NASDC
NCI Awardee Skills Development Consortium

Agonist Antibodies

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- TRM oncology

T-cell Activation

Antitumor immune responses involve multiple steps and cell types

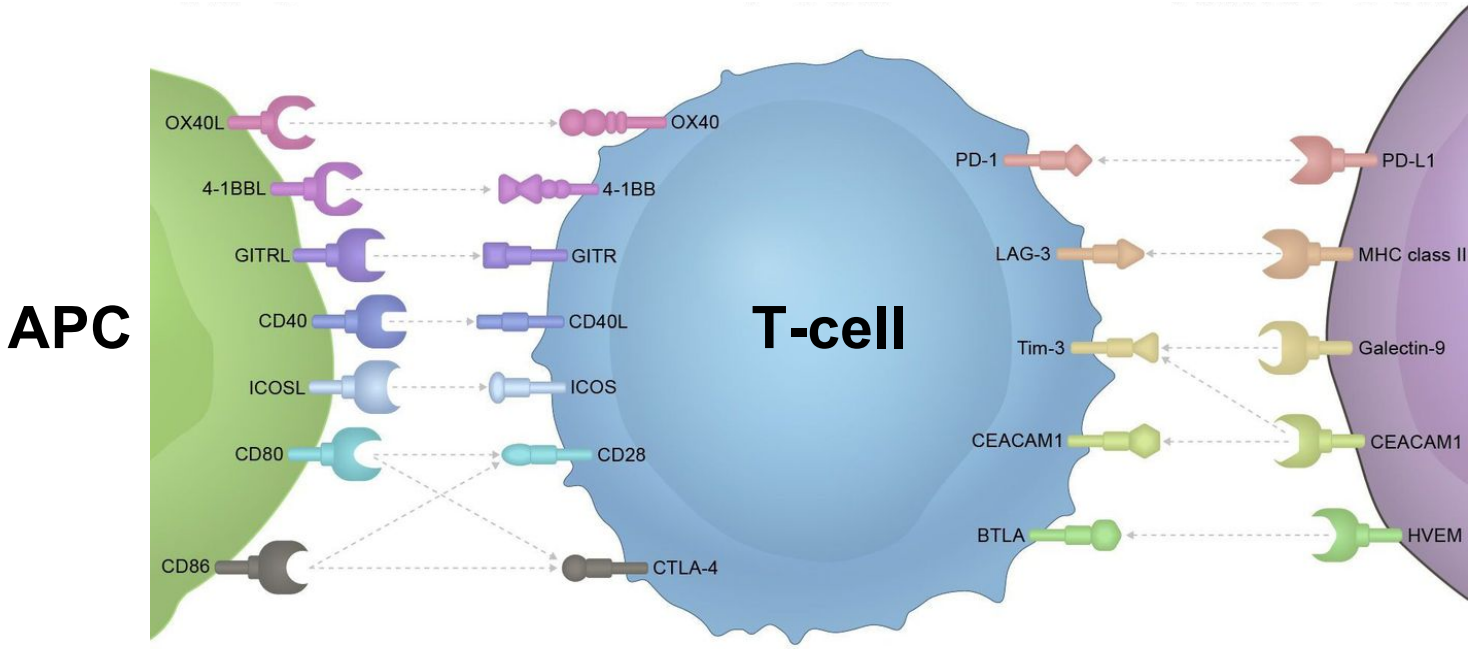
- » depending on interplay of innate and adaptive immune systems

Immunotherapy targeting the adaptive immune system, specifically T-cells, has shown efficacy in several tumor types

T-cell activation requires:

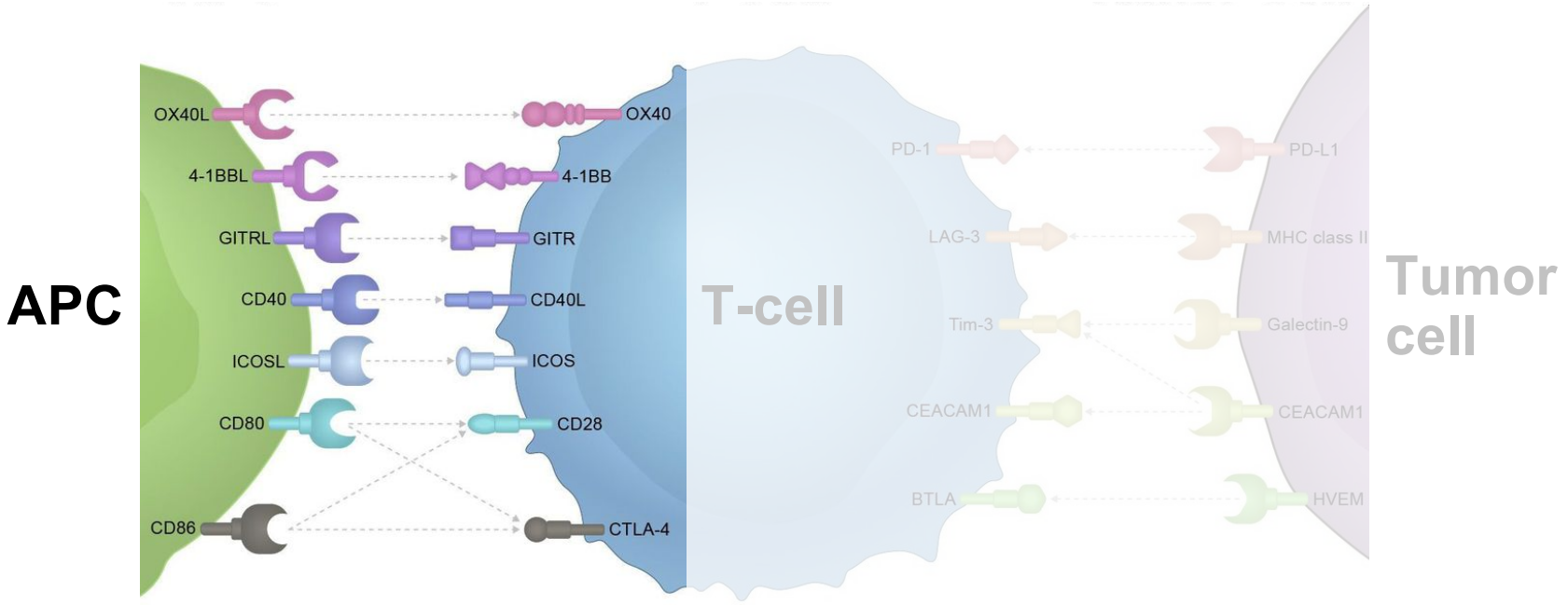
- » T-cell receptor signaling
- » Costimulatory signaling
- » Cytokine support

