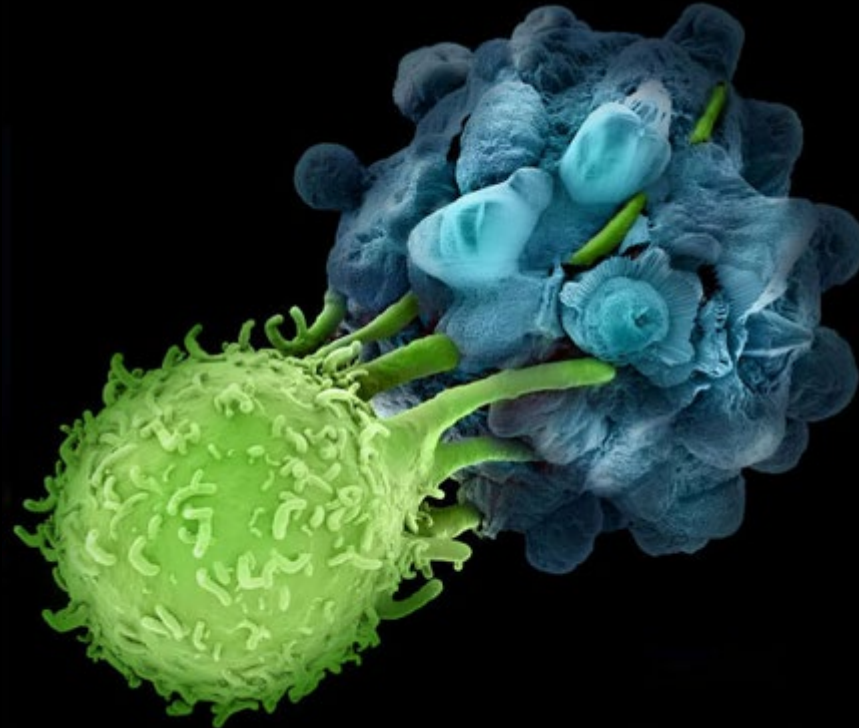


**Using *Low Dose and Intermediate-affinity IL-2 receptor agonist (Nemvaleukin alfa) with XRT to address PD1 Resistance***



James Welsh, MD  
Professor

Thoracic Radiation Oncology  
Head of Immuno Radiation

# Disclosures

Employment: University of Texas MD Anderson

Founder: Healios Oncology, MolecularMatch.com, OncoResponse

Equity Ownership: (Holds/held stock) Alpine, Checkmate, Mavu, Legion Healthcare Partners, MolecularMatch, NanoRobotix, OncoResponse, Reflexion and Healios.

Research Support: GlaxoSmithKline, BMS, Incyte, GSK, Merck, Nanobiotix, **Alkermes**, Artidis, Mavu Pharma, Takeda, Varian, Genentech, Reflexion, Checkmate Pharmaceuticals.

Trademarks: **RadScopal™**

Patents: MP470 (amuvatinib), MRX34 regulation of PDL1, XRT technique to overcome immune resistance

Join steering committee: Nanobiotix

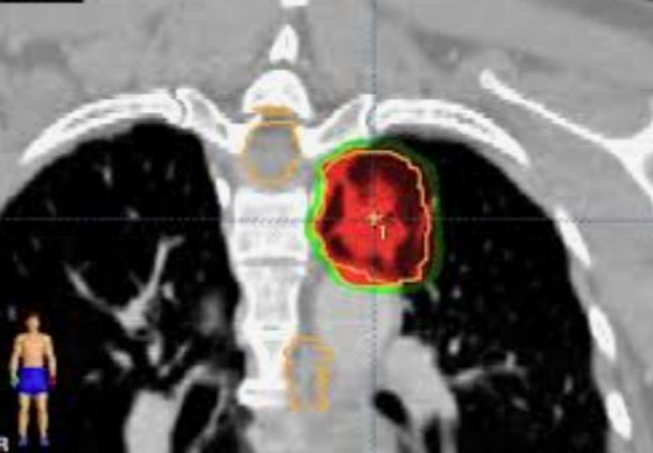
Advisor: Astra Zeneca, OncoResponse, Merck, MolecularMatch, Incyte, Aileron and Nanobiotix

Consultant: Lifescience Dynamics Limited

Scientific Advisory Board: Serves/has served Legion Healthcare Partners, RefleXion Medical, MolecularMatch, Merck, AstraZeneca, Aileron Therapeutics, OncoResponse, Checkmate Pharmaceuticals, Mavu Pharma, Alpine Immune Sciences, Ventana Medical Systems, Nanobiotix, China Medical Tribune, GI Innovation, Genentech and Nanorobotix.

Has/ Had Speaking engagements: Ventana Medical Systems, US Oncology, Alkermes, Boehringer Ingelheim, Accuray

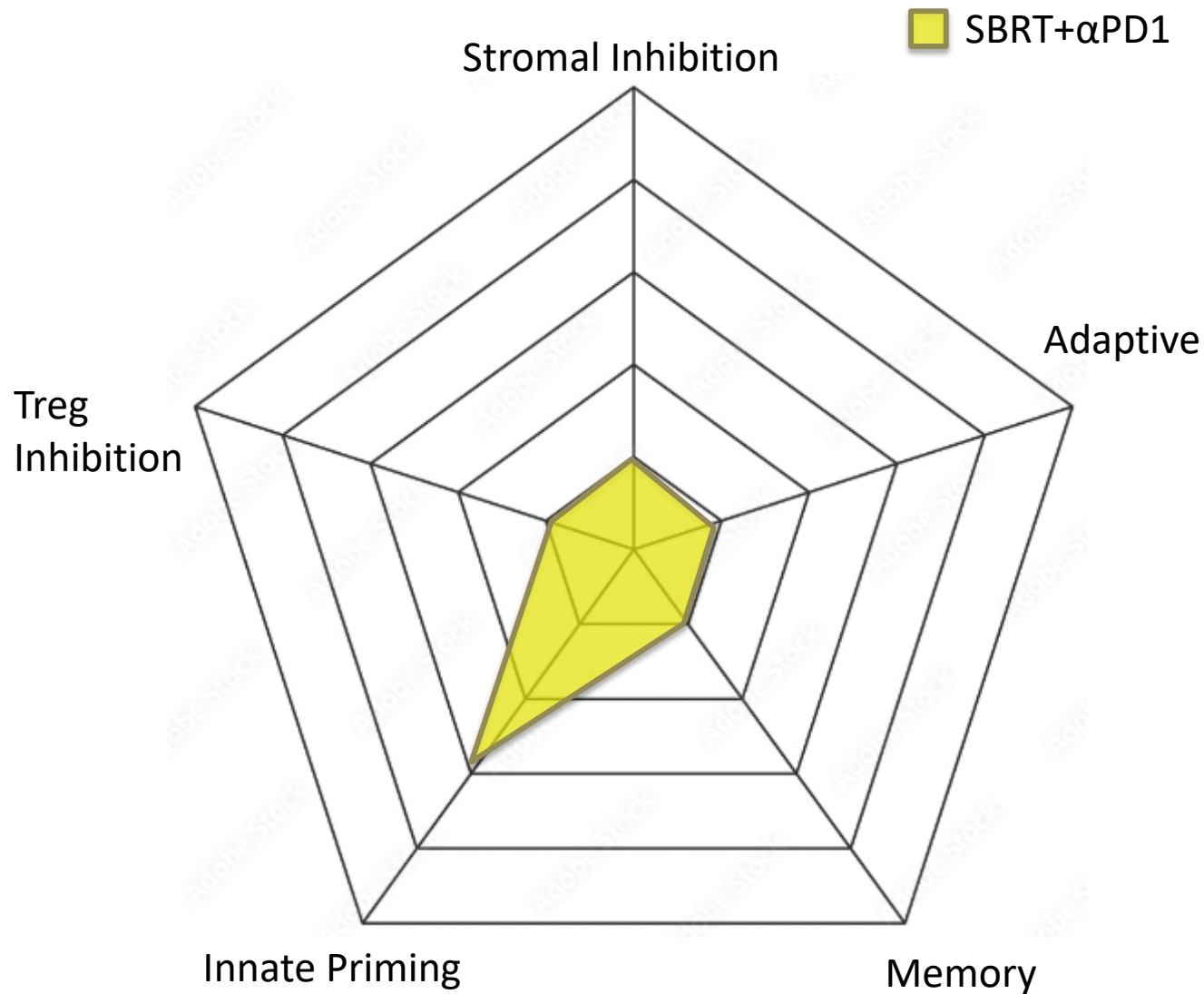
Has accepted honoraria in the form of travel costs from Nanobiotix, RefleXion, Varian, Shandong University, The Korea Society of Radiology, Aileron Therapeutics and Ventana.

