SITC Winter School – 2020

T Cell Agonists

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- Targets: OX40, 4-1BB, CD27, GITR, and ICOS
- Cells that express these targets
- Molecular mechanism(s) of action
- Preclinical activity
- Agonist Abs in Clinical trials
- Outstanding questions in the field

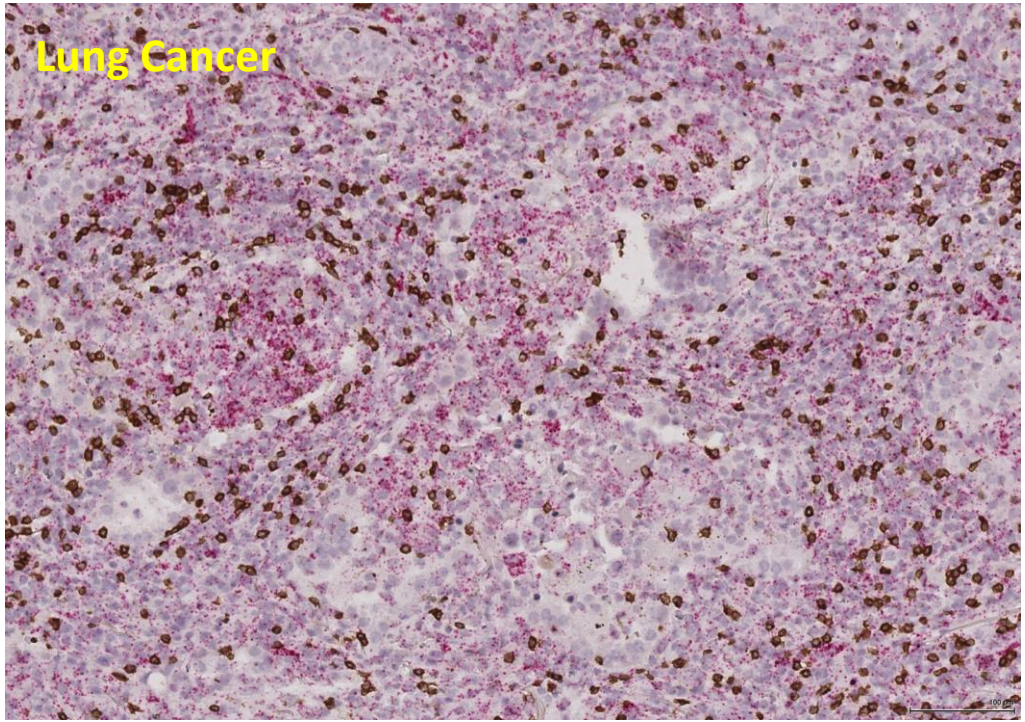
IMMUNOLOGICAL PARADIGM

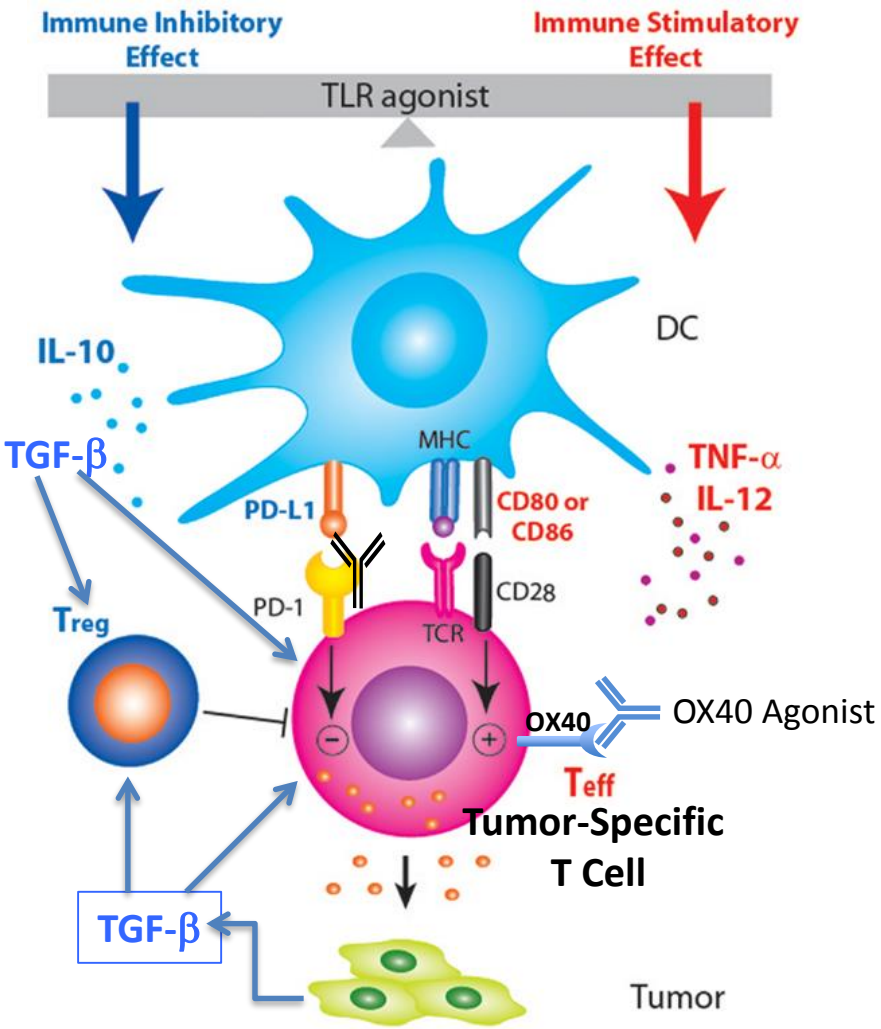
The major function of the immune system is to recognize and eliminate harmful entities within the body without destroying “self” tissue

