Immune Checkpoint Agonists

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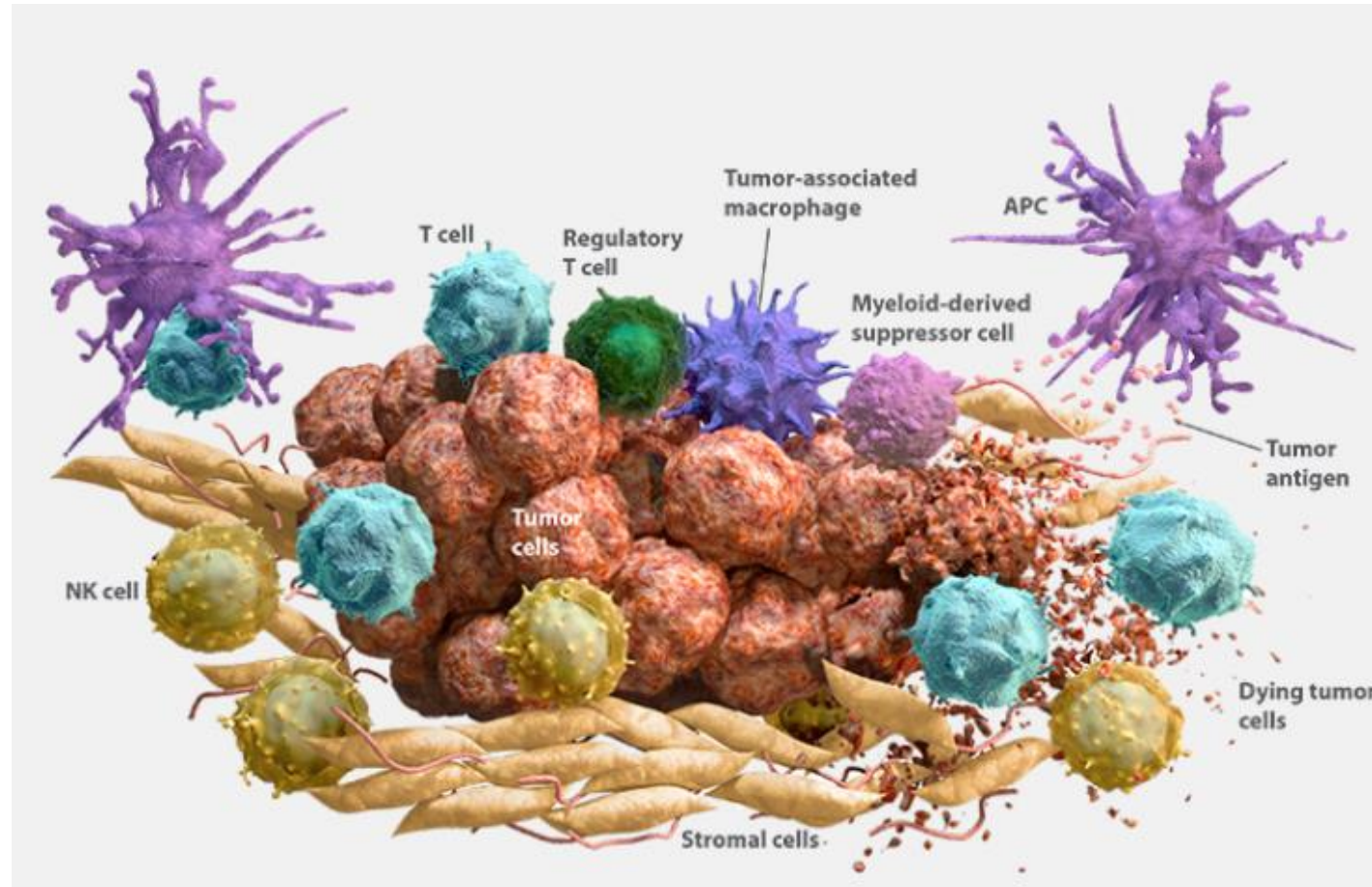**The University of Texas MD Anderson Cancer Center**

Disclosures

- **Research funding from NCI; EMD Serono; MedImmune; Healios Onc. Nutrition; Atterocor; Amplimmune; ARMO BioSciences; Karyopharm Therapeutics; Incyte; Novartis; Regeneron; Merck; BMS; Pfizer, CytomX Therapeutics; Neon Therapeutics; Calithera Biosciences; TopAlliance Biosciences; Eli Lilly; Kymab:**

- **Immune Deficiency Foundation (Spouse)**

- **On advisory board of CytomX Therapeutics and Novartis**

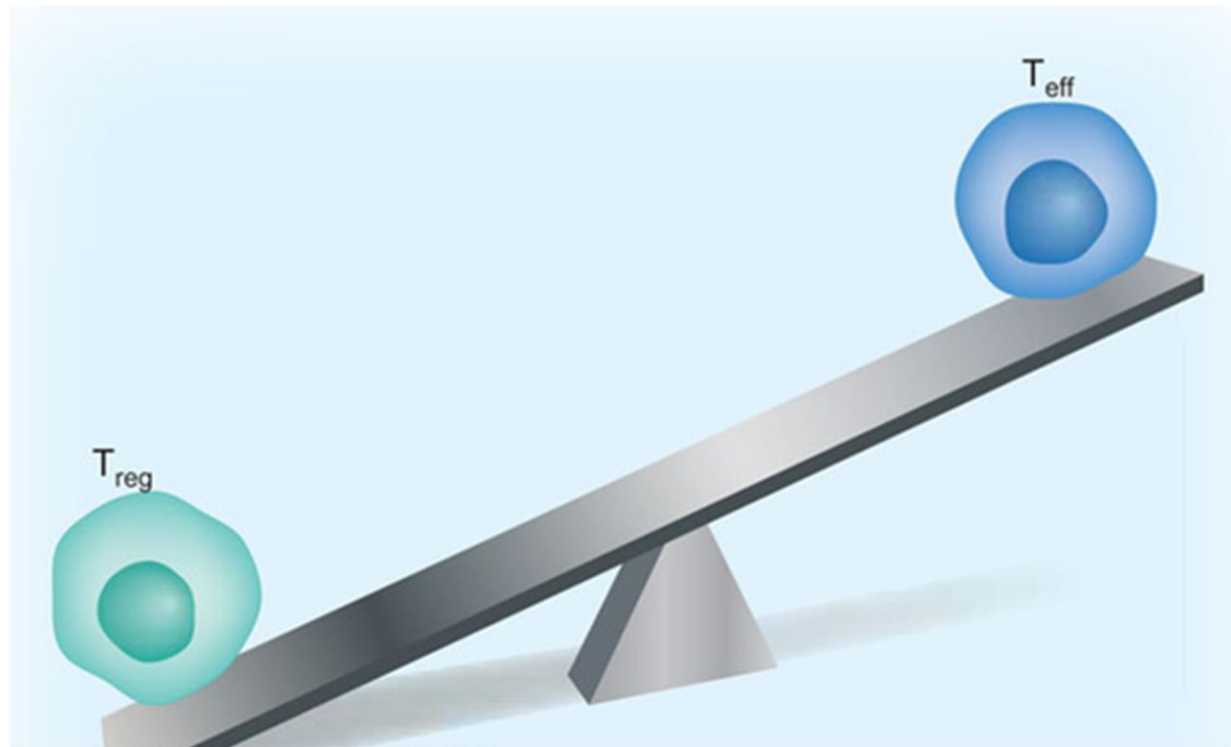- **Travel and accommodation expense from ARMO BioSciences**

Overview

- **Introduction**

- **Immune Checkpoints**

- **What's Next?**
  - **OX40**
  - **4-1BB**
  - **GITR**

- **Challenges Associated with Immunotherapy**
  - **Biomarkers of Response**
  - **Resistance to Treatment**
  - **Immune-related Adverse Events**

- **Summary**

Introduction

Key Players of the Immune System

Immune Tolerance
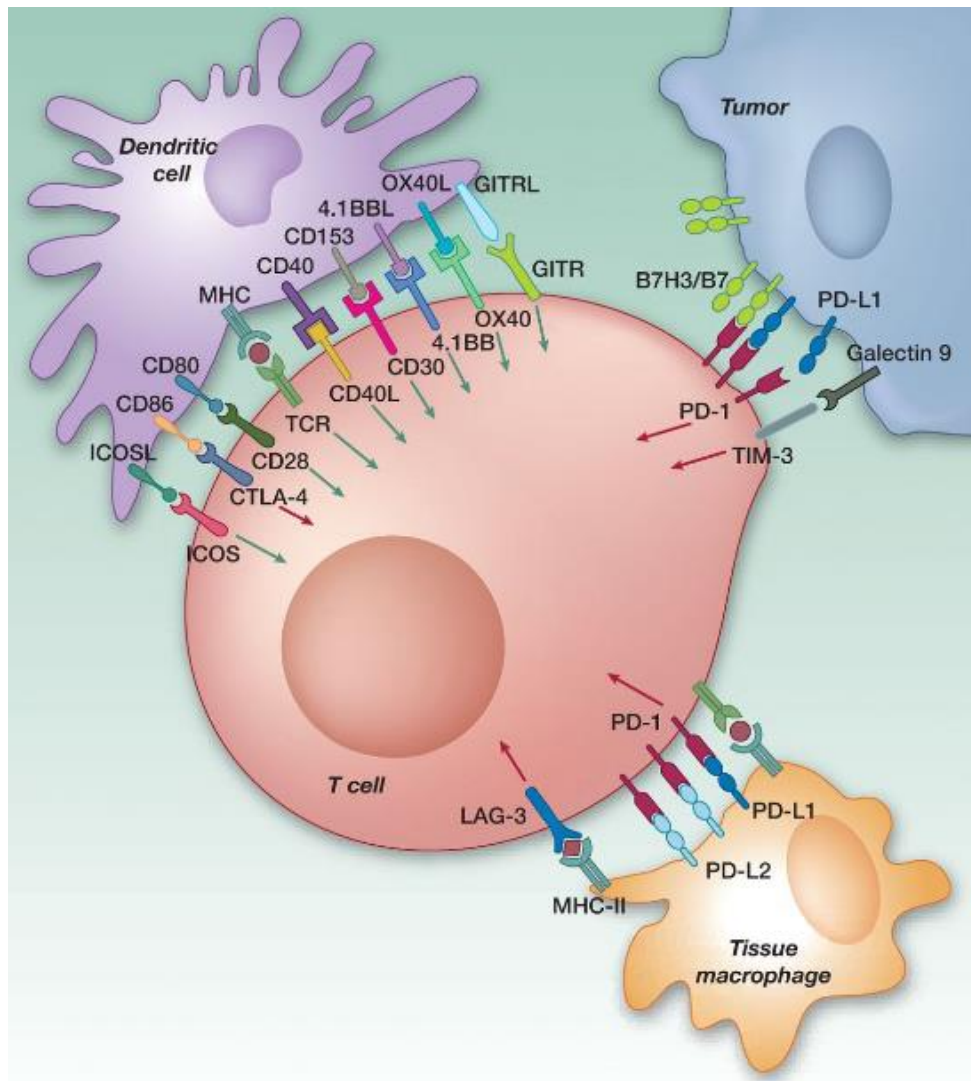
Common Immune Evasion Strategies Used by Tumor Cells

M Davies, New modalities of cancer treatment for NSCLC: Focus on immunotherapy, *Cancer management and research*, 2014.
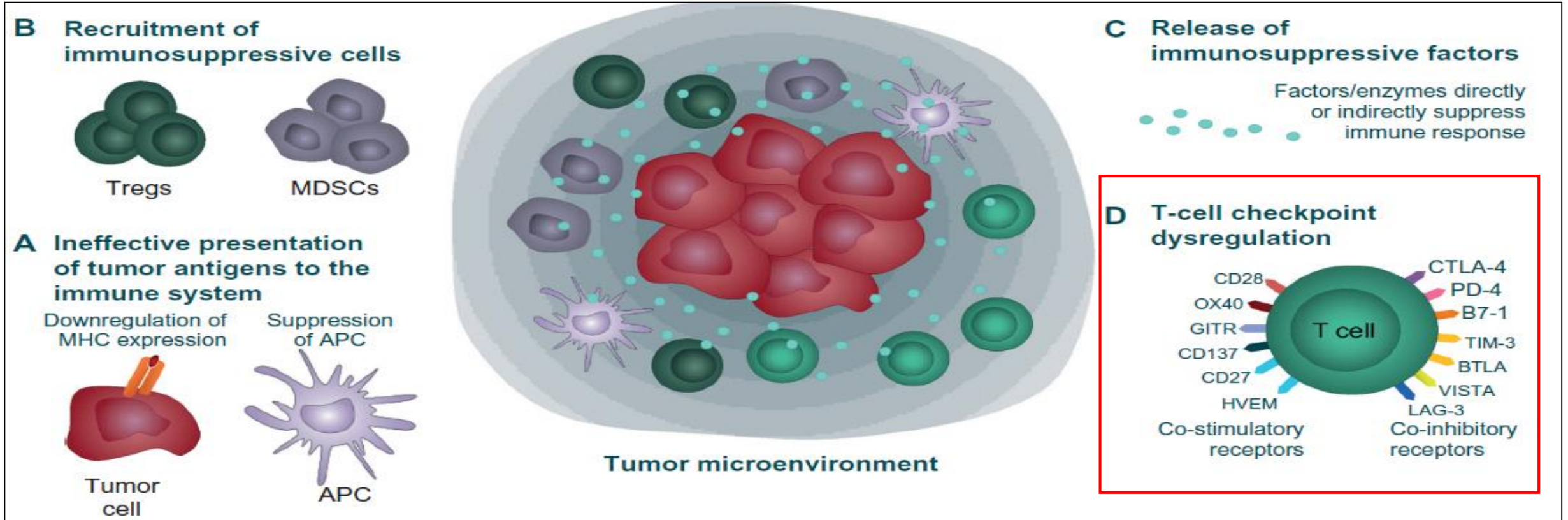
Immune Checkpoints