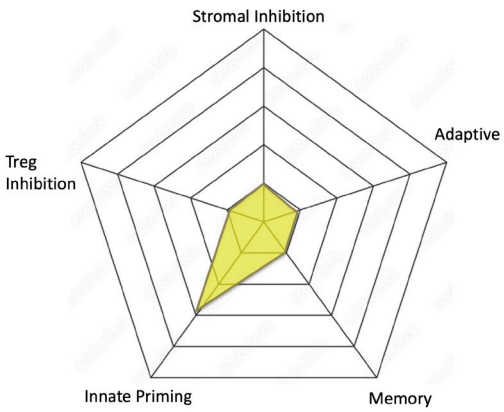


# SBRT Plus anti-PD1

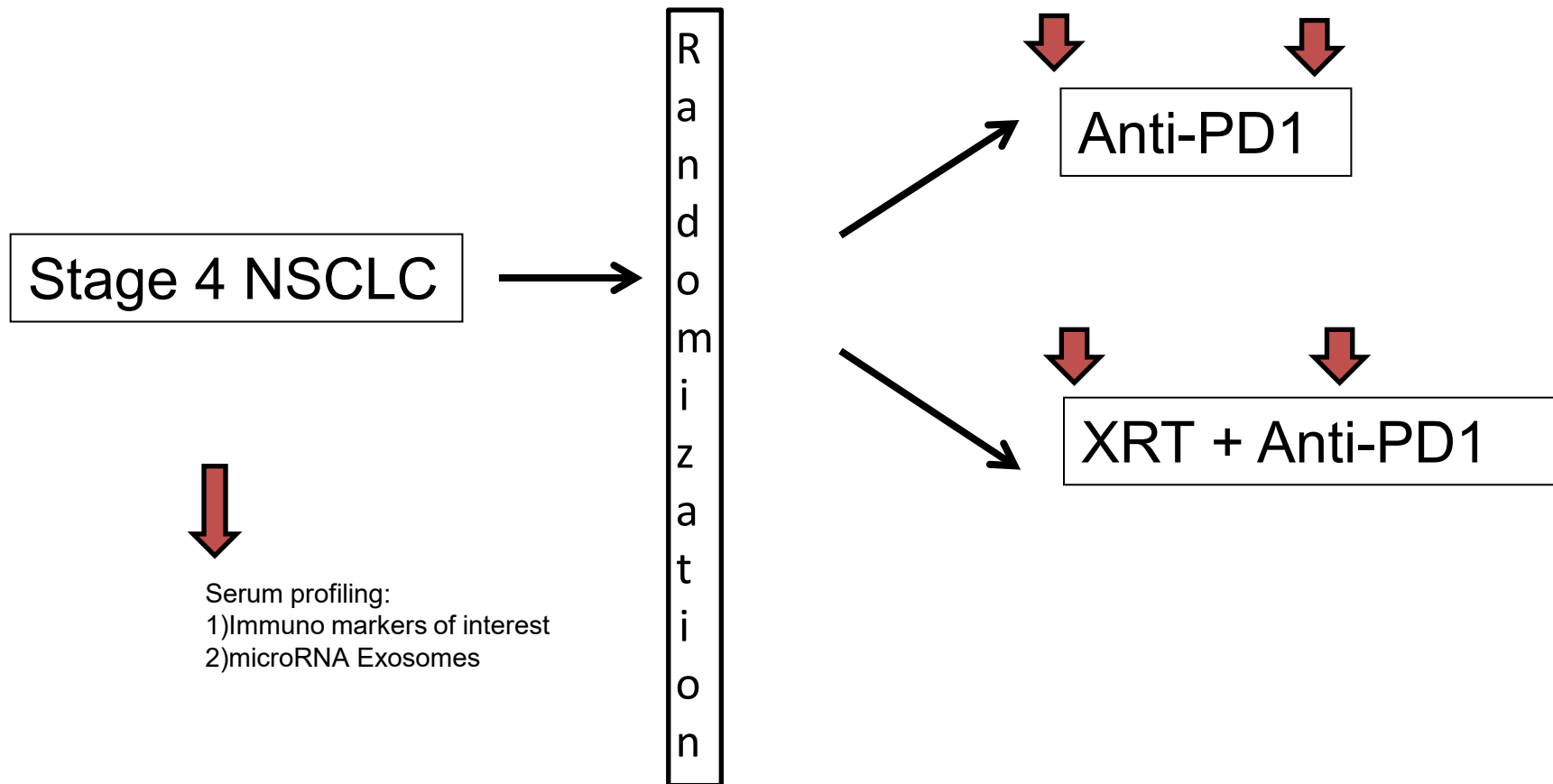
-SBRT in newly diagnosed NSCLC:  
Doubled PFS and doubled OS

-SBRT for PD1 resistance 11%  
response



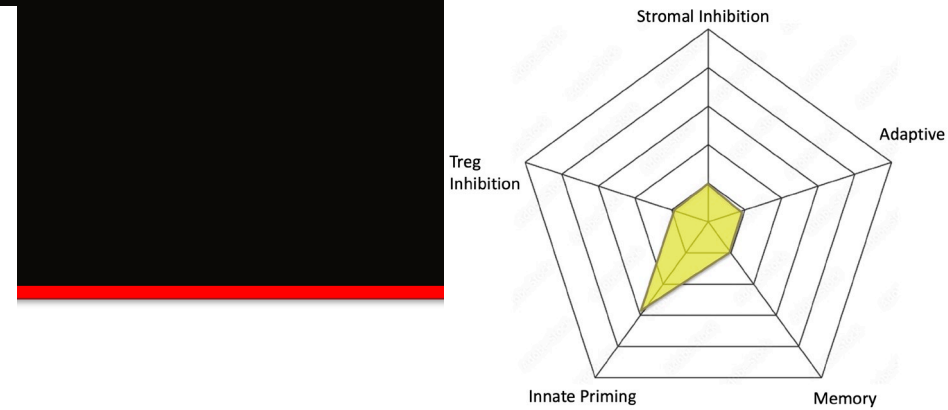


# Phase I/II Randomized Trial of PD1 (Immunotherapy) with or without XRT in Patients with NSCLC

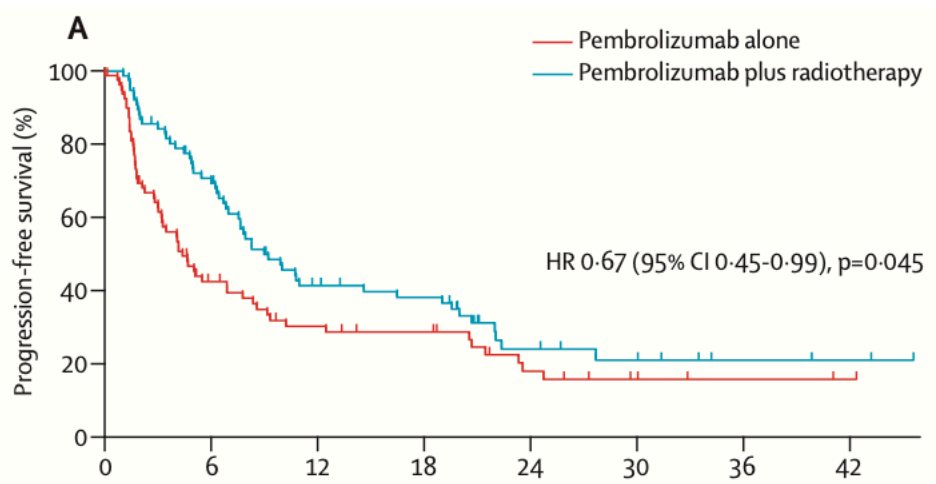


# Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials

Willemijn S M E Theelen\*, Dawei Chen\*, Vivek Verma, Brian P Hobbs, Heike M U Peulen, Joachim G J V Aerts, Idris Bahce, Anna Larissa N Niemeijer, Joe Y Chang, Patricia M de Groot, Quynh-Nhu Nguyen, Nathan I Comeaux, George R Simon, Ferdinandos Skoulidis, Steven H Lin, Kewen He, Roshal Patel, John Heymach†, Paul Baast†, James W Welsh†