Inhibitory and stimulatory receptors on immune cells and cancer cells



Yeonjoo Choi et al. J Immunother Cancer 2020;8:e000966

Inhibitory and stimulatory receptors on immune cells and cancer cells



Yeonjoo Choi et al. J Immunother Cancer 2020;8:e000966

OX40 (CD134)

Member of the TNF receptor superfamily

Expressed on activated CD4/ CD8 T cells and Tregs:

- Driven by T-cell activation and transient
  - Peaks at 24-96 hours and typically lasts 3-4 days
- Intratumoral Tregs have high levels of OX40 expression

OX40L is expressed on activated APCs: Dendritic cells, B cells and macrophages

Choi. J Immunother Cancer 2020; Aspeslagh Eur J Cancer 2016; Ruby J Immunol 2009

OX40 (CD134)

OX40 binding by anti-OX40 agonistic antibodies

- » T-cell expansion and survival
- » Promotes the generation of memory T cells
- » Inhibits the function of Tregs
  - › Under certain situations (e.g.: IFN-γ and IL-4 are absent) may lead to Treg proliferation
  - › Target for depletion via ADCC?

Choi. J Immunother Cancer 2020; Aspeslagh Eur J Cancer 2016; Ruby J Immunol 2009

OX40 Agonist – Clinical Studies

MEDI0562 (phase 1 trial) - 55 patients with advanced solid tumors

- 1.5 to 3.0-fold increase in mean peaks of % peripheral Ki67+ CD4+ and Ki67+ CD8 +memory T cells
- Two irPR (SCC larynx and bladder cancer)

MOXR0916 plus atezolizumab - 51 patients with advanced solid tumors

- The majority of the patients had tolerable safety profiles
- 2/ 51 patients had responses

BMS-986178 ± nivolumab or ipilimumab (NCT02737475)

- 20 pts monotherapy (RR=0%)
- 145 pts combination (RR= 0-13%, as expected from nivo/ipi)

Glisson. Ann Oncol. 2016; Glisson. Ann Oncol. 2018; Infante JCO. 2016; Guttierez. CCR. 2021

OX40 Agonist – Next Steps

Strategies to increase OX40 receptor expression and activated T cells:

- Vaccines
- Toll-like receptor (TLR) agents
- Oncolytic viruses
- Radiation
- Novel combinations

Guttierez. CCR. 2021; Fu. Acta Pharm S. 2020; Gao JCO 2018 (suppl; abstr 12055).

GITR (Glucocorticoid-Induced TNF Receptor)

Member of the TNF receptor superfamily

Highly expressed on Tregs, low levels on naïve and memory T cells

GITR ligand is expressed at low levels in APCs

→ **T-lymphocyte activation**

» Particularly suboptimal TCR stimulation by upregulating IL-2 and IFN-γ

→ **Enhanced T-cell survival by inhibiting TCR activation-induced apoptosis**

» Although may enhance AICD of CD4+ effector cells if very strong TCR stimulus

Choi. J Immunother Cancer 2020; Ephrem. Eur J Immunol 2013; Schaer. Curr Opin Immunol 2012; Nocentini. PNAS.1997