Cancer is “harmful” – Immune Recognition of tumor Ags

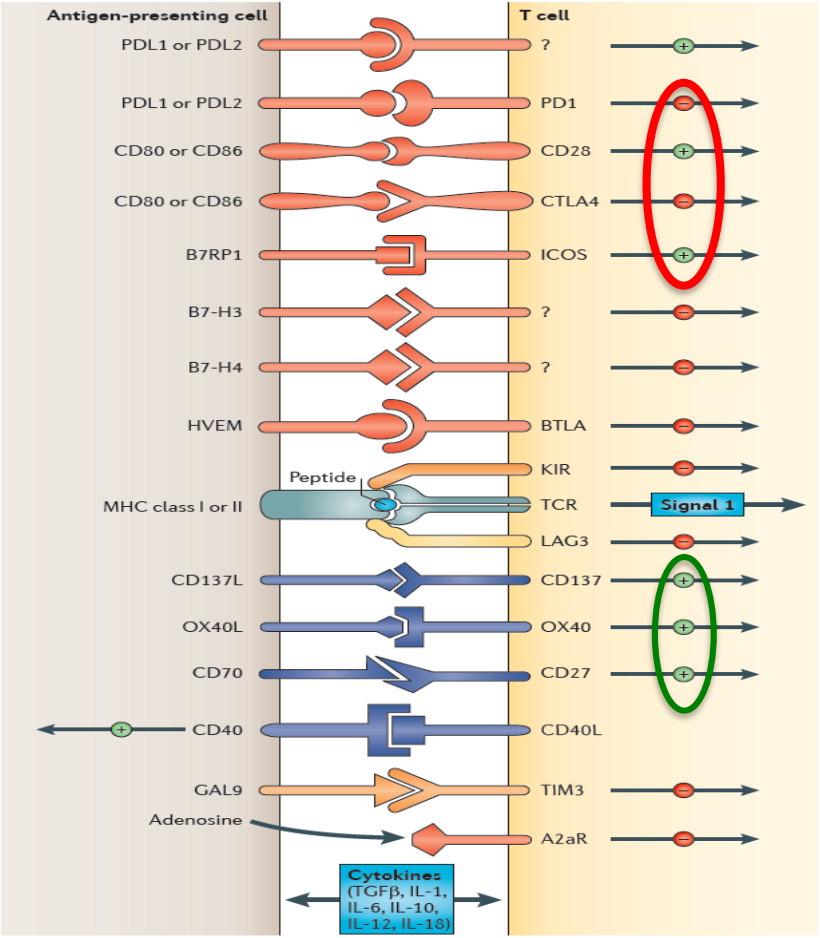
Theoretically, leading to existing immunity in every cancer patient

Tumor-Immune Microenvironment





Multiple co-stimulatory and inhibitory interactions regulate T cell responses



Pardoll: Nature Rev Cancer 12: 254, 2012

T Cell Agonist Expression

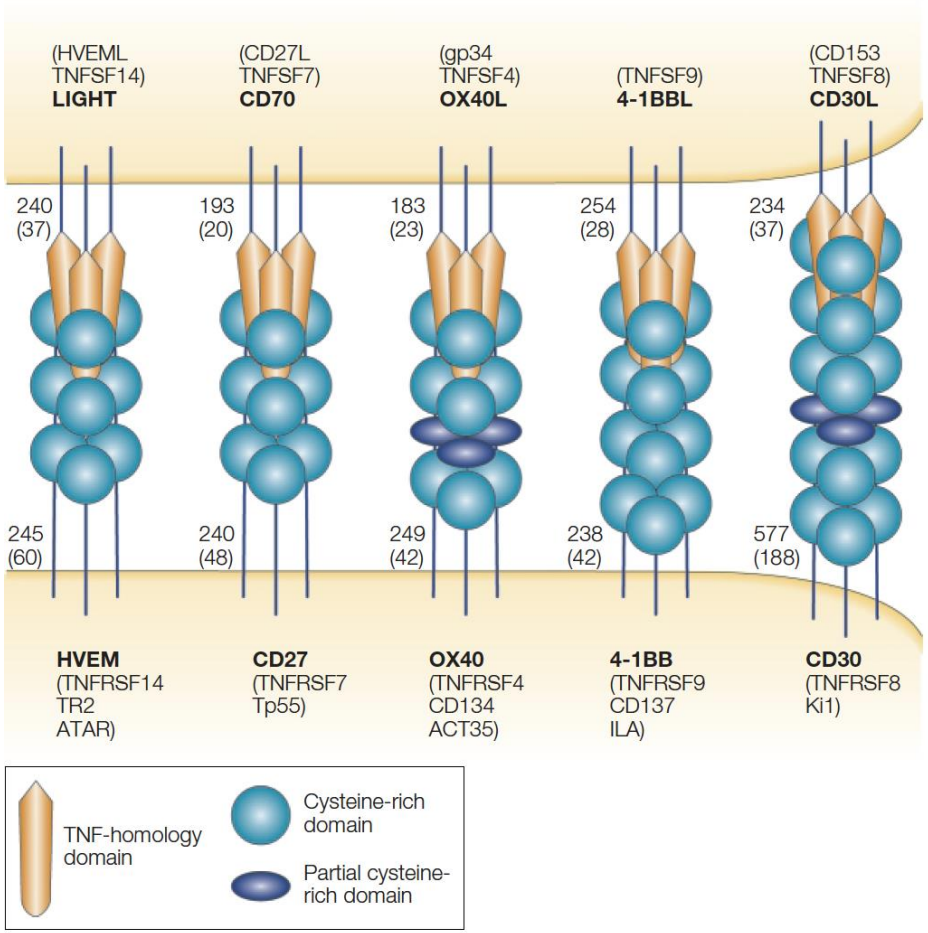
TNF-Receptors

1) **OX40** – CD4s, Tregs, CD8s, and NK T cells
2) **4-1BB** – CD8s, Tregs, CD4s, DCs, B cells, NK, granulocytes, and blood vessel walls
1) **GITR** – Tregs, CD4s, CD8s, NK, B cells, and myeloid cells
2) **CD27** – CD8s, CD4s, Tregs, B cells, and NK cells