Immune Regulatory Receptors on T Cells

FDA-approved Checkpoint Inhibitors*

Drug	Immune Checkpoint(s)	FDA-approved tumor-type**
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma Non-small cell lung cancer Small cell lung cancer Renal cell carcinoma Classical Hodgkin lymphoma Squamous cell carcinoma of the head and neck Urothelial carcinoma Hepatocellular carcinoma Mismatch repair deficient and microsatellite instability high metastatic colorectal cancer
Pembrolizumab	PD-1	Melanoma Non-small cell lung cancer Squamous cell carcinoma of the head and neck Classical Hodgkin lymphoma Urothelial carcinoma Gastric or gastroesophageal junction Microsatellite instability-high or mismatch repair deficient solid tumors Recurrent locally advanced or metastatic Merkel cell carcinoma Cervical cancer Hepatocellular carcinoma
Atezolizumab	PD-L1	Urothelial carcinoma Non-small cell lung cancer
Durvalumab	PD-L1	Urothelial carcinoma Non-small cell lung cancer
Avelumab	PD-L1	Merkel cell carcinoma Urothelial carcinoma
Nivolumab with Ipilimumab	PD-1 and CTLA-4	Melanoma Renal cell carcinoma Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer
Pembrolizumab with carboplatin and either paclitaxel or nab-paclitaxel	PD-1	Non-small cell lung cancer

*List of FDA-approved immune checkpoint inhibitors as of February 18, 2019, adapted from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm
**Tumor type must meet the criteria listed in the above-mentioned website

T cell Targets for Immunoregulatory Therapy

I Mellman et al, Cancer immunotherapy comes of age, *Nature*, 2011
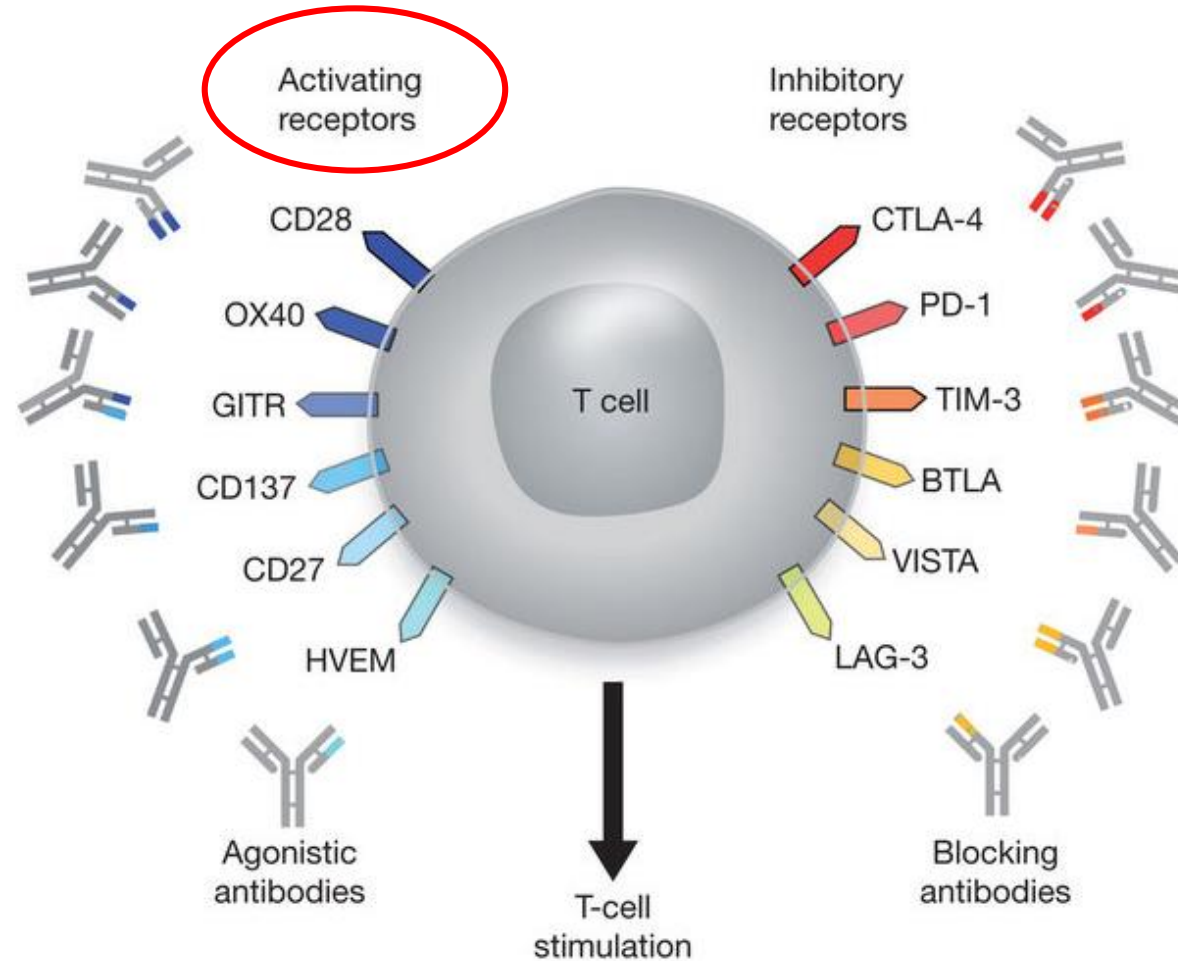
T cell Agonists: Stepping on the Accelerator
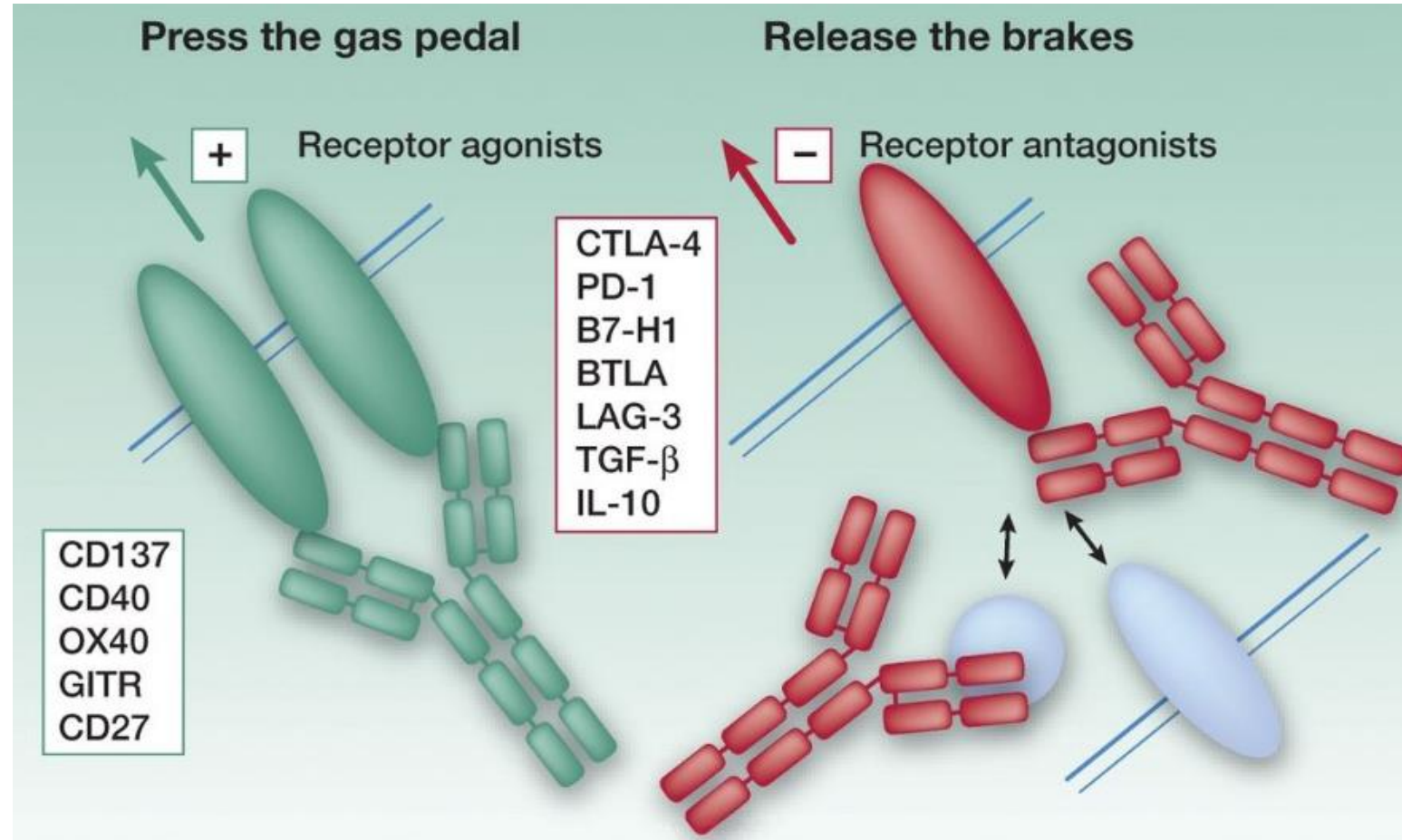
Green means activator receptor and agonist antibody

Red means inhibitory receptor and antagonist antibody

I Melero et al, Clinical Development of Immunostimulatory Monoclonal Antibodies and Opportunities for Combination, *CCR Focus*, 2013

OX40 (CD134)

OX40 (CD134)
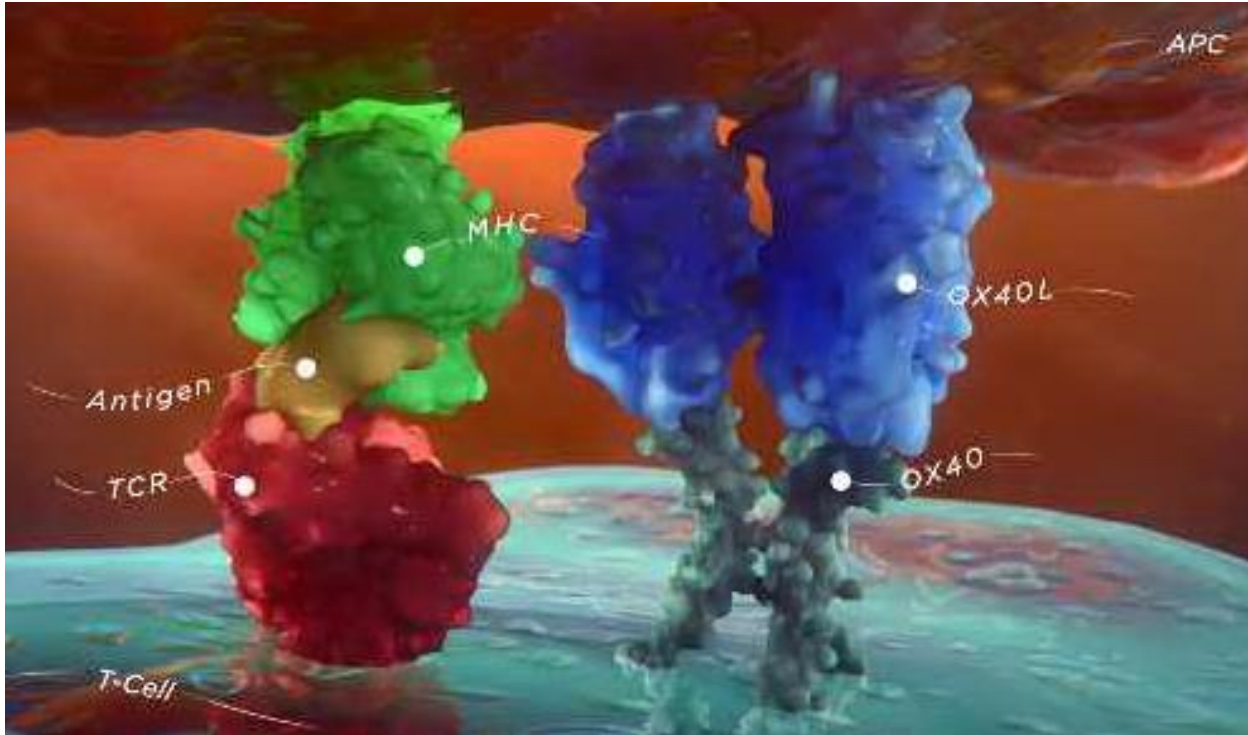
- **Member of the tumor necrosis factor receptor superfamily4**
  - Expressed on <u>activated</u> CD4$^+$ and CD8$^+$ T cells and Foxp3$^+$CD4$^+$ regulatory T cells (Tregs)
  - High level of OX40 expression on <u>Tregs in tumor</u> and not periphery
  - OX40 expression is transient; peaking 24-48 hours after activation
  - Typically lasts 3–4 days

