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Radiotherapie
Medische Oncologie
Hematologie

OX40 agonisten

.. not only releasing the brakes, but also stepping on the gas!

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Medische oncologie, St. Augustinusziekenhuis.

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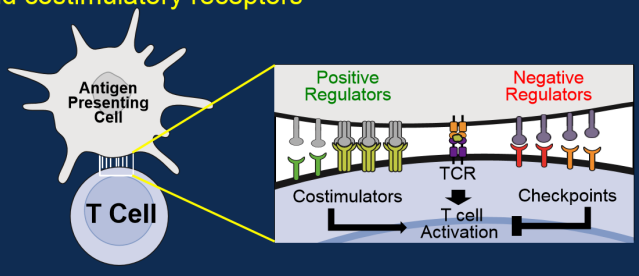
T cel activatie

T cell activation is modulated by a combination of both inhibitory and costimulatory receptors



- Checkpoint molecules such as PD-1, CTLA4 inhibit T cell activation
- Costimulatory molecules augment T cell receptor signaling

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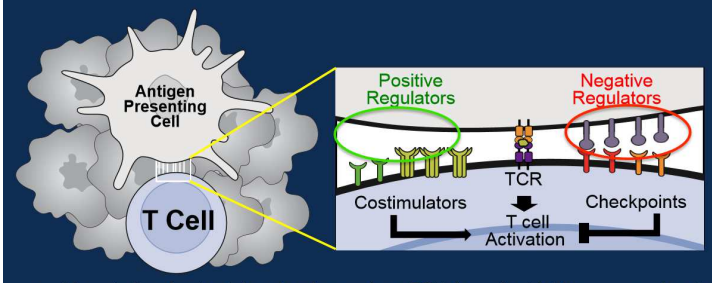
T cel activatie

The tumor microenvironment favors immunosuppression



- Ligands for checkpoint molecules such as PD-L1 can be highly expressed on tumor cells and immune cells
- Ligands for costimulatory receptors are not induced

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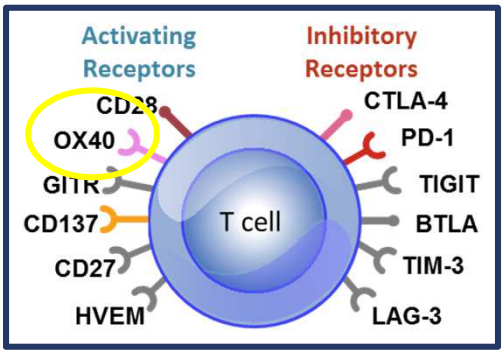
T cel activatie



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OX40

- OX40 < Tumour necrosis factor receptor superfamily
- Co-stimulatory function
- Expressed by **activated CD4+ and CD8+ Tcells**
- OX40 ligand on activated APC's
- Broadly expressed in human cancers

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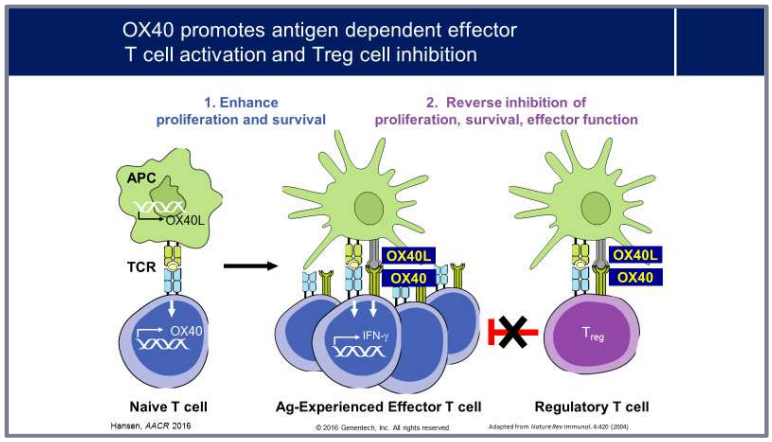
OX40



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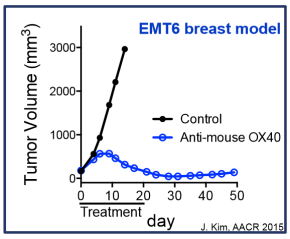
OX40 agonisten

- OX40 agonistic antibodies >>>
  - ⬆ survival and expansion of **effector Tcells**
  - ⬇ suppressive effect of **regulatory Tcells**
- Mice models



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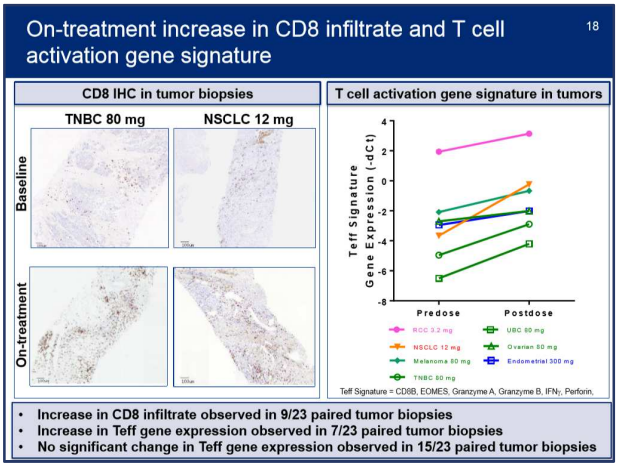
OX40 agonisten