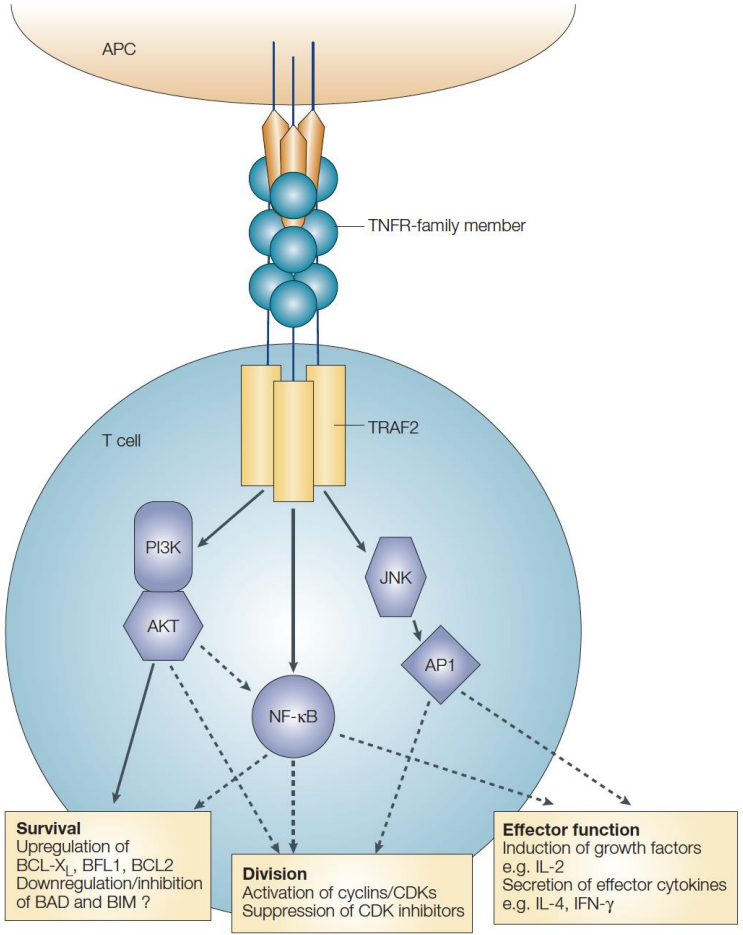
Ig-Super Family Member

1) **ICOS** - CD4, Tregs, and CD8s

Biochemical Structure of the TNF/TNF-receptor Family Members

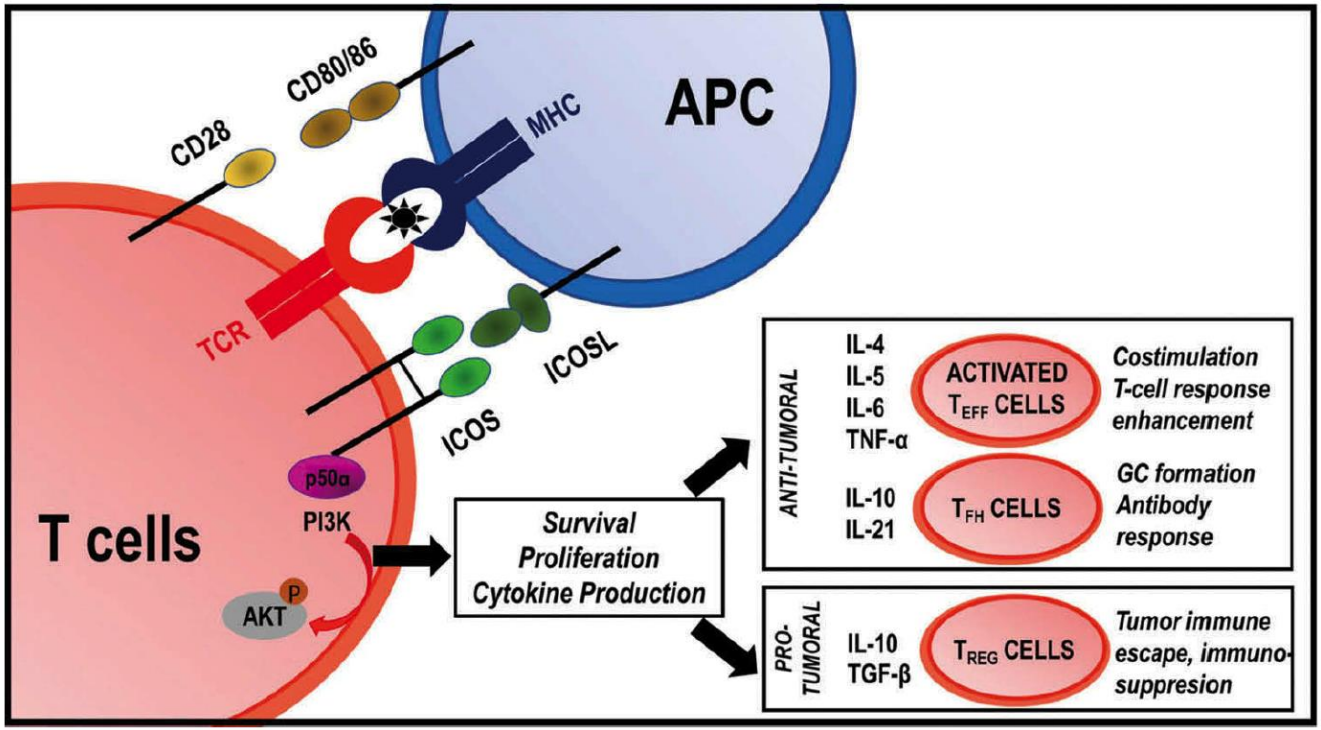


Overview of TNF-R Signaling



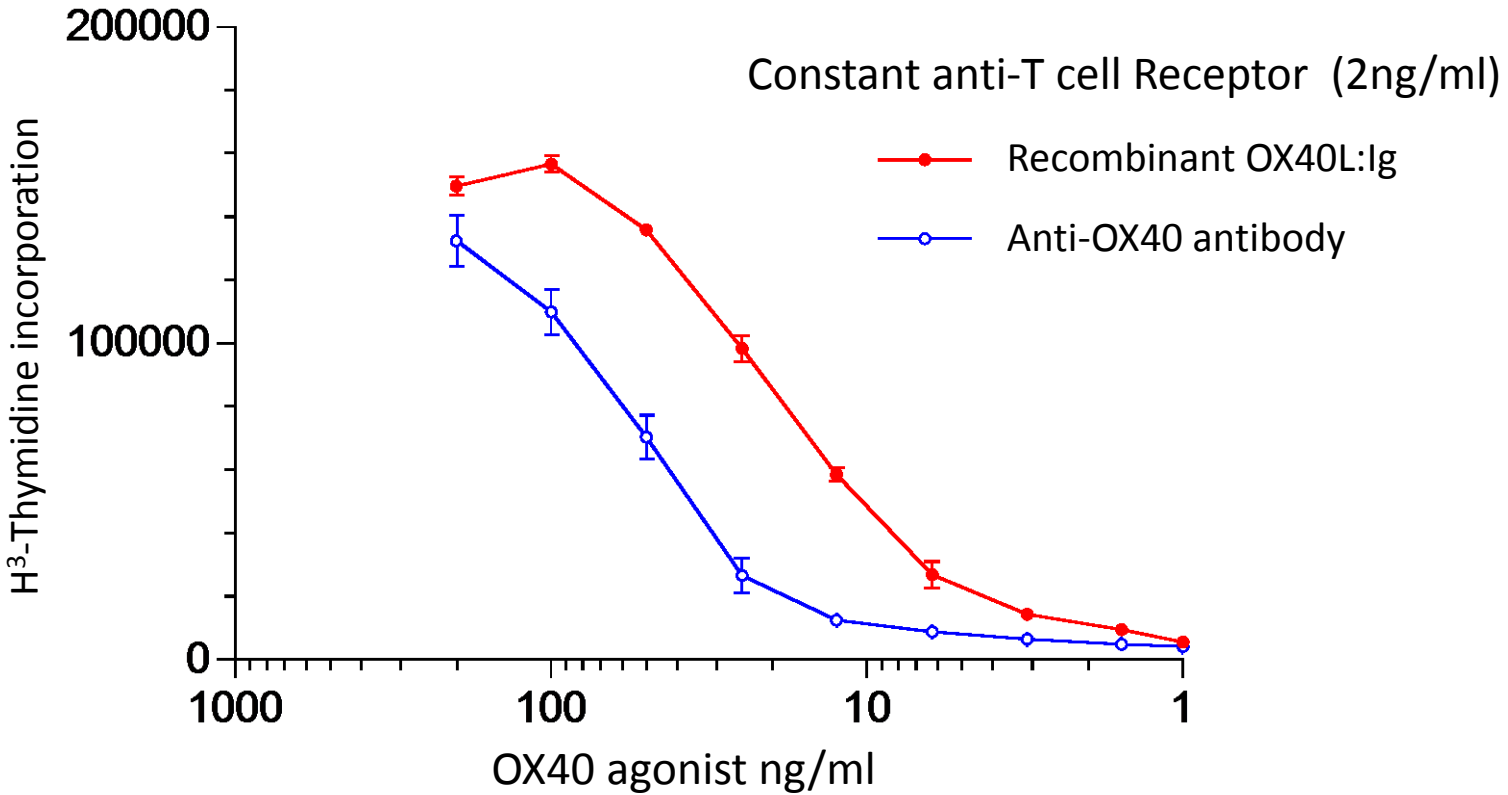
Croft M., Nature Reviews Immunology, 2003, 3:609

