Leiden University
Medical Center

NKG2A checkpoint receptor expression on tumor-infiltrating CD8$^+$ T cells restrains efficacy of immunotherapy

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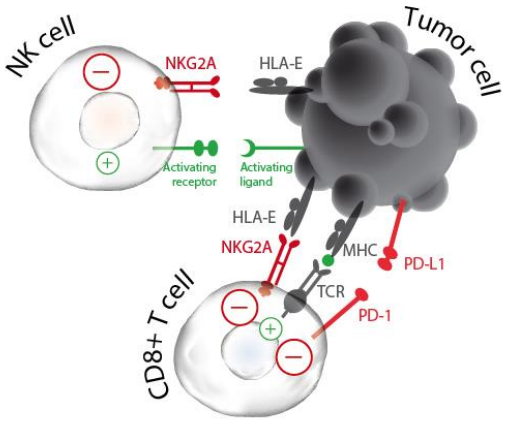

Disclosure Information

AACR, Washington April 2017, Thorbald van Hall PhD

I have the following financial relationships to disclose:

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I will **not** discuss off label use and/or investigational use in my presentation.

HLA-E is generally overexpressed in cancer

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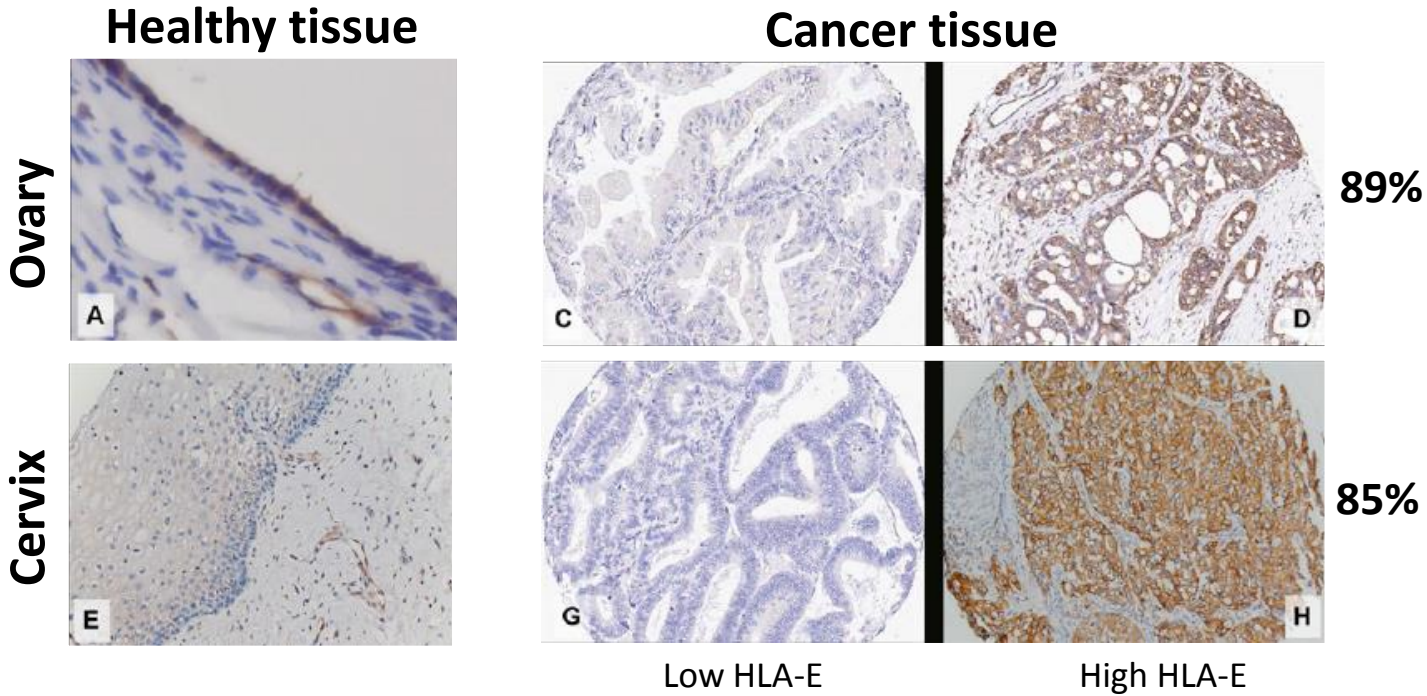

Strong HLA-E expression:

- Colorectal
- Lung
- Gastric
- Melanoma
- Vulva
- HNSCC
- Breast
- Ovarium
- …..