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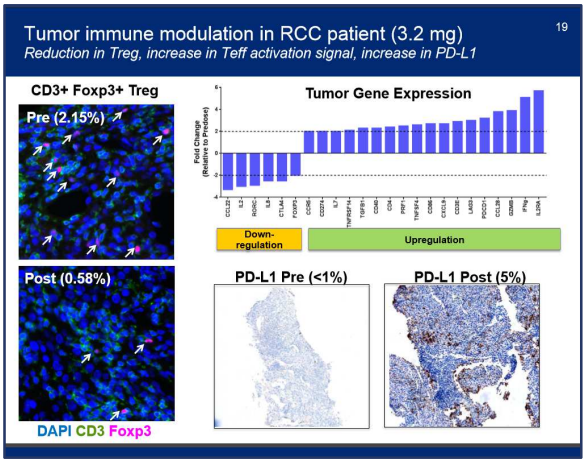
OX40 agonisten



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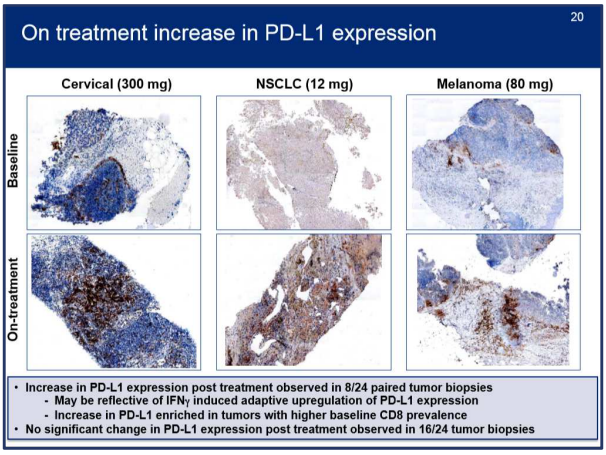
OX40 agonisten



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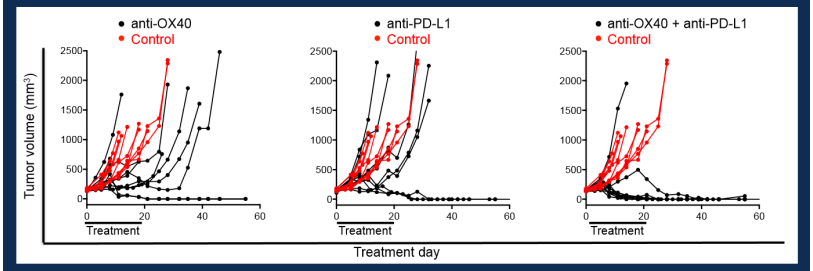
Combination OX40 agonist + PD-L1 inhibitor

Complementary efficacy of an OX40 agonist and a PD-L1 inhibitor in the syngeneic MC38 colorectal model



anti-OX40
2/10 CRs

anti-PD-L1
3/10 CRs

anti-OX40 + anti-PD-L1
9/10 CRs

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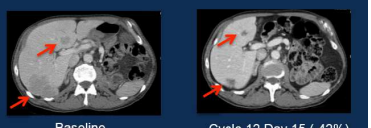
Combination OX40 agonist + PD-L1 inhibitor

Evidence of PD-L1 induction in a patient previously treated with single agent anti-OX40

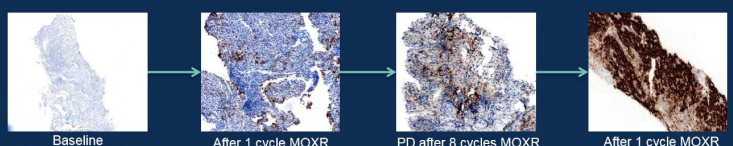
- Clear cell RCC with mets to lung, liver and pancreas s/p sunitinib, everolimus and a Notch inhibitor
- Previously on single agent MOXR0916 with pharmacodynamic response



Baseline

Cycle 12 Day 15 (-42%)

PD-L1 IHC by SP142



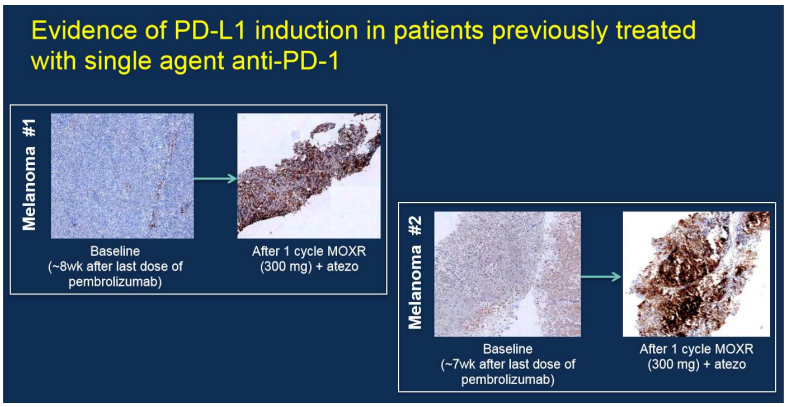
Baseline (pre-dose for PhIa)

After 1 cycle MOXR

PD after 8 cycles MOXR (pre-dose for PhIb)

After 1 cycle MOXR (12 mg) + atezo

Combination OX40 agonist + PD-L1 inhibitor



OX40 agonisten

- OX40 = co-stimulerende receptor geexprimeerd door geactiveerde Tcellen
- Promotie van effector T-cellen en afremmen regulerende T-cellen
- PD-L1 inductie
- Fase I trials: activiteit in monotherapie en in combinatie met anti PD-1.

"Not only releasing the brakes, but also stepping on the gas"