Costimulation of ICOS Pathway/Signaling



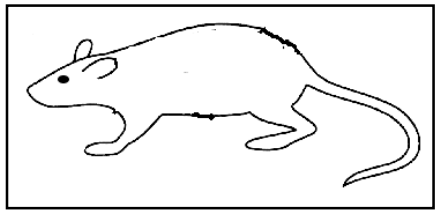
In vitro costimulation anti-OX40 Costimulation Assay

(Effector CD4 T cell proliferation)



Mouse Model to Assess Agonist Ab Activity In Vivo

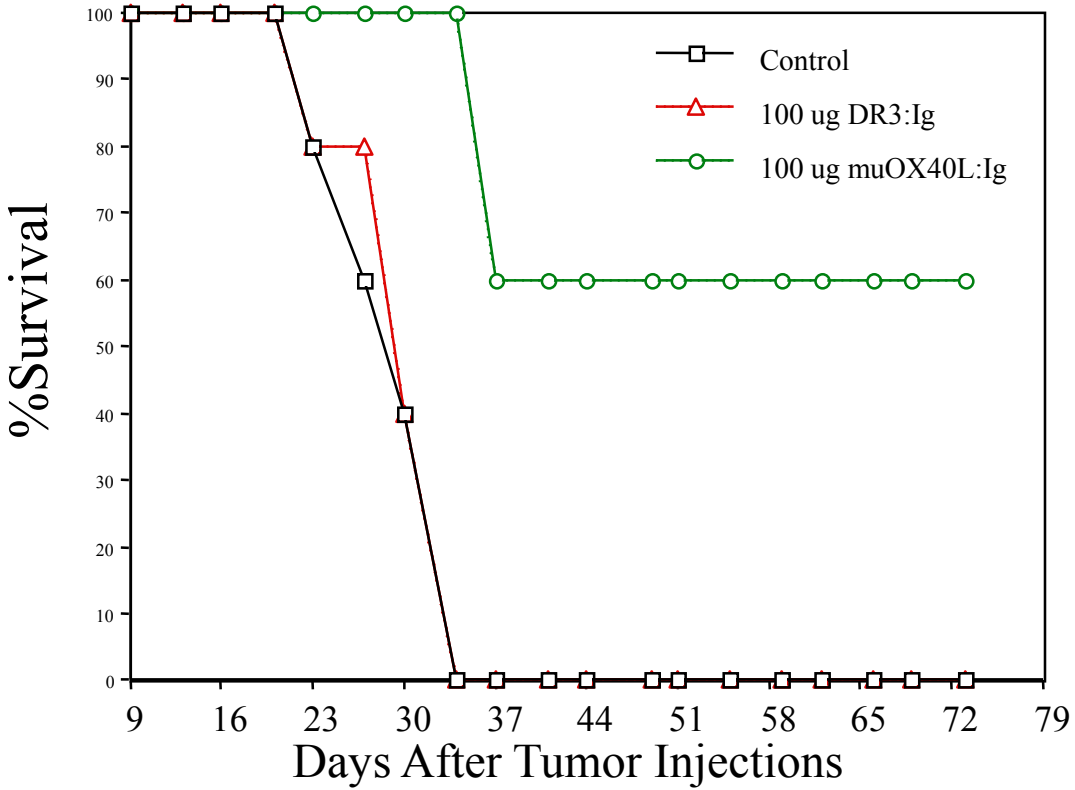
Solid Tumor
Administered s.c.



