

Challenges in the Development of Agonist T cell Antibody Therapy

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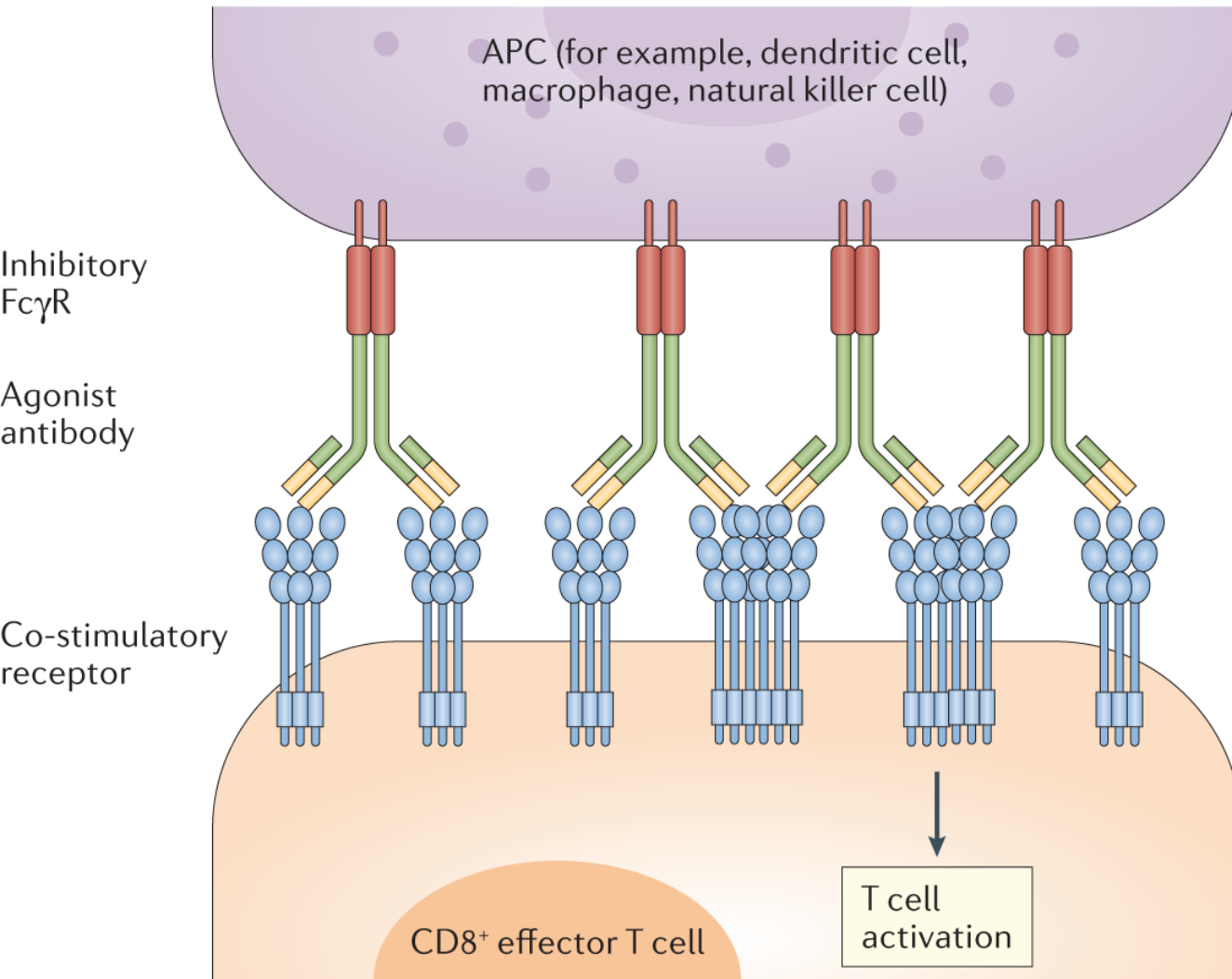
**Addressing Resistance in the Development of
Cancer Immune Modulator Therapeutics
A National Academies of Sciences, Engineering, and Medicine Workshop
November 14-15**