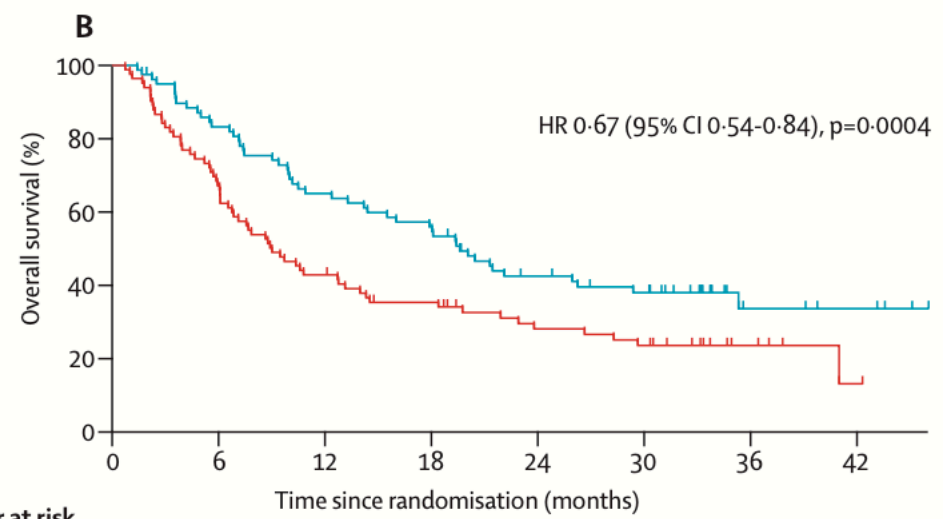


PFS 4.4 m with anti PD1  
PFS 9.0 m with SBRT + anti PD1



	0	6	12	18	24	30	36	42
<b>Number at risk (number censored)</b>								
Pembrolizumab alone	76 (0)	30 (7)	20 (9)	17 (11)	9 (14)	5 (17)	3 (19)	2 (21)
Pembrolizumab plus radiotherapy	72 (0)	53 (2)	28 (5)	25 (7)	11 (14)	8 (16)	4 (20)	3 (21)

OS 8.7 m with anti PD1  
OS 19.2 m with SBRT + anti PD1

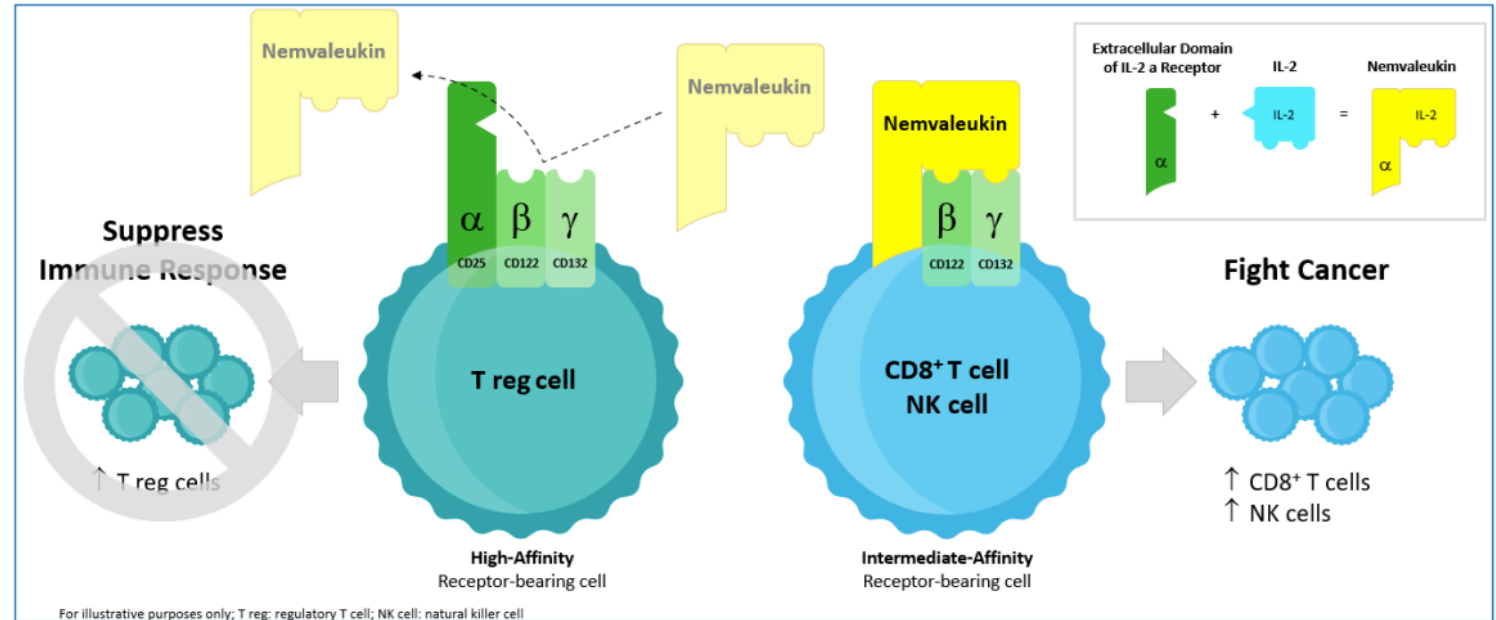


	0	6	12	18	24	30	36	42
<b>Number at risk (number censored)</b>								
Pembrolizumab alone	76 (0)	54 (0)	33 (1)	26 (2)	18 (5)	15 (5)	6 (14)	2 (17)
Pembrolizumab plus radiotherapy	72 (0)	63 (1)	49 (1)	40 (1)	29 (4)	23 (7)	7 (12)	5 (14)

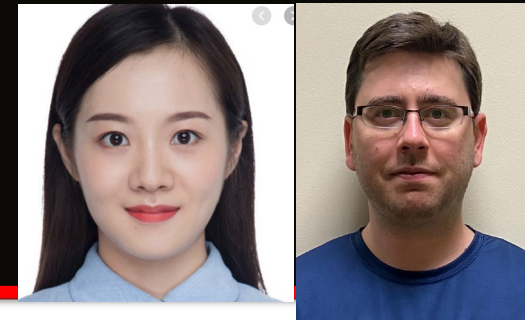
# Nemvaleukin alfa: Engineered to Capture and Expand the Therapeutic Potential of High-Dose IL-2

## Nemvaleukin's design intentions:

- Preferentially expand cancer-fighting CD8<sup>+</sup> T cells and natural killer (NK) cells to potentially improve anti-tumor efficacy
- Prevent engagement with the high-affinity IL-2 receptor to mitigate:
  1. IL-2-derived expansion of immunosuppressive regulatory T cells (T regs)
  2. Activation of vascular endothelial cells, which has been associated with certain side effects of hdIL-2, including vascular leak syndrome

