

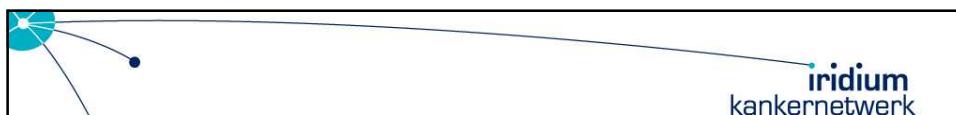


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kankernetwerk  
Radiotherapie  
Medische Oncologie  
Hematologie

## OX40 agonisten

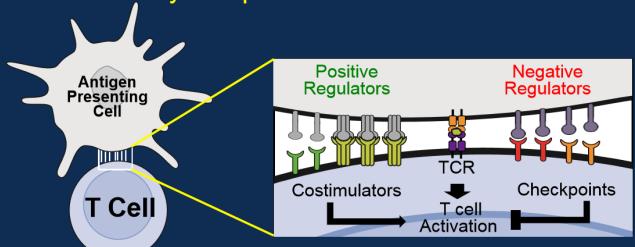
.. not only releasing the brakes,  
but also stepping on the gas!

Dr. Annemie Rutten  
Medische oncologie, St. Augustinusziekenhuis.



### 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

**T cel activatie**

The tumor microenvironment favors immunosuppression

Positive Regulators

Negative Regulators

Costimulators

TCR

T cell Activation

Checkpoints

- 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

**T cel activatie**

Activating Receptors

Inhibitory Receptors

CD28

OX40

GITR

CD137

CD27

HVEM

CTLA-4

PD-1

TIGIT

BTLA

TIM-3

LAG-3

T cell



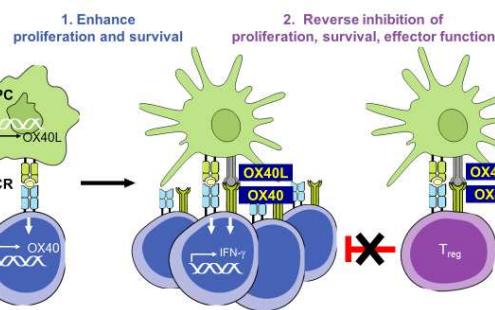
## OX40

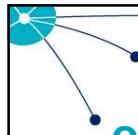
- OX40 < Tumour necrosis factor receptor superfamily
- Co-stimulatory function
- Expressed by **activated CD4+ and CD8+ Tcells**
- OX40 ligand on activated APC's
- Broadly expressed in human cancers



## OX40

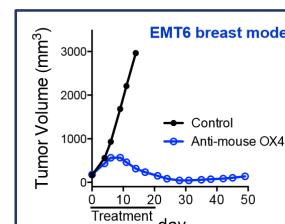
**OX40 promotes antigen dependent effector T cell activation and Treg cell inhibition**



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

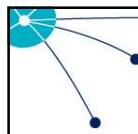


EMT6 breast model

Tumor Volume ( $\text{mm}^3$ )

Treatment day

J. Kim, AACR 2015

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On-treatment increase in CD8 infiltrate and T cell activation gene signature 18

CD8 IHC in tumor biopsies		T cell activation gene signature in tumors	
TNBC 80 mg		NSCLC 12 mg	
Baseline		Baseline	
On-treatment		On-treatment	
<ul style="list-style-type: none"> <li>Increase in CD8 infiltrate observed in 9/23 paired tumor biopsies</li> <li>Increase in Teff gene expression observed in 7/23 paired tumor biopsies</li> <li>No significant change in Teff gene expression observed in 15/23 paired tumor biopsies</li> </ul>			

CD8 IHC in tumor biopsies

Baseline

On-treatment

NSCLC 12 mg

T cell activation gene signature in tumors

Predose Postdose

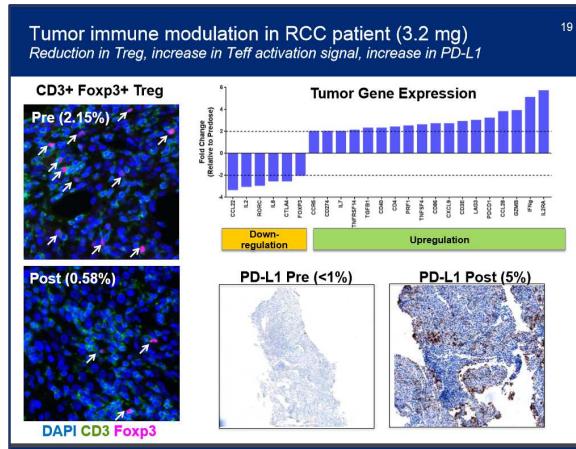
Teff Signature

Gene expression (-Δct)

