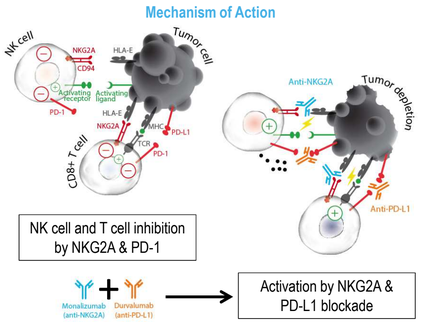
Background

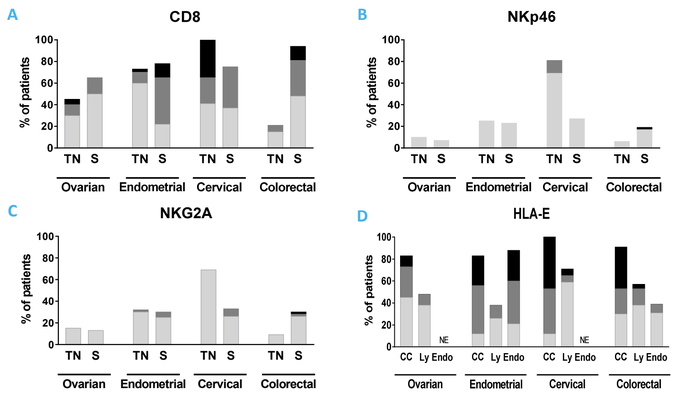
Monalizumab (IPH2201) is a first-in-class humanized IgG_4 targeting NKG2A (Natural Killer Group 2A), which is expressed as a heterodimer with CD94 on subsets of NK cells, γδ T cells and tumor infiltrating $CD8^+$ T cells. This inhibitory receptor binds to HLA-E (Human Leukocyte Antigen-E), in humans and to Qa-1^b in mice. HLA-E is upregulated on cancer cells of several solid tumors, providing a negative regulatory signal to tumor-infiltrating lymphocytes (TILs). Monalizumab blocks binding of CD94-NKG2A to HLA-E, reducing inhibitory signaling and thereby enhancing NK and T cell responses.

PD-1/PD-L1 inhibitors are successfully being used to treat patients with a wide variety of cancers. Combined blockade of NKG2A/HLA-E and PD-1/PD-L1 may be a promising strategy to better fight cancer by activating both the adaptive and innate immune systems.

Here, we describe NK and $CD8^+$ T cell infiltrates in several human solid tumors by immunohistochemistry (IHC) and multicolor flow cytometry. We then studied the effects of *in vitro* targeting both pathways on primary human NK and $CD8^+$ T cells and the efficacy of this combination in a syngeneic mouse model.



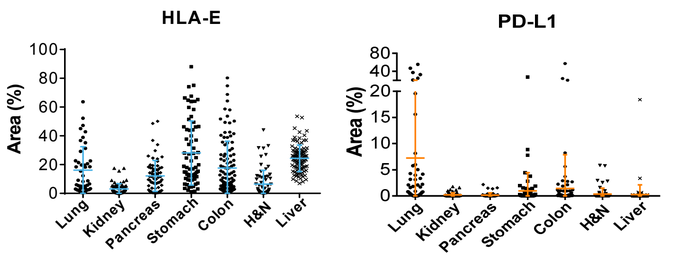
$CD8^+$ T, NK and $NKG2A^+$ immune cells are present in several solid cancer types that express HLA-E



Score 3: ≥66% cells+
Score 2: between 34 and 66% cells+
Score 1: between 1 and 33% cells+