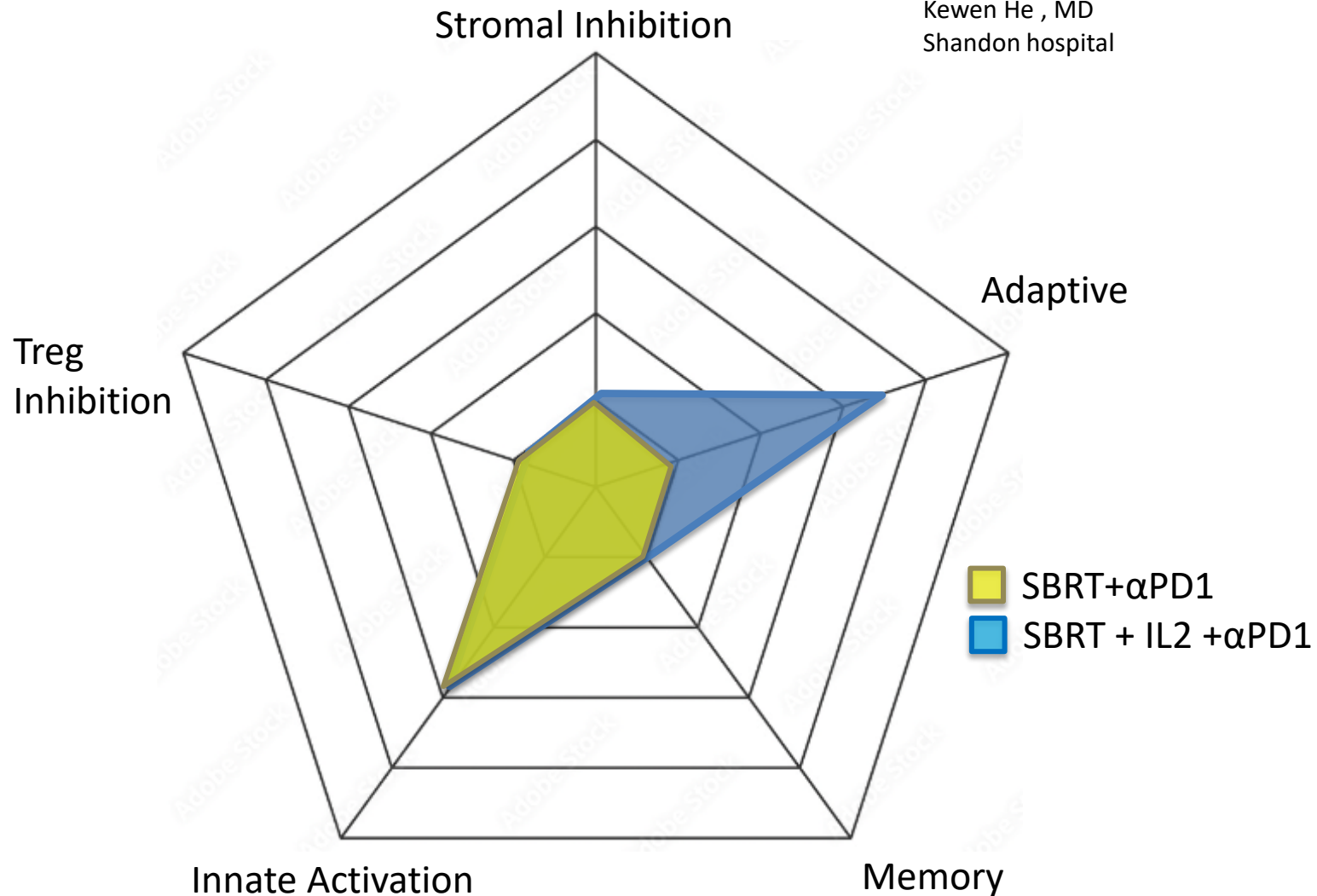


# Selective Agonism of Intermediate-Affinity IL-2 Receptor with Mouse Nemvaleukin (RDB 1462)

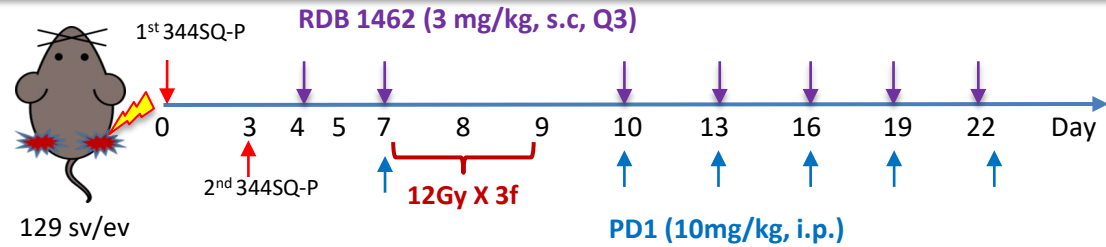


Kewen He , MD  
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Hampartsoum  
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MDACC

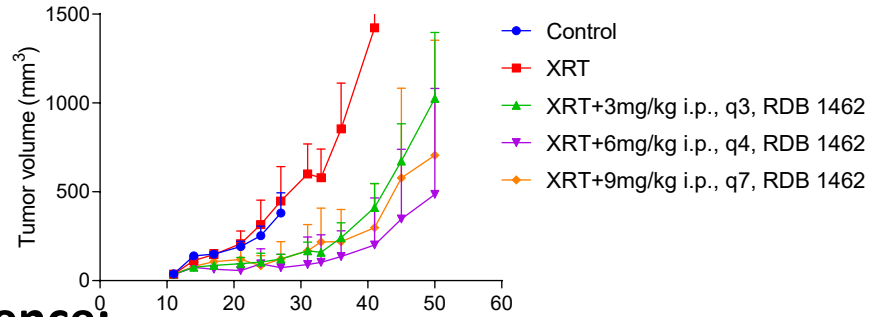


# Effects of RDB 1462 on Abscopal Induction

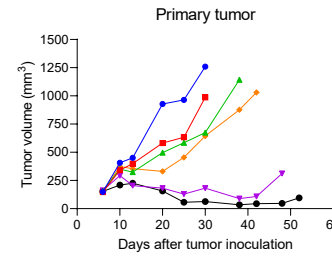
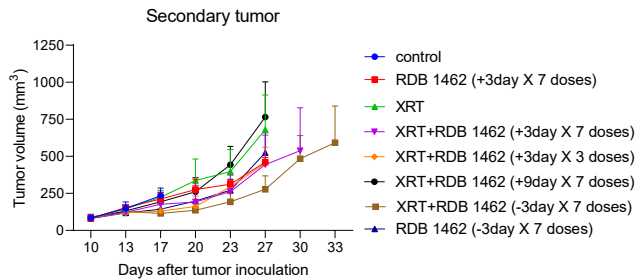
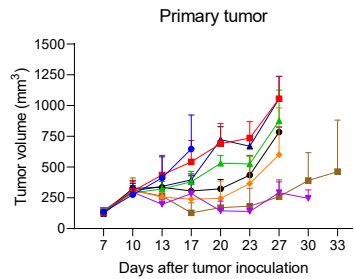