Agonist Antibody Targets

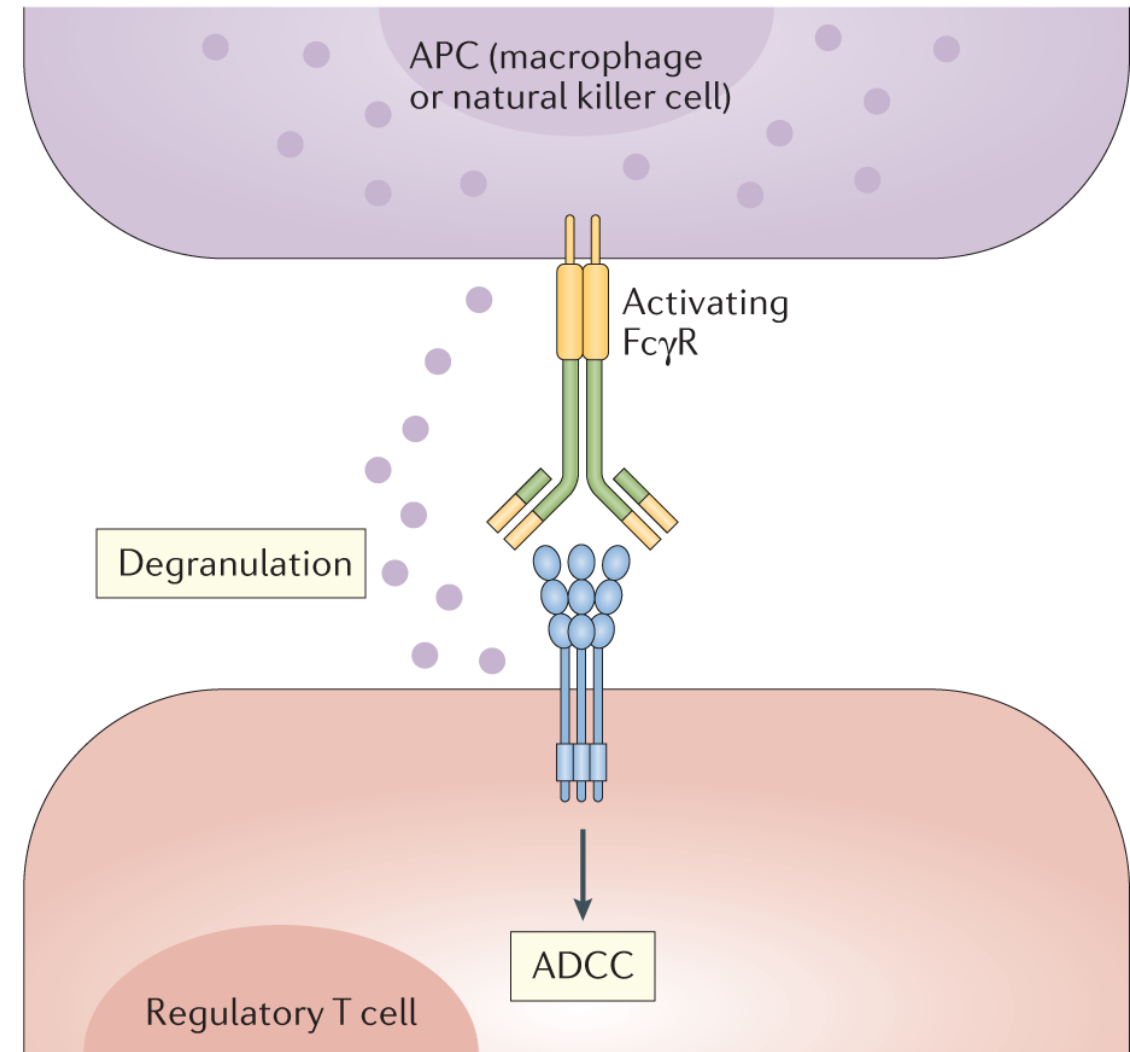
Co-Stimulatory Receptors		
OX40-OX40L	Promotes effector and memory T cell survival	
GITR-GITRL	Treg reduction and activation/proliferation of effector T cells	
4-1BB-4-1BBL	T cell proliferation and Treg reduction	
ICOS-ICOSL	TCR co-stimulation	