GITR – Clinical Studies

TRX-518 (phase 1 study) - 40 patients with metastatic solid tumors

- 4/28 = immune-related SD

AMG228 (phase 1 study) - 30 patients with advanced solid tumors

- 7/27 = immune-related SD

MEDI1873 (phase 1 study) – 40 patients with advanced tumors

- 1 unconfirmed partial response (PNET)
- 17/40 (42.5%) = SD

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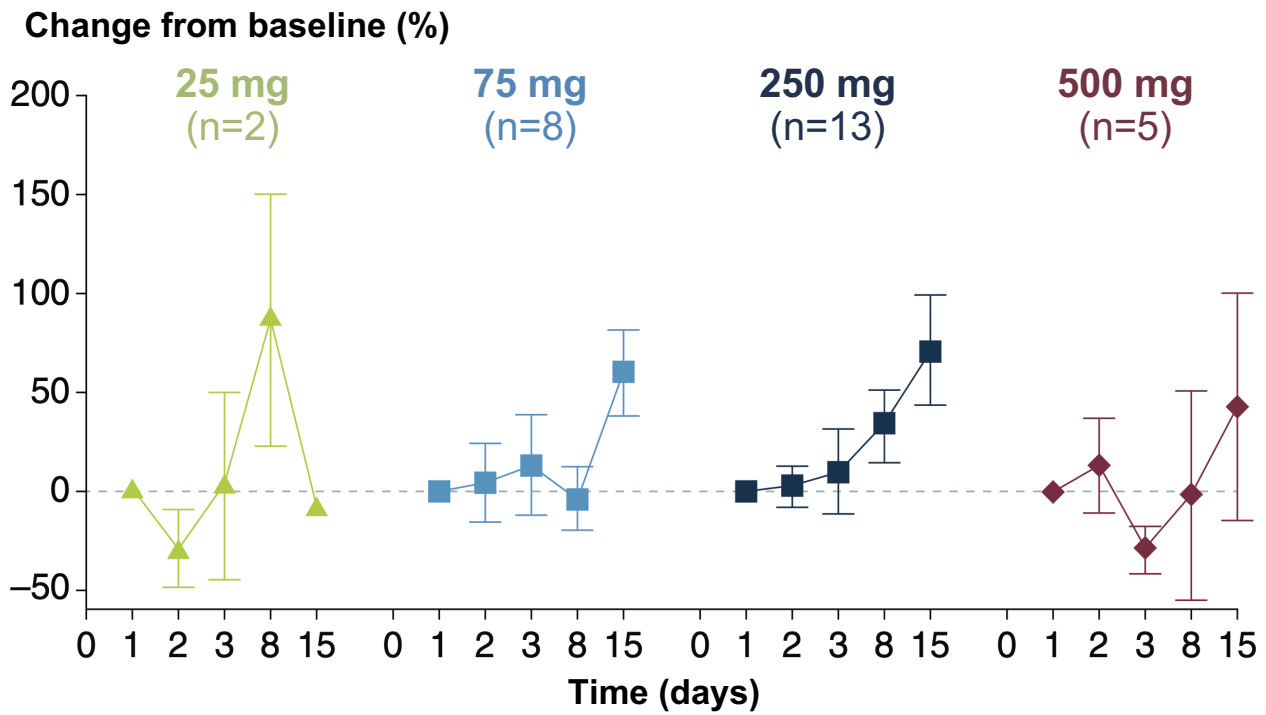
Koon. JCO. 2016; Tran. J Immunother Cancer 2018; Balmanoukian. CCR. 2020

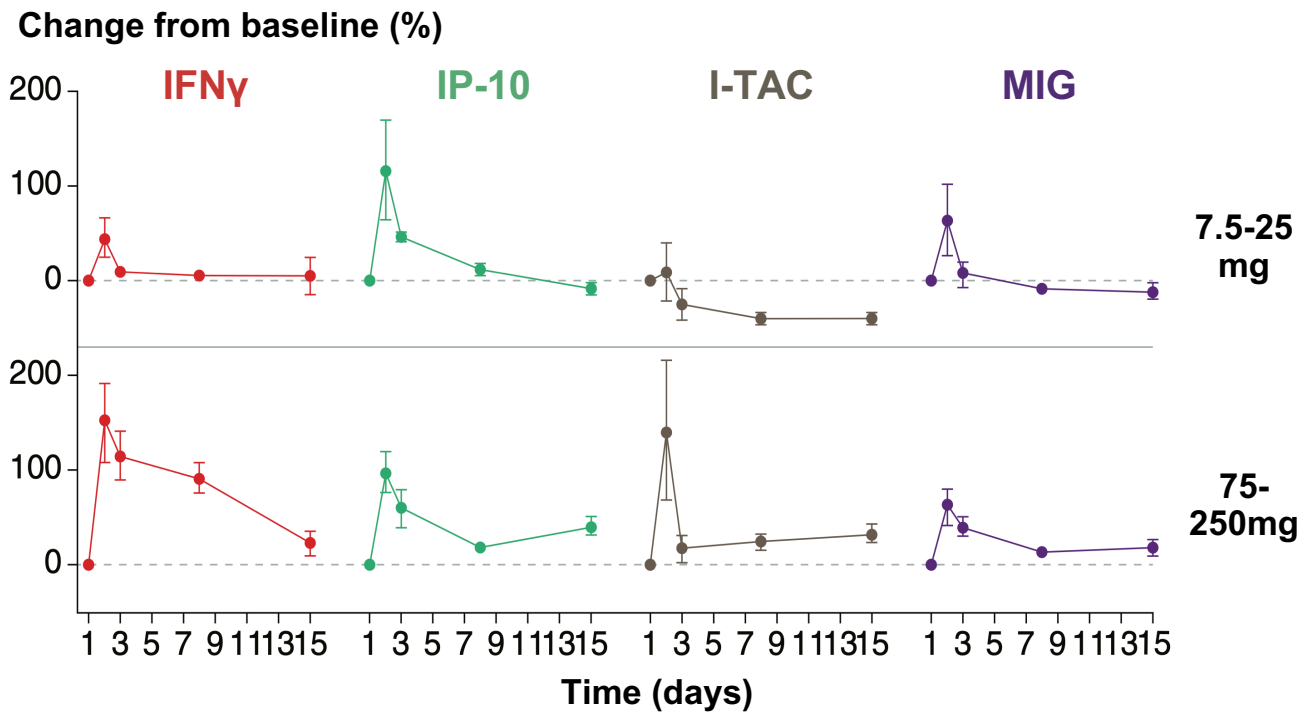
MEDI1873: Change in Peripheral CD4+ Ki67+ T cells



Balmanoukian.
CCR. 2020

MEDI1873: Percent Changes in Soluble Factors

Interferon gamma (IFNγ), IFNγ-induced protein 10 (IP-10), interferon-inducible T cell alpha chemoattractant (I-TAC), monokine induced by IFNγ (MIG)



Balmanoukian.
CCR. 2020

CD40

Member of TNF receptor superfamily

Expressed on:

- **Dendritic cells** → cytokine release, expression of MHC + costimulatory molecules, Ag cross-presentation
- **B lymphocytes** → antigen-presentation, Ig class switching
- **Macrophages** → tumoricidal, deplete tumor stroma
- **Vascular and epithelial cell**s → proinflammatory cytokines
- T cells, activated NK cells, granulocytes, smooth muscle cells, and activated platelets

