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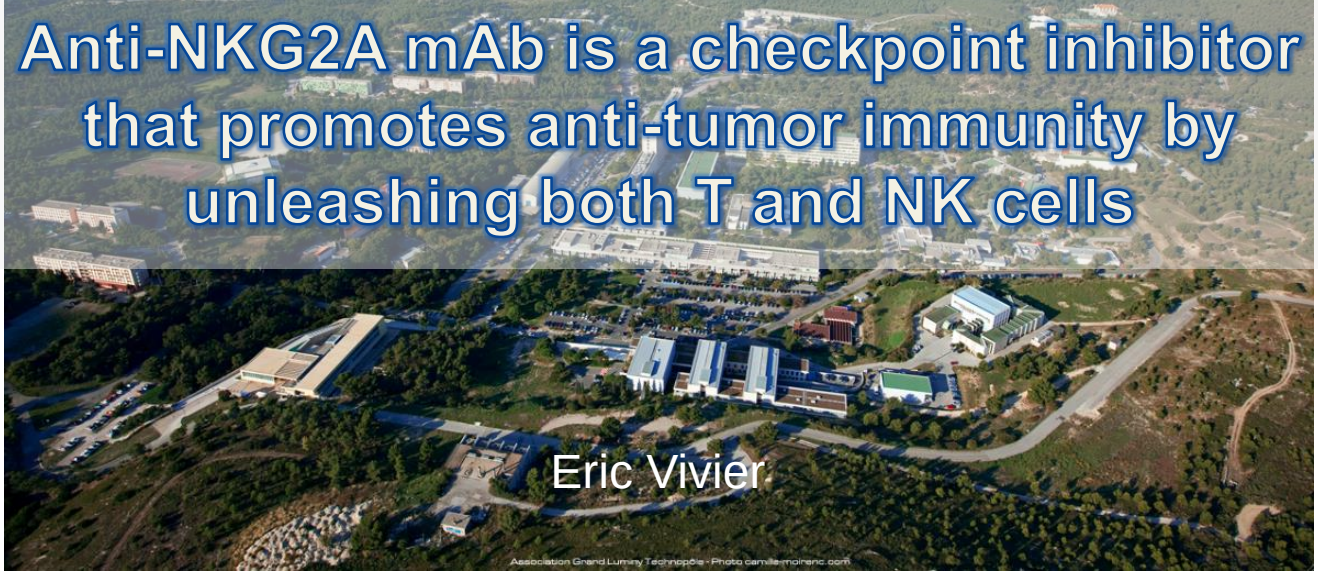
Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells



Eric Vivier

Aix*Marseille université

Inserm

cnrs

AP-HM Assistance Publique Hôpitaux de Marseille

Ciml IMMUNOLOGY

European Research Council erc

ANR

Équipe labellisée par la Ligue contre le cancer

MI MARSEILLE IMMUNOPÔLE

Disclosures

- Innate-Pharma, co-founder + CSO

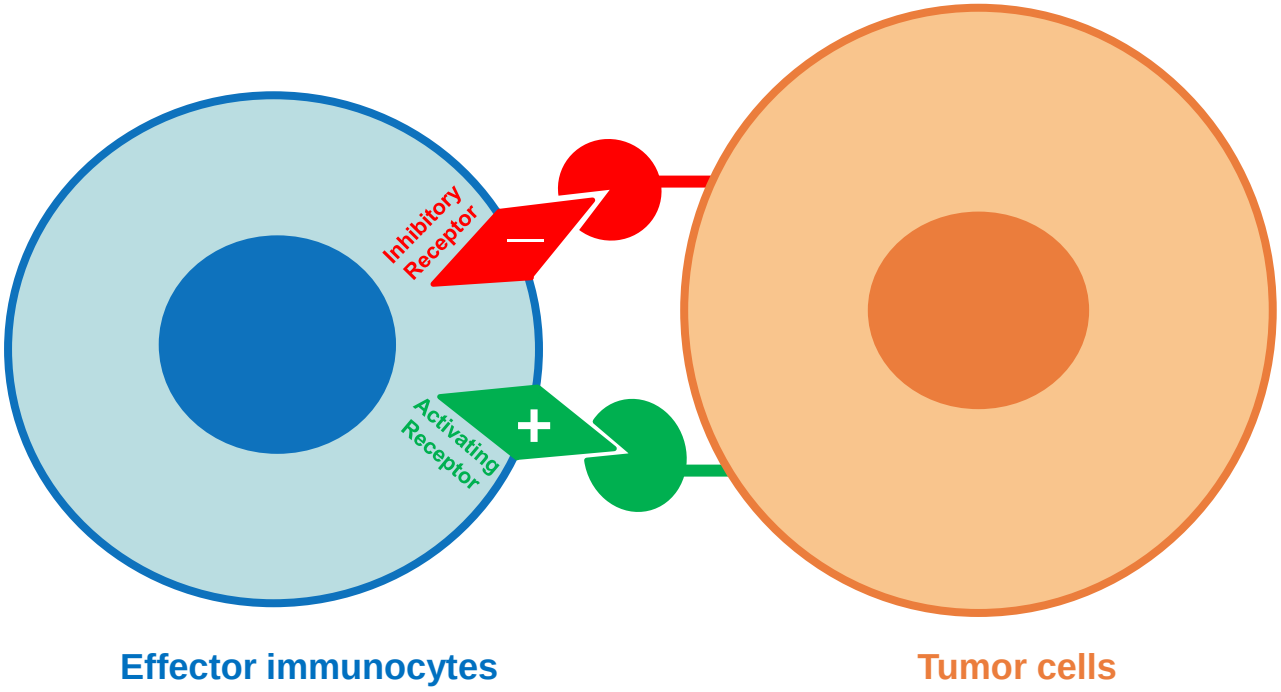
The immuno-oncology revolution

- Shift of cancer treatment from a focus on the tumor to the host with the development of various forms of immune-based therapies that mobilize the immune system to promote or restore an effective antitumor immune response

- Therapeutic blocking antibodies that release immune inhibitory ‘checkpoints’ (immune checkpoint inhibitors, ICIs).