Differential Effects of FcγR on Agonist Antibody Function

a

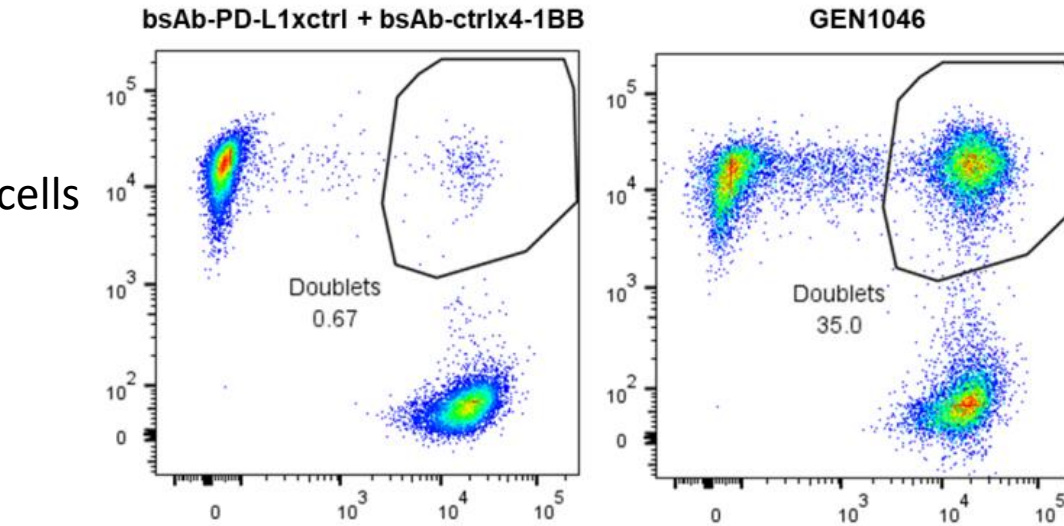


b

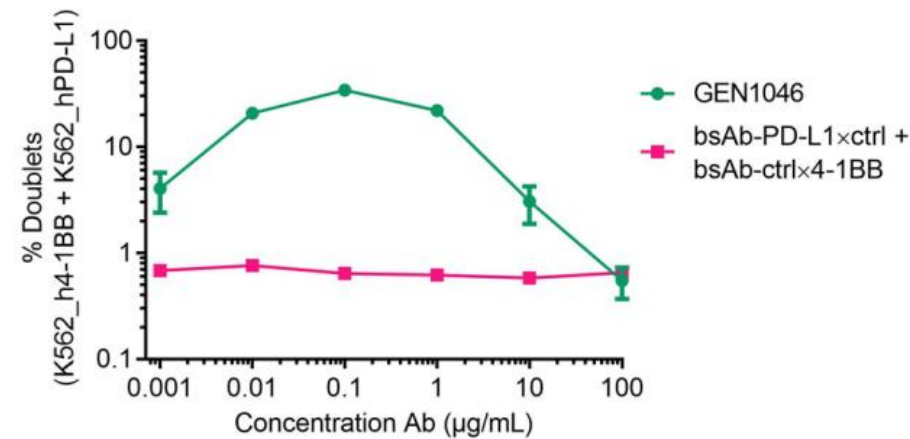


Limitations in Dose Flexibility with Agonist Antibodies

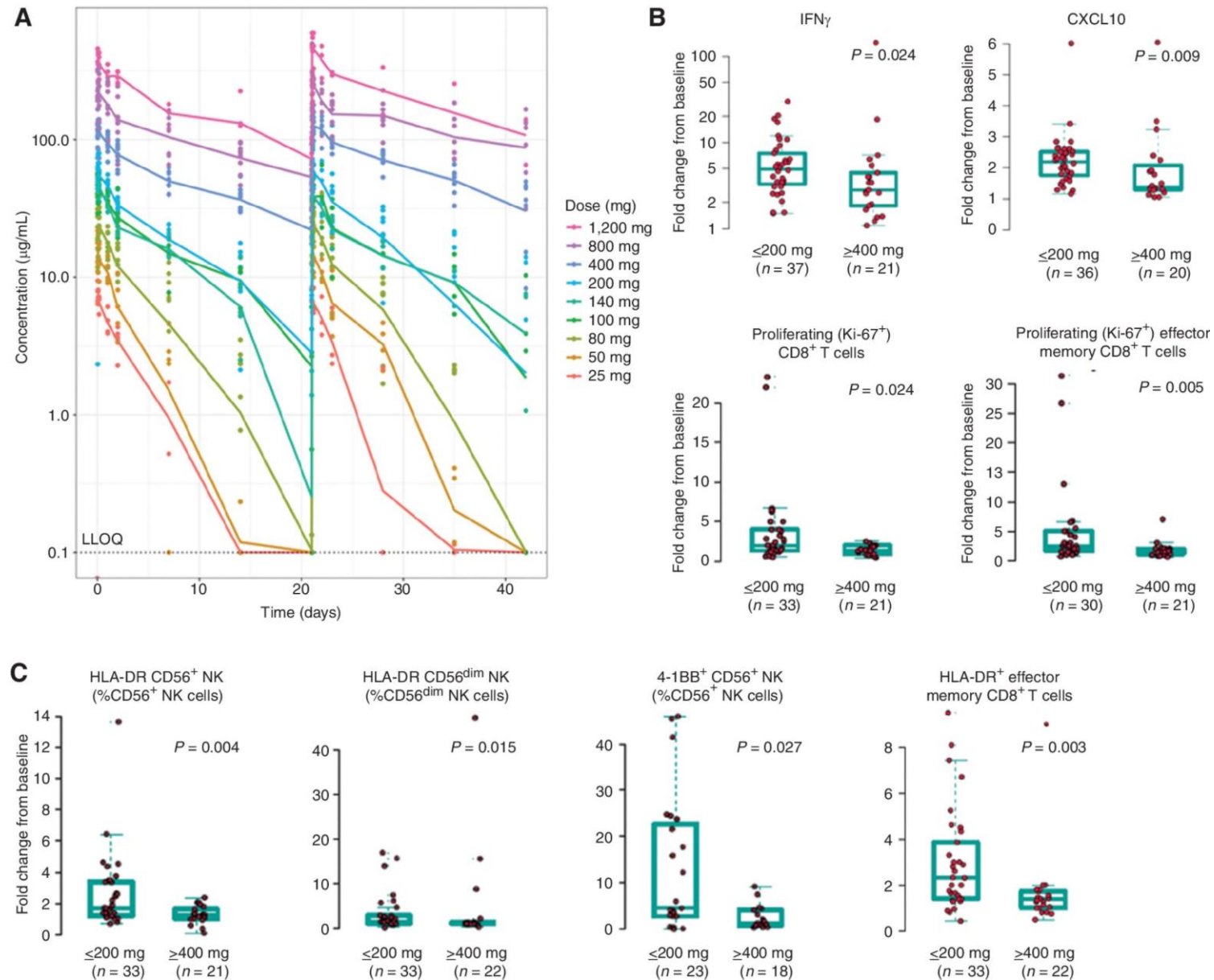
Violet-labeled K562_hPD-L1 cells



FarRed-labeled K562_h4-1BB cells