Days 3 and 7 after tumor injection

- Control
- Sol. mu OX40L
- anti-OX-40

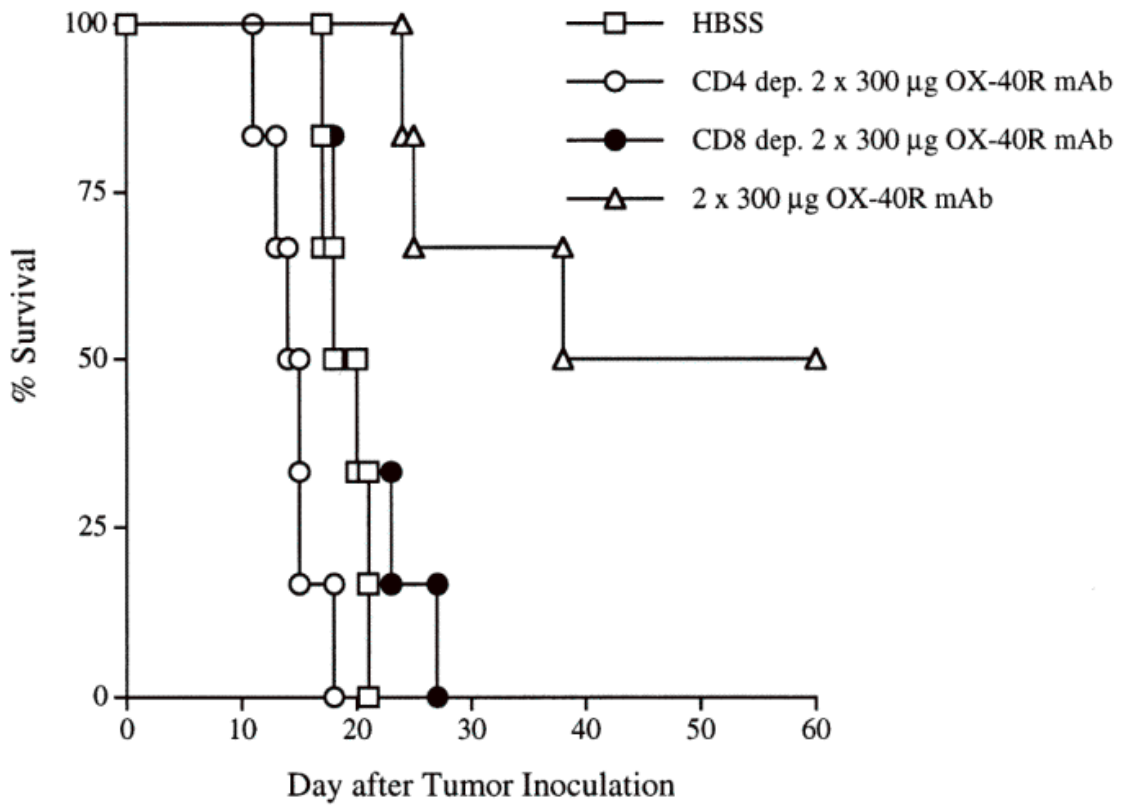
OX40L:Ig Treatment of MCA 303



Tumor Models Successfully Treated with OX40 Engagement

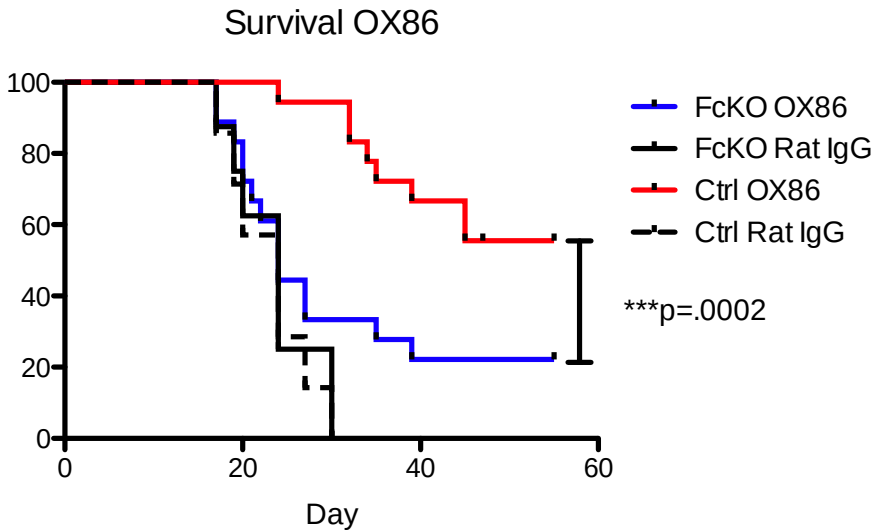
- Breast (4T1, SM1, EMT-6)
- Sarcoma (MCA 303, 205, 203)
- Colon (CT-26)
- Glioma (GL261)
- Melanoma (B16/F10)
- Prostate (TRAMP-C1)
- Lung (Lewis Lung)

CD4 and CD8 T cells Roles in anti-OX40 Enhanced Tumor Immunity (Glioma Model)



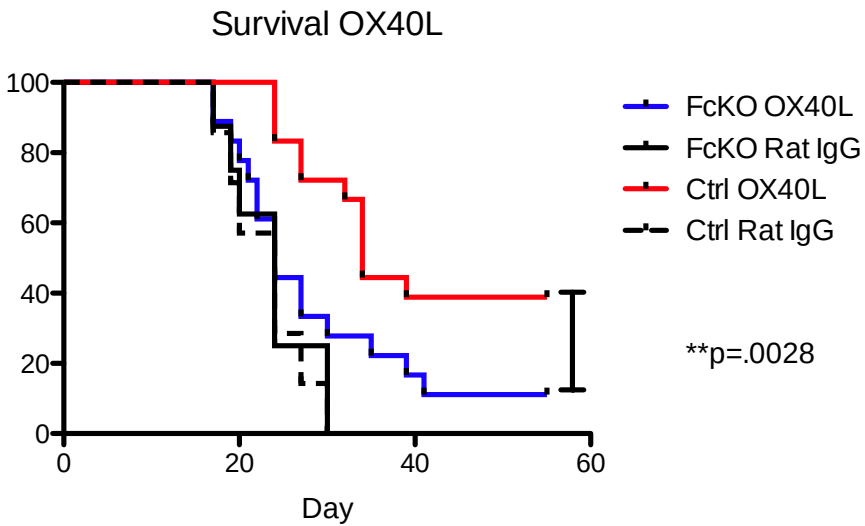
Fc-Receptor Importance for Therapeutic Effects of Agonist Abs

(OX40 agonists performed in Fc-Receptor ko mice)



FcKO 4/18 = 22% Cure Rate

WT 10/18 = 56% Cure Rate



FcKO 2/18 = 11% Cure Rate

WT 7/18 = 39% Cure Rate

First OX40 Agonist Trial in Cancer Patients

Microenvironment and Immunology

Cancer Research

OX40 Is a Potent Immune-Stimulating Target in Late-Stage Cancer Patients

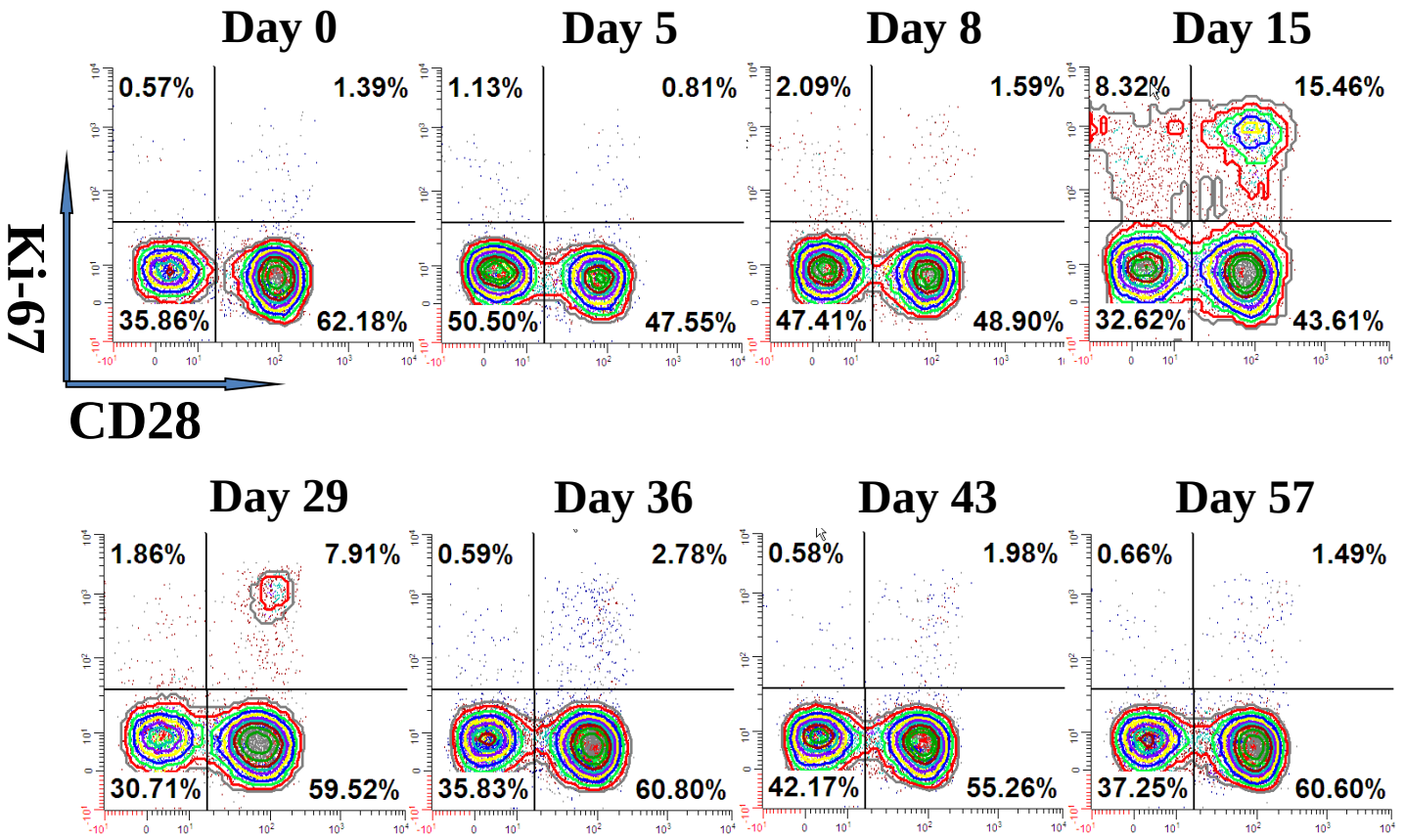
Brendan D. Curti[1], Magdalena Kovacsovics-Bankowski[1], Nicholas Morris[1], Edwin Walker[1], Lana Chisholm[1], Kevin Floyd[1], Joshua Walker[2], Iliana Gonzalez[1], Tanisha Meeuwsen[1], Bernard A. Fox[1], Tarsem Moudgil[1], William Miller[1], Daniel Haley[1], Todd Coffey[1], Brenda Fisher[1], Laurie Delanty-Miller[1], Nicole Rymarchyk[1], Tracy Kelly[1], Todd Crocenzi[1], Eric Bernstein[1], Rachel Sanborn[1], Walter J. Urba[1], and Andrew D. Weinberg[1]

Cancer Res 2013;73:7189-7198.