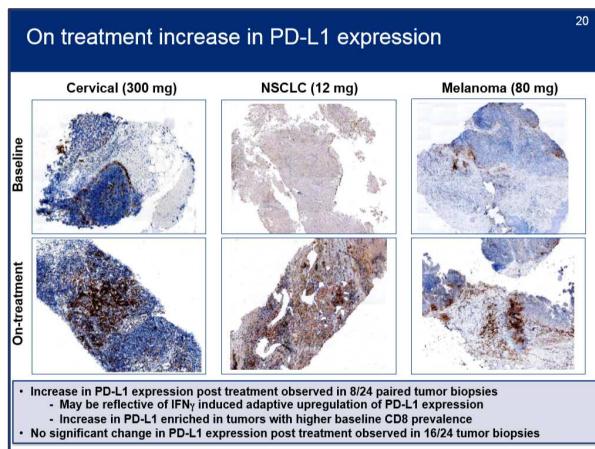
Teff Signature = CD68, EDMS, Granzyme A, Granzyme B, IFN $\gamma$ , Perforin.

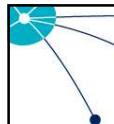
- RCC 3.2 mg
- NSCLC 12 mg
- Melanoma 80 mg
- TNBC 80 mg
- UBC 80 mg
- Ovarian 80 mg
- Endometrial 300 mg

# OX40 agonisten



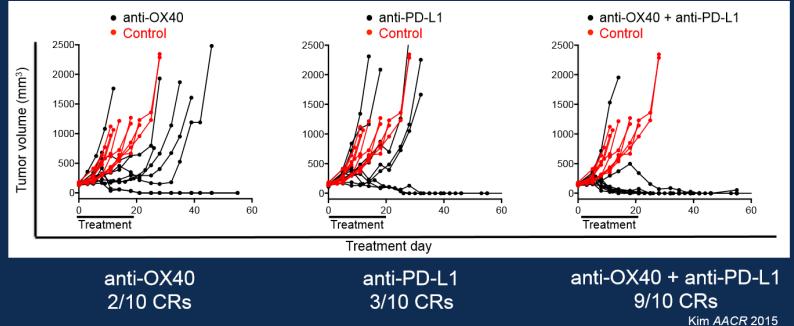
## OX40 agonisten



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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

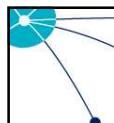


anti-OX40  
2/10 CRs

anti-PD-L1  
3/10 CRs

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

Kim AACR 2015

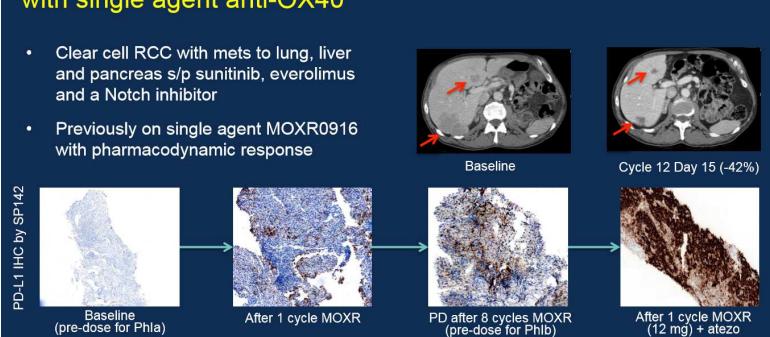
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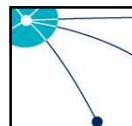
## Combination OX40 agonist + PD-L1 inhibitor

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

PD-L1 IHC by SP142





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## Combination OX40 agonist + PD-L1 inhibitor

Evidence of PD-L1 induction in patients previously treated with single agent anti-PD-1

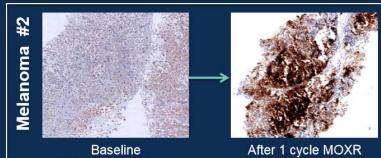
**Melanoma #1**



Baseline (~8wk after last dose of pembrolizumab)

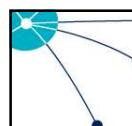
After 1 cycle MOXR (300 mg) + atezo

**Melanoma #2**



Baseline (~7wk after last dose of pembrolizumab)

After 1 cycle MOXR (300 mg) + atezo



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## OX40 agonisten

- OX40 = co-stimulerende receptor geëxprimeerd door geactiveerde Tcellen
- Promotie van effector T-cell en afremmen regulerende T-cell
- 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"*