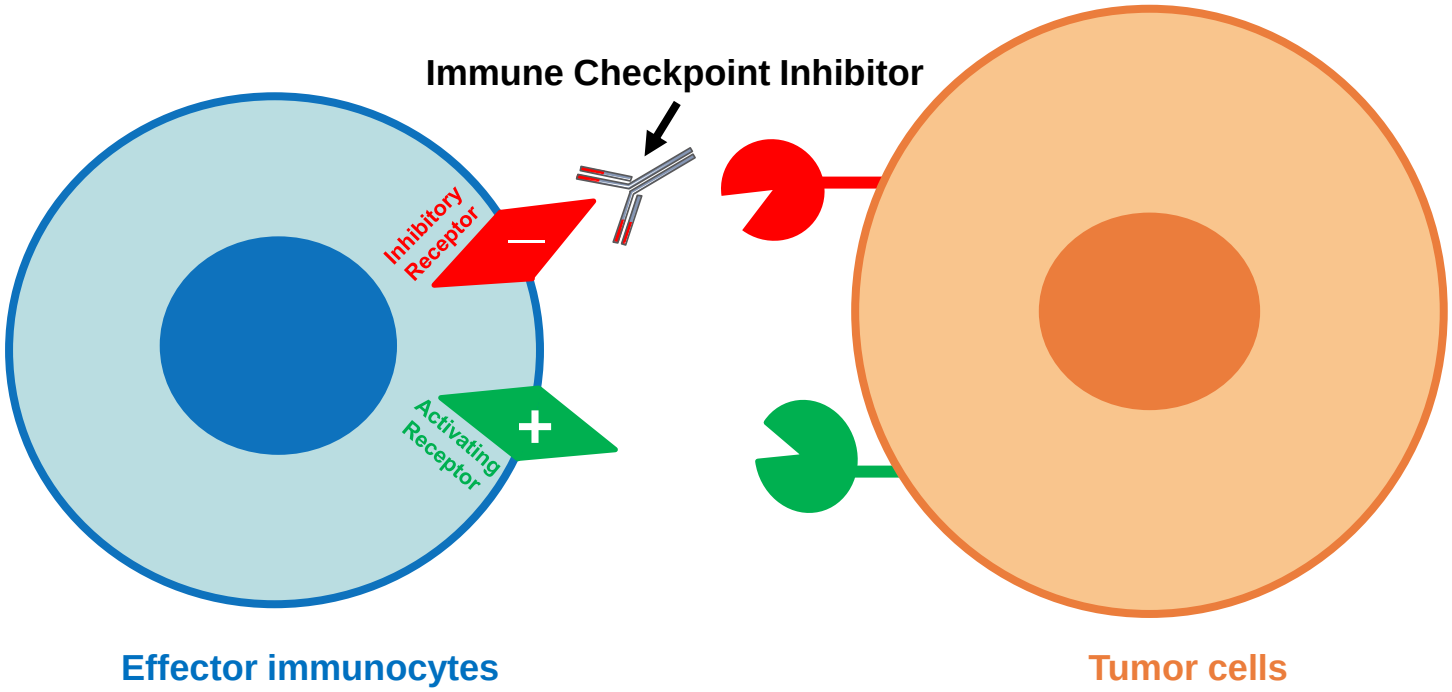
The immuno-therapy revolution

The dynamic equilibrium between activating and inhibitory receptors

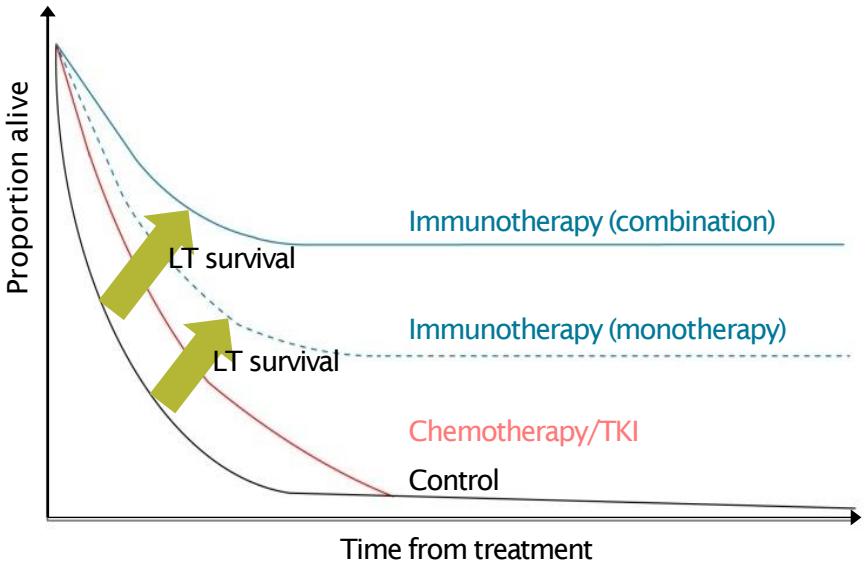


Various shades of immuno-therapies - I

Blocking the inhibition



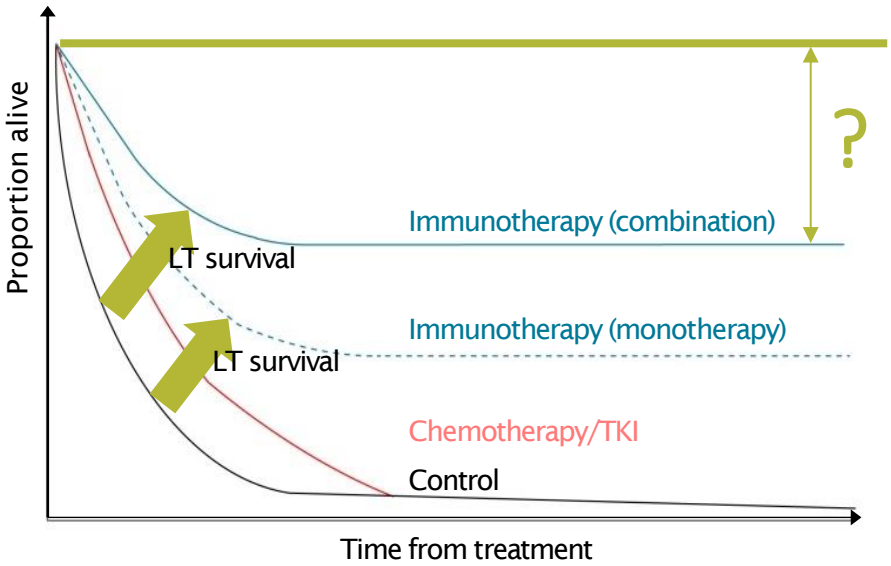
The Immuno-Oncology Revolution



Immune Checkpoint Inhibitors

- anti-CTLA-4
  - > Ipilimumab (***YERVOY***, BMS)
  - > Tremelimumab (MEDIMMUNE-ASTRAZENECA)
- anti-PD-1
  - > Nivolumab (***OPDIVO***, BMS/ONO)
  - > Pembrolizumab (***KEYTRUDA***, MERCK)
- anti-PD-L1
  - > Avelumab (***BAVENCIO***, MERCK KGaA/PFIZER)
  - > Durvalumab (***IMFINZI***, MEDIMMUNE-ASTRAZENECA)
  - > Atezolizumab (***TECENTRIQ***, GENENTECH/ROCHE)

The Immuno-Oncology Revolution



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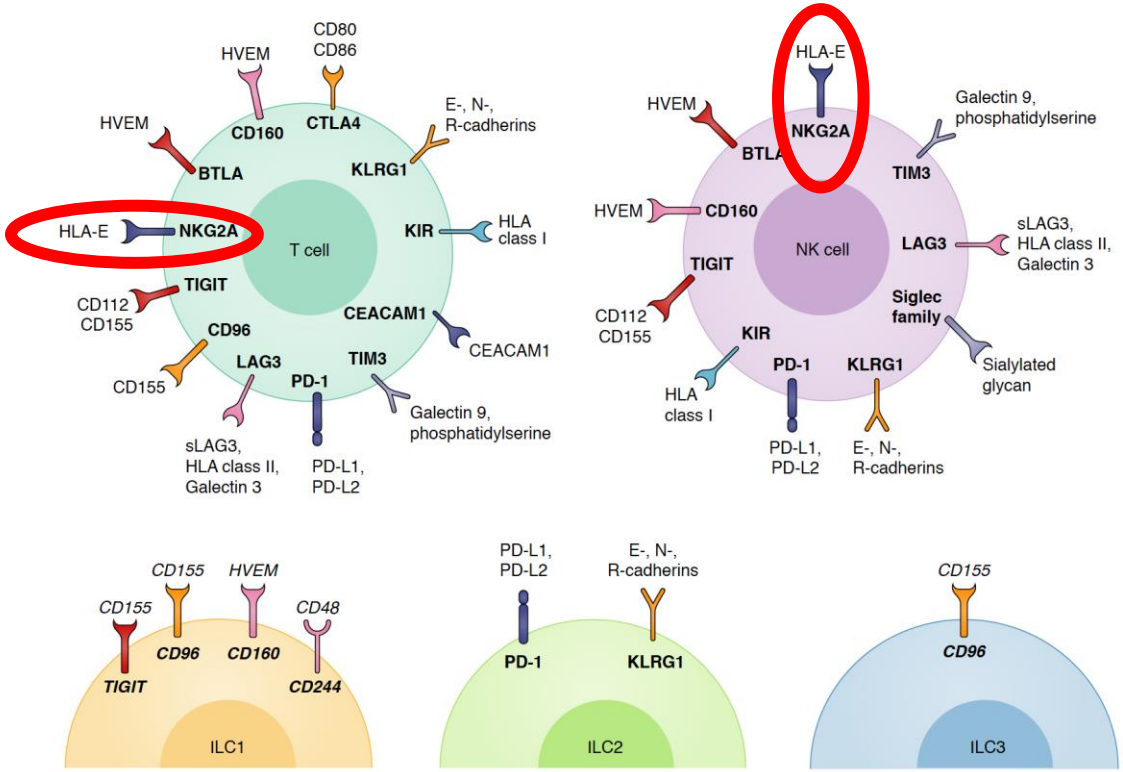
What’s next in immuno-oncology?

- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity

What’s next in immuno-oncology?

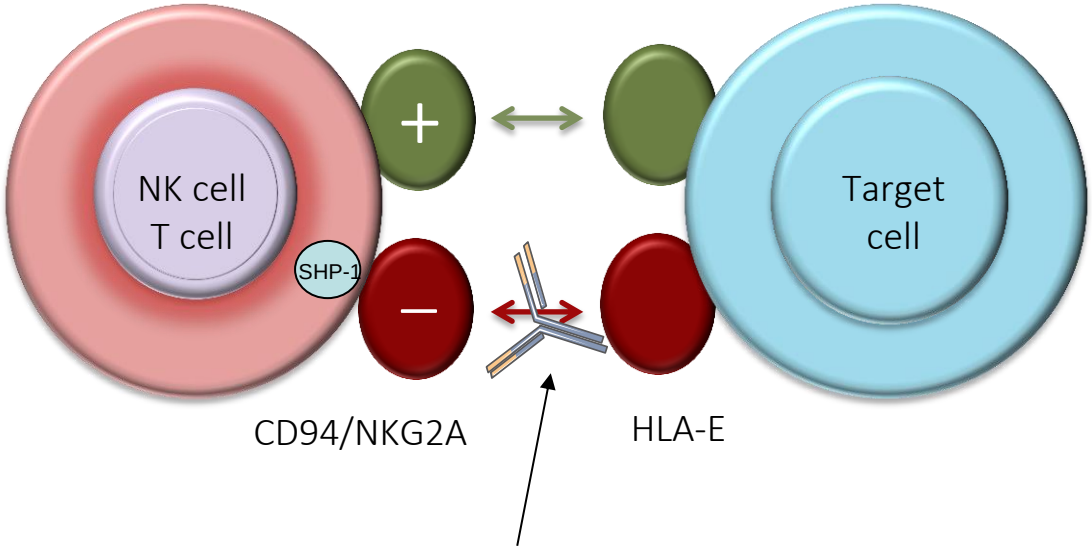
- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity
- Identify new targets (cells and molecules)
- Identify biomarkers

Immune checkpoints



Chiossone & Vivier, J. Exp. Med., 2017

Blocking anti-NKG2A mab as a novel immune checkpoint inhibitor in cancer immunotherapy?