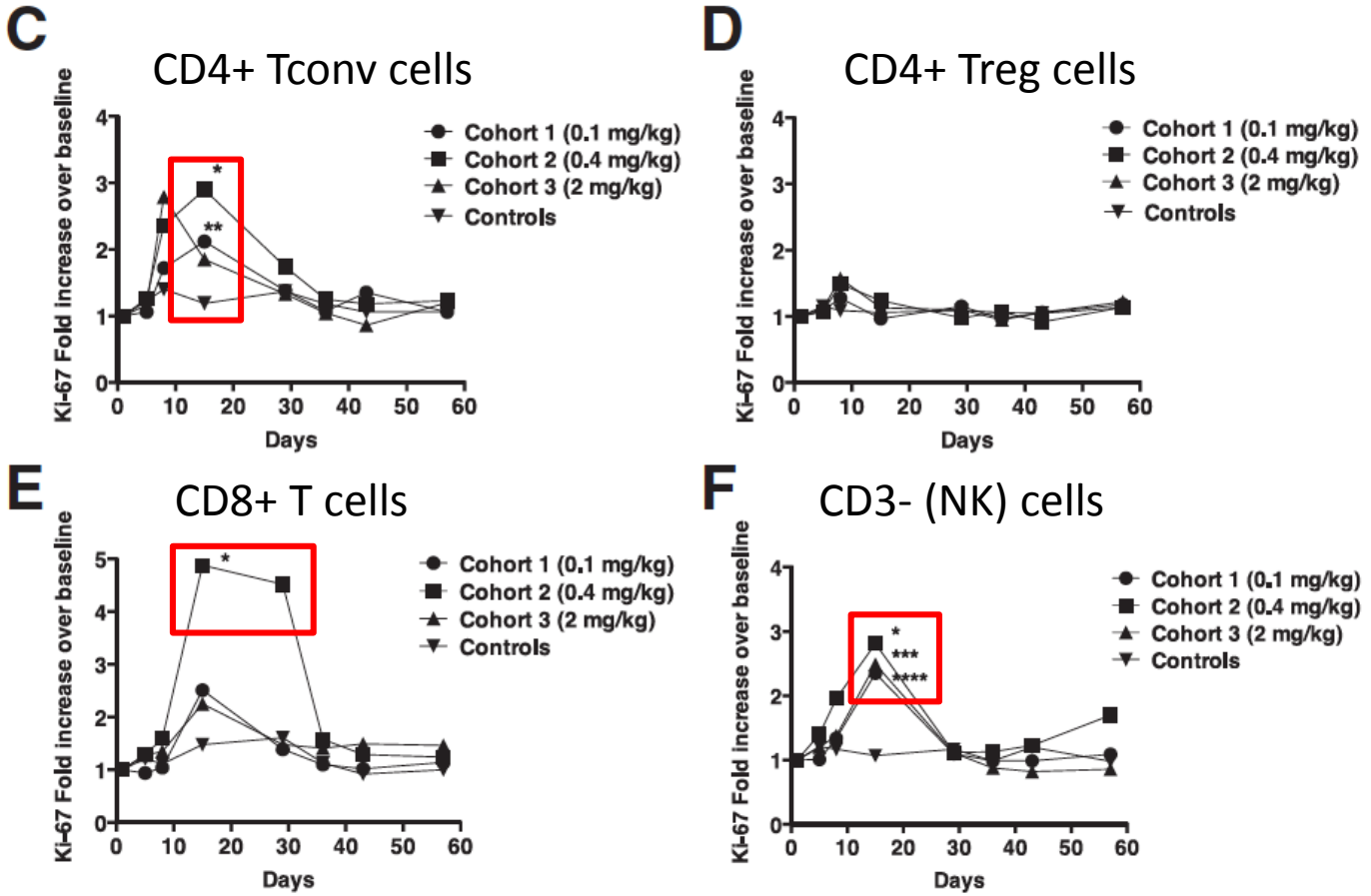
- Phase I: Three doses delivered in a one week span
- Anti-OX40 was well-tolerated
- No CRs or PRs; however,
  - 12 patients had regression of at least one tumor nodule
  - 17/30 had SD by RECIST criteria for 56 days

Patient #14

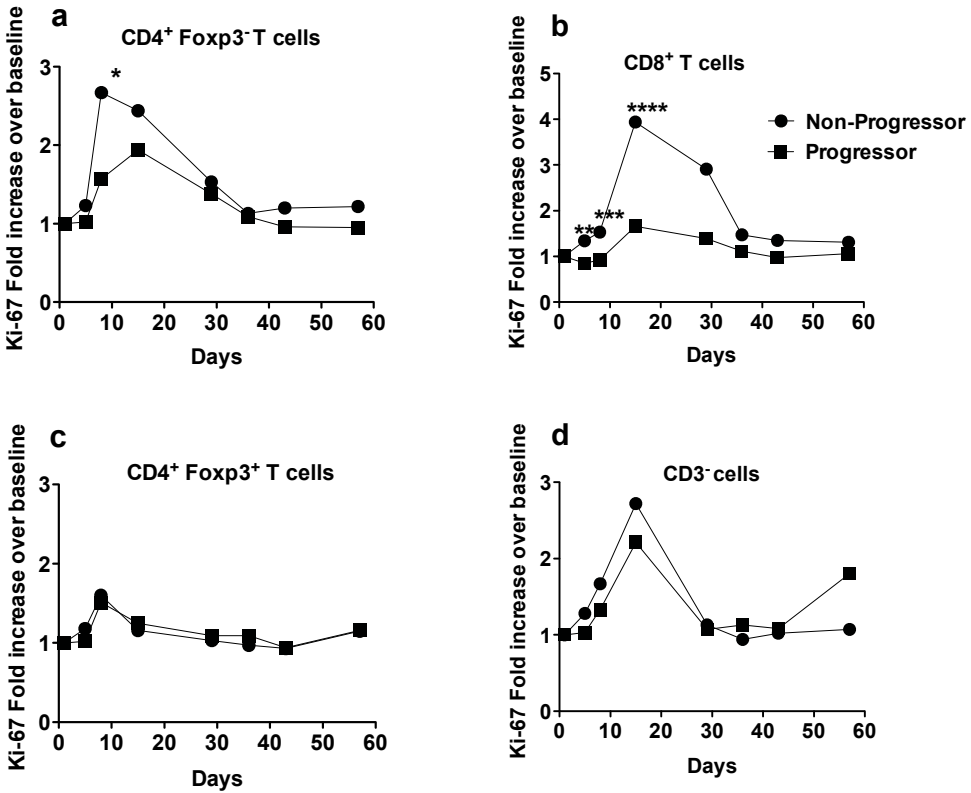
$CD8^+CD95^+$ T cell (PBLs)