- **One known ligand OX40L**
  - Expressed on <u>activated</u> APCs

OX40 Signaling
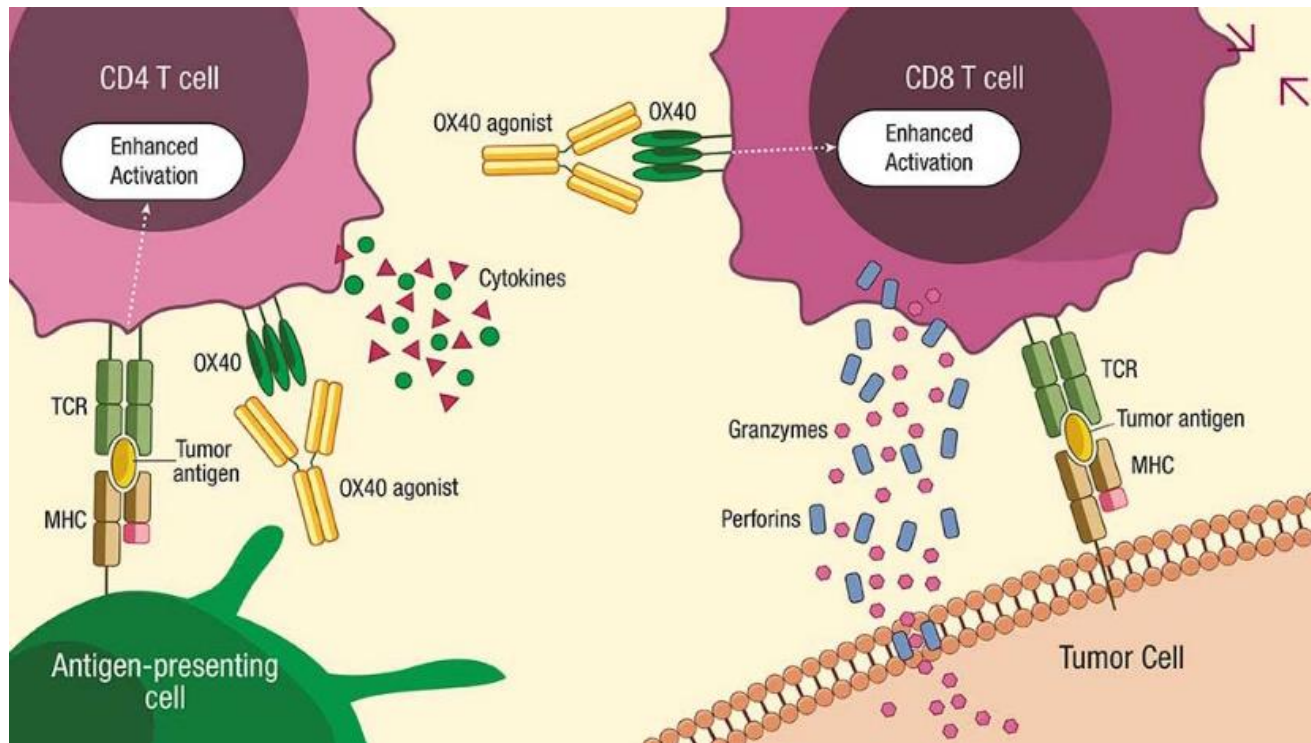
- **Promotes effector T cell expansion and survival**

- **Enhances expression of survivin, cyclin A, cyclin-dependent kinases, Bcl-2 anti-apoptotic molecules, cytokines, and cytokine receptors**

- **Impairs conversion of naïve T-cells into FoxP3$^+$ Tregs**

- **Depletes <u>tumor infiltrating</u> Tregs that Impairs suppressing ability of Tregs in the tumor**

OX40 and Tregs

- **OX40 blocks the suppressive function of Treg cells in vivo**

- **In TGF-β1-treated cultures, OX40 agonist increased IFN-γ and IL-4 production and blocked TGF-β1-mediated Treg conversion of activated T cells**

- **However, in the absence of IFNγ or IL-4, OX40 stimulation in naive mice, enhanced Treg proliferation and accumulation in vivo.**

- **OX40 can push Treg cells in both directions, <u>depending</u> upon the context of stimulation and the <u>cytokine milieu</u>**

Ruby CE et al. Cutting Edge: OX40 agonists can drive regulatory T cell expansion if the cytokine milieu is right. *J Immunol.* 2009
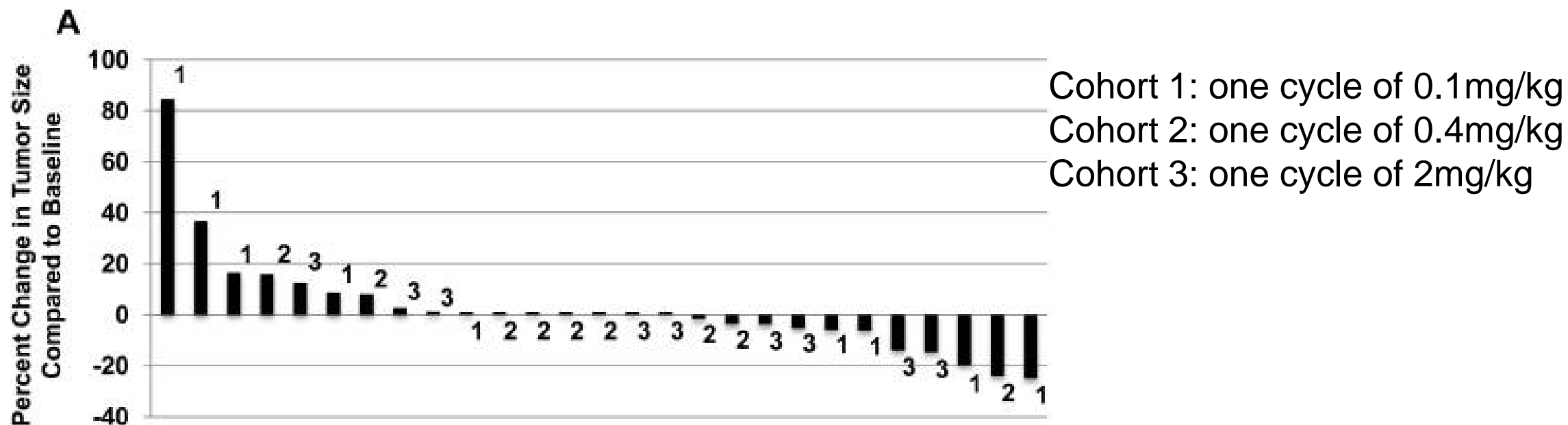
OX40 Agonist: Phase I Proof-of-principle Study

- N=30 patients with advanced cancer
- <u>Murine agonistic</u> anti-human OX40 mAb used
- Single cycle of anti-OX40 given intravenously (IV) on days 1, 3 and 5
- 3 dose levels: 0.1mg/kg; 0.4mg/kg; 2mg/kg
- Most common toxicities: Lymphopenia, fatigue, rash and flu-like symptoms with fever and chills
- MTD was not reached within the dose levels tested

Adverse events				
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Lymphopenia	3	10	6	1
Fatigue	7	12		
Rash/Skin Changes	4	6		
Pruritis	5	1		
Fever/Chills	11	2		
Splenomegaly	7			
Arthralgias/Myalgias	5	5		
Nausea/Vomiting	4	3		
Increased AST, ALT or alkaline phosphatase	2	1		
Anemia	1	8		

Curti BD et al. OX40 is a potent immune stimulating target in late stage cancer patients. *Cancer Research*. 2013

OX40 Agonist: Efficacy Results

- **Tumor shrinkage in 12 and no change in 6 patients**
- **SD in patients with melanoma, renal cancer, squamous cell carcinoma of the urethra, prostate cancer and cholangiocarcinoma**
- **Longest interval of SD lasted 470 days in a patient with renal cancer**

Cohort 1: one cycle of 0.1mg/kg
Cohort 2: one cycle of 0.4mg/kg
Cohort 3: one cycle of 2mg/kg

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Curti BD et al. OX40 is a potent immune stimulating target in late stage cancer patients. *Cancer Research*. 2013

OX40 Agonist: Immunologic Results
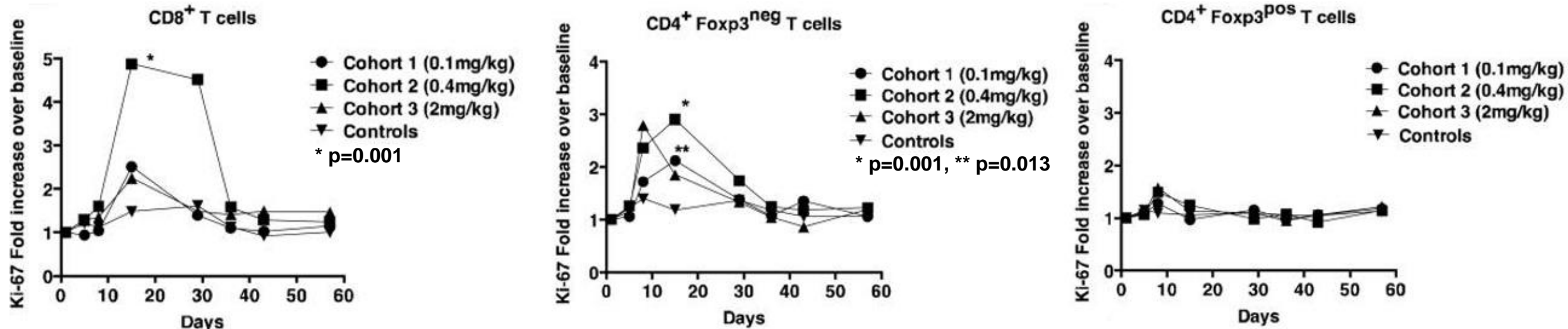
- **Significant increase in proliferation of both CD4+ and CD8+ T cells**

- **Did not increase CD4+/FoxP3+ Treg proliferation**

- **Preferential upregulation of OX40 in TIL Tregs than PBL Tregs**

- **Major limitation: High human Anti-mouse Ab production, which precluded the administration of multiple cycles**

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Curti BD et al. OX40 is a potent immune stimulating target in late stage cancer patients. *Cancer Research*. 2013

OX40 Agonist Monotherapy: in Clinical Development

OX40	Tavolimab (MEDI0562)	IgG1	AstraZeneca	Phase I
	PF-04518600	IgG2	Pfizer	Phase II
	BMS-986178	IgG1	Bristol-Myers Squibb	Phase II
	MOXR-0916	IgG1	Roche	Discontinued; phase at termination: phase II clinical
	GSK-3174998	IgG1	GlaxoSmithKline	Phase I
	INCAGN01949	IgG1	Incyte	Phase II

PF-8600, fully human IgG2 agonistic mAb against human OX40: Phase I

- **N=52 [melanoma (n = 15), HCC (n = 19), head and neck squamous cell (n = 9) or renal cell carcinoma (n = 9)]**

- **Most commonly-reported AE (all grade): fatigue, nausea, decreased appetite**

- **No DLTs up to 10mg/kg.**

- **Dose expansion in HCC to find RP2D**

- **PR=2 (melanoma & HCC; n=1 each), SD=28, PD=19**

El-Khoueiry Ab et al, The relationship of pharmacodynamics (PD) and pharmacokinetics (PK) to clinical outcomes in a phase I study of OX40 agonistic monoclonal antibody (mAb) PF-04518600 (PF-8600). *J Clin Oncol* 35, 2017 (suppl; abstr 3027)

MEDI0562, a humanized IgG4 OX40 monoclonal antibody: Phase I

- **N=55 pts with advanced solid tumors**

- **TRAe in 67%; most common trAEs were fatigue (31%) and infusion-related reaction (15%).**
- **Gr 3 TRAEs in 16%; most common pyrexia (4%)**

- **No Gr 4 or 5 TRAEs.**

- **No DLT; suggested MEDI0562 Phase 2 dose of ≥ 3 mg/kg Q2W was selected.**
- **50 evaluable; 2 PR (SCC of larynx and bladder cancer [n=1 each]), SD in 22 (>3 months in 20),**

OX40 agonism + PD-1 blockade: Timing is Important

- **Orthotopically-transplanted murine mammary tumor virus polyoma middle T (MMTV-PyMT) mammary cancer model**
  - Model is refractory to PD-1 blockade
  - With sequencing, tumor progression delayed significantly.