MONALIZUMAB (IPH2201) IS A FIRST-IN-CLASS ANTI-NKG2A HUMANIZED IGG4 BLOCKING MAB

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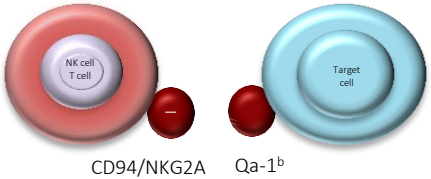
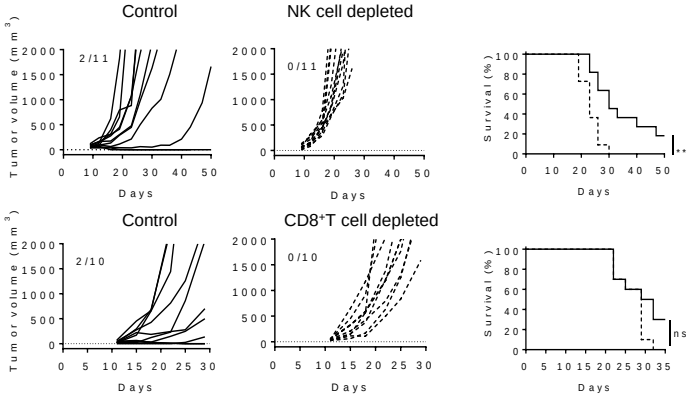
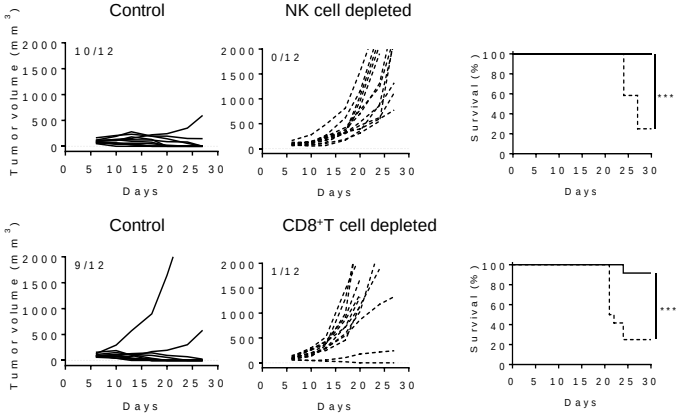
Qa-1^{b} expression blocks the anti-tumor efficacy of NK and CD8^{+} T cells



A20



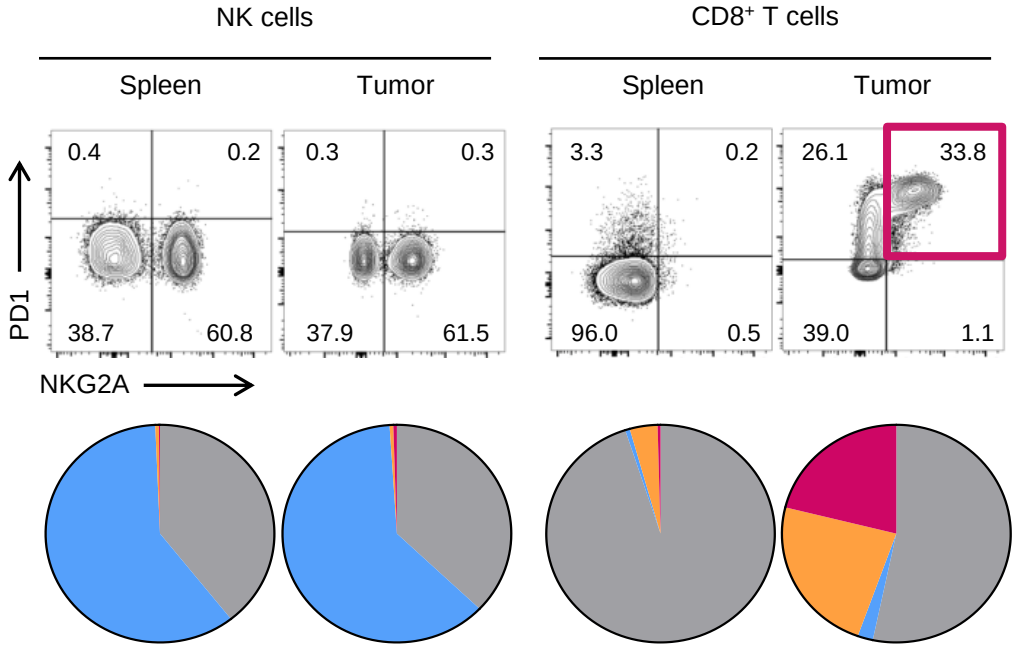
A20 Qa-1^{b} KO



P. André et al.

Co-expression of NKG2A and PD-1

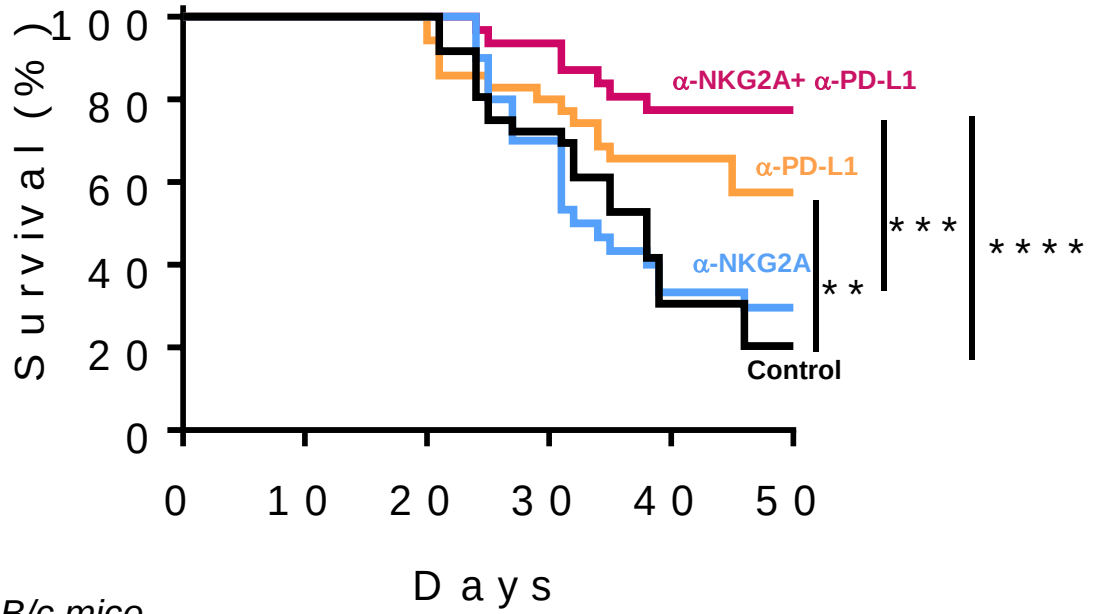
A20 tumor-bearing BALB/c mice



	NK cells Spleen	NK cells Tumor	CD8⁺ T cells Spleen	CD8⁺ T cells Tumor
NKG2A⁺PD1⁻	60 ± 0.4	61.9 ± 2.9	0.7 ± 0.5	2.2 ± 0.9
NKG2A⁻PD1⁺	0.5 ± 0.3	0.5 ± 0.7	3.9 ± 2.1	23.4 ± 12.1
NKG2A⁺PD1⁺	0.1 ± 0.1	0.5 ± 0.6	0.4 ± 0.4	21.1 ± 10
NKG2A⁻PD1⁻	39.4 ± 1.3	37.1 ± 3.4	95.0 ± 0.8	53.3 ± 20.9