Gooden et al, PNAS 2011; van Esch et al, CII 2014; van Esch et al, Int J Cancer 2014; Talebian Yazdi et al, Oncotarget 2015.

The NKG2A --- HLA-E axis in cancer

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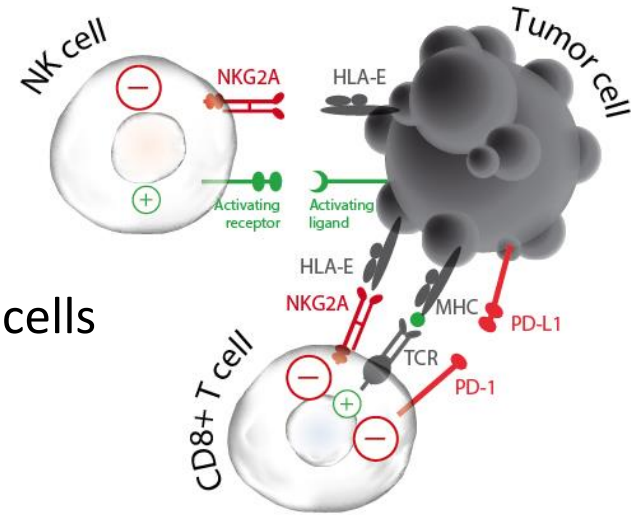
In homeostasis:

- HLA-E is a conserved, non-classical HLA molecule
- Expressed in immune privileged tissues
- Low expression in healthy tissues
- Engaged by inhibiting receptor NKG2A
- NKG2A is only expressed on killers: NK and killer T cells



In cancer:

- Overexpression of HLA-E correlates with worse prognosis
- Neutralizes beneficial effect of T cell infiltrate

NKG2A expression on human TIL

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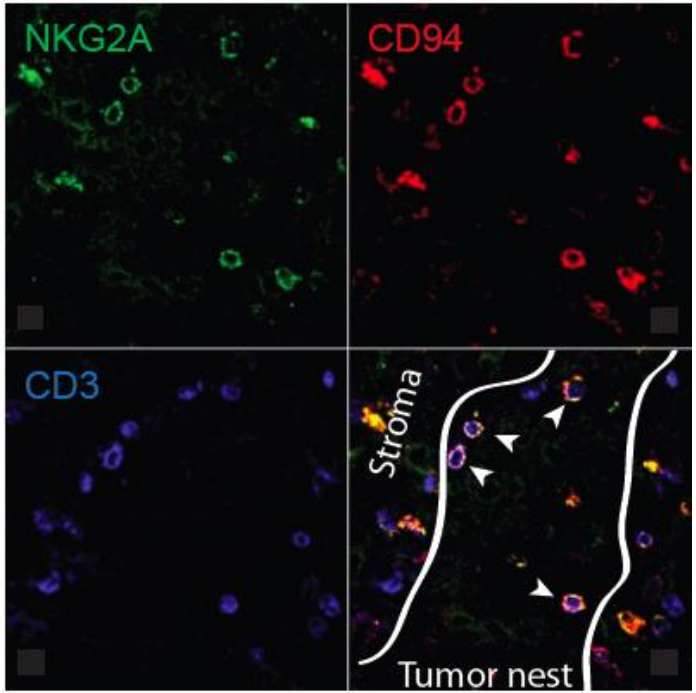
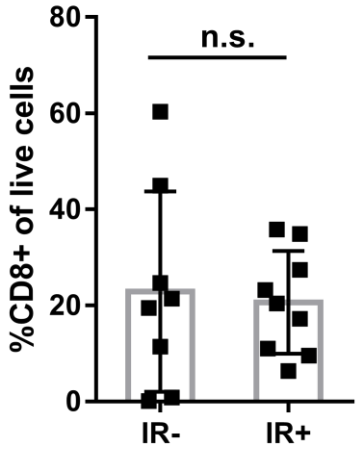
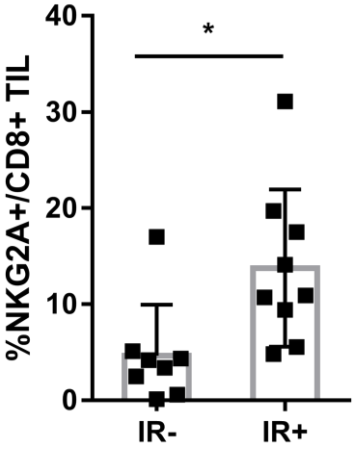