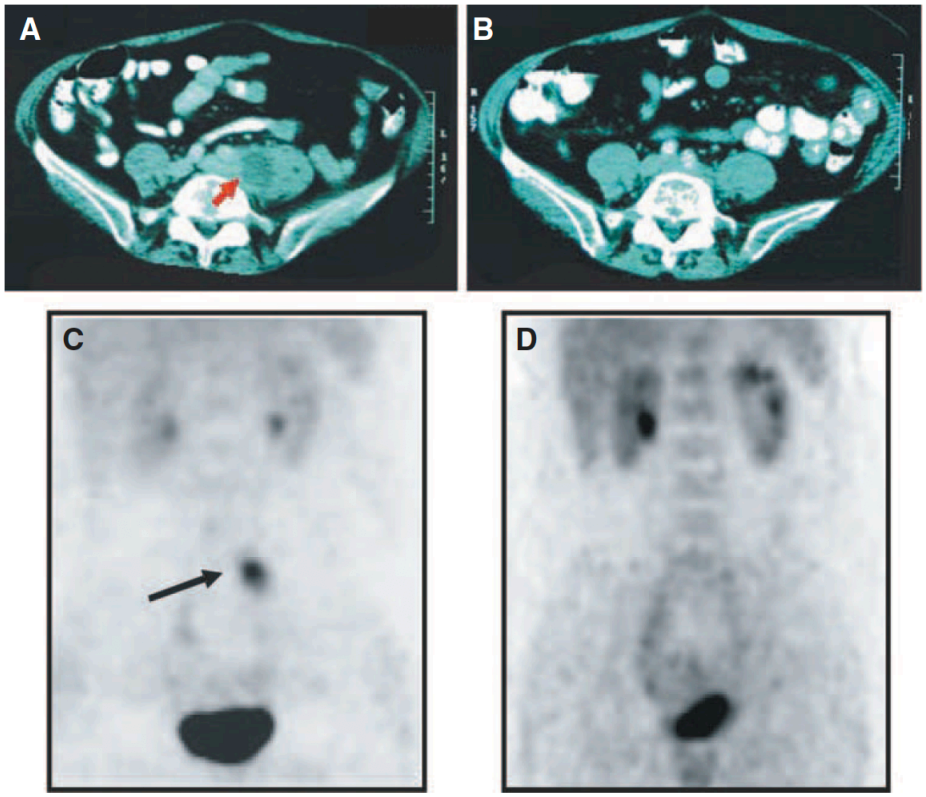
CD40L (CD154) expressed on activated T cells, B cells and NK cells; granulocytes, endothelial cells, smooth muscle cells, and activated platelets.

Vonderheide. Clin Cancer Res. 2007; Beatty. Expert Rev Anticancer Ther. 2018

CD40 – Clinical Studies

CP-870,893 (single dose) -
29 patients with advanced tumors

- The most common AE was CRS:
  - Within minutes to hours after infusion
  - Transient chills, rigors, and fevers
  - Associated with elevations of serum TNF-α and IL-6
- Four patients with melanoma had objective responses at restaging:
  - 14% of all patients
  - 27% of melanoma patients

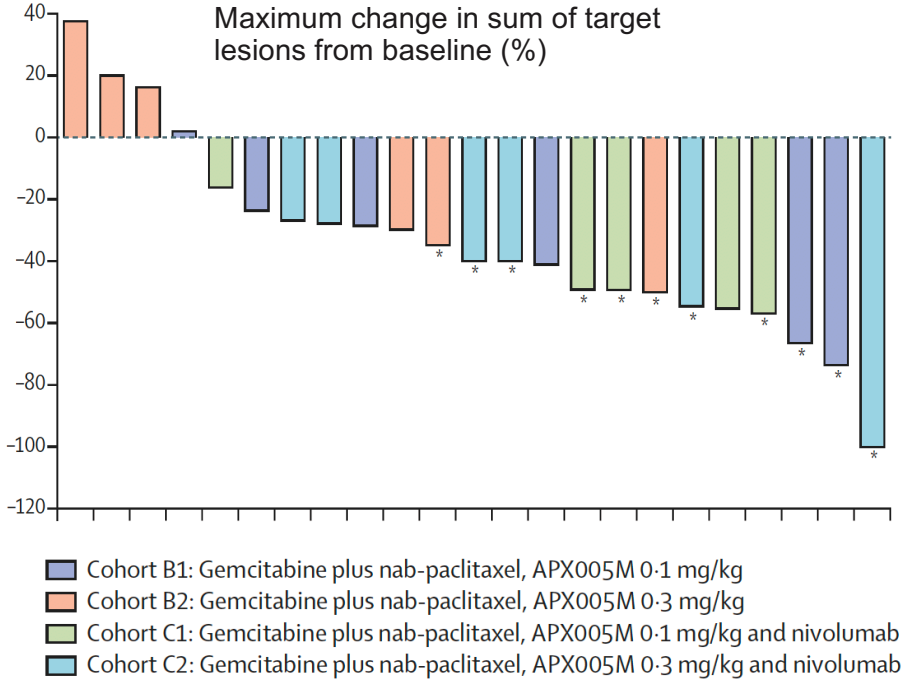


Vonderheide. JCO. 2007

CD40 – Clinical Studies

Sotigalimab + gemcitabine/nab-paclitaxel +/- nivolumab (Phase 1b)

- » Patients (n=30) with previously untreated metastatic pancreas cancer
- » Treatment considered tolerable
- » ORR = 58% in DLT evaluable patients (n=24)
- » Further studies are ongoing



O'Hara. Lancet Oncology. 2020

ICOS (Inducible Costimulatory receptor)

Member of the CD28 superfamily of costimulatory molecules

ICOS induced upon T-cell receptor (TCR) engagement

- Unlike CD28, not expressed on naïve T_{Eff} cells

Relative expression varies between T-cell subtypes:

- Intratumoral Treg > CD4+ > CD8+ Teff cells
  - (may represent a target for Treg depletion strategy)

Ligand is mostly expressed on APCs (can be induced by IFN-γ and TNF-α)

Modestly promotes T-cell proliferation and differentiation

↑ cytokine production (pro or anti-inflammatory: IL-4, IL-5, IL-10, IFN-γ, TNF-α)

Prognostic marker

- ↑ICOS+ CD4 TEff is associated with ↑prognosis (pts treated with anti–CTLA-4)
- ↑ICOS+ Tregs in the TME is associated ↓prognosis

Hutloff. Nature. 1999; Swallow. Immunity. 1999; Sharpe. Nat Rev Immunol 2002; Sainson. Cancer Immunol Res. 2020; Ng. Cancer Immunol Res. 2013; Tu. Sci Rep. 2016

ICOS – Clinical Studies

GSK3359609 +/- pembrolizumab (phase 1 trial)

- HNSCC expansion cohort
  - Monotherapy (prior PD/L-1): RR = 8% (1/8)
  - Combination (PD/L-1 naïve): RR = 24% (8/34), 4 PR and 4 CR

Randomized, double-blind, II/III studies in recurrent/ metastatic HNSCC:

- Pembrolizumab +/- GSK3359609 (n=600) (INDUCE-3/ NCT04128696)
- Pembrolizumab plus 5-FU/platinum +/- GSK3359609 (n=640) (INDUCE-4/ NCT04428333)

Rischin. Ann Onc (abstract 1119PD). 2019; Angevin. JCO (abstract 6517). 2020

4-1BB/CD137

Activated T-cell: ↑ function and survival

» Peak ~12 hrs after TCR engagement, decline within 72 hrs

Activated NK cells: ↑Fc receptor and ↑ADCC

Treg effect is controversial:

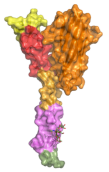
» Downregulates Foxp3 and inhibit inducible Tregs

» Soluble 4-1BBL may promotes Treg expansion

Ligand is inducible on activated APCs, myeloid progenitor and hematopoietic stem cells

Wang. Immunol Rev. 2009; Bartkowiak. Front Oncol. 2015; Houot. Oncoimmunology 2012

4-1BB Agonist Antibodies

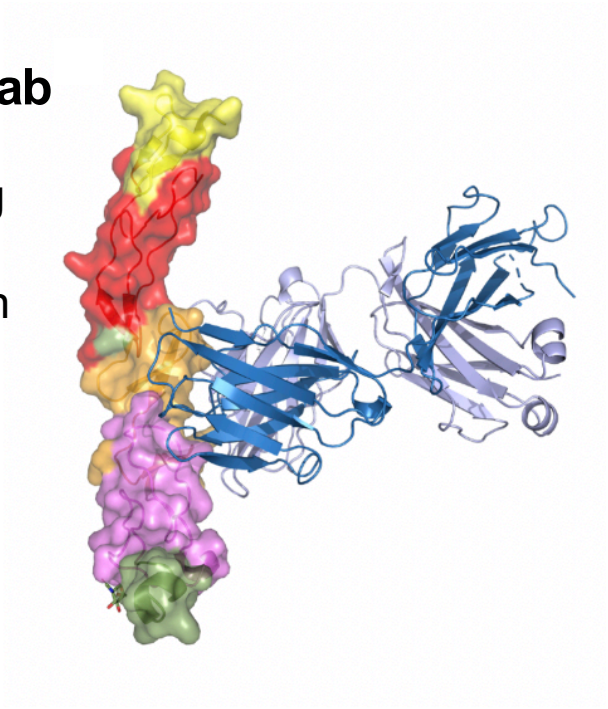


Urelumab

- » Binds CRD-1
- » Away from ligand-binding site

Utomilumab

- » Ligand-blocking
- » Binds between CRDs 3 and 4



Chin. Nature Comm. 2018

Urelumab

2005:

Evaluated as a monotherapy in two studies, CA186-001 and CA186-006

December 2008:

enrolment was stopped for all urelumab studies following the occurrence of two hepatotoxicity-related deaths (1 and 5 mg/kg)

Dose was the most important factor contributing to the development of severe transaminitis

February 2012:

Study CA186-011 aimed to evaluate monotherapy doses <1 mg/kg

- » Selected dose was 0.1 mg/kg, 8 mg flat dose

Segal. Clin Cancer Res. 2017

Efficacy

Study 001: 83 pts (54 melanoma, 15 RCC, 13 ovarian and 1 prostate)

- 3 PRs (18+ mo, 3+ mo, 1.5+ mo, all melanoma)
- 4 SD (10 mo, 6 mo, 6 mo, 4+ mo)

Preliminary biomarker analysis showed:

- ↑ expression of IFN-inducible genes in peripheral blood
- ↑% circulating activated CD8 and CD4 T-cells
- ↑ expression CD8α and IFNγ in post- treatment biopsies in a subset of pts

Sznol. ASCO. 2016

Utomilumab (PF-05082566)

» Phase I dose escalation study

» 12 dose levels: 0.006 - 10 mg/kg Q4W

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Segal. Clin Cancer Res. 2018

Table 1. Patient demographics and baseline characteristics	**Utomilumab** ***N* = 55**
Male : Female, *n*	37: 18
Mean age, years (range)	59.7 (27–85)
≥65 years	21 (38.2)
Race, *n* (%)	
White	34 (61.8)
Black	3 (5.5)
Asian	14 (25.5)
Other	3 (5.5)
Unspecified	1 (1.8)
ECOG PS, *n* (%)	
0	24 (43.6)
1	31 (56.4)
Primary cancer, *n* (%)	
Merkel cell carcinoma of the skin	15 (27.3)
Colorectal cancer	12 (21.8)
Gastric cancer	4 (7.3)
Pancreatic cancer	4 (7.3)
Lung cancer	3 (5.5)
Hepatobiliary cancer	3 (5.5)
Breast cancer	2 (3.6)
Lymphoma	2 (3.6)
Soft tissue sarcoma	2 (3.6)
Other[a]	8 (14.5)