**Dose:**

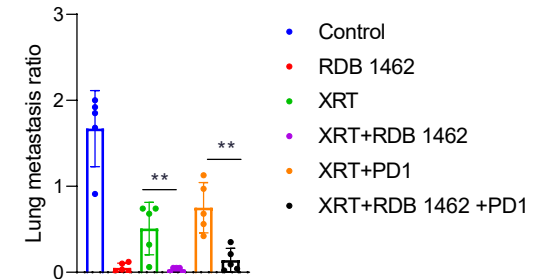
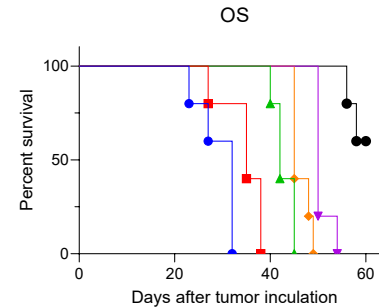
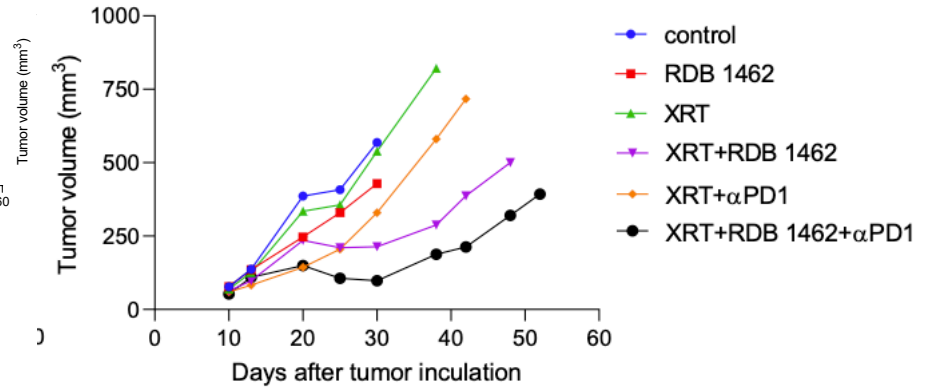
Secondary tumor



**Sequence:**



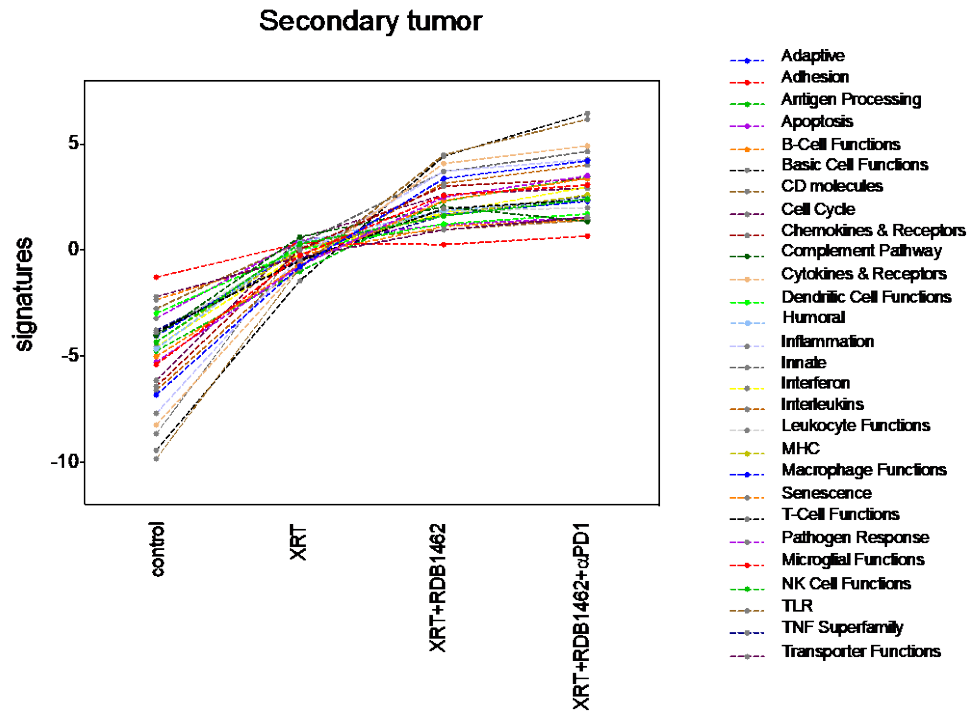
Secondary tumor



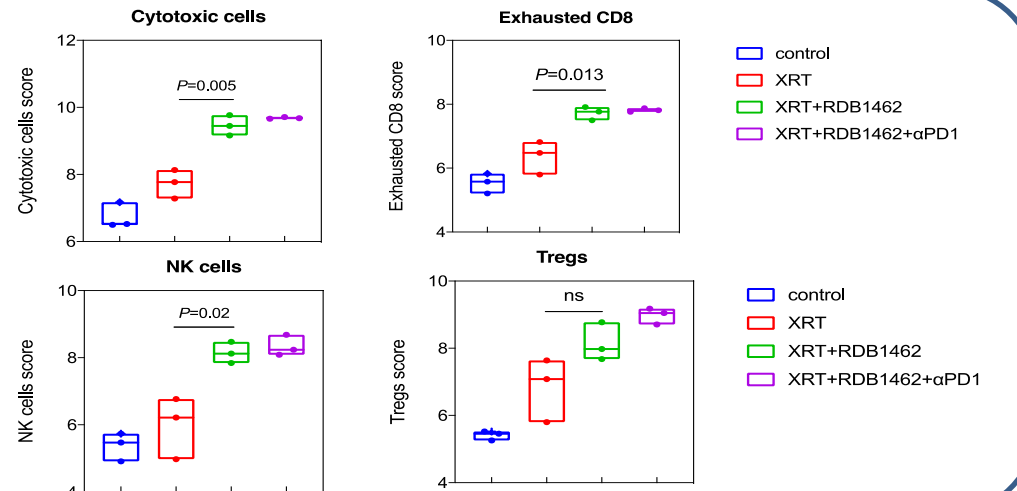
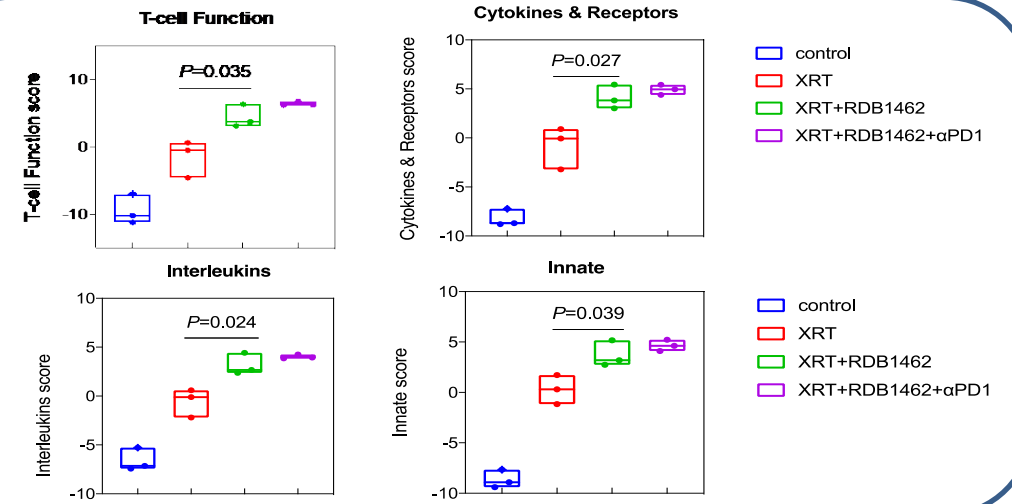
RDB 1462 = mouse equivalent of nemvaleukin