Gooden et al, PNAS 2011

% CD8 T cells of TIL



% NKG2A^{+} of CD8^{+}



HNSCC: IR= *ex vivo* immune response

Co-inhibitors on human TIL: unique populations

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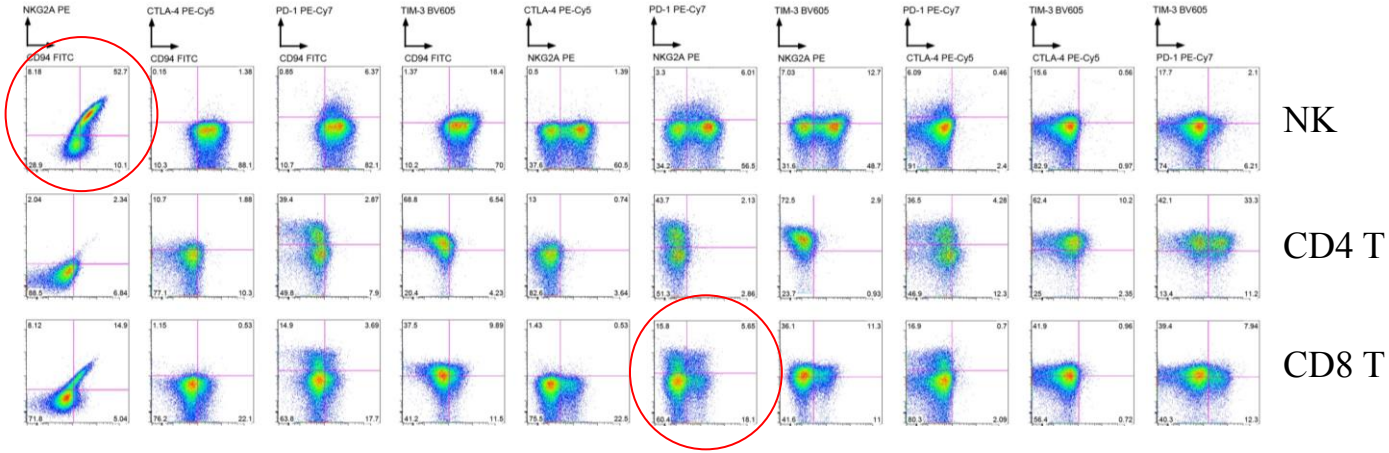
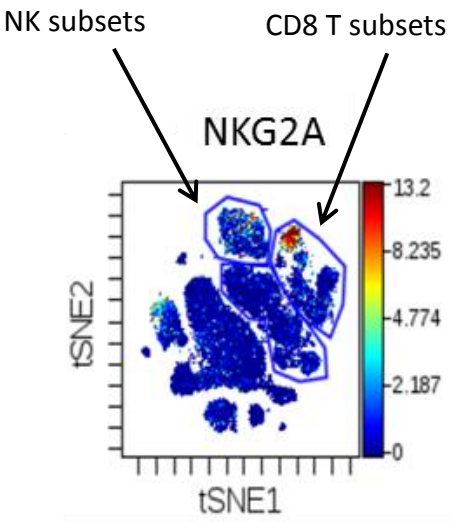
Co-expression of PD-1 and NKG2A