Messenheimer DJ et al, Timing of PD-1 Blockade Is Critical to Effective Combination Immunotherapy with Anti-OX40. *Clin Cancer Res.* 2017
Curti BD presentation at *2017 ASCO-SITC Clinical Immuno-Oncology Symposium*
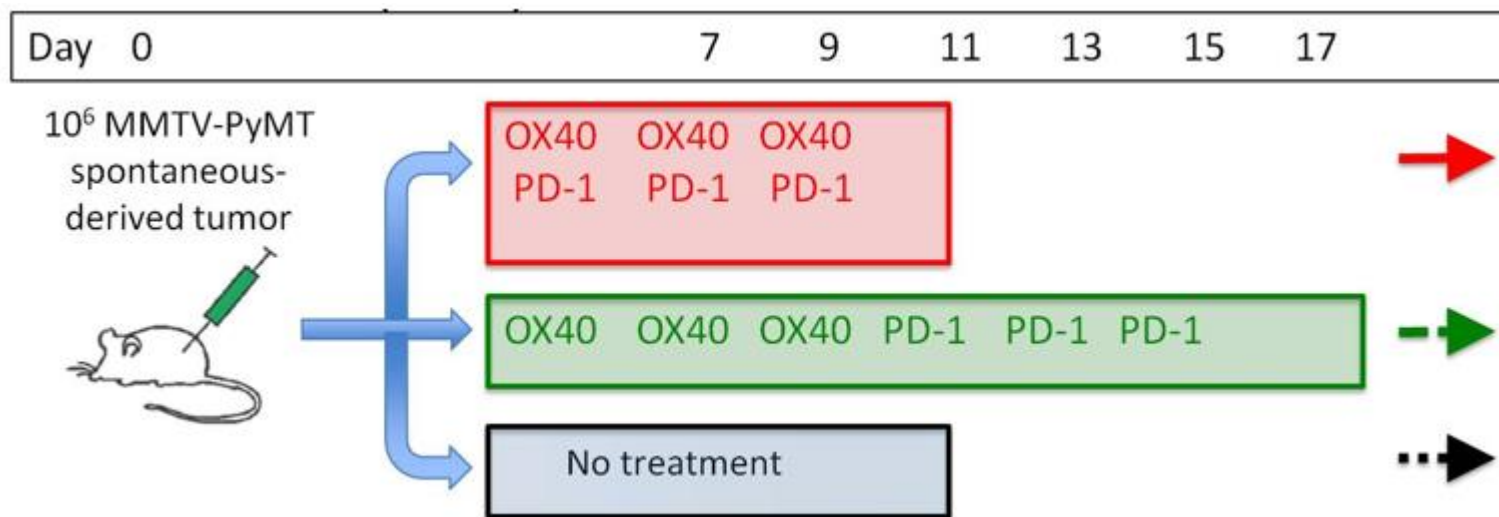
Concurrent Administration

- **Increases proliferation of TILs but short lived and this metric does not correlate with therapeutic response**

- **Weakened anti-tumor effect**
  - **Suppressed the therapeutic effect of anti-OX40 antibody**

- **Heightened expression of immune checkpoint proteins CTLA-4 and TIM-3 on T cells**

- **Acute increase in serum cytokines**
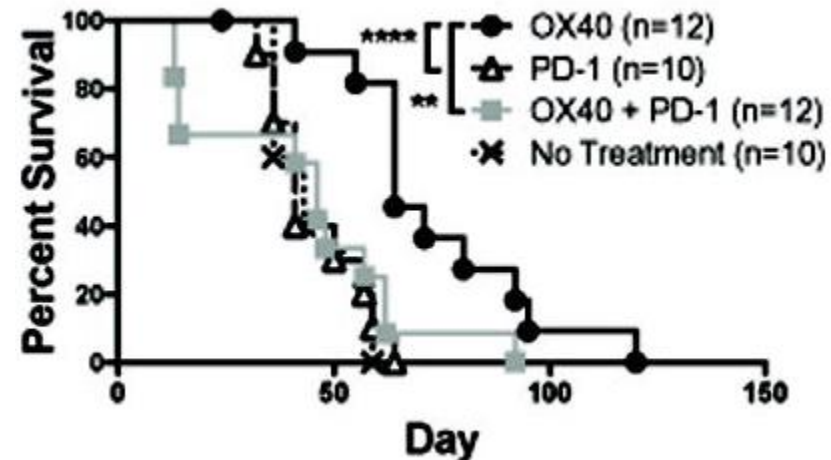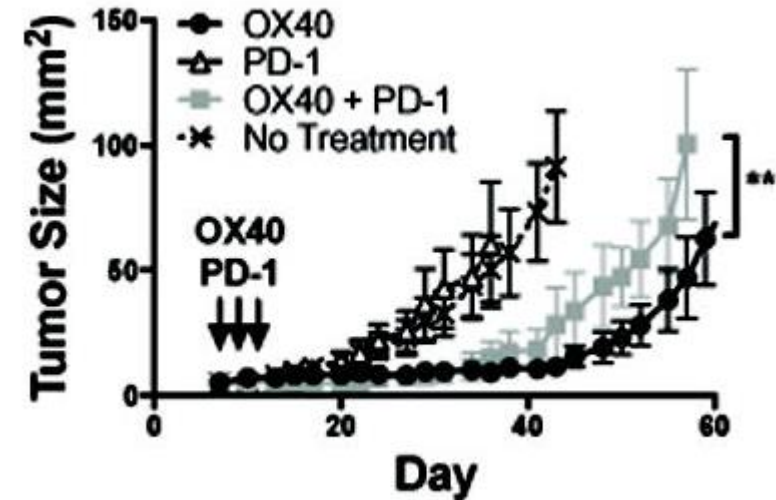
Sequential Administration

Anti-OX40 plus delayed anti-PD-1 is superior to concurrent combination
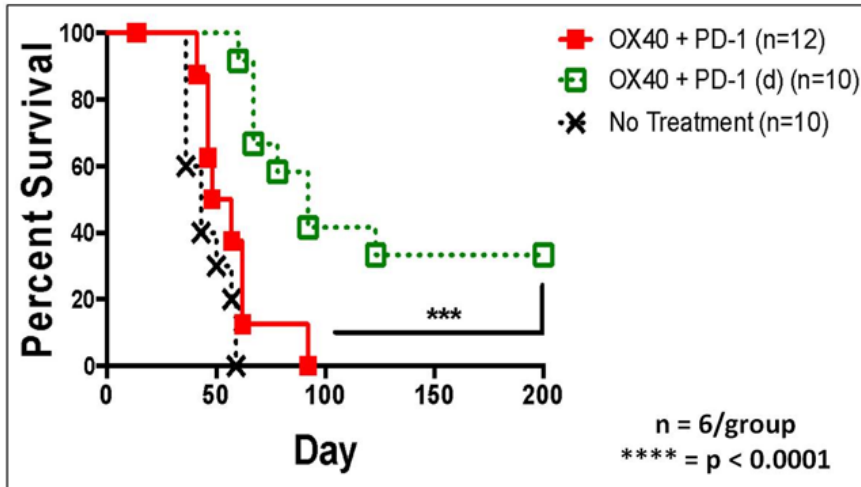
Anti-OX40 plus delayed anti-PD-L1 is also superior to concurrent combination
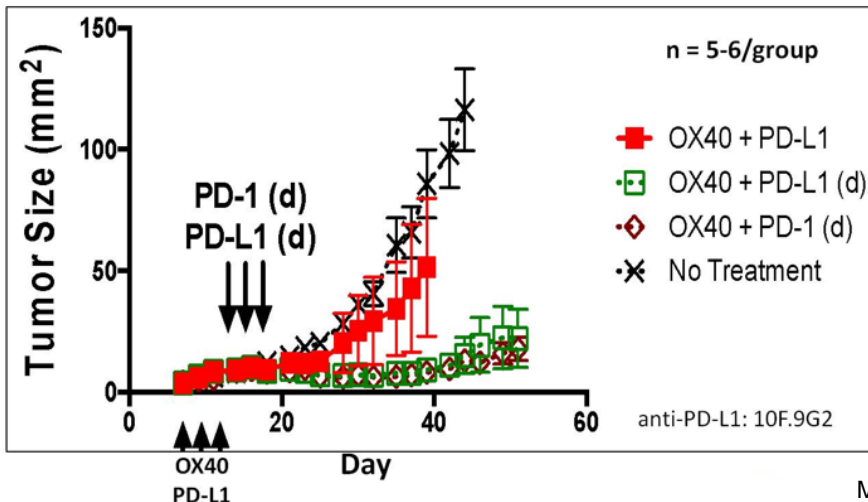
- **Delaying anti-PD-1 administration**
  - Greatly enhanced the effects of anti-OX40 monotherapy
  - Complete regression of tumors in about 30 percent of the mice
  - Provided durable responses dependent on both CD4+ and CD8+ T cells that eliminated tumors in a substantial portion of animals.

Timing is Important

Proposed Model: Anti-OX40 + delayed anti-PD-1 provides improved therapy

OX40 + PD-1 delay

OX40

OX40 + PD-1

Immune Response

Time

Improved Therapy
* Block exhaustion
* Maintain T cells

Reduced Therapy
↑ inhibitory receptors
↑ T$_{reg}$ cells

Messenheimer DJ et al, Timing of PD-1 Blockade Is Critical to Effective Combination Immunotherapy with Anti-OX40. *Clin Cancer Res.* 2017
Curti BD presentation *at 2017 ASCO-SITC Clinical Immuno-Oncology Symposium*

OX40 Combinations in Clinical Development
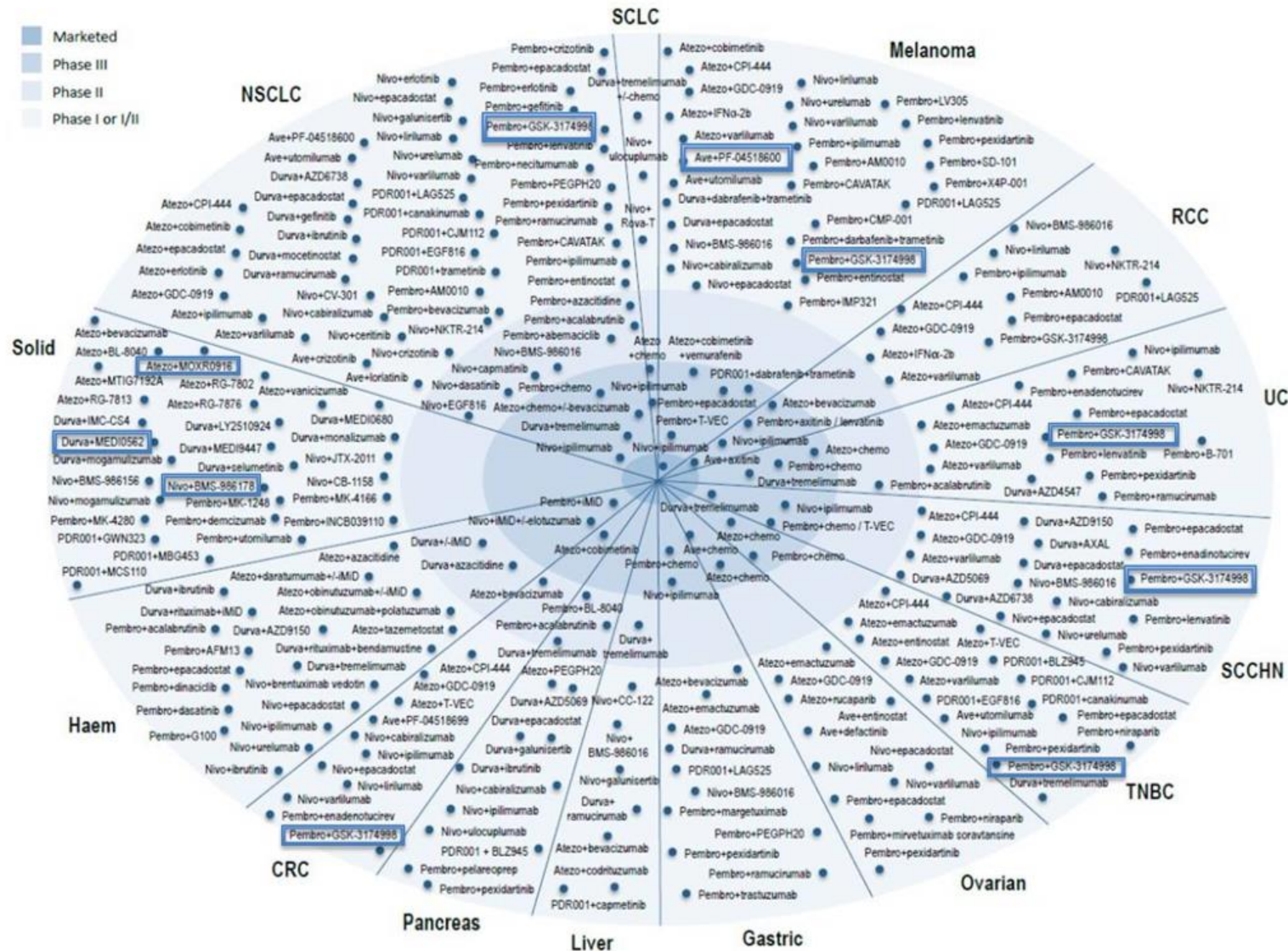
4-1BB (CD137)

4-1BB (CD137)