# RDB 1462 Increases T cell function but not Tregs

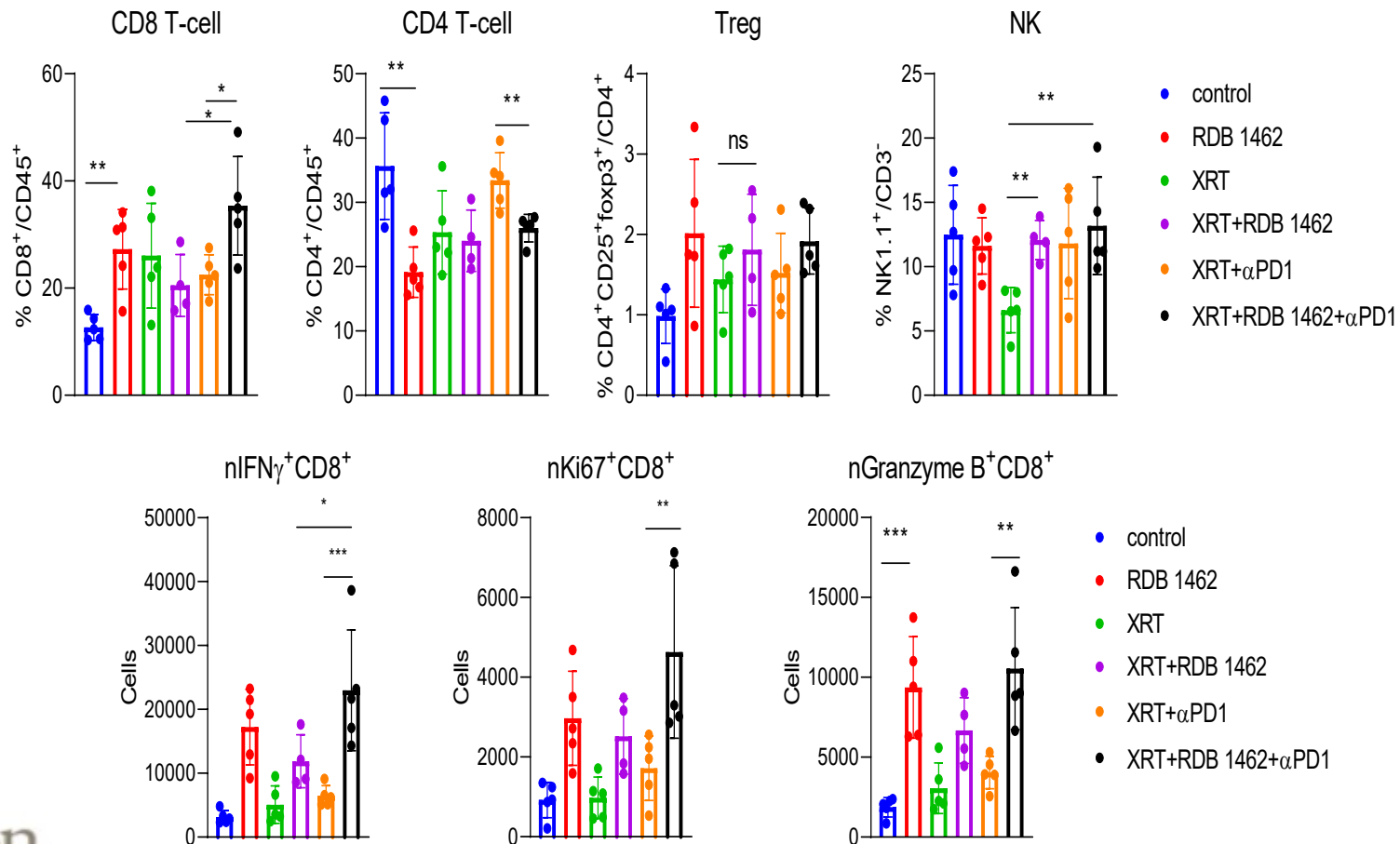


RDB 1462 = mouse equivalent of nemvaleurin

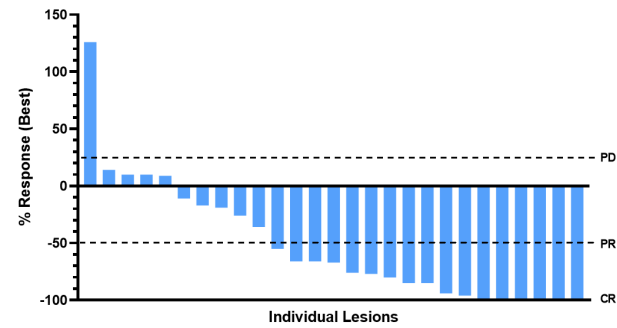


# Immune responses in NON XRT treated tumors

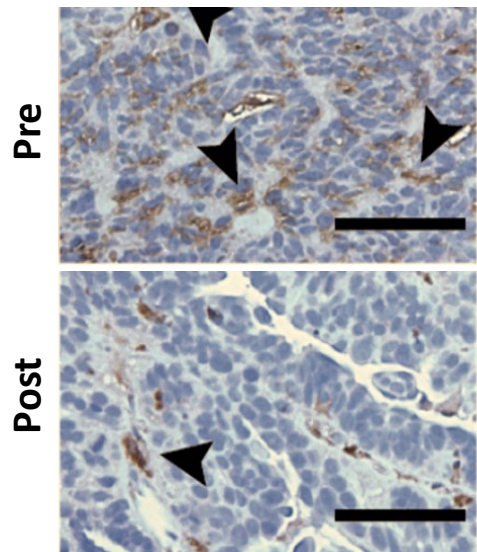
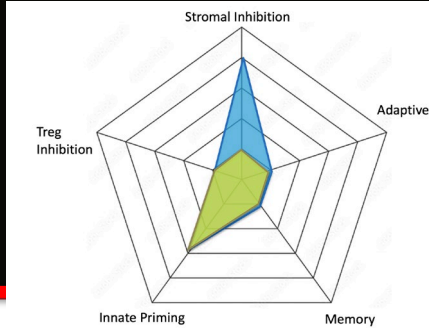
## Secondary Tumors



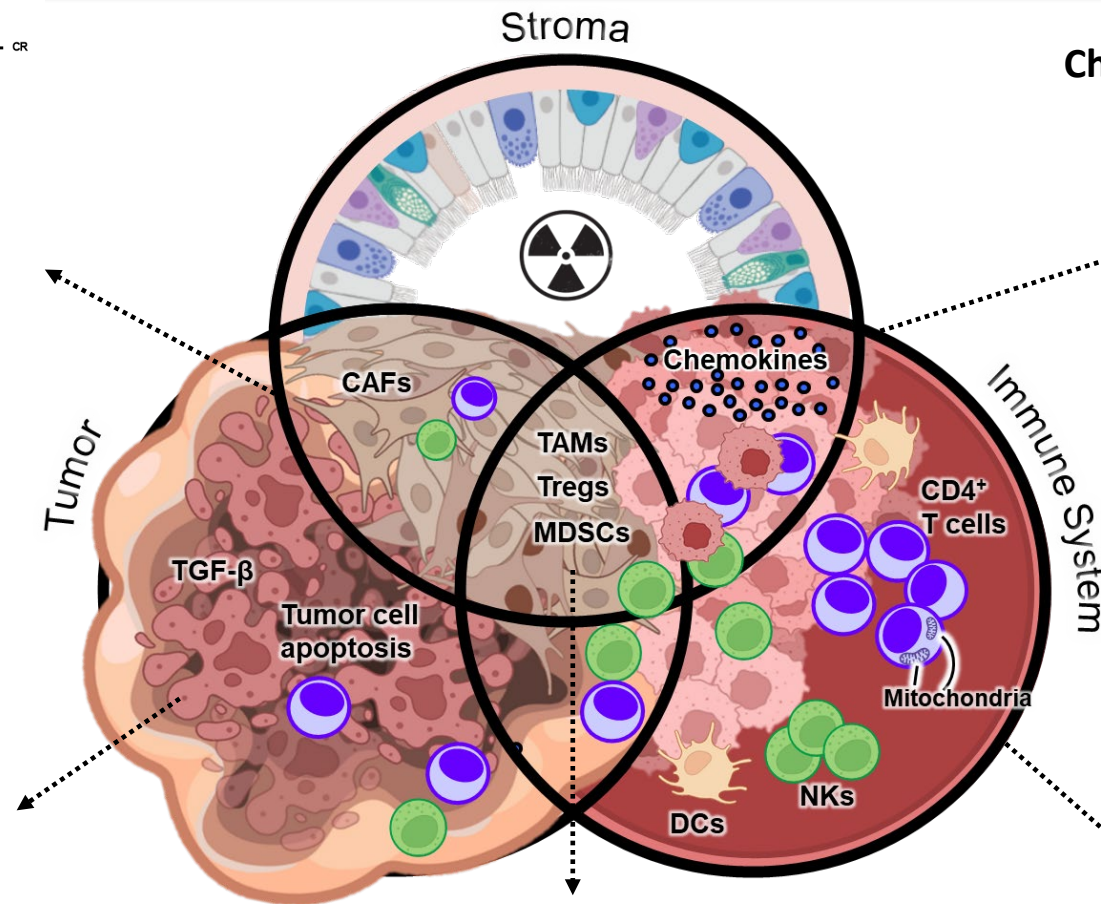
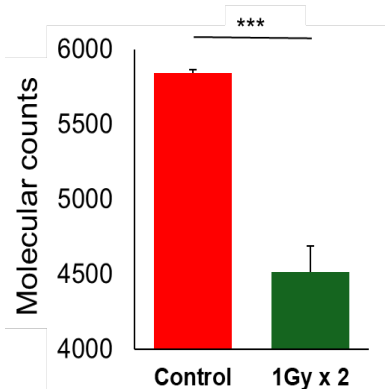
Response of Low-Dose Irradiated Lesions in Patients Who Progressed on Immunotherapy