Flow analysis of TIL (HNSCC)



Mass cytometry analysis of TIL

Co-expression of inhibitory receptors on mouse TIL
(Mouse model 1: TC-1 in C57BL/6 mice)

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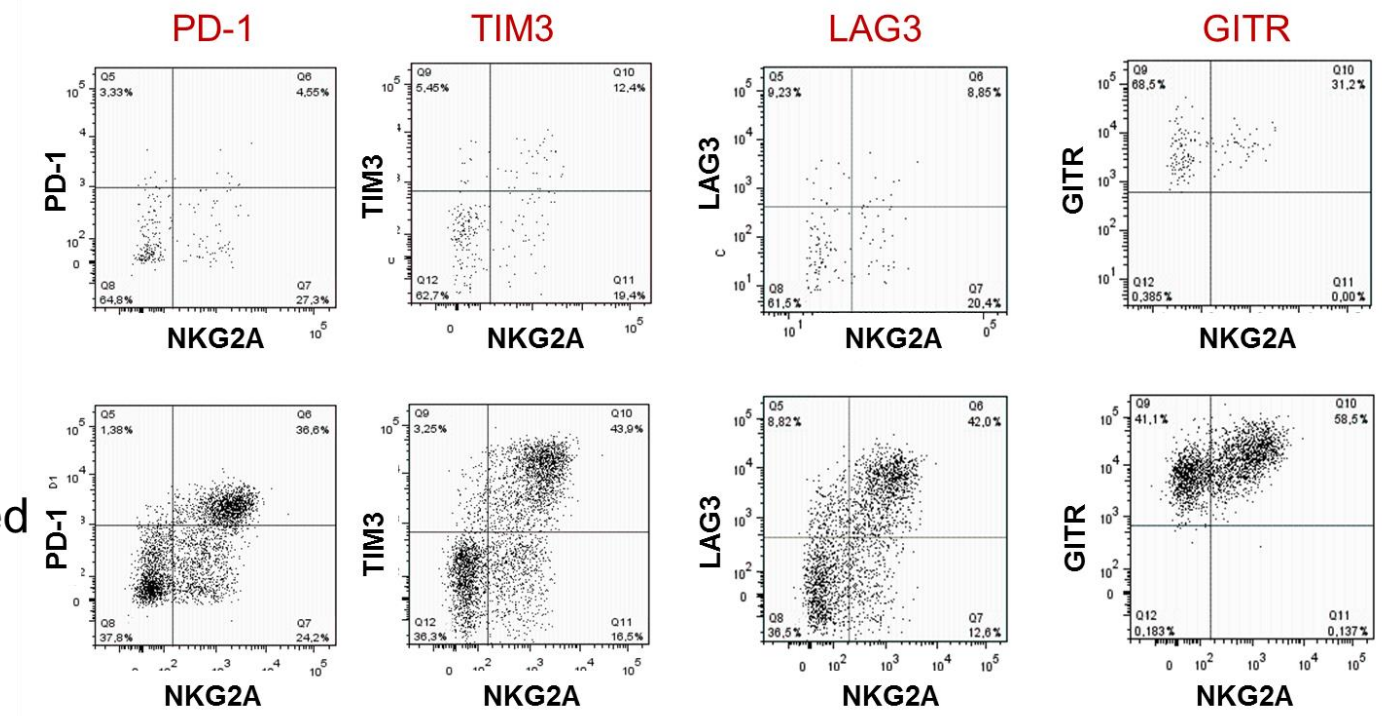
CD8 T cells in TIL



TC-1 model

Therapeutic vaccination increases NKG2A and Qa-1
(Mouse model 1: TC-1 in C57BL/6 mice)