P. André, C. Soulas, C. Denis et al.

The combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity



A20 tumor-bearing BALB/c mice

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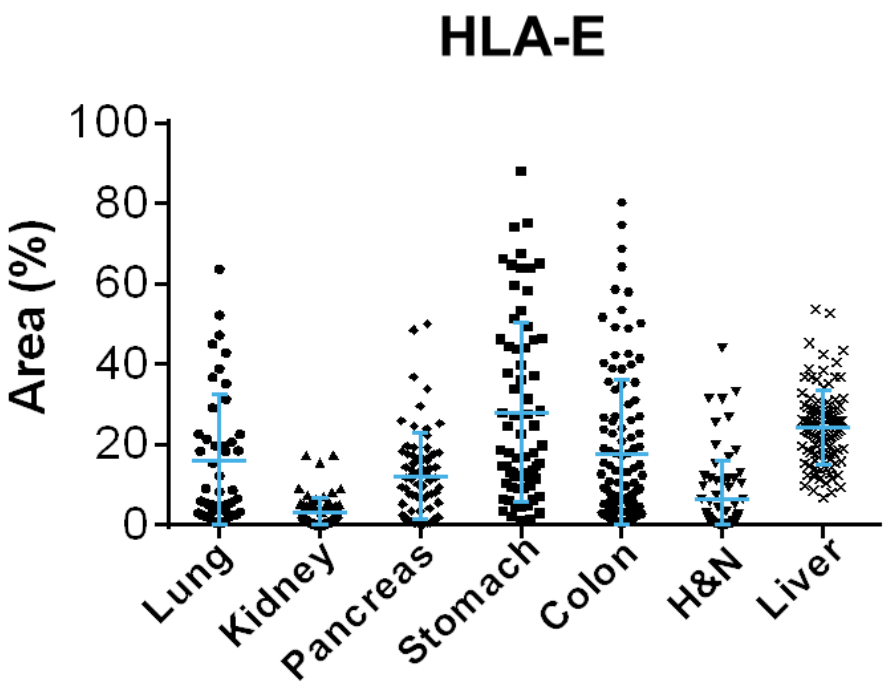
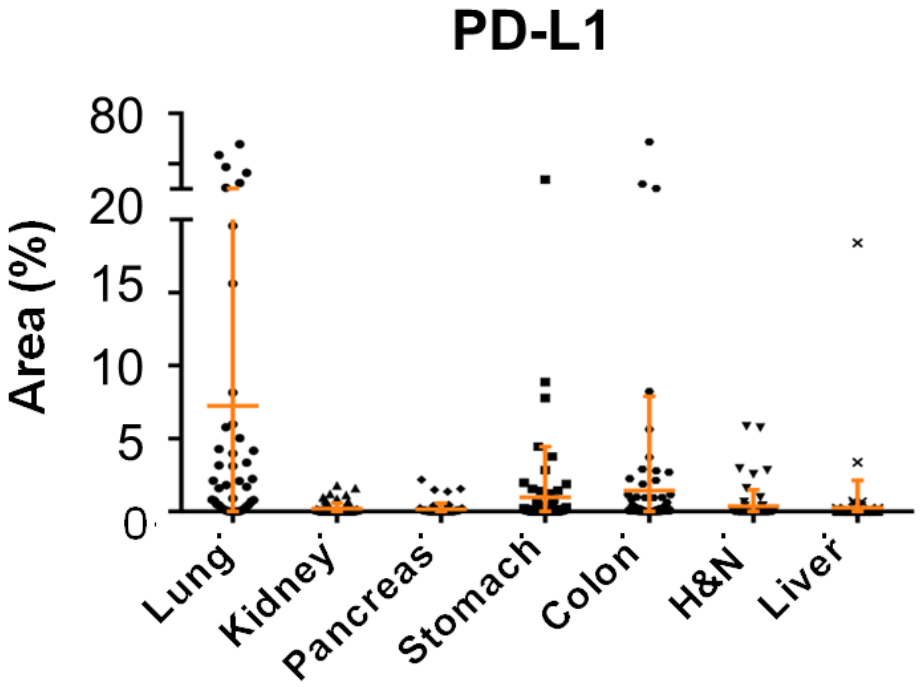
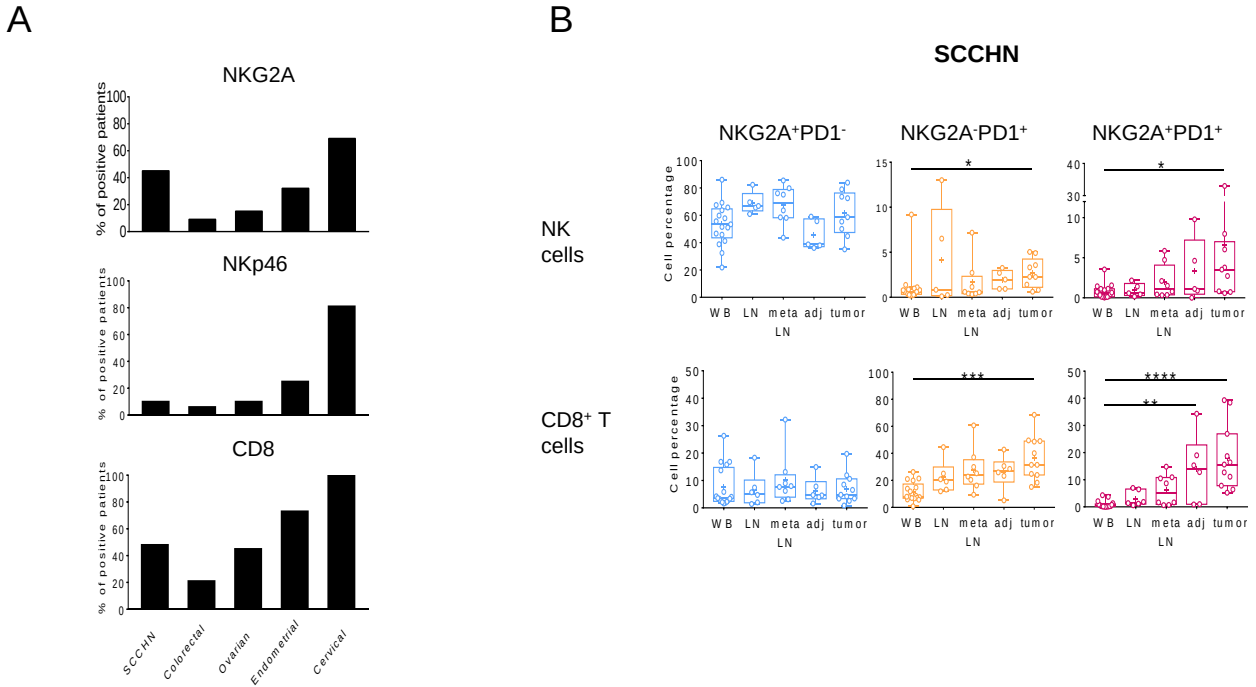
HLA-E expression in human solid tumors



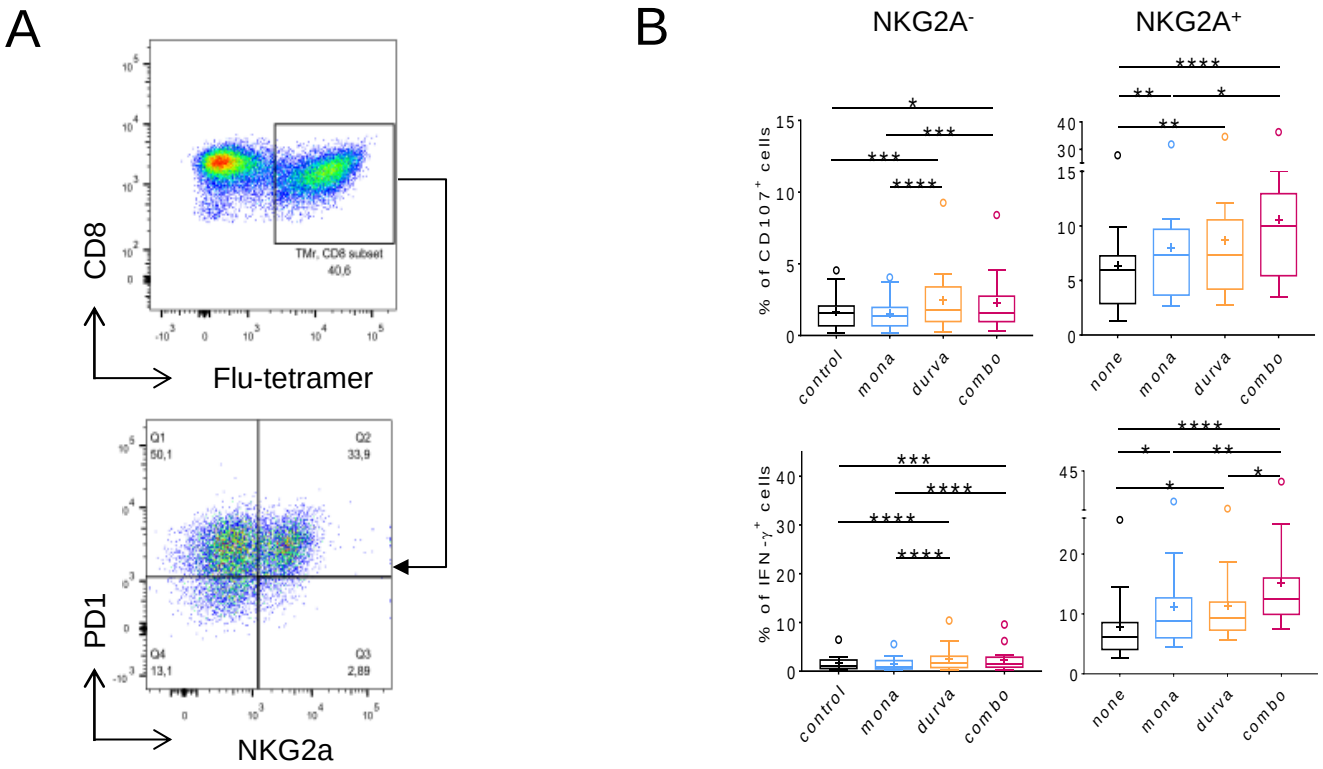


Pascale André et al.