CD137/4-1BB stimulated tumor cell killing
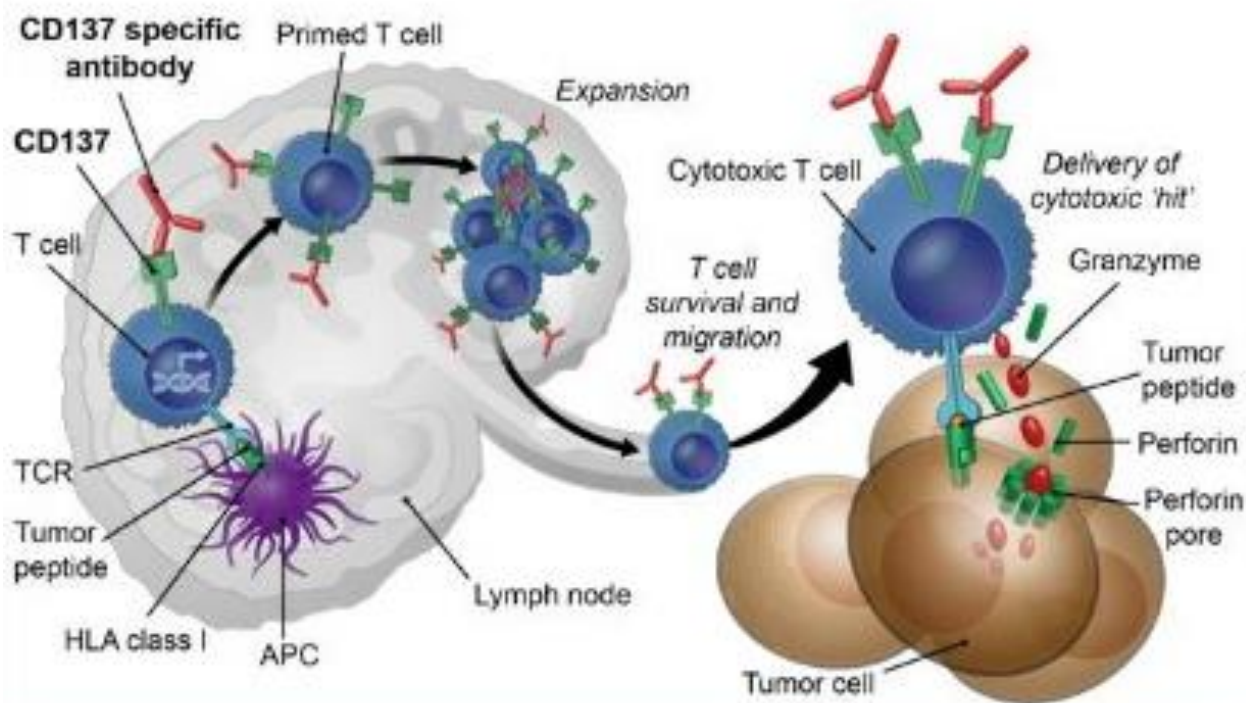
- **Member of the tumor necrosis factor receptor superfamily[9]**

  o **Expressed on <u>activated</u> CD8^{+} and CD4^{+} T cells, activated natural killer (NK) and natural killer T (NKT) cells, regulatory T cells, dendritic cells (DC), stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, and eosinophils**

  o **Peaks 12-24 hours following stimulation**

  o **Declines by 72 hours**

Ligand: 4-1BBL

  o **Expressed on activated APCs**

  o **Myeloid progenitor cells and hematopoietic stem cells**

Wang C et al. Immune regulation by 4-1BB and 4-1BBL: complexities and challenges, *Immunological Reviews, 2009*
Bartkowiak T and Curran MA. 4-1BB Agonists: Multi-Potent Potentiators of Tumor Immunity, *Front Oncol.* 2015.
Segal NH et al, A phase 1 study of PF-05082566 (anti-4-1BB) in patients with advanced cancer. *J Clin Oncol,* 2014

Multi-potent Roles of 4-1BB
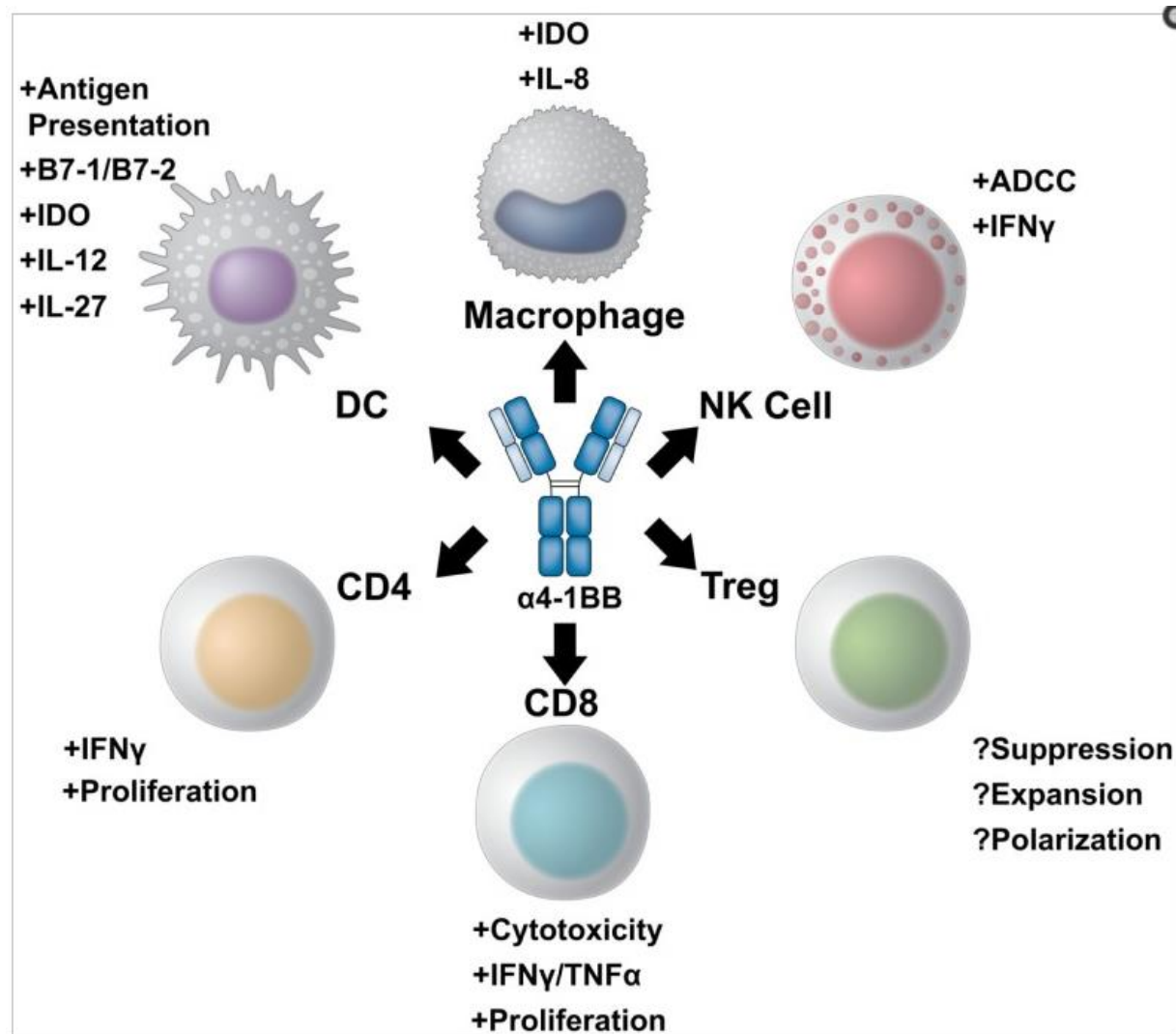
- **Diverse immune effector responses on both the innate and adaptive immune arms.**

- **Most potent action on CD8+ cytotoxic T cells:**
  - Increased T cell proliferation and effector potential through increased IFN γ production and expression of multiple granzymes; prolonged CD8 T cell survival

- **CD4+ effector T cells: stimulated to expand and produce pro-inflammatory cytokines.**

- **Controversial role on Tregs:**
  - Either inhibit differentiation of conventional effector cells into Tregs and inhibit Treg suppression
  - Or maintain Treg expansion and suppressive capacity

- **NK cells: stimulate antibody-dependent cell-mediated cytotoxicity through Fc/FcR interactions,**

- **DC: Induce maturation and antigen presentation. In addition, α4-1BB stimulated DCs begin to express IL-12 and IL-27 as well as the enzyme IDO to modulate T cell function.**

- **4-1BB+ macrophages: stimulated to increase antigen presentation and produce IL-8 as well as IDO.**

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Bartkowiak T and Curran MA. 4-1BB Agonists: Multi-Potent Potentiators of Tumor Immunity, *Front Oncol.* 2015.
Segal NH et al, A phase 1 study of PF-05082566 (anti-4-1BB) in patients with advanced cancer. *J Clin Oncol*, 2014

4-1BB Signaling/Agonist Action

- **Ligation recruits** TNFR-associated factor (TRAF) 1 and TRAF2 and induces signaling through the NF-kB and MAPKs.

- Increase co-stimulatory molecule expression and markedly enhance cytolytic T lymphocyte responses

- Results in durable anti-tumor protective T-cell memory responses

- Promotes T-cell migration into tumor lesions due to increased expression of the cellular adhesion molecules ICAM-1, VCAM-1, and E-selectin on tumor vasculature

- Fully human mAbs against CD137 (urelumab or BMS-663513, Utomilumab or PF-05082566) have been developed

- Liver toxicity associated with 4-1BB agonist antibodies has dampened the clinical development of the agent

Fisher et al, Targeting of 4-1BB by monoclonal antibody PF-05082566 enhances T-cell function and promotes anti-tumor activity, *Cancer Immunol Immunother*, 2012.

4-1BB Monotherapy: Preclinical Data

- **In several tumor models, 4-1BB agonists have demonstrated antitumor efficacy**

- **CD-137 agonist antibodies show a dose dependent inhibition of tumor growth:**

CT26 Mouse Model

Segal NH et al, A phase 1 study of PF-05082566 (anti-4-1BB) in patients with advanced cancer. *J Clin Oncol,* 2014
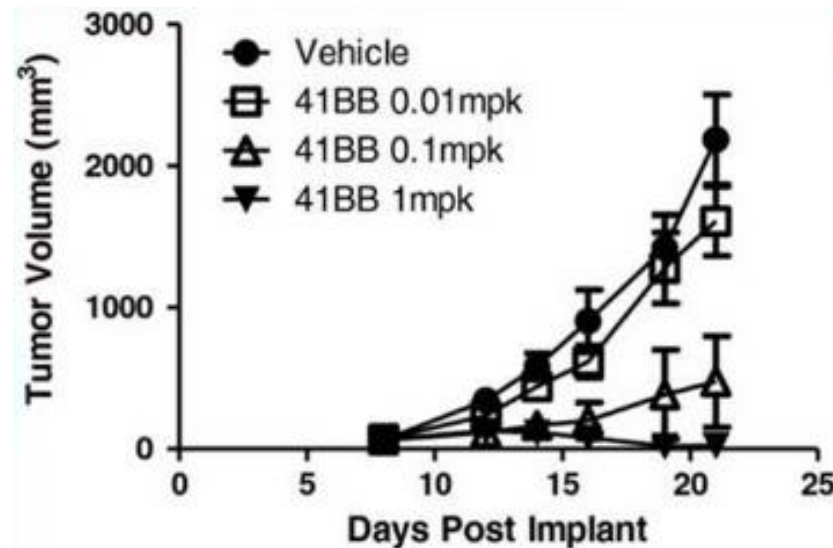
Urelumab: Proof-of-concept Study

- **A fully human IgG4 with a point mutation (S228P)**

- **Phase I/ II trial in 115 patients with advanced/metastatic solid tumors**

- **Most frequent AE fatigue, transaminitis, neutropenia, rash, and diarrhea**

- **Grade ≥2 laboratory abnormalities were: increases in alanine aminotransferase (ALT) (15%), aspartate transaminase (AST) (12%), leukopenia (8%), neutropenia (6%), thrombocytopenia (4%), and hyperbilirubinemia (<1%)**

- **Optimal dose was not identified**

- **Partial remissions and sustained stable diseases were observed.**

- **Increase peripheral activated CD8 T cells and IFN-inducible genes**

Sznol M et al, Phase I study of BMS-663513, a fully human anti-CD137 agonist monoclonal antibody, in patients (pts) with advanced cancer (CA) [abstract], *J Clin Oncol*, 2008.

Urelumab: Phase II

- Randomized, multi-dose study in previously treated melanoma patients with stage IV disease

- Four arms:
  - arm 1, 0.1 mg/kg every 3 weeks
  - arm 2, 1 mg/kg every 3 weeks
  - arm 3, 1 mg/kg every 6 weeks
  - arm 4, 5 mg/kg every 3 weeks

- The study was terminated in May 2009 due to unusually high incidence of grade 4 hepatitis

- Cause is related to increased CD8+ T cell accumulation and activation in the liver following treatment

- In December 2008, enrolment was stopped for all urelumab studies following the occurrence of two hepatotoxicity-related deaths

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Wen-Jen Hwu, Targeted therapy for metastatic melanoma: From bench to bedside, *HemOnc Today*, 2010.
Mayes PA et al, The promise and challenges of immune agonist antibody development in cancer, *Nature Reviews Drug Discovery*, 2018

Urelumab: Phase Ib

- 3 monotherapy studies restarted in February 2012

- N=347; doses ranging from 0.1 to 15 mg/kg every 3 weeks

- TRAEs in urelumab doses between 1 and 15 mg/kg greater than than in doses of 0.1 or 0.3 mg/kg

- Two deaths occurred at the higher dose range (1 and 5 mg/kg).