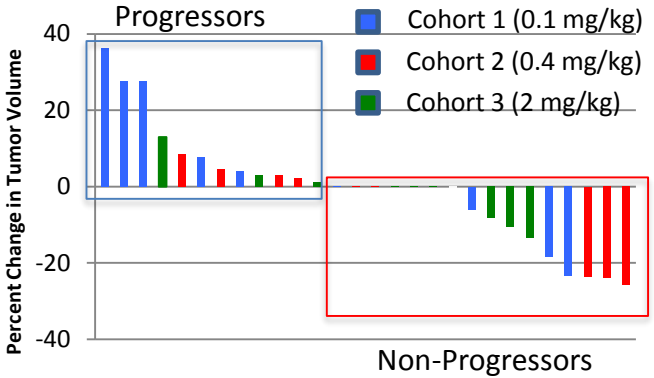


Anti-OX40 induces robust proliferation in peripheral blood

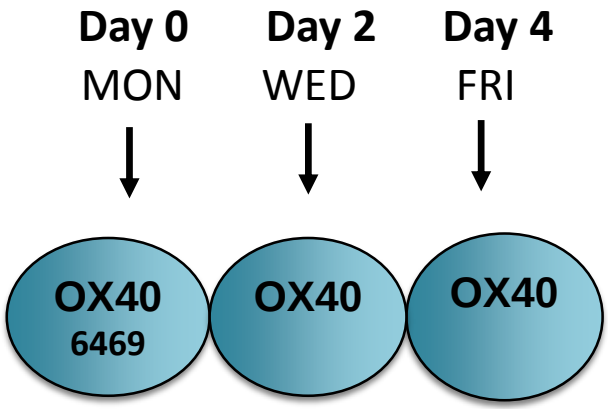


Do increases in PBL-Ki-67 predict clinical outcome?





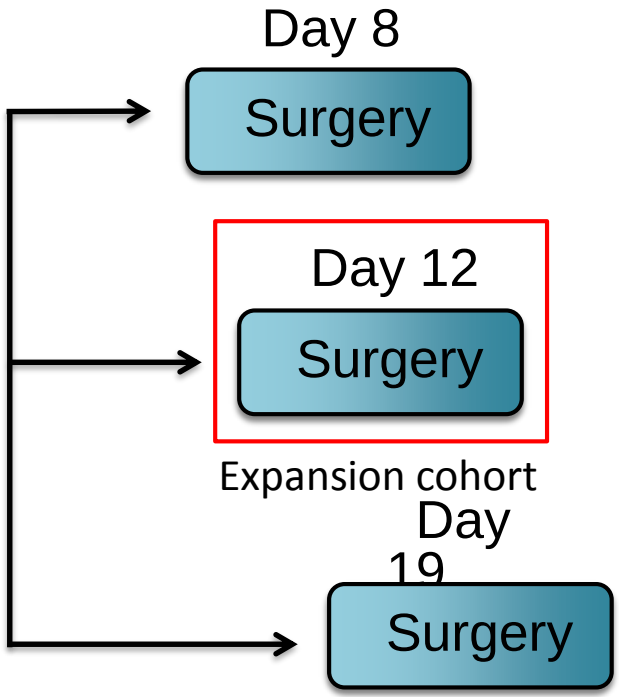
Pre-op anti-OX40: 3-arm Surgical Window Study in H&N Cancer



0.4 mg/kg

Pre-treatment immune assessment

- Incisional tumor biopsy
- Peripheral whole blood



Post-treatment immune assessment

- Resected tumor
- Draining nodes (normal and metastatic)
- Peripheral whole blood

Cytometry
Immunophenotype and activation status in blood and tumor

Multiplex IHC
Immunophenotype & digital quantification
Spatial cell-cell quant

WES

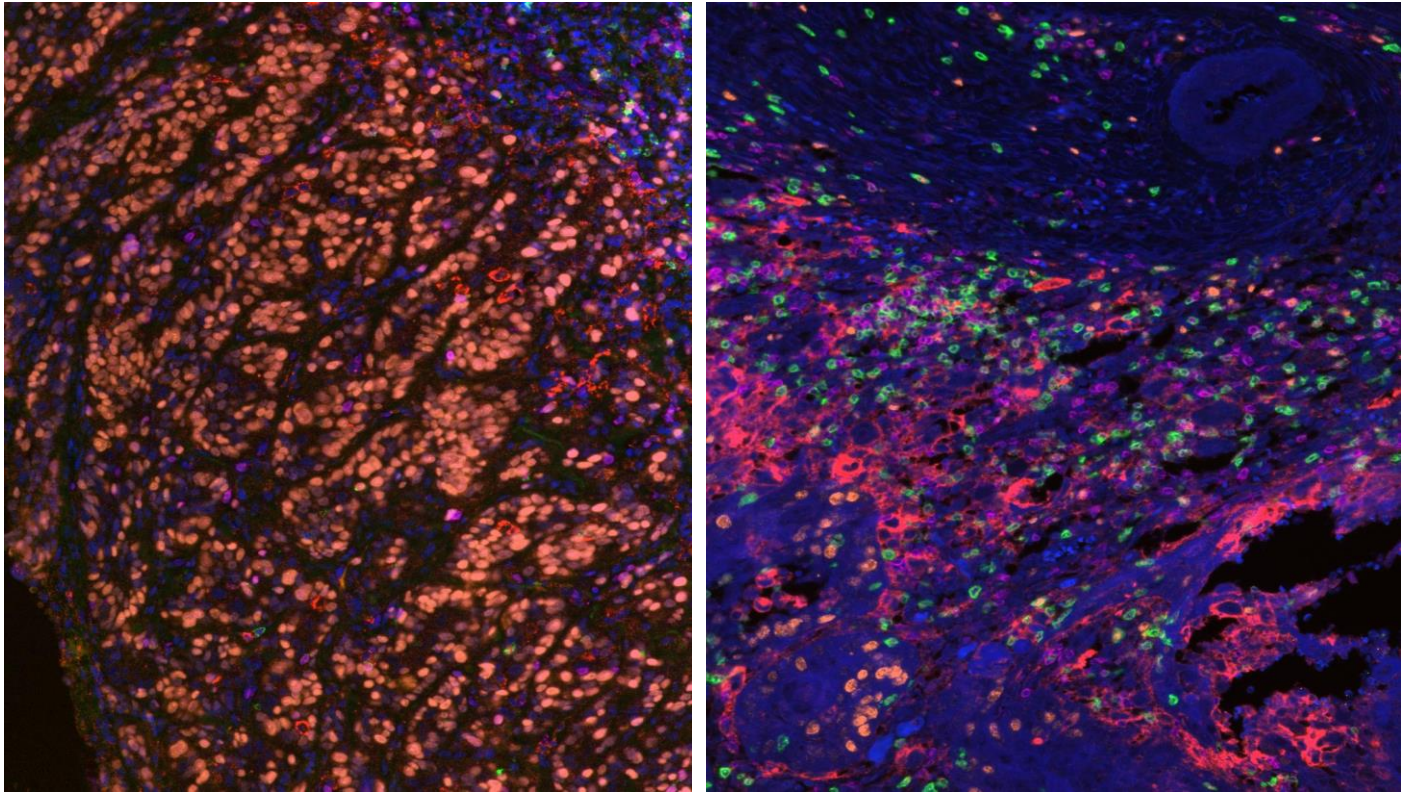
Multi-Plex Immune Fluorescence FFPE:HOX04