CD8+, NKp46+ or NKG2A+ immune cells are present in several types of HLA-E-expressing solid cancers



Monalizumab unleashes human CD8$^+$ T cell function *in vitro* alone and with durvalumab

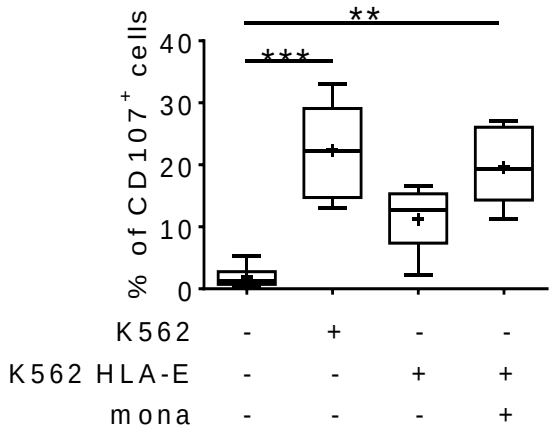


CD8$^+$ T cells cultured in vitro with monocytes, flu peptide and IL-15 (day 10)

Flu-specific CD8$^+$ T cells challenged with flu peptide-pulsed K562 cells expressing PD-L1, HLA-E and HLA-A2

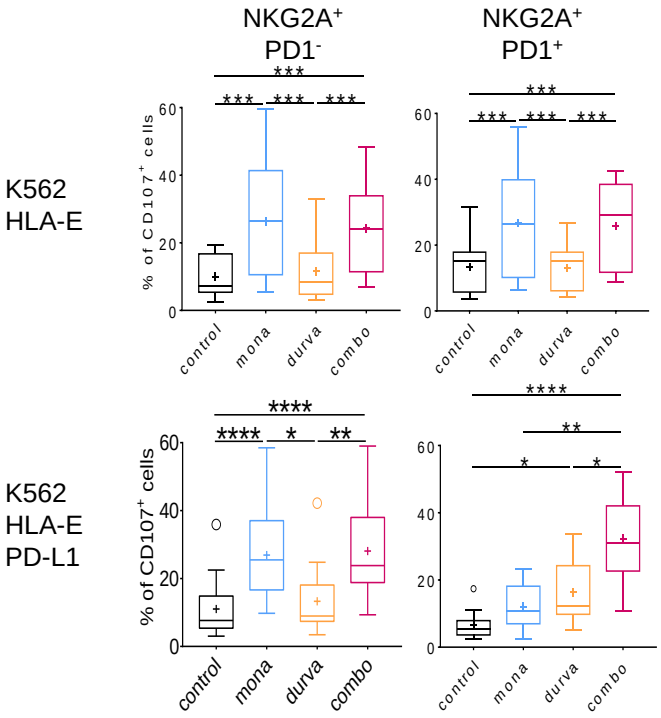
Monalizumab unleashes human NK cell function *in vitro* alone and with durvalumab

A



Resting NKG2A⁺ NK cells

B

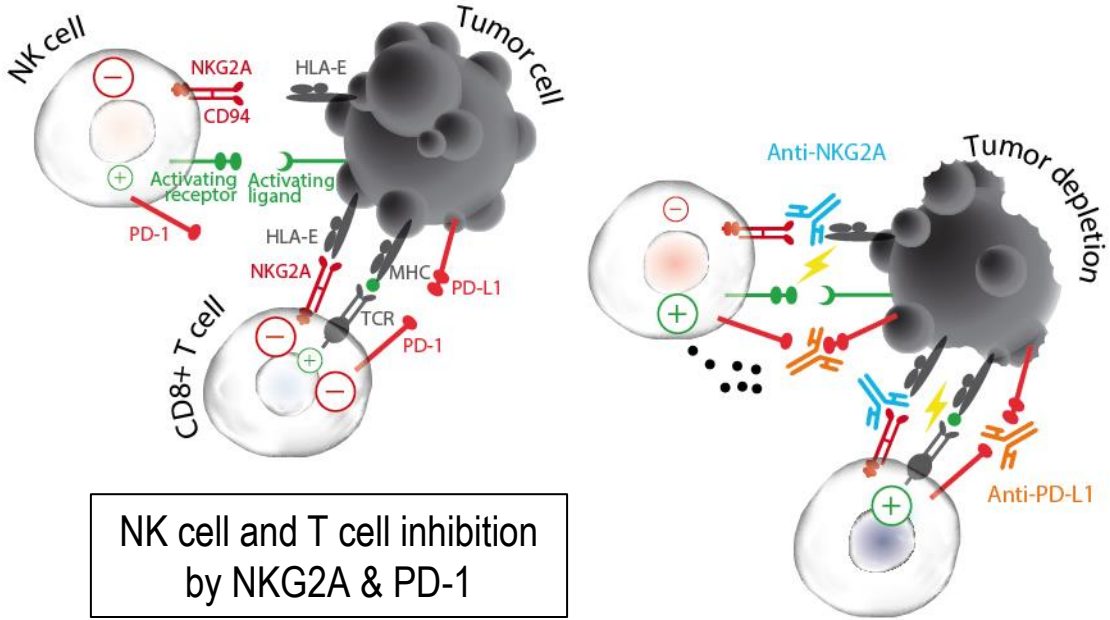


NK cells stimulated in vitro with IL-15 for 9 days

Combination of monalizumab and durvalumab in cancer immunotherapy

- 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
- Blocking both NKG2A/HLA-E and PD-1/PD-L1 pathways can enhance responses of NK and $CD8^+$ T cells