- 15 of 25 patients rechallenged at the same dose did not have recurrence of same AEs

- Urelumab 0.1 mg/kg every 3 weeks was demonstrated to be safe

- **More marked agonistic activity on the receptor than utomilumab**

Event	Urelumab 0.1 mg/kg ($n = 61$)[c]	Urelumab 0.3 mg/kg ($n = 56$)[c]	Urelumab ≥1 mg/kg ($n = 229$)[c]
Any grade ≤4 AEs[a], % (grade 3–4, %)[d]			
AST increased	8.2	14.3 (3.6)	27.1 (13.5)
ALT increased	6.6 (1.6)	10.7 (3.6)	26.6 (16.6)
Fatigue	16.4	14.3	24.0
Rash	4.9	7.1	19.7
Nausea	13.1	3.6	13.5
Pruritus	4.9	5.4	13.1
Decreased appetite	8.2	3.6	12.2
Pyrexia	4.9	1.8	12.2
Diarrhea	3.3	3.6	12.2
Asthenia	8.2	0	7.9
Headache	1.6	1.8	7.0
Neutropenia	4.9 (3.3)	0	6.1 (2.6)
Vomiting	3.3	0	5.2

Segal NH et al, Results from an Integrated Safety Analysis of Urelumab, an Agonist Anti-CD137 Monoclonal Antibody, *Clin Cancer Res.,* 2016
Perez-Ruiz EAnti-CD137 and PD-1/PD-L1 antibodies en route toward clinical synergy. *Clin Cancer Res.* 2017

Utomilumab: Phase I

- **A fully human IgG2**

- **N=34 patients with advanced cancer**

- **3+3 design (0.006 to 0.3 mg/kg) Time-To-Event CRM design for higher doses (0.6 to 5 mg/kg)**

- **Grade 1 AEs: Rash (n=3), fever, nausea/vomiting (n=2 each), weight loss, fatigue, thrombocytopenia (n=1 each)**

- **Grade 3 elevation in alkaline phosphatase (n=1) at 0.06 mg/kg dose**

- **No dose-limiting toxic effects in humans at doses up to 10 mg/kg**

- **Best overall response of stable disease was observed in 22% (6/27) patients**

Segal NH et al, A phase 1 study of PF-05082566 (anti-4-1BB) in patients with advanced cancer. *J Clin Oncol*, 2014

- **T-cell activation and cytokine production (e.g., IFNγ) by 4-1BB may induce increased PD-L1 expression, limiting T cell function**

- **Combination has complementary action and may produce additive or synergistic antitumor activity**
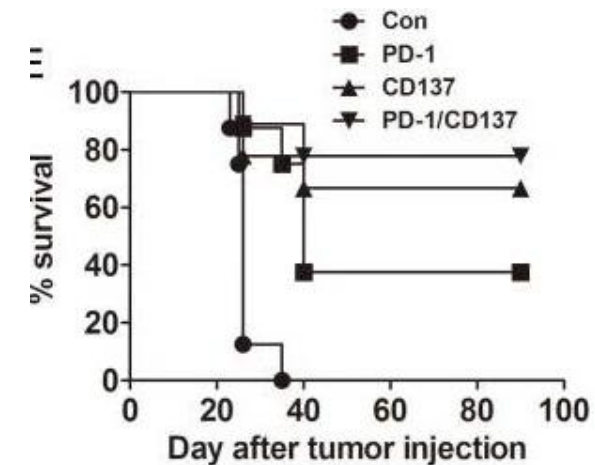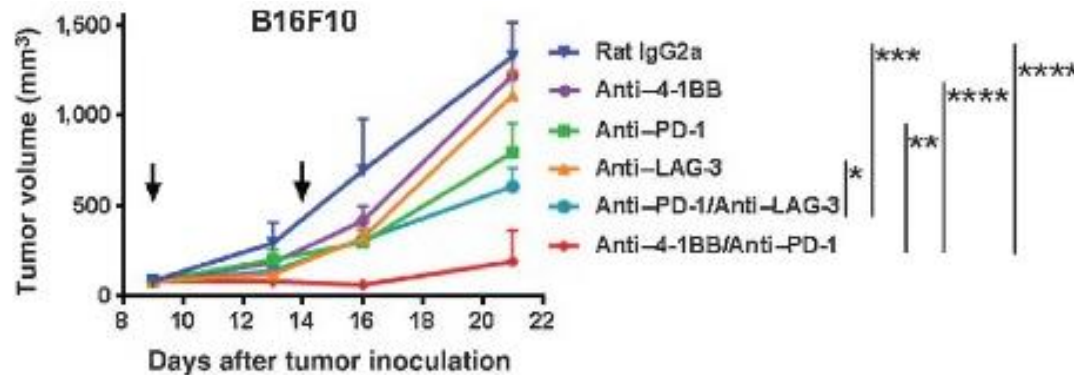
- **Poorly immunogenic B16F10 melanoma model,**
  - Combination produced antitumor activity
  - Elevated CD8+/regulatory T-cell ratio
  - Increased activity of tumor-specific cytotoxic T lymphocytes

- **Ovarian cancer model,**
  - Improved survival
  - Increase in effector CD8+ T cells
  - Decrease in Tregs and MDSCs

Chen S et al, Combination of 4-1BB agonist and PD-1 antagonist promotes antitumor effector/memory CD8 T cells in a poorly immunogenic tumor model. *Cancer Immunol Res* 2015
Wei H et al, Dual targeting of CD137 co-stimulatory and PD-1 co-inhibitory molecules for ovarian cancer immunotherapy. *Oncoimmunology* 2014
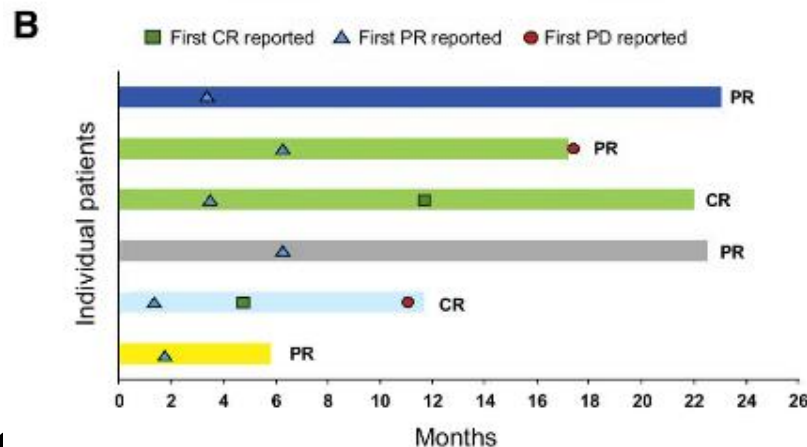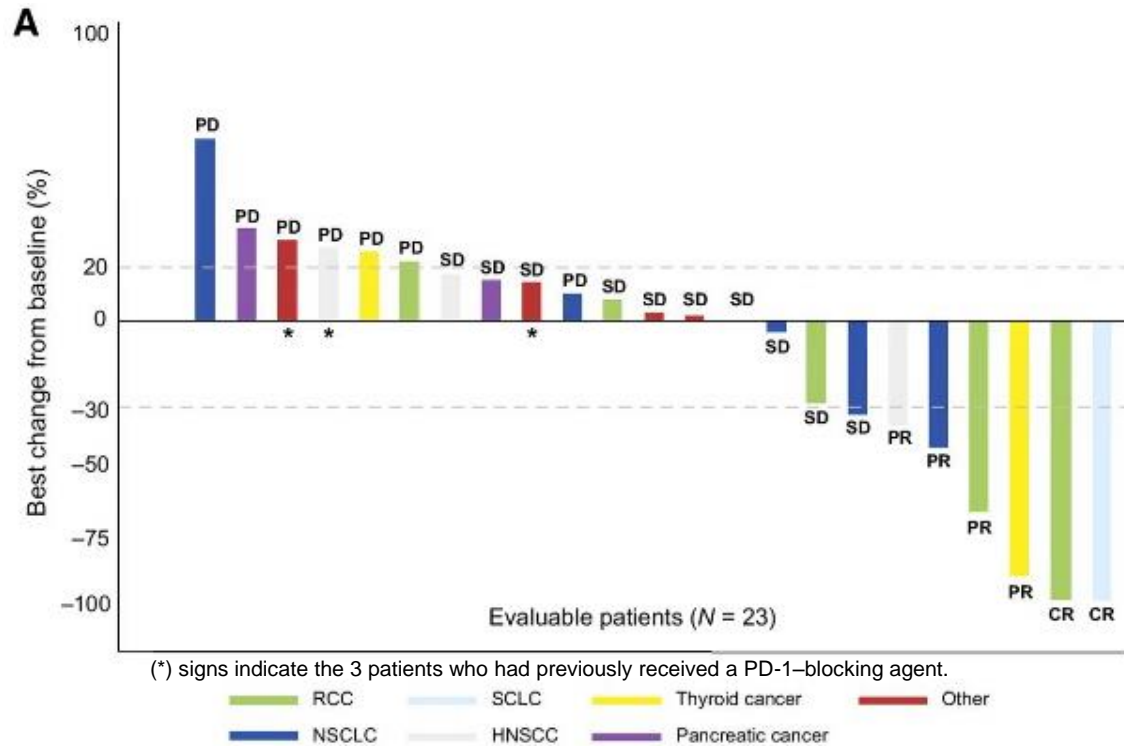
Utomilumab + Pembrolizumab: Phase Ib

- **N=23 patients**
  - 6 had NSCLC
  - 5 had RCC
  - 3 had HNSCC
  - 2 each had pancreatic or thyroid cancer
  - 1 each had small-cell lung cancer (SCLC), colon cancer, sarcoma, thymic cancer, or ocular melanoma

- **Utomilumab (0.45–5.0 mg/kg) and pembrolizumab (2 mg/kg) every 3 weeks.**

- **No DLTs were reported.**

- **TRAEs were mostly Grade 1/2**

Adverse event[a]	Pembrolizumab (2 mg/kg) + utomilumab (N = 23)			
	Treatment emergent		Treatment related	
	All grades	Grade 3–4[b]	All grades	Grade 3–4
Fatigue	10 (43.5)	1 (4.3)	8 (34.8)	0
Rash	10 (43.5)	0	8 (34.8)	0
Cough	8 (34.8)	0	1 (4.3)	0
Decreased appetite	7 (30.4)	0	3 (13.0)	0
Nausea	7 (30.4)	0	3 (13.0)	0
Constipation	6 (26.1)	0	1 (4.3)	0
Pruritus	6 (26.1)	0	5 (21.7)	0
Pyrexia	5 (21.7)	0	3 (13.0)	0
Vomiting	5 (21.7)	0	1 (4.3)	0
Anemia	4 (17.4)	3 (13)	0	0
Dyspepsia	4 (17.4)	0	2 (8.7)	0
Upper respiratory tract infection	4 (17.4)	0	0	0

[a]None of the patients discontinued due to treatment-related adverse events.
[b]Treatment-related grade 3 adverse events reported in this study included adrenal insufficiency and hypokalemia (n = 1 each).

Tolcher AW et al., Phase Ib Study of Utomilumab (PF-05082566), a 4-1BB/CD137 Agonist, in Combination with Pembrolizumab (MK-3475) in Patients with Advanced Solid Tumors, *CCR*, 2017

Utomilumab+ Pembrolizumab: Phase Ib

A

(*) signs indicate the 3 patients who had previously received a PD-1–blocking agent.

Legend: RCC, NSCLC, SCLC, HNSCC, Thyroid cancer, Pancreatic cancer, Other

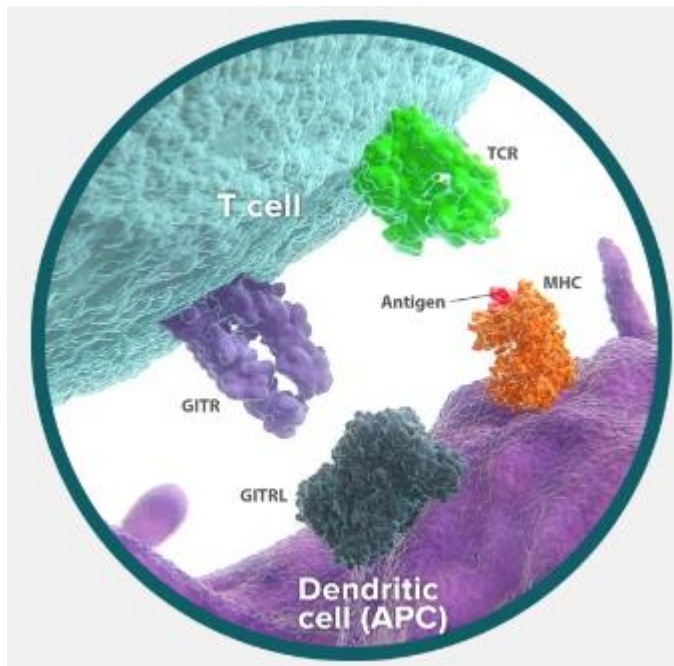B — First CR reported, First PR reported, First PD reported

- **ORR: Six out of 23 treated patients (26%) per RECIST 1.1**
- **CR in SCLC (n=1), PRs in RCC (n=2), NSCLC (n=1), H&N (n=1) and anaplastic thyroid (n=1)**
- **Median duration of response has not been reached**
- **Five of the 6 responders maintained a response for >6 months**

Tolcher AW et al., Phase Ib Study of Utomilumab (PF-05082566), a 4-1BB/CD137 Agonist, in Combination with Pembrolizumab (MK-3475) in Patients with Advanced Solid Tumors, *CCR, 2017*

4-1BB Agonist + Chemotherapy

- **α4-1BB with 5-FU:**
  - Profound tumor regressions
  - Increased overall survival rates

- **α4-1BB with the DNA-alkylating platinum-containing derivatives, particularly cisplatin:**
  - Produced cooperative anti-tumor responses; complete rejection of CT26 colon adenocarcinoma
  - Increased survival
  - Protection from cisplatin-induced nephrotoxicity

- **α4-1BB with cyclophosphamide (CTX):**
  - Increased overall survival by eliciting polyclonal expansion of anti-tumor T cells
  - Significantly enhanced effector function

Ju SA et al. Eradication of established renal cell carcinoma by a combination of 5-fluorouracil and anti-4-1BB monoclonal antibody in mice. *Int J Cancer*. 2008
Kim YH et al. Combination therapy with cisplatin and anti-4-1BB: synergistic anticancer effects and amelioration of cisplatin-induced nephrotoxicity. *Cancer Res*. 2008
Kim YH et al, Mechanisms involved in synergistic anticancer effects of anti-4-1BB and cyclophosphamide therapy. *Mol Cancer Ther*. 2009

Glucocorticoid induced TNFR (GITR)

GITR (CD357)

Cell type	GITR expression	
	Naïve	**Activated**
Regulatory T cells	High	Very high
T cells (CD4/CD8)	Intermediate	High
NK cells	Intermediate	High
Granulocytes	Intermediate	High
Mast cells	Intermediate	Intermediate
Eosinophils	Intermediate/low	
Basophils	Intermediate/low	
Monocytes/macrophages	Low	Intermediate