Limitations in Dose Flexibility with Agonist Antibodies

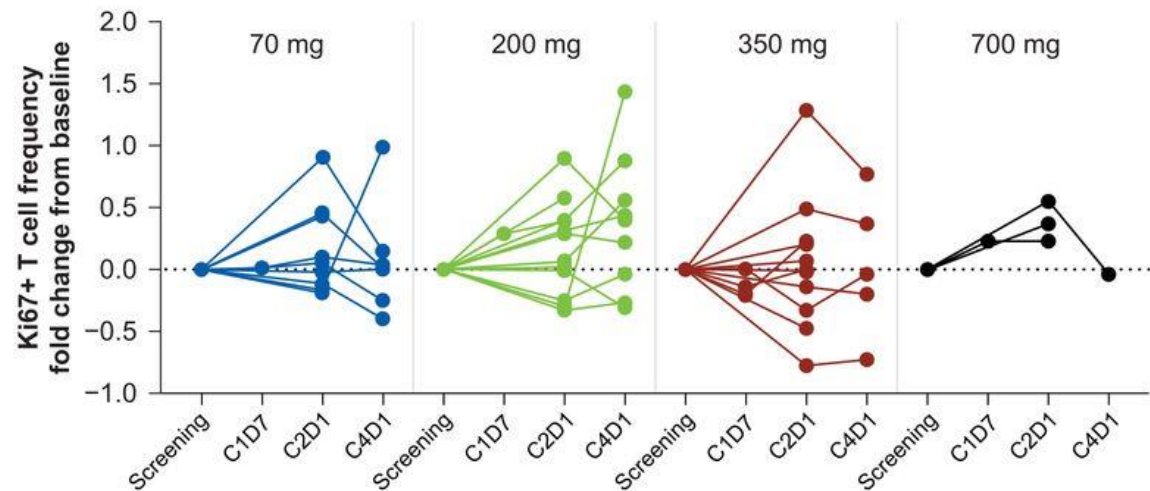


Design of INCAGN01949

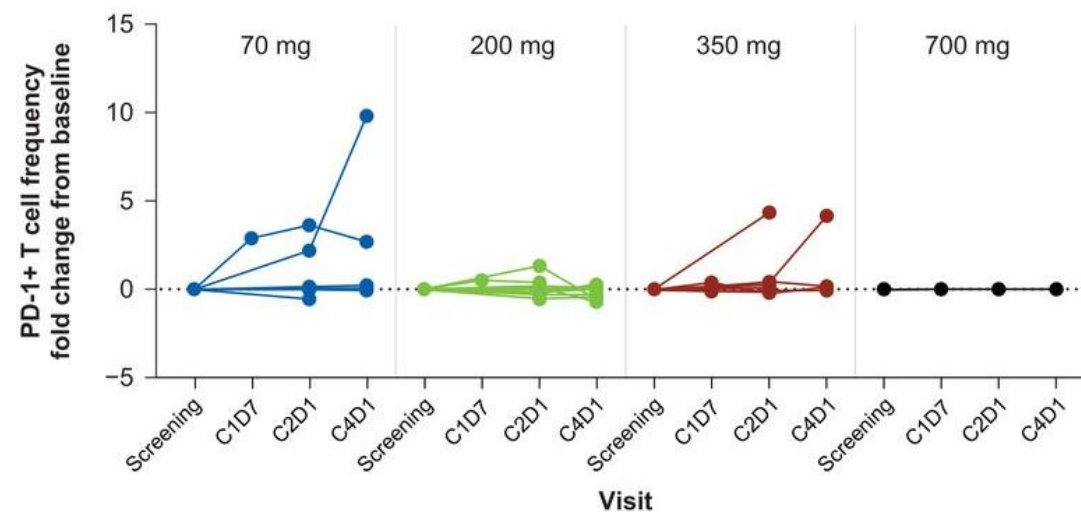
- Bell shaped activity curve for T cell stimulation in vitro was altered
- Antibody stimulated T cell proliferation in a dose-dependent fashion