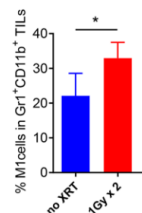
# RadScopal™ Low dose XRT impact on TME



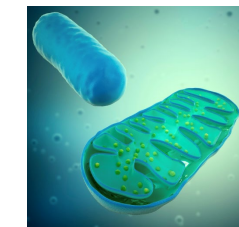
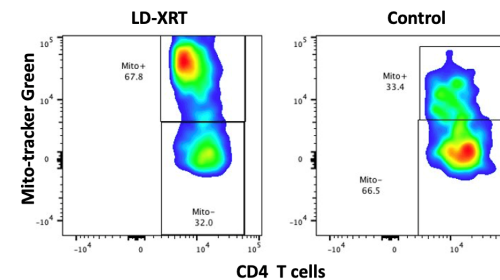
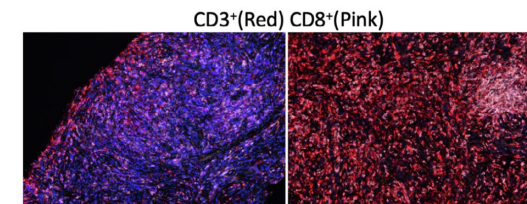
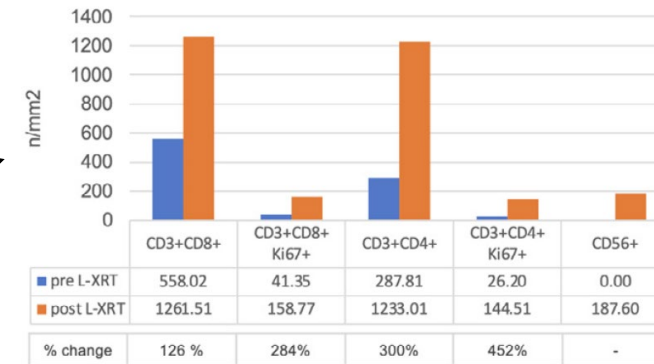
Downregulates TGF-β1