Safety

- No DLTs (0.006– 10 mg/kg)
- Grade ≥3 event: Fatigue (G3) in one (1.8%) patient.
- No treatment-related grade 3–4 hepatoxicity

Segal. Clin Cancer Res. 2018

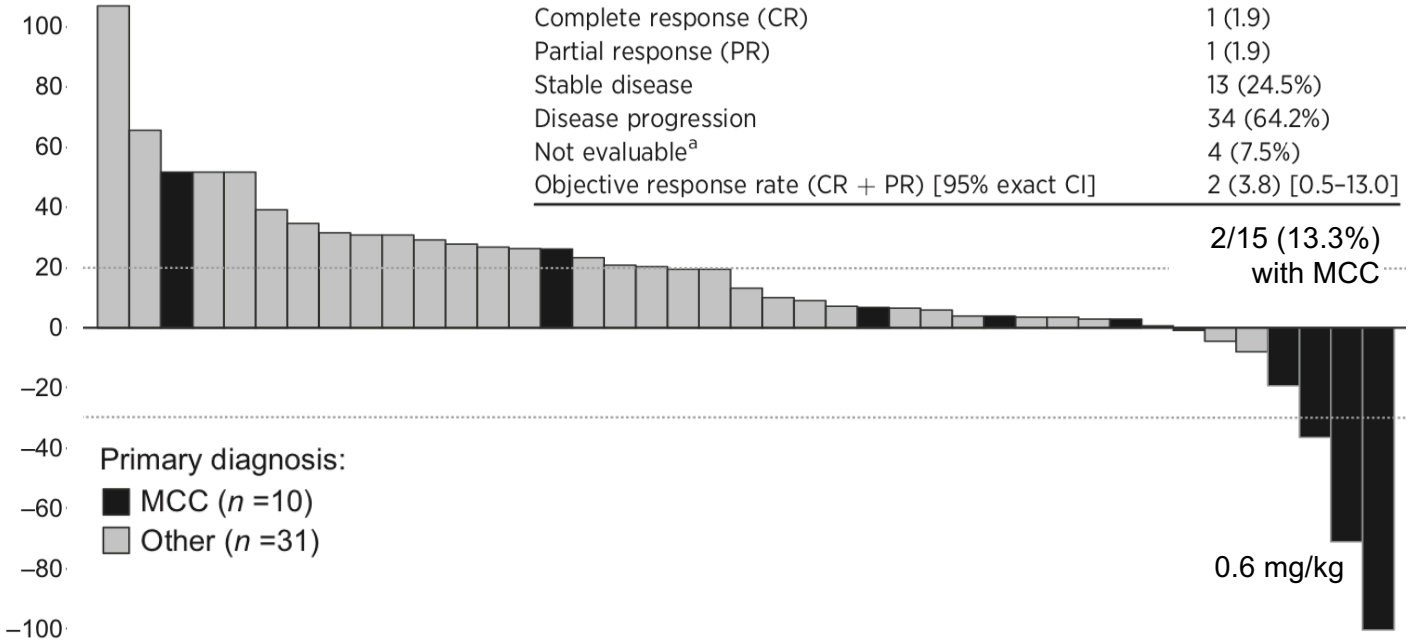
Table 2. Treatment-related AEs reported in >1 patient

AE	Grade 1–2 *n* (%)	Grade 3–4 *n* (%)	Total *n* (%)
Any AE	18 (32.7)	1 (1.8)	19 (34.5)
Fatigue	4 (7.3)	1 (1.8)	5 (9.1)
Pyrexia	5 (9.1)	0	5 (9.1)
Decreased appetite	3 (5.5)	0	3 (5.5)
Dizziness	3 (5.5)	0	3 (5.5)
Rash	3 (5.5)	0	3 (5.5)
Abdominal pain	2 (3.6)	0	2 (3.6)
Diarrhea	2 (3.6)	0	2 (3.6)
Vomiting	2 (3.6)	0	2 (3.6)
Dyspnea	2 (3.6)	0	2 (3.6)
Paresthesia	2 (3.6)	0	2 (3.6)

Efficacy

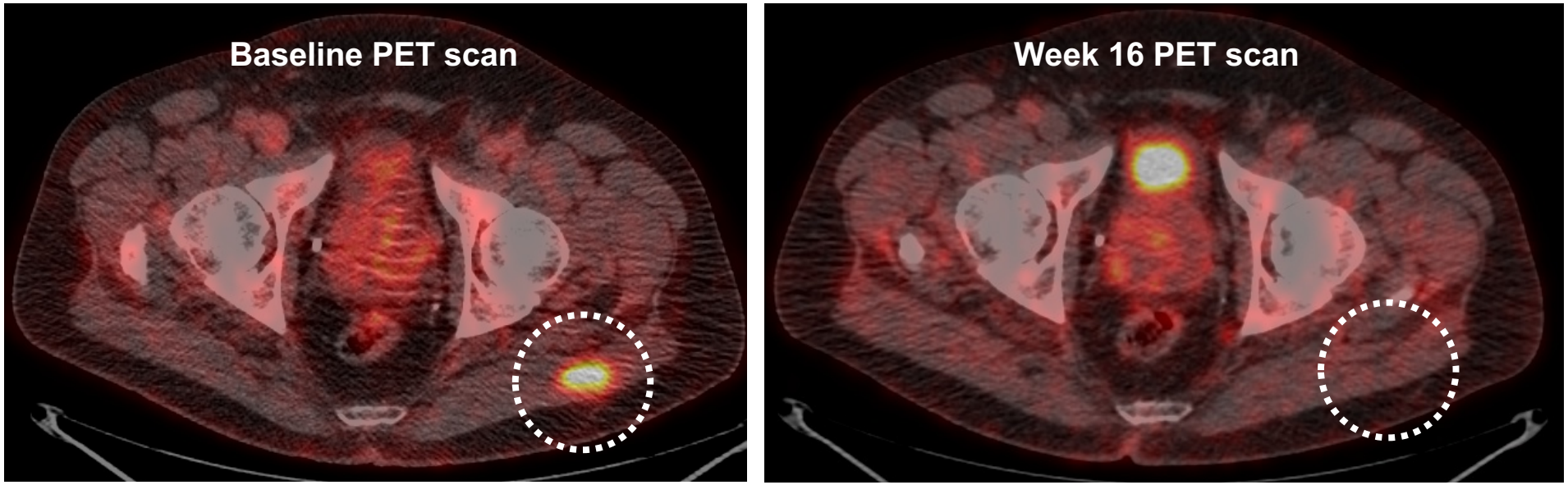
Table 3. Best overall response in patients with solid malignancies