Anti-NKG2A as a novel immune checkpoint inhibitor in cancer

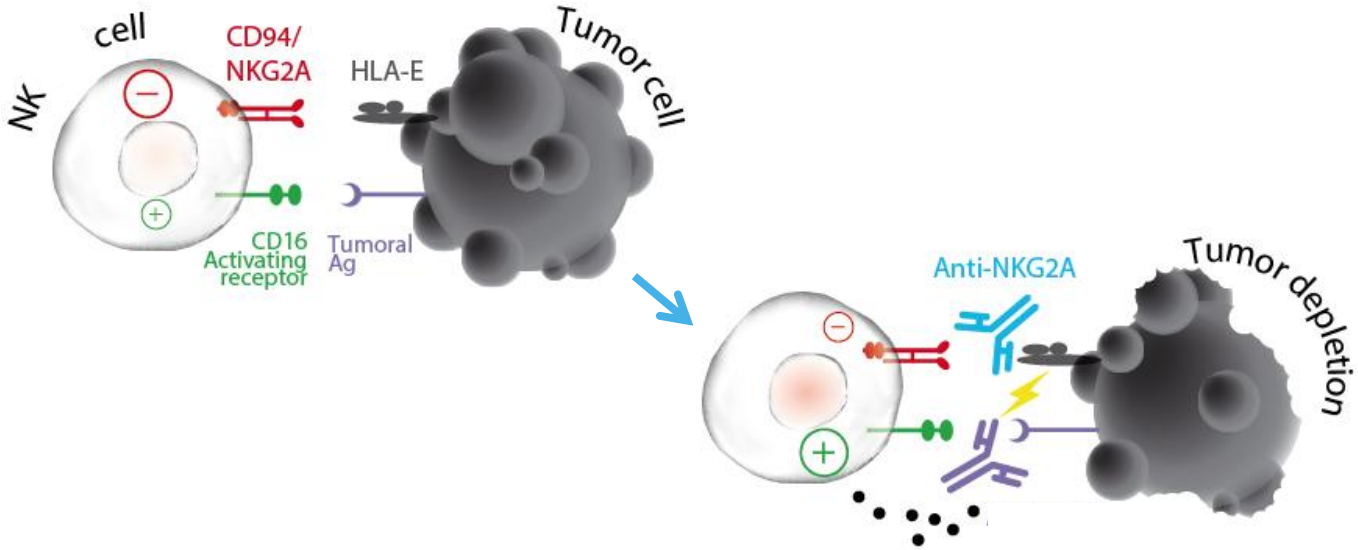


NK cell and T cell inhibition by NKG2A & PD-1

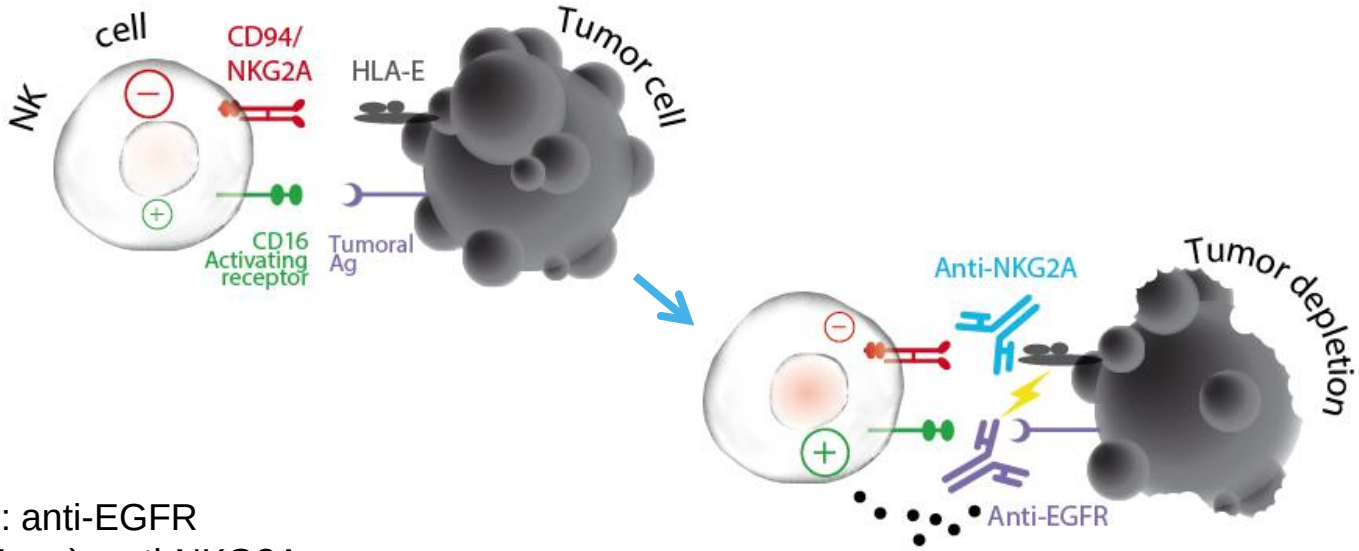
Activation by NKG2A & PD-L1 blockade

In vitro data support the rationale for ongoing clinical trial investigating the combination monalizumab/durvalumab (NCT02671435)

Can the NKG2A immune checkpoint blockade potentiate ADCC?



Can the NKG2A immune checkpoint blockade potentiate cetuximab-induced ADCC in head and neck cancer?

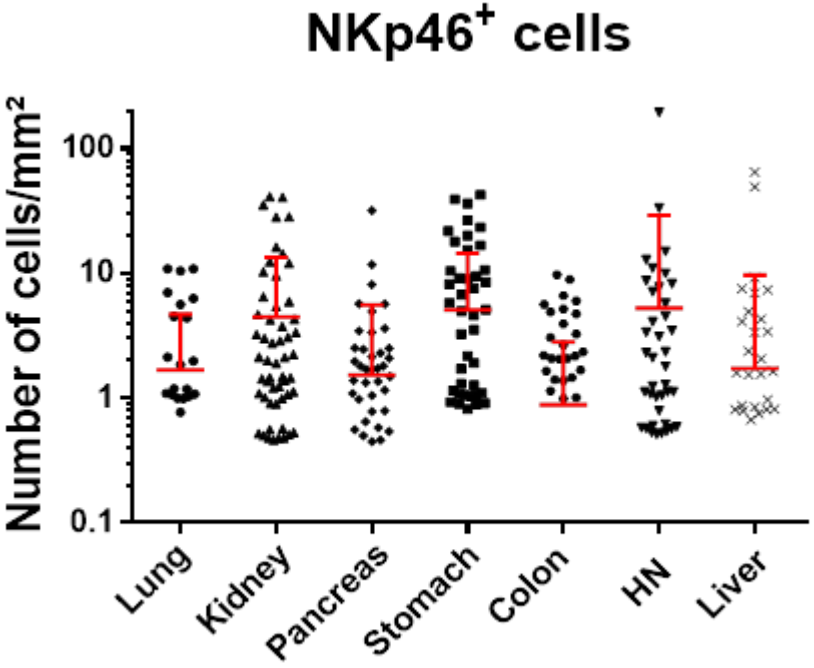


Cetuximab (Ctx): anti-EGFR
Monalizumab (Mona): anti-NKG2A

ADCC enhancement by NKG2A blockade?

SCCHN is one of the tumor types with high NK cell density

A



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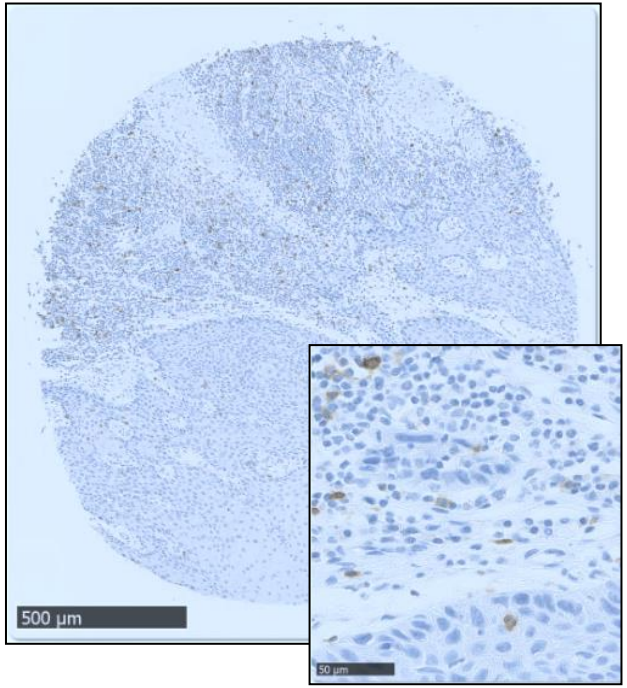
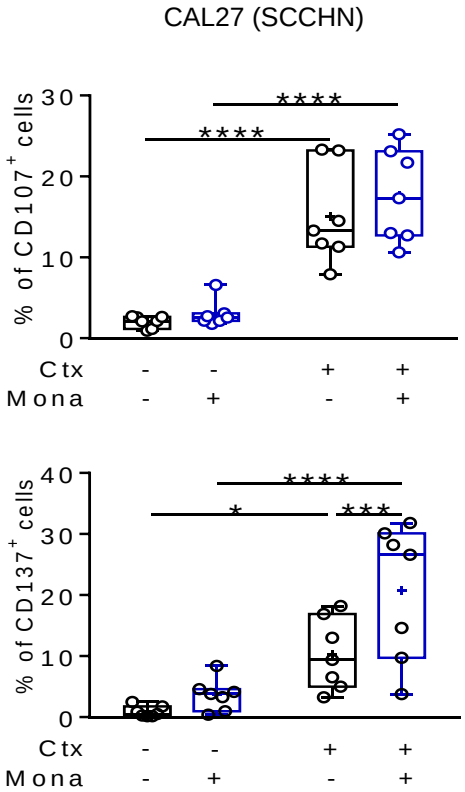


Pascale André et al.

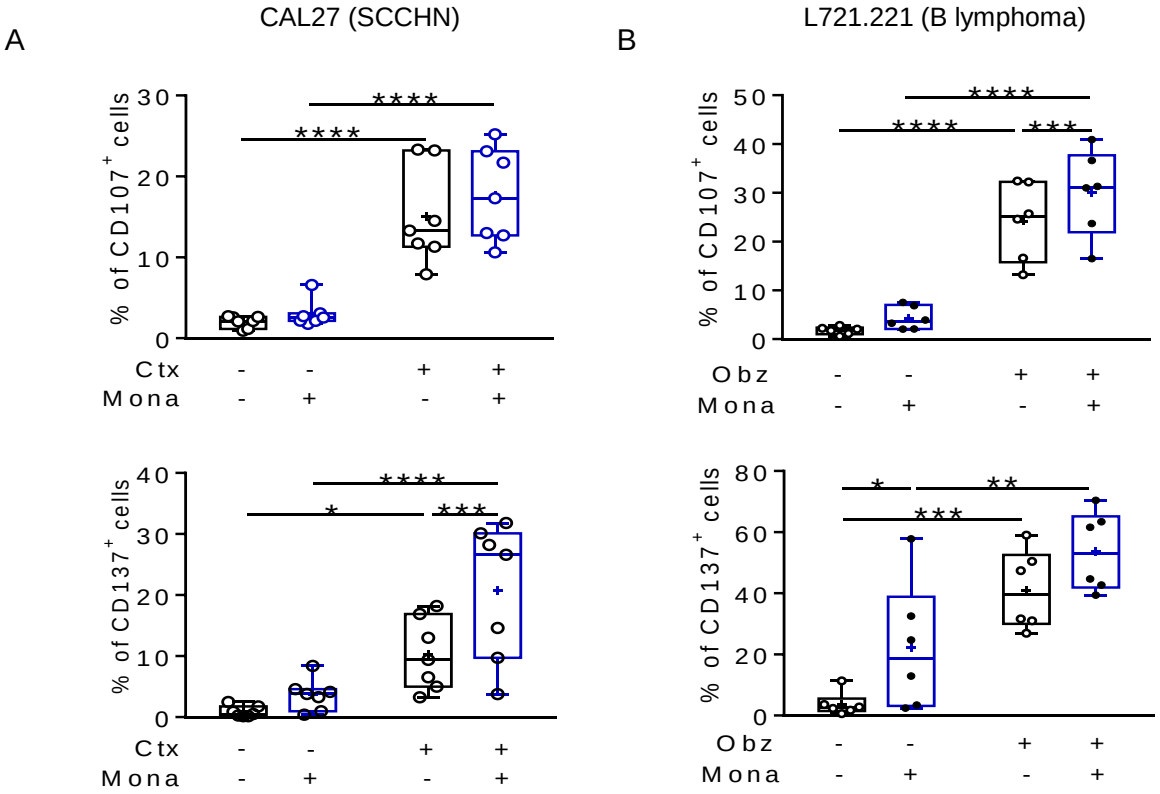
Monalizumab enhances human NK cell-mediated ADCC