- **Member of the tumor necrosis factor receptor superfamily18**
  - **Peaks after 2-3 days**
  - **Declines by day 5**

- **GITR ligand (GITRL)**
  - **Expressed at low levels by antigen-presenting cells such as dendritic cells (DCs), macrophages, and B cells**
  - **Upregulated upon activation**

Riccardi C et al, Glucocorticoid-induced TNFR-related gene (GITR) as a therapeutic target for immunotherapy, *Expert Opinion on Therapeutic Targets* , 2018

Schaer et al, Modulation of GITR for cancer immunotherapy, *Curr Opin Immunol.* 2012

https://www.immunooncologyhcp.bmsinformation.com/antitumor-immunity/pathways/additional-effector-t-cell-pathways/

Role of GITR

a

CD4 — TCR, CD4, CD25/IL-2R, IL-2, GITR, GITRL — activation/proliferation

CD8 — TCR, CD8, CD25/IL-2R, IL-2, GITR, GITRL — activation

Increased T cell activation

b

GITR, GITRL, COX-2, iNOS → ↑MMP-9, MMP-13, MMP-2, MCP-1, PGE₂, NO, TNFα

increased macrophage activation

c

T cell activation — TCR, CD4, RANTES, E-selectin, P-selectin, GITRL, GITR

endothelial cell activation — VCAM-1, ICAM-1

macrophage activation

increased adhesion/extravasation

- **TCR-stimulated T lymphocytes:**
  - **Increases activation and proliferation,** particularly in the setting of suboptimal TCR stimulation
  - Protects T cell from activation-induced cell death
  - upregulates IL-2Rα, IL-2 and IFNγ

- **Macrophages: upregulation of**
  - Matrix metalloproteinase (MMP)-2, -9, and 13, monocyte chemoattractant protein (MCP)-1, TNFα, COX-2 and inducible nitric oxide synthase enzymes

- **Favors leukocyte activation, migration and extravasation**
  - Upregulates the adhesion molecules VCAM-1 and ICAM-1
  - Activate T cells that upregulate the chemotactic molecule CCL5 or RANTES and the adhesion molecules E-selectin and P-selectin

- **Tregs:**
  - Induces Treg expansion, inhibits Treg suppressive function and promotes Teff resistance to Treg suppression
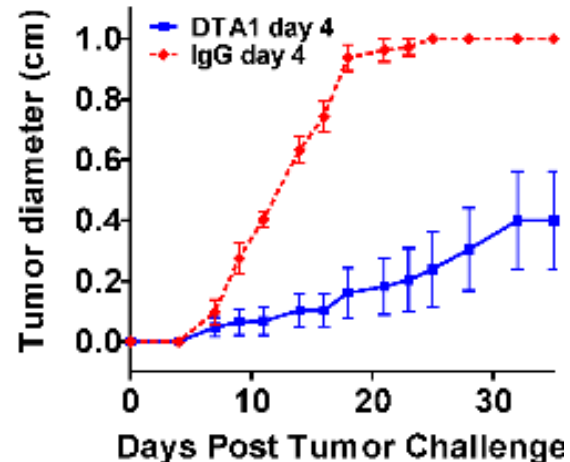
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GITR Signaling
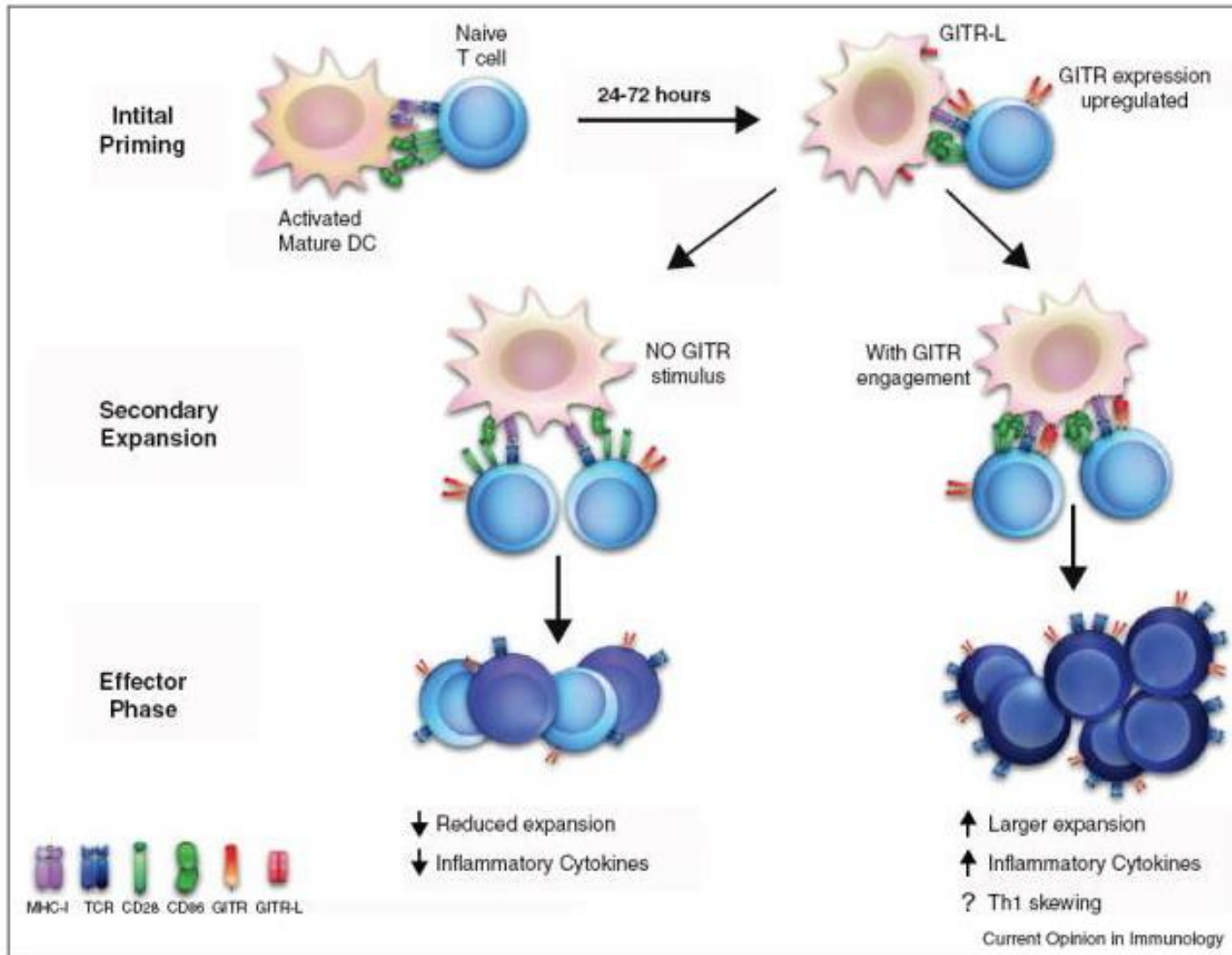
- **Initial priming:**
  - **Naïve T cells are activated by interaction between TCR and MHC molecule**

- **Secondary priming and expansion:**
  - **Upregulation of GITR on activated T cells 24–72 h after initial activation**

- **If GITR-L is expressed by DCs:**
  - **Enhances the Teff to Treg ratio**
    - **In part through its costimulatory role of enhancing the CD8+ T cell population,**
    - **Also through its depletion of Tregs**
  - **Increased persistence of the antigen-specific T cells**

B16 Melanoma tumor model
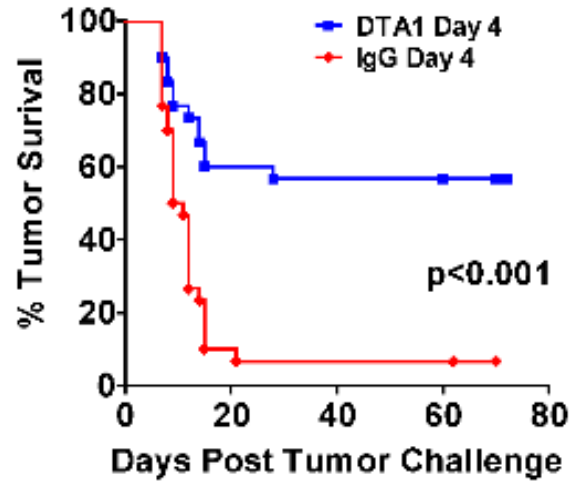
- **The most widely used agonist antibody is DTA-1 (rat IgG2b anti-mouse GITR agonist antibody)**

- **In wide range of syngeneic mouse models:**
  - Compelling antitumor activity attributed to:
    - **Costimulatory role on CD4+ and CD8+ T cells**
    - **Inhibition or depletion of intratumoral Tregs**
      - **GITR+ Tregs are killed by myeloid and NK cells present in the tumor (Treg-specific and tumor-specific action)**

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Knee DA et al, Rationale for anti-GITR cancer immunotherapy, *European Journal of Cancer.* 2016
Cohen AD et al, Agonist Anti-GITR Monoclonal Antibody Induces Melanoma Tumor Immunity in Mice by Altering Regulatory T Cell Stability and Intra-Tumor Accumulation, *PLoS One,* 2010

GITR Agonist: in Clinical Development

| GITR	TRX-518	Aglycosyl IgG1	Leap Therapeutics	Phase I
	MK-4166	IgG1	Merck & Co.	Phase I
	MK-1248	IgG4	Merck & Co.	Phase I
	GWN-323	IgG1	Novartis	Phase I
	INCAGN01876	IgG1	Incyte	Phase I/II
	BMS-986156	IgG1	Bristol-Myers Squibb	Phase I/II
	AMG-228	IgG1	Amgen	Phase I
	MEDI 1873	GITR-ligand/IgG1 agonist fusion protein	MedImmune	Phase I

AMG 228: Phase I

- **N=30 patients with refractory CRC, head and neck squamous cell carcinoma, urothelial carcinoma, NSCLC and melanoma**

- **Most common TRAEs: fatigue (13%), infusion-related reaction (7%), pyrexia (7%), decreased appetite (7%), and hypophosphatemia (7%)**

- **3 fatal AEs: pneumonitis (related), acute hypoxemic respiratory failure (not related), and progressive disease (melanoma)**

- **No DLT; MTD not reached**

- **27 evaluable for response by irRC; CR/PR=0; SD=7; PD=17**

- **Despite GITR coverage in peripheral blood and tumor biopsies, there was no evidence of T-cell activation or anti-tumor activity, so not expanded**

MEDI1873: Phase I

- **N=40, dose escalation (n=28) and pharmacodynamic (n=12) cohorts**

- **Any-grade drug-related AEs in 82.5% of patients**
  - Headache (25%) and infusion related reaction (20%)
  - Grade 3 TRAEs occurred in 22.5% of pts; Amylase increase was the only one reported in > 1 pt (n = 2)
  - No drug-related Grade 4 or 5 AEs

- **Three DLTs occurred:**
  - Grade 3 worsening tumor pain at 250 mg
  - Grade 3 nausea and vomiting at 500 mg
  - Grade 3 non-STEMI at 750 mg

- **MTD was not reached (maximum administered dose was 750 mg)**

- **Best overall response was stable disease (SD) in 42.5% of patients**
  - 17.5% had SD ≥ 24 weeks
  - Three pts (pancreatic neuroendocrine tumor, lung cancer and mesothelioma) stayed for ≥52 weeks without PD

- **Translational data:**
  - MEDI1873 engaged GITR on CD4$^+$ T cells
  - Increased CD4$^+$Ki67$^+$ T cells at doses ≥25 mg
  - Intratumorally, induced a ≥ 25% decrease in GITR$^+$/FOXP3$^+$ T cells in 5 of 5 pts with evaluable cells.

Denlinger CS et al, A Phase 1 study of MEDI1873, a novel GITR agonist, in advanced solid tumors, *ESMO 2018 Congress*.