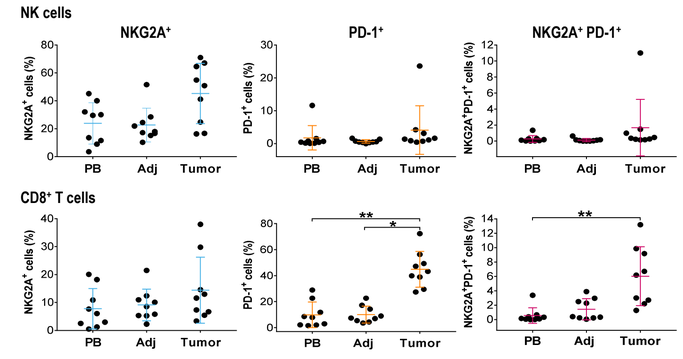
Semi-quantitative analysis of $CD8^+$ (A), NKp46+ (B), $NKG2A^+$ (C) cells and HLA-E expression (D) on human frozen cancer samples (ovarian (n=40), endometrial (n=40), cervical (n=17) and colorectal cancers (n=48)). $CD8^+$, NKp46+ and $NKG2A^+$ cells were quantified in two different tumor regions, stroma (S) and tumor nests (TN). HLA-E expression was assessed on cancer cells (CC), lymphocytes (Ly) and endothelial cells (Endo). Frozen tissues were stained by IHC using anti-CD8 (clone C8/144B), -NKp46 (clone 9E2), -HLA-E (clone 3D12) or -NKG2A (clone Z270) antibodies.. For each marker stacked bars represent the percentage of patients with score 1, 2 or 3. *NE, Not Evaluated*.

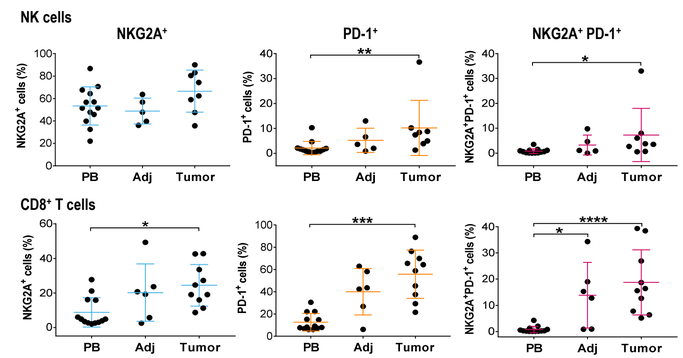
Higher HLA-E expression is observed on solid tumors compared to PD-L1



Quantifications were done using Halo (Indicalabs) in lung (n=45), kidney (n=75), pancreas (n=79), stomach (n=76), colon (n=109), SCCHN (n=70) and liver tumors (n=106). Formalin-fixed paraffin-embedded (FFPE) tissue microarrays were stained by IHC using anti-HLA-E (clone MEM-E/02) or anti-PD-L1 (clone E1L3N). For each indication, scatter plots represent the percentage of HLA-E or PD-L1 stained area on each spot. Colored bars indicate the mean (±SD).

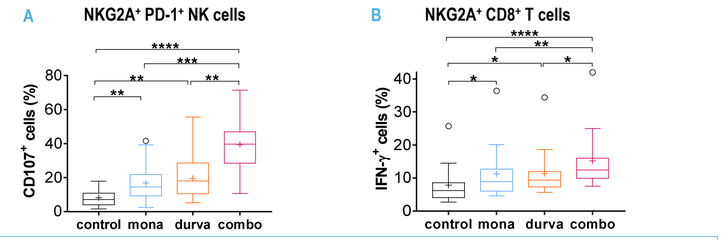
$NKG2A^+$ and PD-1 are expressed on tumor infiltrating NK and $CD8^+$ T cells from cancer patients





Distribution of NK and $CD8^+$ T cells expressing NKG2A and PD-1 in lung cancer patients (A) and in SCCHN patients (B). Cells from peripheral blood (PB), adjacent tissue (Adj) and tumor were analyzed by flow cytometry. Percentages of NK cells (upper rows) and $CD8^+$ T cells (lower rows) were determined and expression of NKG2A and PD-1 was analyzed on each population. A: n=9 patients. Friedman test followed by Dunn's test. * p=0.0140, ** p=0.0012. B: n=17 patients. Kruskall Wallis followed by Dunn's test. * p<0.05, ** p≤0.01, *** p≤0.001, ****p≤0.0001.