T-cell activity in patients treated with INCAGN01949.

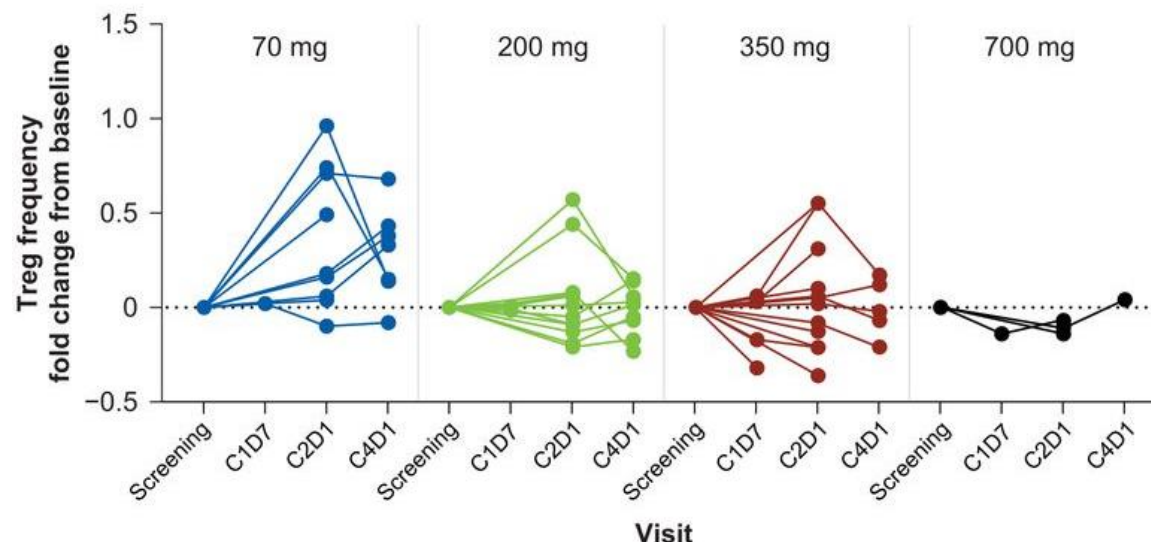
A



B



C



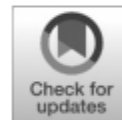
Concurrent PD-1 Blockade Negates the Effects of OX40 Agonist Antibody in Combination Immunotherapy through Inducing T-cell Apoptosis