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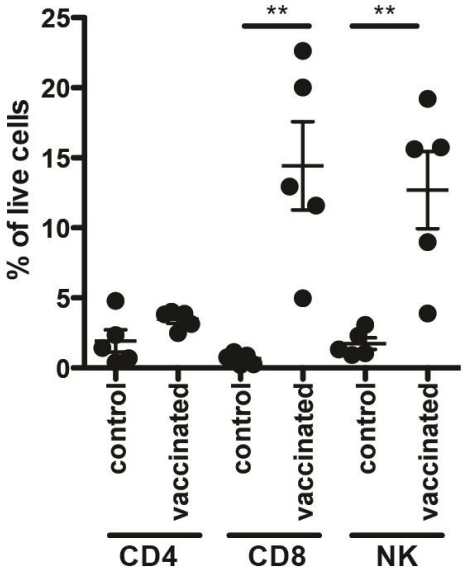
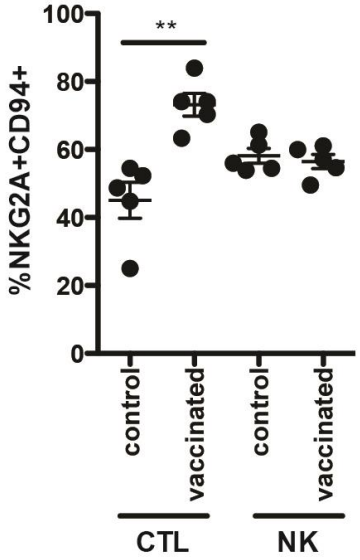
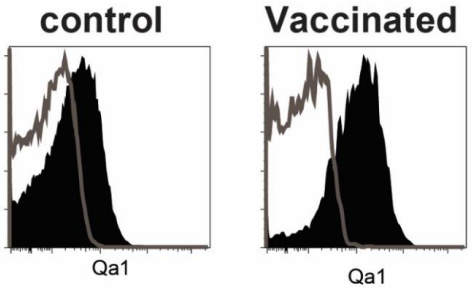
Influx of immune cells



NKG2A$^+$ TIL



Enhanced Qa-1 expression on tumor



Also found in B16 model

TC-1 model

Enhanced efficacy of vaccination in absence of Qa-1
(Mouse model 1: Qa-1 knockdown TC-1 in C57BL/6 mice)

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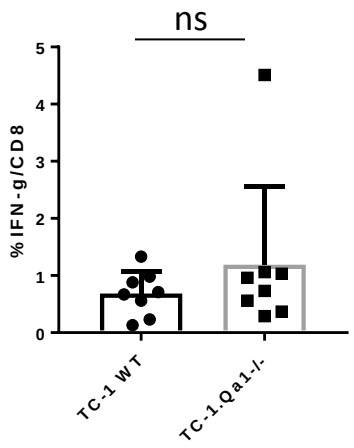
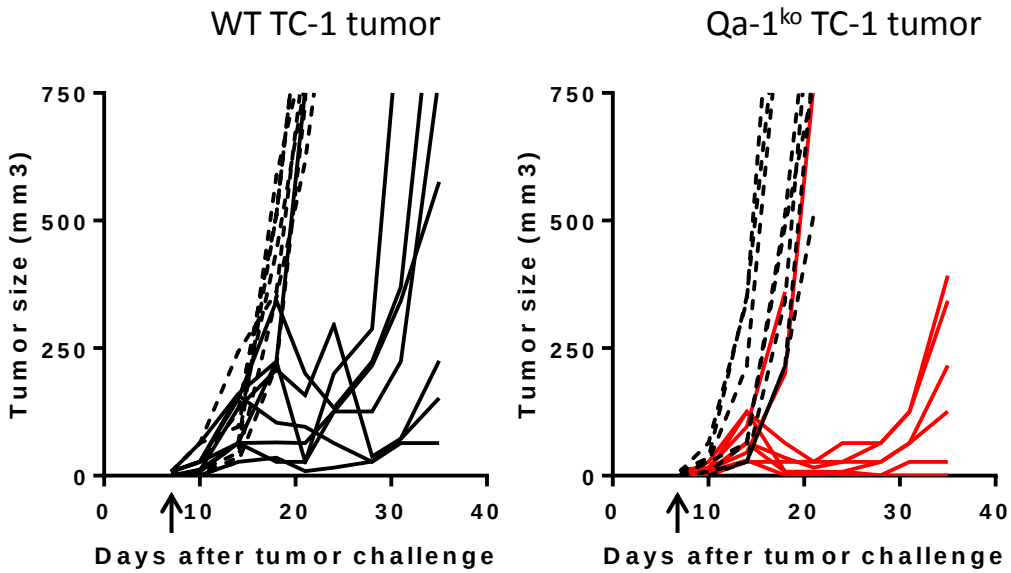
Similar T cell induction