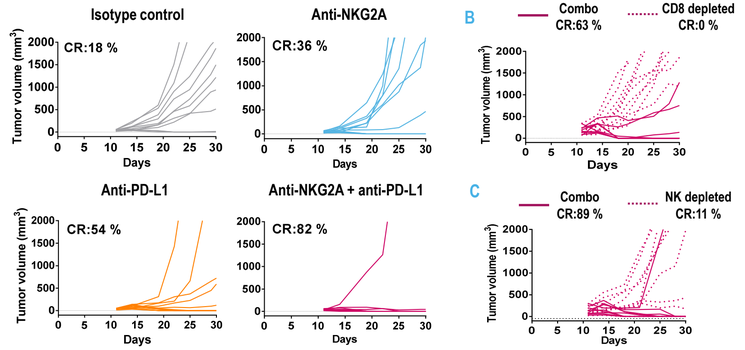
Monalizumab and durvalumab combination enhances NK and Ag-specific $CD8^+$ T cell responses



A. CD107 mobilization on $NKG2A^+$ PD-1^+ NK cells: IL-15-stimulated PBMC (9 days) were co-cultured (4 hours) with HLA-E and PD-L1 transfected-K562 cells in the presence of monalizumab (mona) or durvalumab (durva) as single agents, or combined together (combo). % $NKG2A^+$ PD-1^+ NK cells: 9.7% ± 7.8%, range [1.1% - 30.5%], n=25 healthy volunteers. One-way ANOVA followed by Dunn's test. Box and whiskers (Tukey) with means indicated as "+". ** p<0.001, *** p=0.0001, **** p< 0.0001.

B. IFN-γ induction on $NKG2A^+$ $CD8^+$ T cells: IL-15 and Flu-peptide-stimulated co-cultures of monocytes and $CD8^+$ T cells (9 days) were incubated (4 hours) with Flu-peptide-pulsed K562 cells co-expressing HLA-A2, HLA-E and PD-L1 in the presence of indicated mAbs. % $NKG2A^+$ $CD8^+$ T cells: 11.8 % ± 7.5%, range [2.6% - 30.4%], n=14 healthy volunteers. One-way ANOVA followed by Dunn's test. Box and whiskers (Tukey) with means indicated as "+". * p<0.05, ** p=0.0077, *** p<0.0001.

Combined NKG2A and PD-L1 blockade increases complete response rate in a $CD8^+$ T and NK cell-dependent manner



A20 tumor bearing BALB/c mice (n=8-11) were randomized when tumor volume reached around 40 mm^3 and treated with anti-NKG2A (200 µg, iv, days 11, 14 and 18) or anti-PD-L1 (50 µg, ip, twice a week for 3 weeks from day 11) with mAbs alone or combined. A. Individual tumor volumes. One representative experiment out three is shown. B & C. Individual tumor volumes of mice treated with combined anti-NKG2A and anti-PD-L1 mAbs with (dashed lines) or without (full lines) lymphocyte depletion: $CD8^+$ T cell (B) and NK cell depletion (C) from the day of randomization.

CR: complete tumor regression.

Conclusions

- Tumor infiltrating NK and $CD8^+$ T cells expressing NKG2A and /or PD-1 are present in several cancer types.
- HLA-E is expressed by tumor cells in the large majority of solid tumors compared to PD-L1.
- Blocking both NKG2A/HLA-E and PD-1/PD-L1 pathways could enhance responses of NK and $CD8^+$ T cells that are present in close contact to tumor cells and therefore boost innate and adaptive immunity.
- Together, these data support the rationale for ongoing clinical trial investigating the monalizumab/durvalumab combination (NCT02671435).