2 week post-therapy

PRE

Ki67 = orange
CD8 = green
PD-L1 = red
CD3 = purple

POST



Costimulatory Agonist Antibodies in Development

Drug	Company	Molecule type	Status
ICOS			
GSK3359609	GlaxoSmithKline	IgG4	Phase III
Vopratelimab	Jounce Therapeutics	IgG1	Phase II
KY-1044	Kymab	IgG1	Phase I
OX40			
PF04518600	Pfizer	IgG2	Phase II
BMS-986178	Bristol-Myers Squibb	IgG1	Phase I/II
ABBV-368	AbbVie	IgG1	Phase I
GSK3174998	GlaxoSmithKline	IgG1	Phase I
MEDI0562	AstraZeneca, AgonOx	Not disclosed	Phase I
4-1BB			
CTX-471	Compass Therapeutics	IgG4	Phase I
AGEN2373	Agenus	IgG1	Phase I
ATOR-1017	Alligator Bioscience	IgG4	Phase I
GITR			
TRX518	Leap Therapeutics	IgG1	Phase I/II
ASP1951 (PTZ522)	Astellas Pharma	IgG4	Phase I

Combinations with Agonist Abs for Future Trials

Combining Agonist Abs

1) anti-OX40 with anti-4-1BB (several publications showing additive/synergistic effects). OX40 more CD4 dominant and 4-1BB more CD8 dominant.
2) anti-OX40 combined with anti-ICOS (publication showing additive/synergy)
3) GITRL:Ig fusion protein with anti-OX40 (publication showing additive/synergy)

Combining Agonist Abs with Checkpoint Blockade

1) anti-4-1BB with PD-1 or CTLA-4 blockade (publications showing additive/synergistic effects)
2) anti-OX40 combined with PD-1 or CTLA-4 blockade (publications showing additive/synergy)
3) GITRL:Ig fusion protein with anti-PD-1 (publication showing additive/synergy)
4) Anti-CD27 with anti-PD-1 (publication showing additive/synergy)

Combining Agonist Abs with Vaccines

1) anti-CD27 with DC vaccine in prostate cancer (publications showing additive effects)
2) anti-OX40 combined with cell-based or peptide vaccines (publications show additive effects)
3) Anti-GITR with cell-based and Listeria vaccine (publications show additive effects)
4) Anti-ICOS with cell-based vaccine (publication showing additive/synergy)

Outstanding Questions for Agonist Abs

1) Why has the efficacy in the clinic been underwhelming as single agent or combination?

2) Dosing and schedule different than checkpoint blockade, although to date all trials have been dosed identical to checkpoint blockade.

3) How should combination therapies be delivered? With checkpoint blockade delivered at the same time as agonist Abs? Publications have indicated that is probably not optimal.

4) What about blocking negative signals delivered in tumor microenvironment in combo with agonist Abs? Blocking TGF-β signaling in combo with anti-OX40 shown dramatic effects.

5) Bi-specifics? Agonist Ab:Checkpoint blockade Ab or Agonist Ab:Agonist Ab?

6) Are there new costimulatory pathways to be exploited?

Concurrent vs Sequenced anti-OX40 with anti-PD-1: 2017

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

David J. Messenheimer[1,2], Shawn M. Jensen[1], Michael E. Afentoulis[1], Keith W. Wegmann[1], Zipei Feng[1,3], David J. Friedman[1], Michael J. Gough[1], Walter J. Urba[1], and Bernard A. Fox[1,2,3,4]

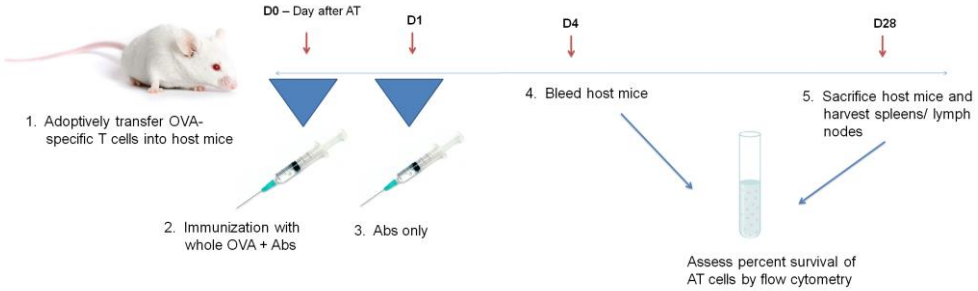
Clin Cancer Res; 23(20); 6165–77.

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

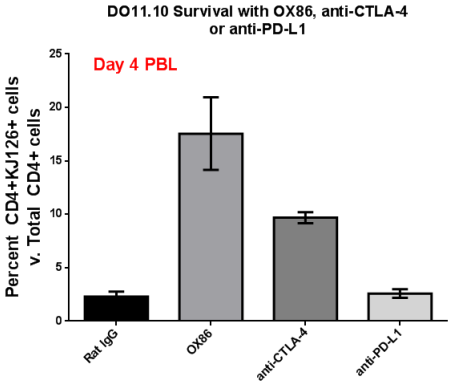
Rajeev K. Shrimali[1], Shamim Ahmad[1], Vivek Verma[1], Peng Zeng[1], Sudha Ananth[1], Pankaj Gaur[1], Rachel M. Gittelman[2], Erik Yusko[2], Catherine Sanders[2], Harlan Robins[2,3], Scott A. Hammond[4], John E. Janik[1], Mikayel Mkrtichyan[1], Seema Gupta[1], and Samir N. Khleif[1]

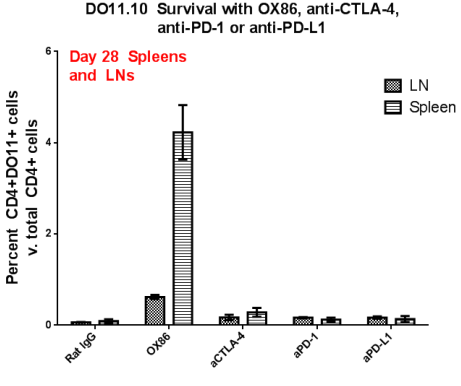
Cancer Immunol Res; 5(9); 755–66.

Anti-OX40 Enhancing Vaccine: Comparison to CTLA-4 and PD-1 Blockade



CD4s





CD8s