	Utomilumab ***N* = 53**
Complete response (CR)	1 (1.9)
Partial response (PR)	1 (1.9)
Stable disease	13 (24.5%)
Disease progression	34 (64.2%)
Not evaluable[a]	4 (7.5%)
Objective response rate (CR + PR) [95% exact CI]	2 (3.8) [0.5–13.0]



Segal. Clin Cancer Res. 2018

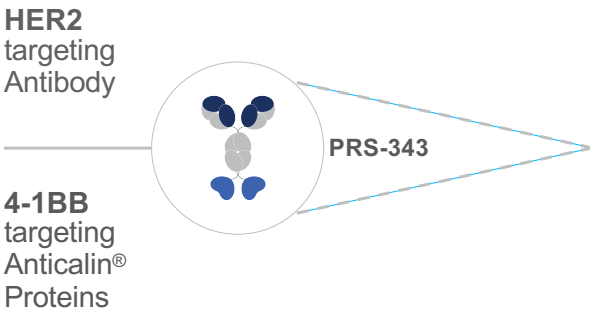
Tumor Response in Merkel Cell Carcinoma
Patient Treated At 0.6 mg/kg



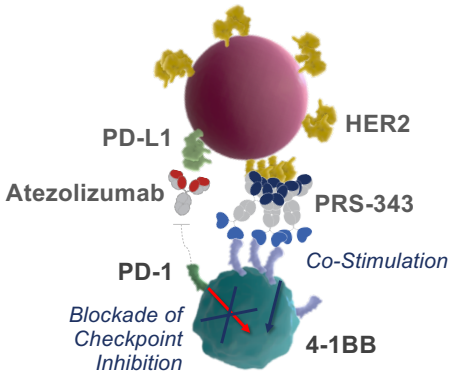
Segal. ASCO. 2014

PRS-343, a HER2 4-1BB Bispecific, Drives 4-1BB Agonism in the Tumor Microenvironment in HER2 Positive Solid Tumors

HER2-targeting moiety of the drug localizes to the tumor microenvironment and facilitates 4-1BB cross-linking

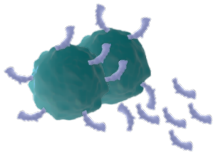


4-1BB cross-linking ameliorates T-cell exhaustion and is critical for T-cell expansion

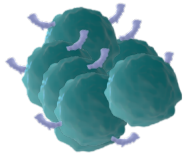


Clinically-Relevant Biomarkers

4-1BB Pathway Activation
Soluble 4-1BB



T-cell Proliferation
CD8⁺ and CD8⁺/Ki67⁺



Piha-Paul. ESMO. 2020

Summary of Responses at Active Dose Range of PRS-343 in Monotherapy

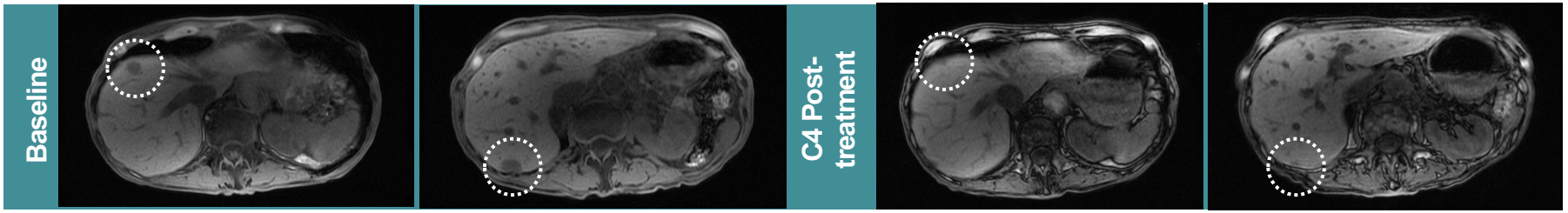
Based on clinical data, serum concentration of > 20 µg/ml defines active dose range (beginning at Cohort 9)