Cetuximab (Ctx): anti-EGFR
Monalizumab (Mona): anti-NKG2A

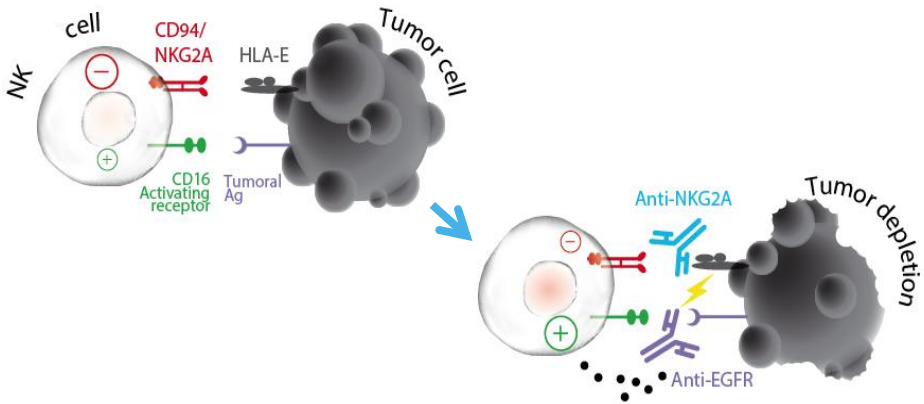


Monalizumab enhances human NK cell-mediated ADCC

Cetuximab (Ctx): anti-EGFR
Monalizumab (Mona): anti-NKG2A
Obinutuzumab (Obz): anti-CD20



NKG2A immune checkpoint blockade potentiates cetuximab-induced ADCC in head and neck cancer



ADCC enhancement by NKG2A blockade

- SCCHN are infiltrated by NK and CD8^{+} T cells expressing CD94/NKG2A
- HN tumor cells express HLA-E
- NKG2A blockade enhances cetuximab-mediated ADCC towards HN tumor cell lines
- These data support the rationale for investigating monalizumab in SCCHN patients and in combination with cetuximab in clinical trials (NCT02643550)

Phase II clinical trial in recurrent or metastatic SCCHN

Patient Characteristics N=31		n (%)
Age, median [range]		64 [34-76]
Sex	Female Male	10 (32%) 21 (68%)
ECOG	0 1	12 (39%) 19 (61%)
HPV status	Positive Negative To be determined	4 (13%) 15 (48%) 12 (39%)
Tobacco	Never Former Current	6 (19%) 20 (65%) 5 (16%)
Tumor site	Oral cavity Oropharynx Larynx Hypopharynx Nasopharynx	14 (45%) 10 (32%) 4 (13%) 2 (6%) 1 (3%)
Type of recurrence	Local Distant	18 (58%) 13 (42%)
Prior lines of systemic therapy (overall)		
Number of previous lines 1 2 3		 16 (52%) 10 (32%) 5 (16%)
Prior platinum		31 (100%)
Prior IO		14 (45%)
Prior cetuximab		3 (10%)

Study Design and Dosing regimen

Multicenter, international (US and France), open label, single arm study to evaluate the antitumor activity of monalizumab in combination with cetuximab (NCT02643550).
Five doses of monalizumab (0.4, 1, 2, 4, 10 mg/kg every 2 weeks) in combination with the approved dosage of cetuximab (400 mg/m² load then 250 mg/m² weekly) were explored. The highest dose tested (10 mg/kg) was used for the phase II cohort expansion. A one-stage Fleming design with a futility analysis after the first 11 patients was used; the overall phase II study will include 40 patients.

Key eligibility criteria

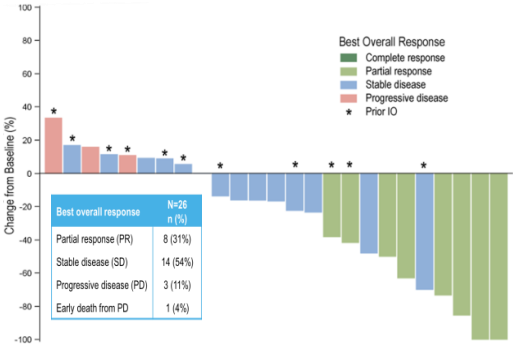
- R/M SCCHN histologically confirmed, HPV (+) or HPV (-)
- Progression after platinum-based chemotherapy
- Maximum of 2 prior systemic treatment regimens for R/M disease; prior IO allowed; prior cetuximab allowed if used for the treatment of locally advanced disease, with no progressive disease for at least 4 months

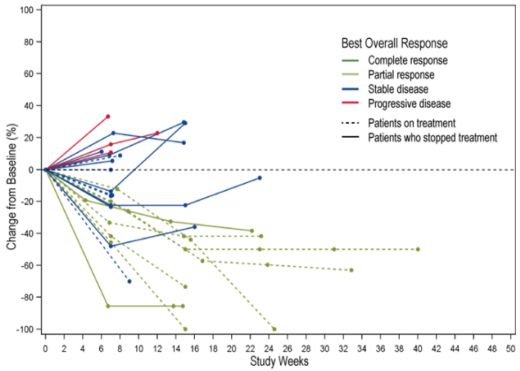
Anti-tumor activity of monalizumab and cetuximab

A

As of March 9, 2018, 31 patients with R/M SCCHN were treated and evaluable for safety, 26 patients were evaluable for activity

B





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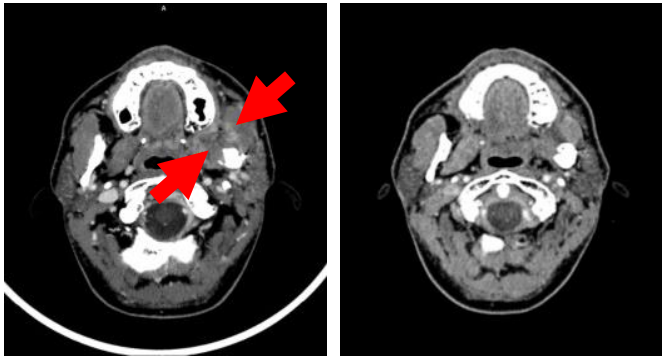


Baseline (July 2017)
Target lesion = 41mm

Under treatment (February 2018)
Target lesion = 0 mm

100% reduction in target lesion, no non-target lesions, no new lesions.

Anti-tumor activity of monalizumab and cetuximab

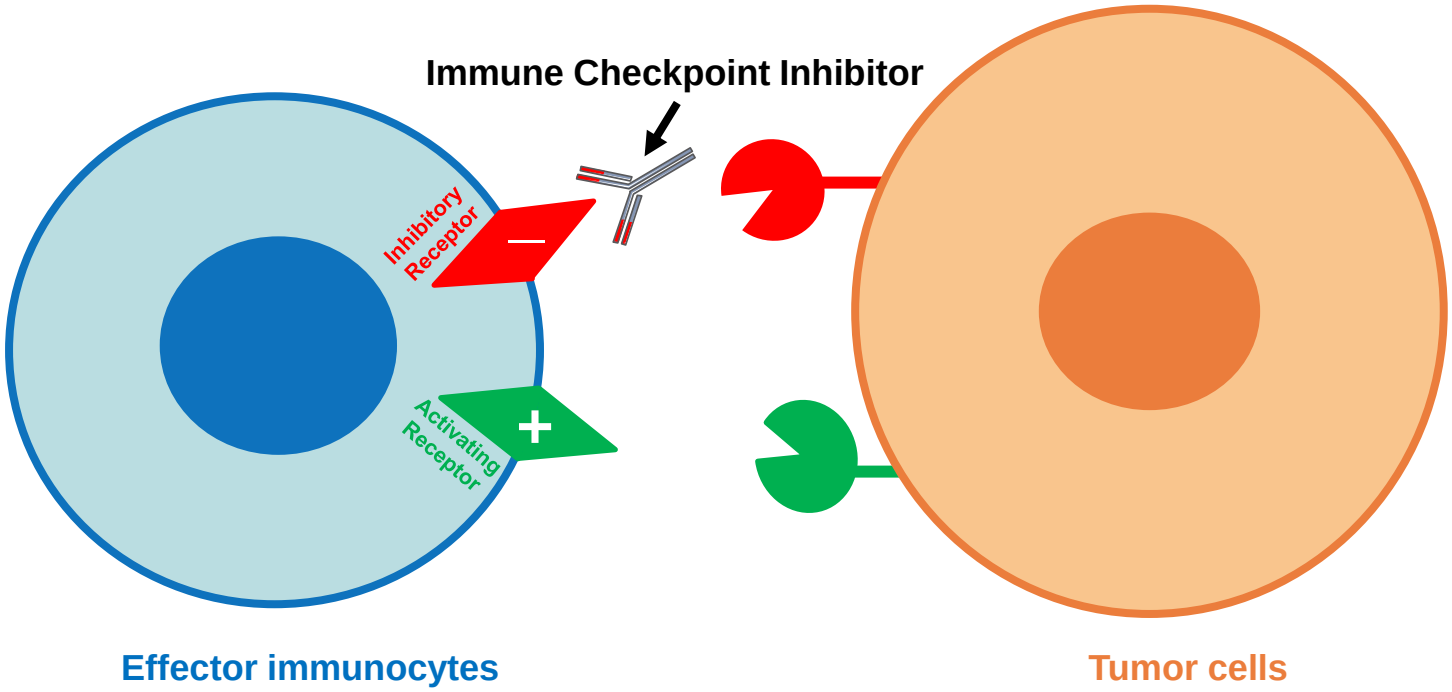
- This is the first report of activity of monalizumab, an anti-NKG2A monoclonal antibody, in combination with cetuximab in patients with SCCHN
- The safety profile is similar to the single agent experience with either agent. No potentiation of the cetuximab side-effects, no new or unusual safety signals were observed with the combination monalizumab and cetuximab
- According to the hypothesis of ORR of 25%, using 10% as inactivity cut-off rate, α =0.05, power 0.76, the predefined number of eight responses to declare the trial positive has been reached
- The trial is ongoing to enroll the 40 patients and allow long term assessment of duration of response, PFS and OS and final results will be presented with 40 patients