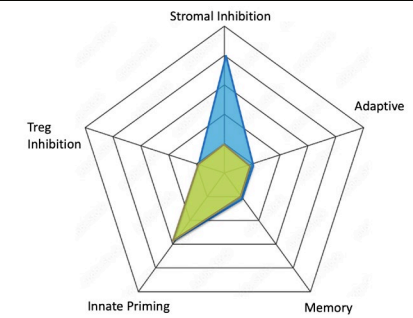
Polarizes M2 macrophages to M1



Chemokines which "pull" in CD8, CD4 and NK

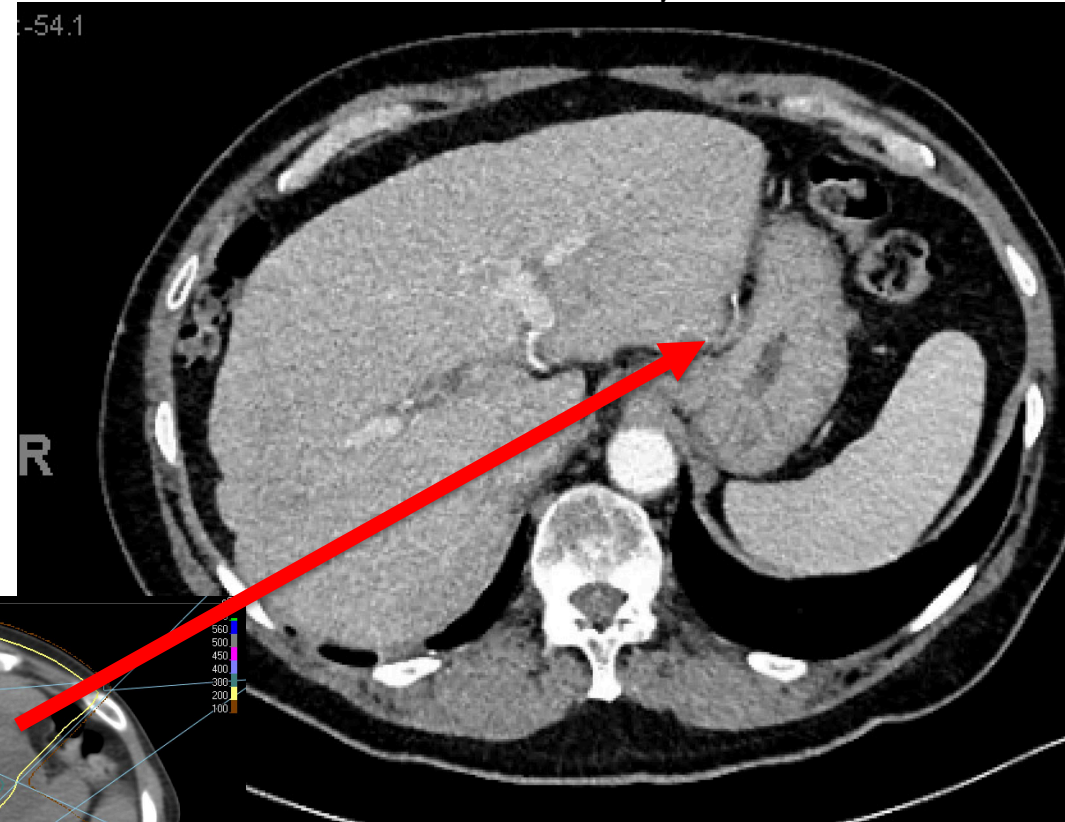


# Low-Dose Radiotherapy AFTER progression from 150 Billion TIL

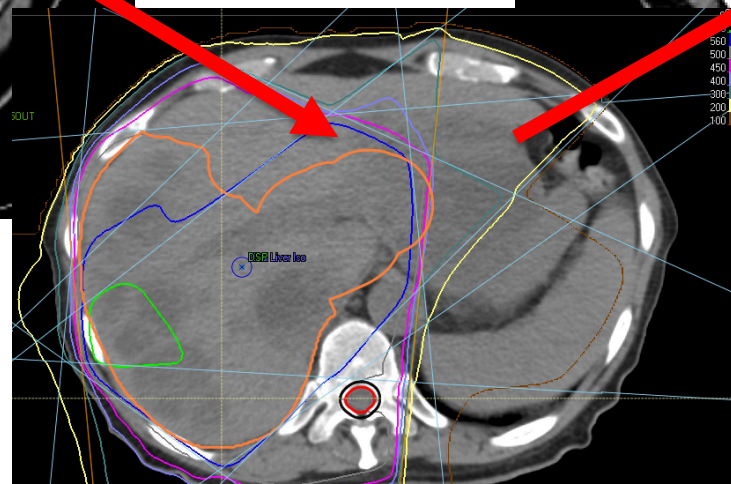


CT CAP 9/2019

CT CAP 10/2021



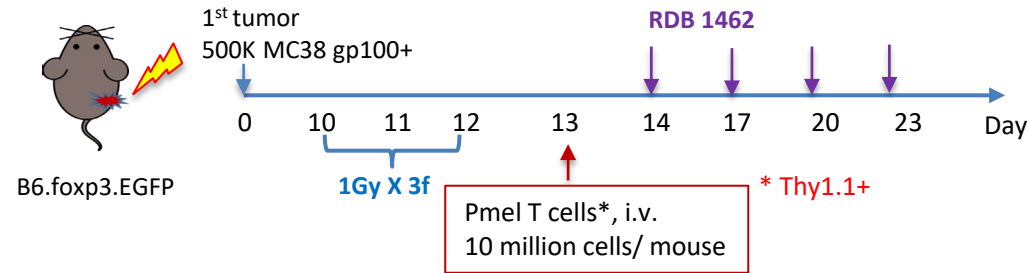
10/8-10/11:  
Low-dose RT



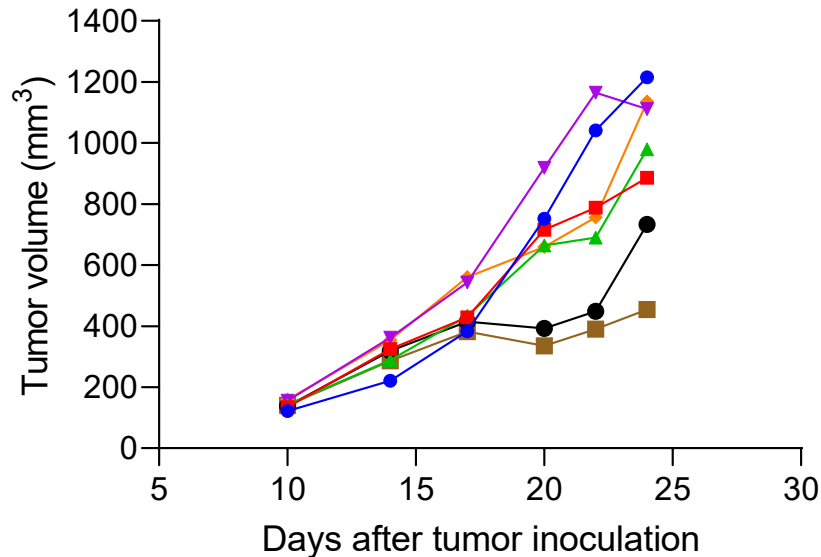
7/18/2019: Cell Therapy

Low dose XRT 1.4Gy x 4 = 5.6Gy

# Low Dose XRT and RDB 1462 Improve Cell Therapy

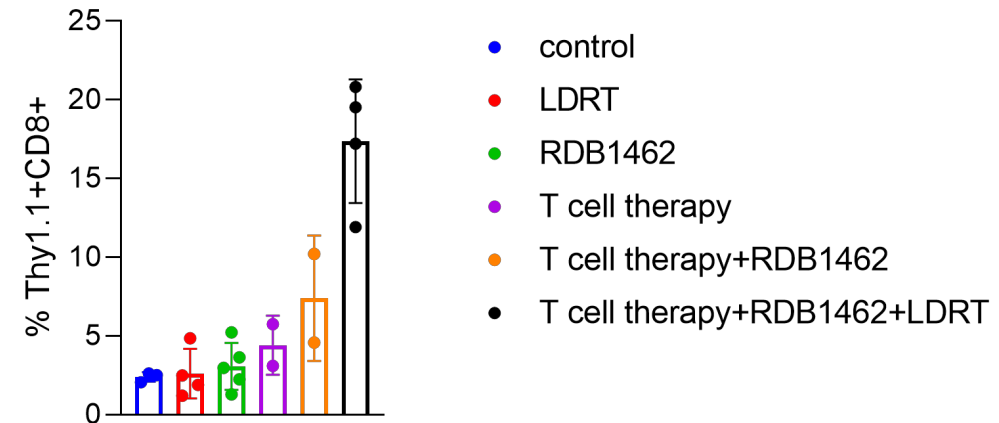


Tumor growth



- control
- LDRT
- ▲ RDB1462
- ▼ T cell therapy
- ◆ T cell therapy+RDB1462
- LDRT+RDB1462
- T cell therapy+RDB1462+LDRT

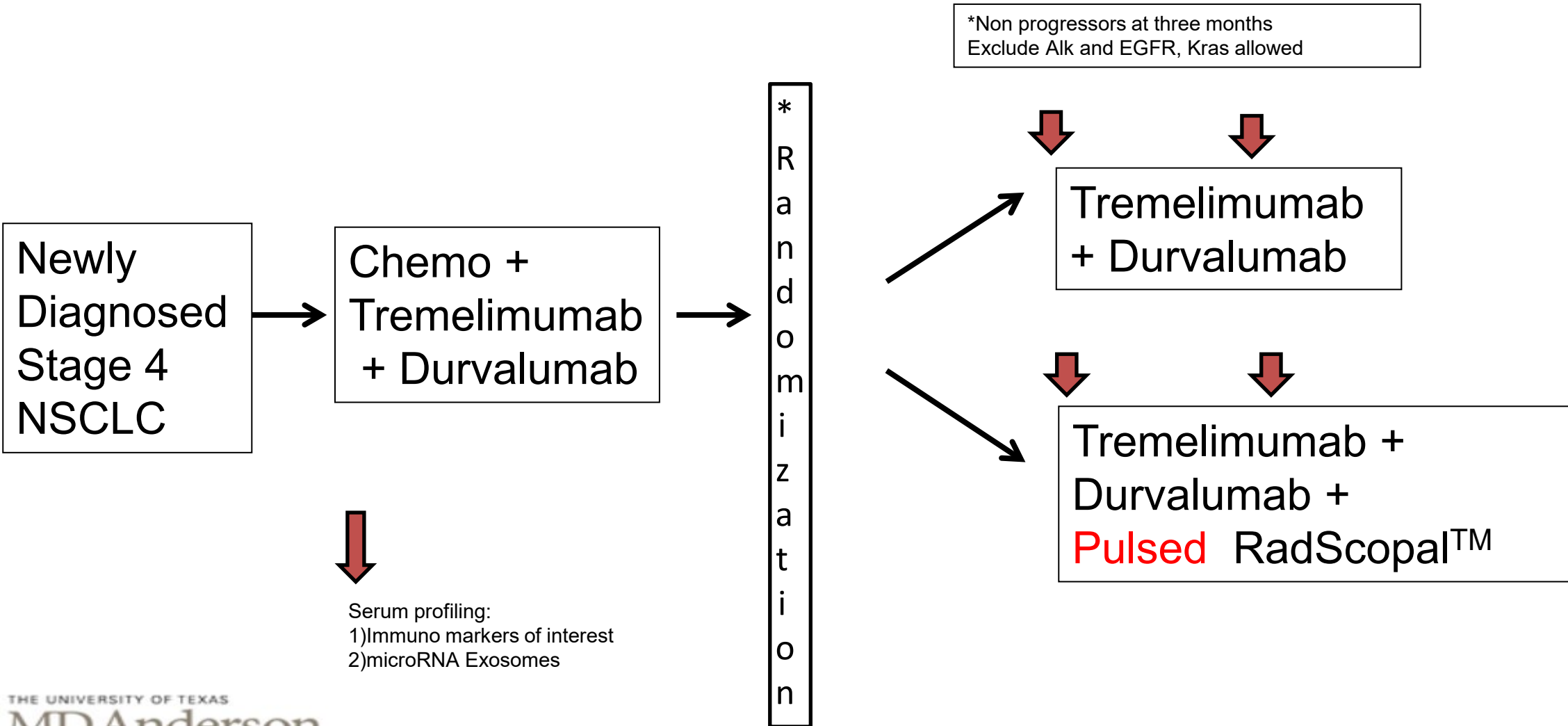
Pmel-1 T cell



- control
- LDRT
- RDB1462
- T cell therapy
- T cell therapy+RDB1462
- T cell therapy+RDB1462+LDRT

RDB 1462 = mouse equivalent of nemvaleurin

# NRG LU 2146/ SWOG : Phase II/III Randomized trial of CTLA 4 + PDL1 with or without RadScopal™ for Metastatic Non-Small Cell lung Cancer





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