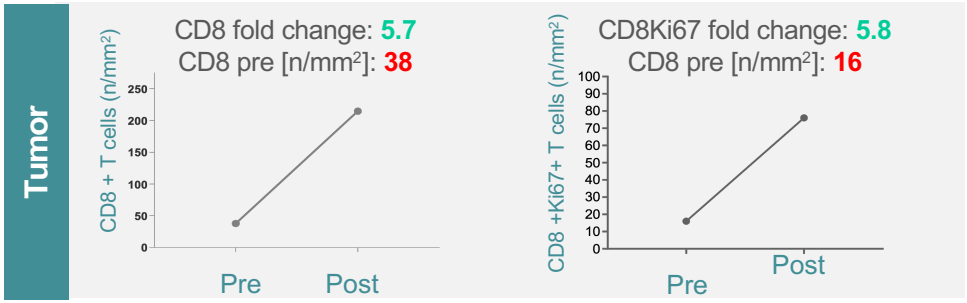
Cohort	13b	12b	11c	Obi	11b	11	10	9	Total
Best Response	18 mg/kg, Q2W	12 mg/kg, Q2W	8 mg/kg, QW	8 mg/Kg, Q2W	8 mg/kg, Q2W	8 mg/kg, Q3W	5 mg/kg, Q3W	2.5 mg/kg, Q3W	
Evaluable Patients	3	2	4	2	7	4	6	5	33
CR	1	-	-		-	-	-	-	1
PR	-	-	-		3	-	-	-	3
SD	-	-	1	1	3	3	3	2	13
ORR	33%	0%	0%	0%	43%	0%	0%	0%	12%
DCR	33%	0%	25%	50%	86%	75%	50%	40%	52%

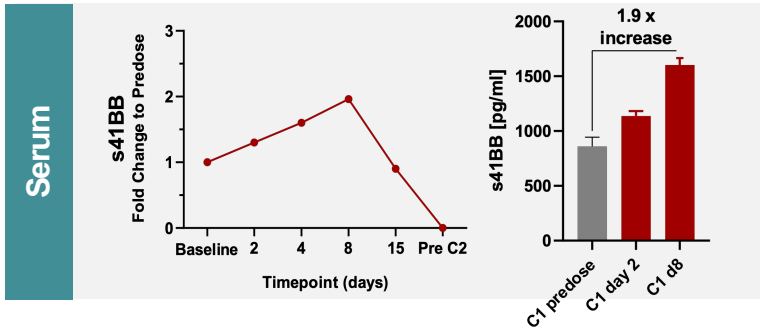
Data cut-off: 27-Jul-20

Piha-Paul. ESMO. 2020

CD8+ T Cell Numbers in the Tumor and Circulating s4-1BB Increase Post-Treatment in responding Gastric Cancer Patient (107-012)

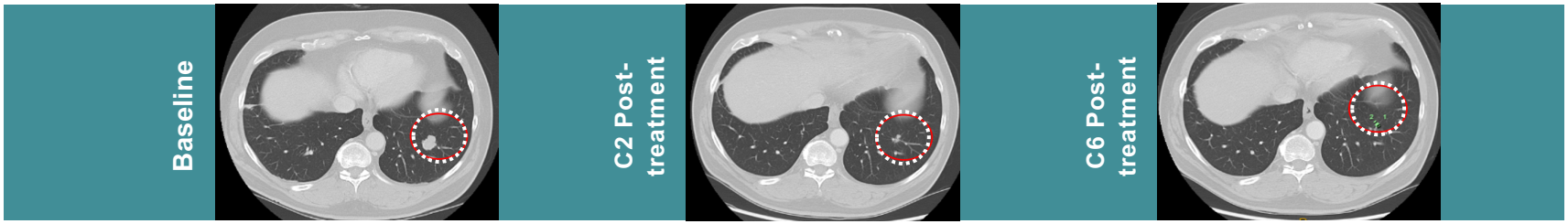


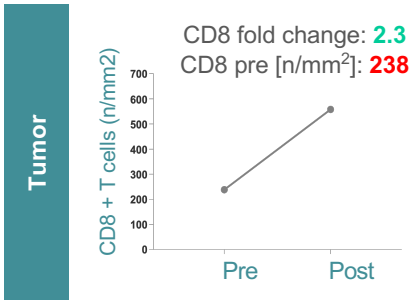


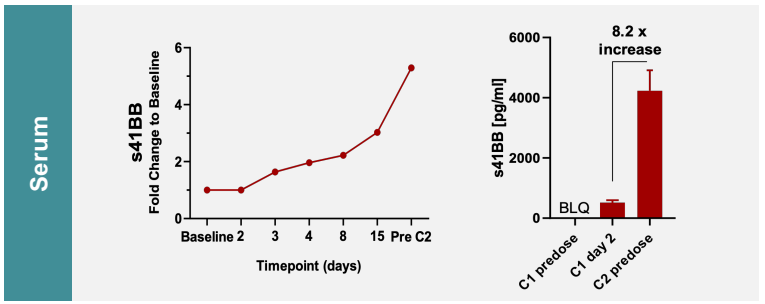


Piha-Paul. ESMO. 2020

CD8+ T Cell Numbers in the Tumor and Circulating s4-1BB Increase Post-Treatment in CR Rectal Cancer Patient (103-021)







Piha-Paul. ESMO. 2020

Take-Home Points

Immune checkpoint blockade has led to unpresented benefit, durable in some patients

- » Varies by tumor type. Response rates ~20%
- » New and rational strategies are very much needed

With the identification of immune agonists, we have compelling new targets to enhance anti-tumor immunity

- » Supported by preclinical rationale and models
- » Goal is to enhance and maintain T-cell proliferation and survival, without Treg expansion
- » However, response rates to single agent agonists are 0-10%

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Take-Home Points

Challenge:

Costimulatory molecules may be expressed for only a brief period following stimulation, repeat stimulation can lead to exhaustion, and there may be inhibitory effects

Important questions include:

- Optimal combination – more than one agonist, CTLA-4 or PD/L-1, blockade, chemotherapy, RT, …
- Timing, duration and sequencing (agonist ↔ antagonist, or concurrent)
- Identify responsive tumor types and subtypes
- Correlative studies, eg: T-cell infiltration and cell type (Treg v. Teff)

There is work to do

NASDC
NCI Awardee Skills Development Consortium

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Questions