Rajeev K. Shrimali¹, Shamim Ahmad¹, Vivek Verma¹, Peng Zeng¹, Sudha Ananth¹, Pankaj Gaur¹, Rachel M. Gittelman², Erik Yusko², Catherine Sanders², Harlan Robins^{2,3}, Scott A. Hammond⁴, John E. Janik¹, Mikayel Mkrtichyan¹, Seema Gupta¹, and Samir N. Khleif¹

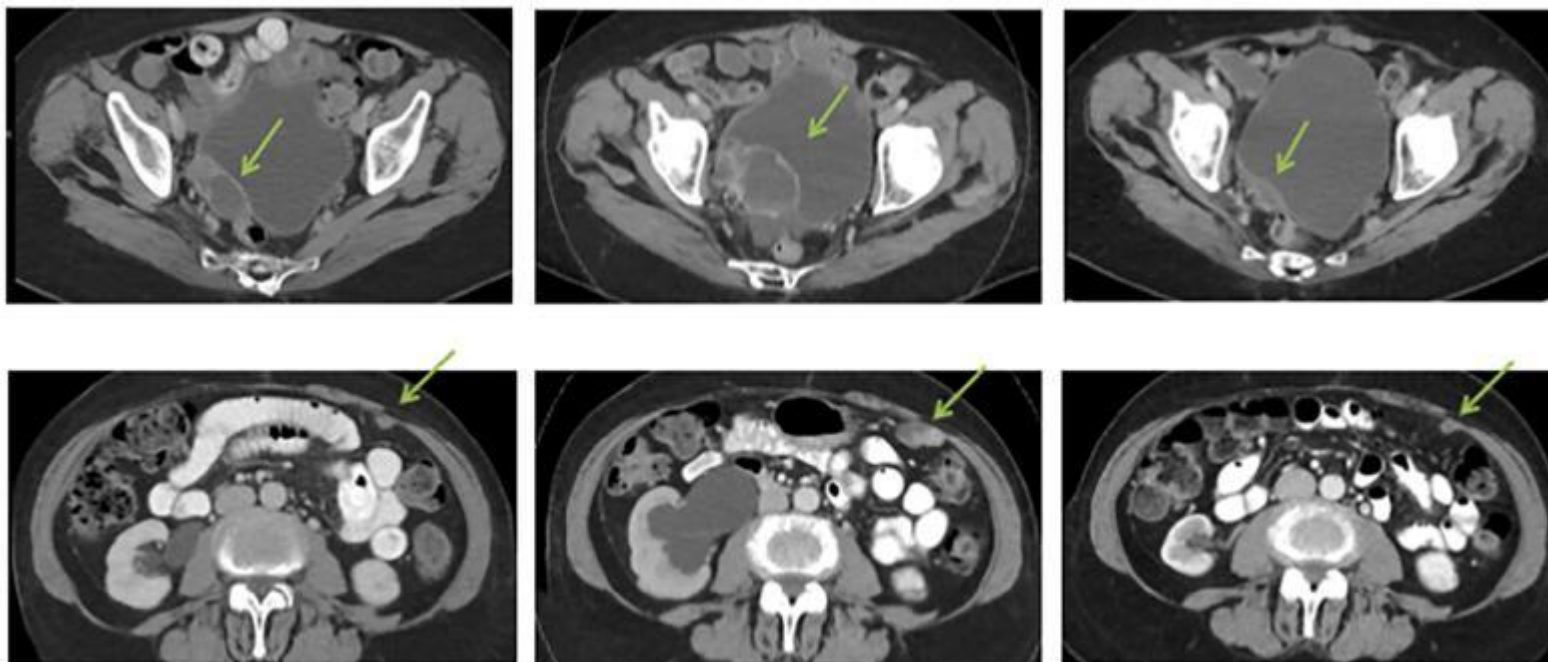


Timing of PD-1 Blockade Is Critical to Effective Combination Immunotherapy with Anti-OX40