Stronger vaccination efficacy



TC-1 model

NKG2A blocking mAb recapitulates genetic model
(Mouse model 1: TC-1 in C57BL/6 mice)

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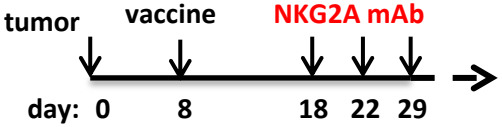

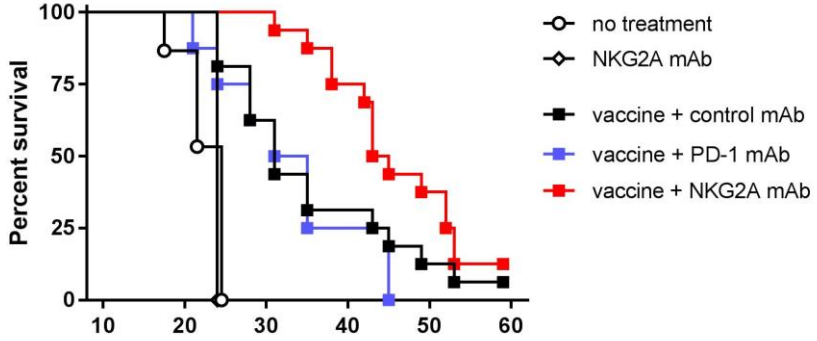

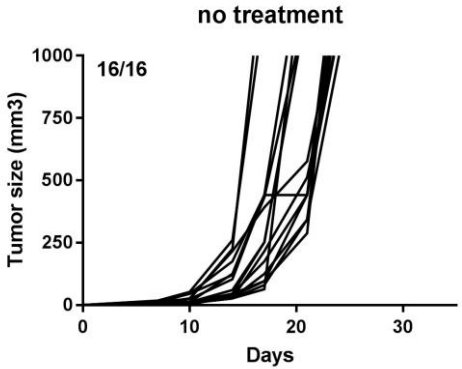

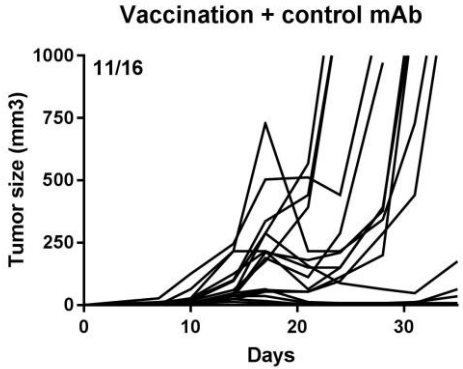

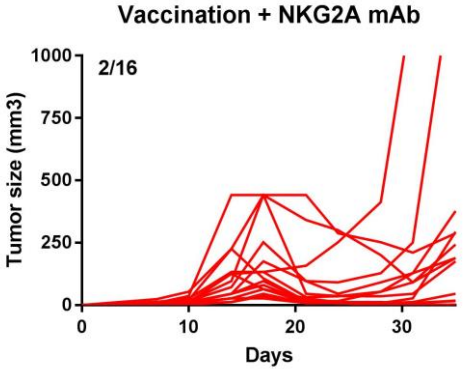

TC-1 model

NKG2A expression and blockade therapy with PD-1
(Mouse model 2: A20 in BALB/c mice)