GITR Agonist + PD-1 inhibitor

- **Poorly immunogenic ID8 murine ovarian cancer model**
  - Inhibited peritoneal ID8 tumor growth
  - **Memory immune response** conferred by CD4+ cells and CD8+ T cells.
  - Increased the frequencies of interferon-γ-producing effector T cells
  - Decreased immunosuppressive regulatory T cells and myeloid-derived suppressor cells, **shifting an immunosuppressive tumor milieu to an immunostimulatory state**
  - Antigen-specific immune response as evidenced by antigen-specific IFN-γ production and cytolytic activity of spleen cells from treated mice.
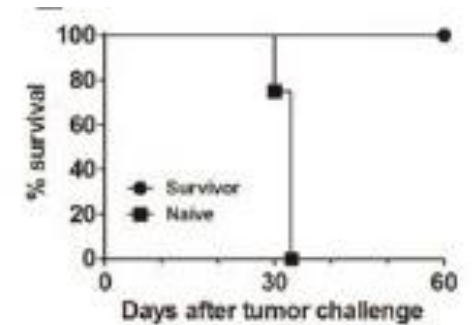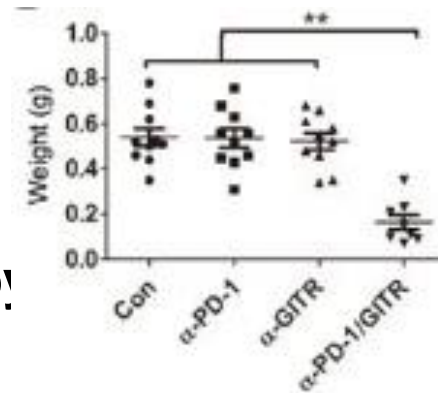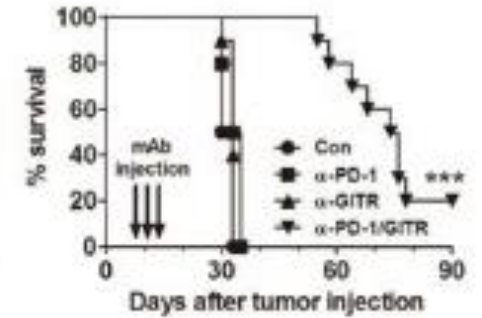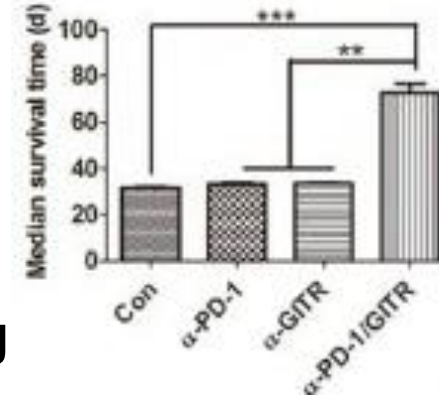
Rechallenged with ID8 cells and their overall survival was recorded. Naïve mice were challenged with ID8 cells as control

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Lu L et al, Combined PD-1 blockade and GITR triggering induce a potent antitumor immunity in murine cancer models and synergizes with chemotherapeutic drugs, *Journal of Translational Medicine,* 2014
Riccardi C et al, Glucocorticoid-induced TNFR-related gene (GITR) as a therapeutic target for immunotherapy, *Expert Opinion on Therapeutic Targets* , 2018
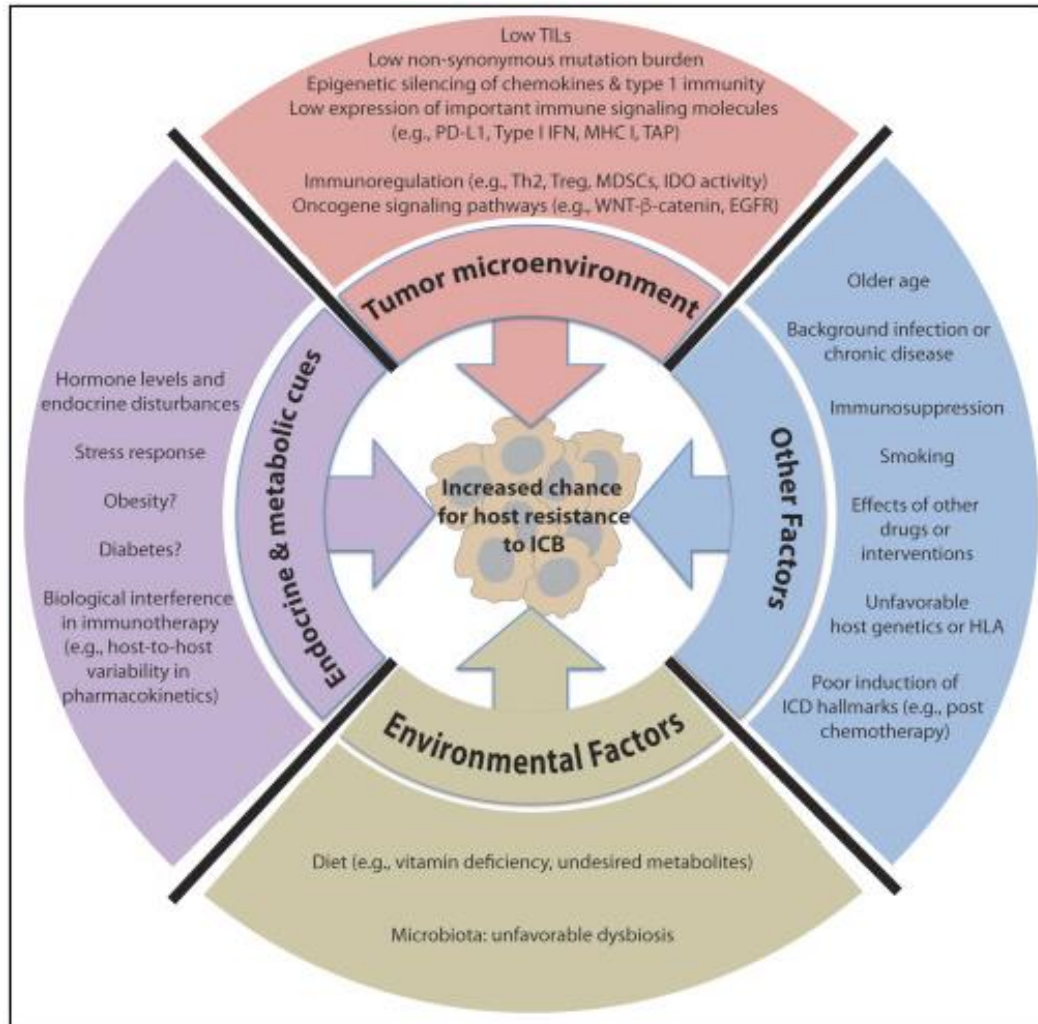
MK1248 +/- Pembrolizumab

- **N=37 patients; Monotherapy (n=20), Combination (n=17)**

- **Tumor types: CRC (8 pts), melanoma (5 pts), RCC (4 pts) and 20 pts with 16 other solid tumors.**

- **MK-1248 at the dose up to 170 mg as monotherapy and 60 mg in combination with pembrolizumab was well tolerated**

- **17 pts (48.6%) had ≥1 TRAEs; 3 (8.1%) had grade 3-5 TRAEs**

- **No DLT or treatment-related deaths were observed**

Geva R et al, First-in-human phase 1 study of MK-1248, an anti-human glucocorticoid-induced tumor necrosis factor receptor (GITR) monoclonal antibody, as monotherapy or in combination with pembrolizumab in patients with advanced solid tumors. *J Clin Oncol 36, 2018 (suppl; abstr 3029).*

Challenges Associated with Immunotherapy

Resistance to Treatment

Resistance Mechanisms

Despite initial response, eventual relapse or progression is inevitable

Pitt JM et al. Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors, *Immunity*. 2016; 44; 1255–1269

Mechanisms to Overcome Resistance

- **Combination therapies are potentially synergistic and are far more effective than monotherapies**

- **As tumors use multiple pathways to evade immune elimination, a multi-pronged attack of complimentary pathways may be beneficial**

- **Tumors may prevent initiation of a local endogenous immune response, in whom pre-conditioning regimens such as chemotherapy or radiotherapy may be beneficial**
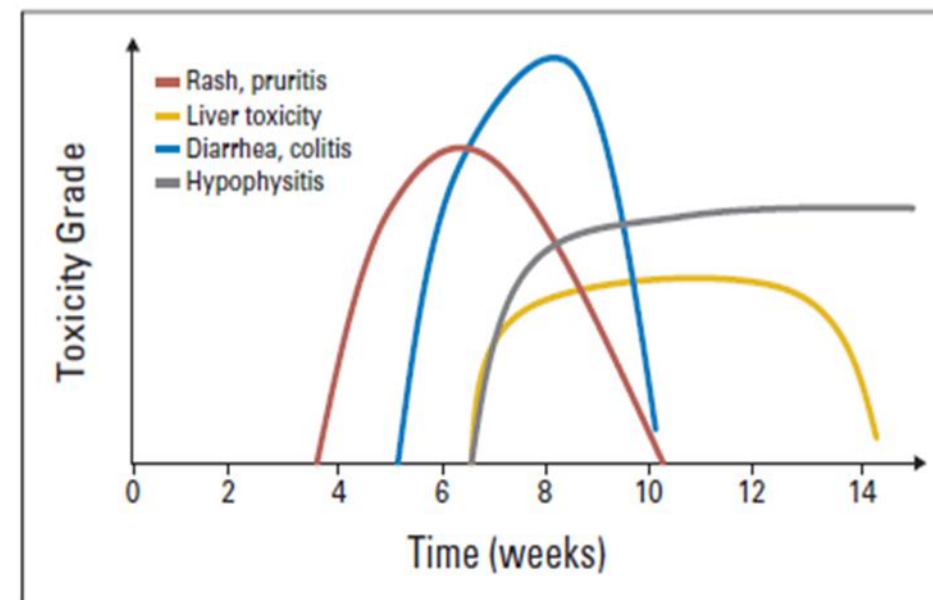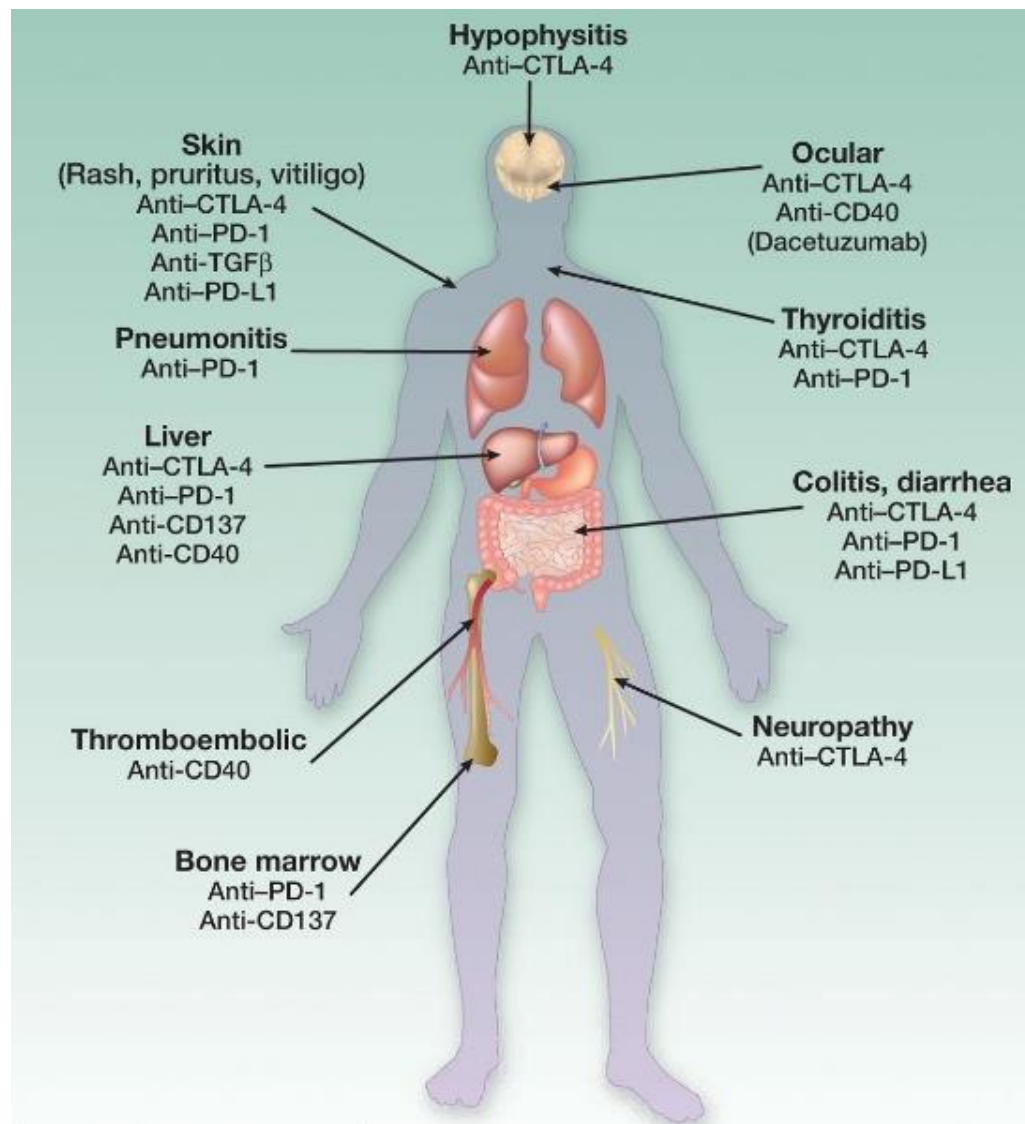
Topalian SL et al, *J Clin Oncol.* 2011;29(36):4828-36;
Gajewski TF. *Mol Oncol.* 2012;6(2):242-50.

Immune-Related Adverse Events (irAEs)
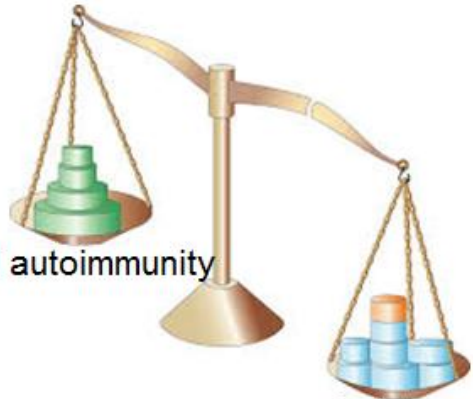
Most Frequent irAEs

Summary

- **OX40, 4-1BB and GITR share similarities in their expression patterns and downstream signaling pathways, they also exhibit unique characteristics, suggesting they are not redundant molecules.**

- **"Combination" is the key word to overcome resistance to therapy, with emphasis on study design**

- **Immune system is dynamic; the success of any of these agents, especially as combination partners, will depend heavily on the interrogation of the TME and pharmacodynamics of these agents**

- **Immune signatures predictive of response is much needed**

- **Prompt identification and treatment of irAE critical**

Thank You

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