David J. Messenheimer^{1,2}, Shawn M. Jensen¹, Michael E. Afentoulis¹, Keith W. Wegmann¹, Zipei Feng^{1,3}, David J. Friedman¹, Michael J. Gough¹, Walter J. Urba¹, and Bernard A. Fox^{1,2,3,4}



Sequential Therapy with OX40 Antibody followed by Nivolumab/Ipilimumab



2/15/2017

Pretreatment
INCAGN01949

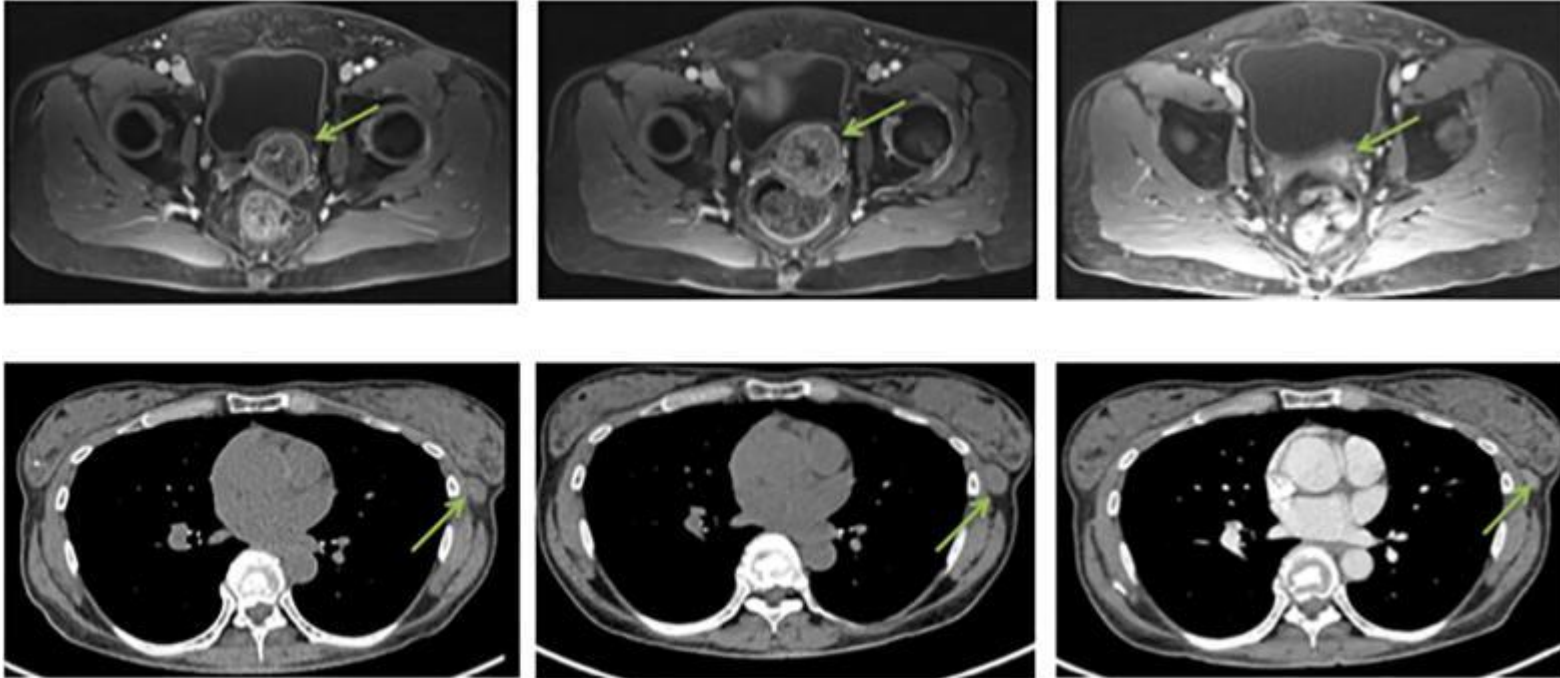
8/30/2017

End of treatment
INCAGN01949

2/18/2018

Post Nivolumab and Ipilimumab

Sequential Therapy with OX40 Antibody followed by Nivolumab/Ipilimumab



4/10/2017

6/19/2017

10/31/2017

Pretreatment
INCAGN01949

End of treatment
INCAGN01949

Post Nivolumab and Ipilimumab