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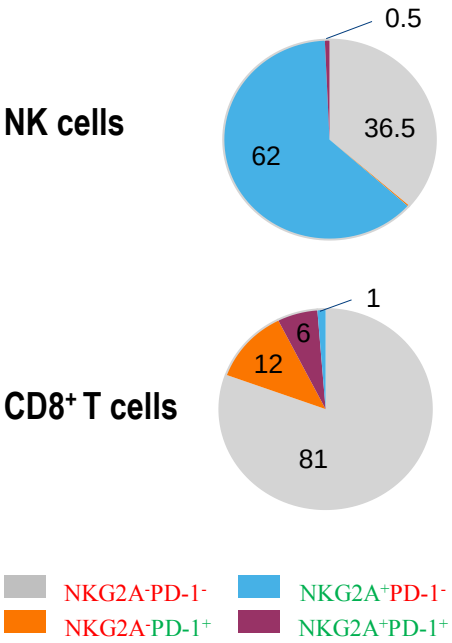
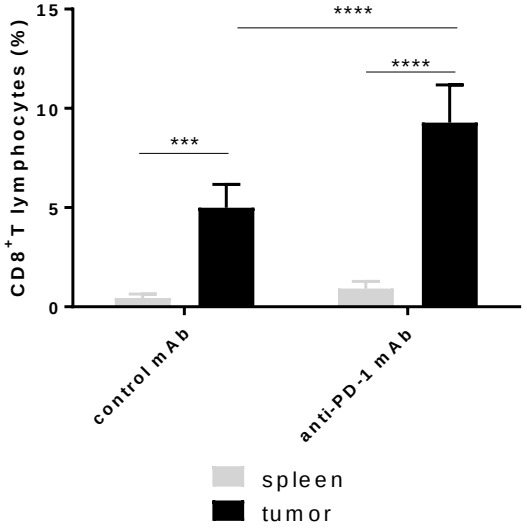
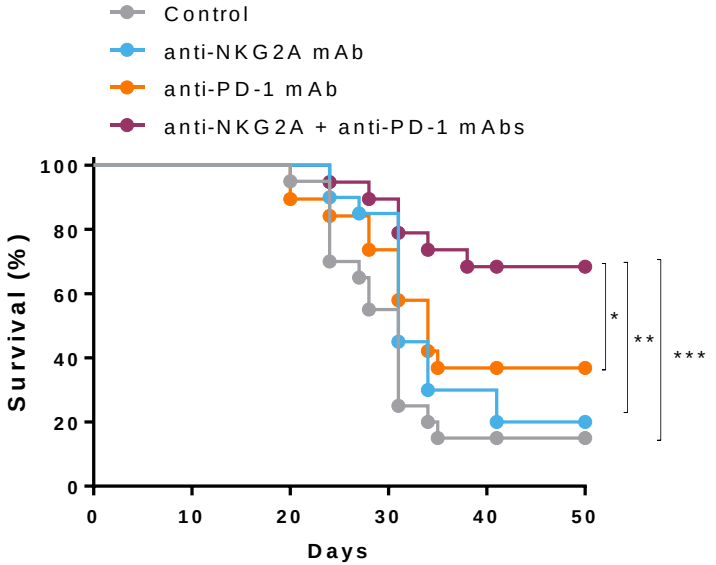
NKG2A expression on TIL



….on CD8 T cells after PD-1 therapy



Combination therapy



Conclusions

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- NKG2A checkpoint receptor:
  - is expressed on intratumoral NK (~60%) and CD8 T cells (~15%)
  - enhanced frequencies after PD-1 blockade therapy and after vaccination
- The ligand HLA-E (=Qa-1 in mice):
  - is generally overexpressed in cancer
  - is upregulated after vaccination

- The NKG2A-HLA-E axis may confer adaptive resistance to immunotherapy
- Combo treatment with NKG2A and PD-1 blockade, or with vaccination is powerful

Leiden University Medical Center

People involved

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Nadine van Montfoort

Marjolein Sluijter

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Innate Pharma:

Pascale Andre

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innate pharma

KWF KANKER BESTRIJDING