NKG2A targeting with monalizumab

Monalizumab is a novel checkpoint inhibitor promoting anti-tumor immunity by enhancing the activity of both T and NK cells, which may complement the activity of the first generation of active immunotherapies against cancer

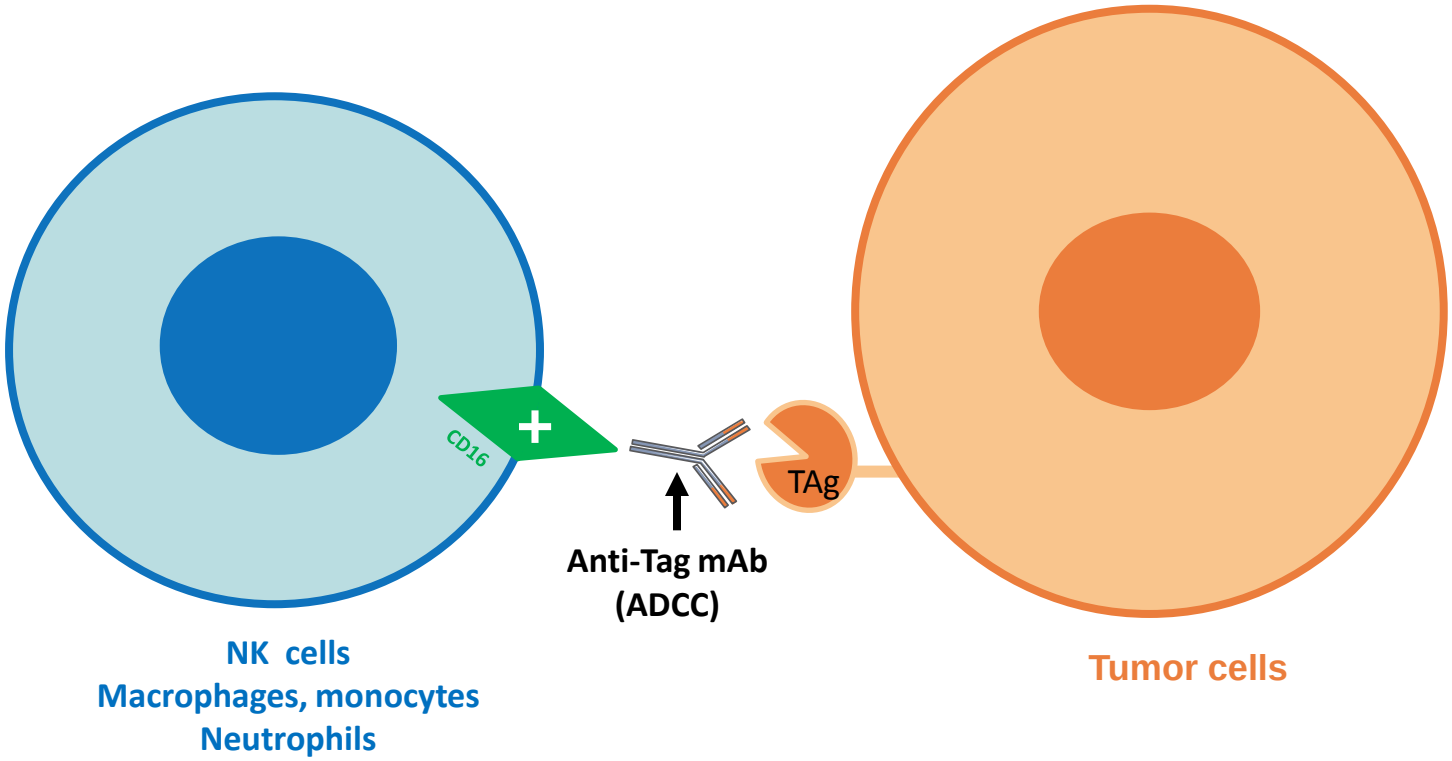
Various shades of immuno-therapies - I

Blocking the inhibition



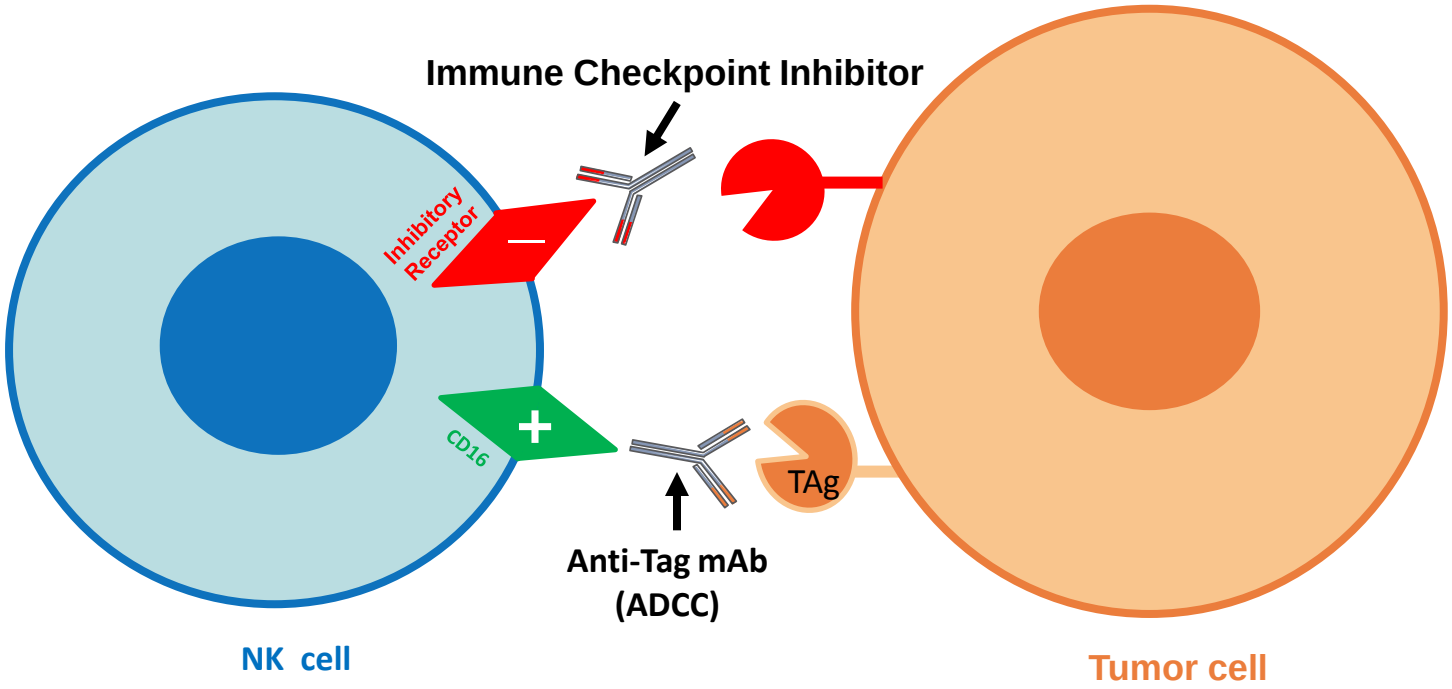
Various shades of immuno-therapies - II

Targeting the tumor via tumor antigens (Tag) with mAbs



Various shades of immuno-therapies - III

Blocking the inhibition and providing activation via anti-TAg mAbs



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ÉQUIPE LABELLISÉE PAR LA LIGUE CONTRE LE CANCER

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ANR AGENCE NATIONALE DE LA RECHERCHE

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THANKS to PATIENTS
and their FAMILIES

MARSEILLE IMMUNOPÔLE

Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells

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