SITC 2019

Gaylord National Hotel
& Convention Center

Nov. 6-10

NATIONAL HARBOR, MARYLAND

sitc

Society for Immunotherapy of Cancer

SITC 2019
Gaylord National Hotel & Convention Center Nov. 6-10
NATIONAL HARBOR, MARYLAND

CD40: A Target for Systemic Immune Modulation

Michael Yellin, MD

VP, Clinical Science

Celldex

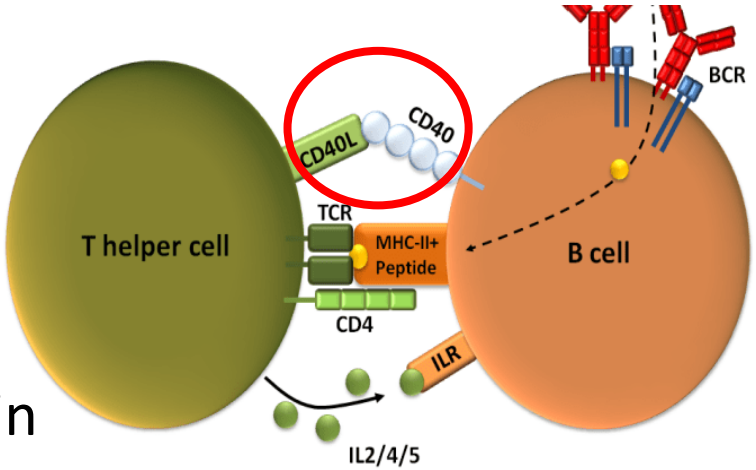
Disclosure: I am employed by Celldex Therapeutics and own stock in the company

Topics

- CD40 biology
- Potential mechanisms by which targeting CD40 may modify the tumor microenvironment and enhance anti-tumor innate and adaptive immune responses
- Clinical data of agonist anti-CD40 mAb in solid tumors

CD40 Biology

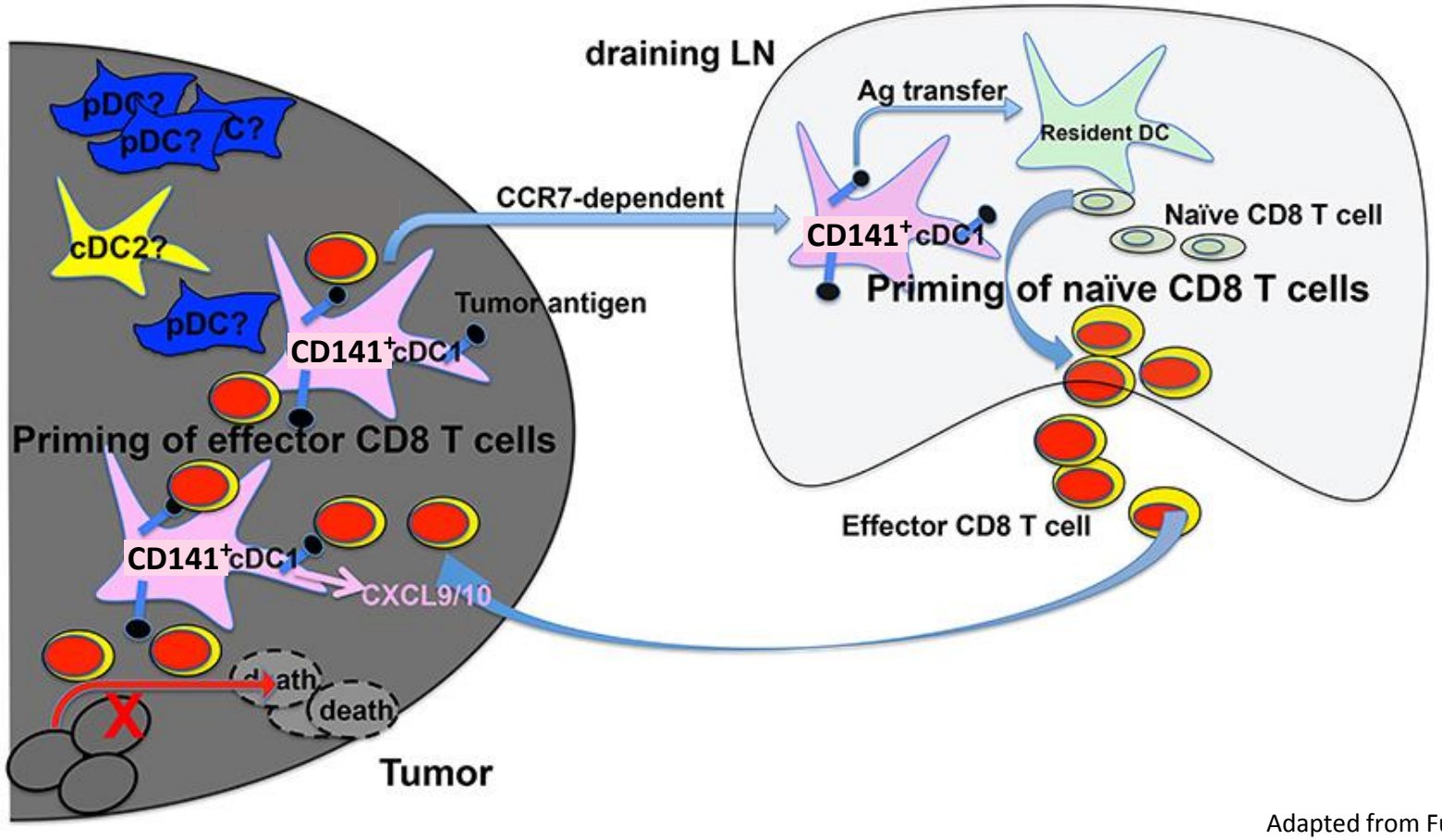
- CD40 was first identified in 1985 and cloned in 1989[1,2]
  - Functionally expressed on B cells
- CD40L (CD154) first identified in 1992[3,4,5]
  - Mainly expressed on activated CD4+ T cells
- Initial studies focused on the role of CD40L-CD40 interactions in T cell dependent B cell responses (T cell help)
  - Key for Ig class switching and germinal center formation
  - Initial therapeutic focus was on blocking the pathway to treat autoimmune diseases
- Subsequently demonstrated that CD40 is functionally expressed on many different types of normal cells, including dendritic cell and macrophages



1. Paulie. Immunother. 1985.
2. Stamenkovic. EMBO J. 1989.
3. Armitage. Nature. 1992.
4. Noelle. PNAS. 1992
5. Lederman. J Exp Med. 1992

Key Role of CD40L-CD40 Interactions in T Cell Immune Responses

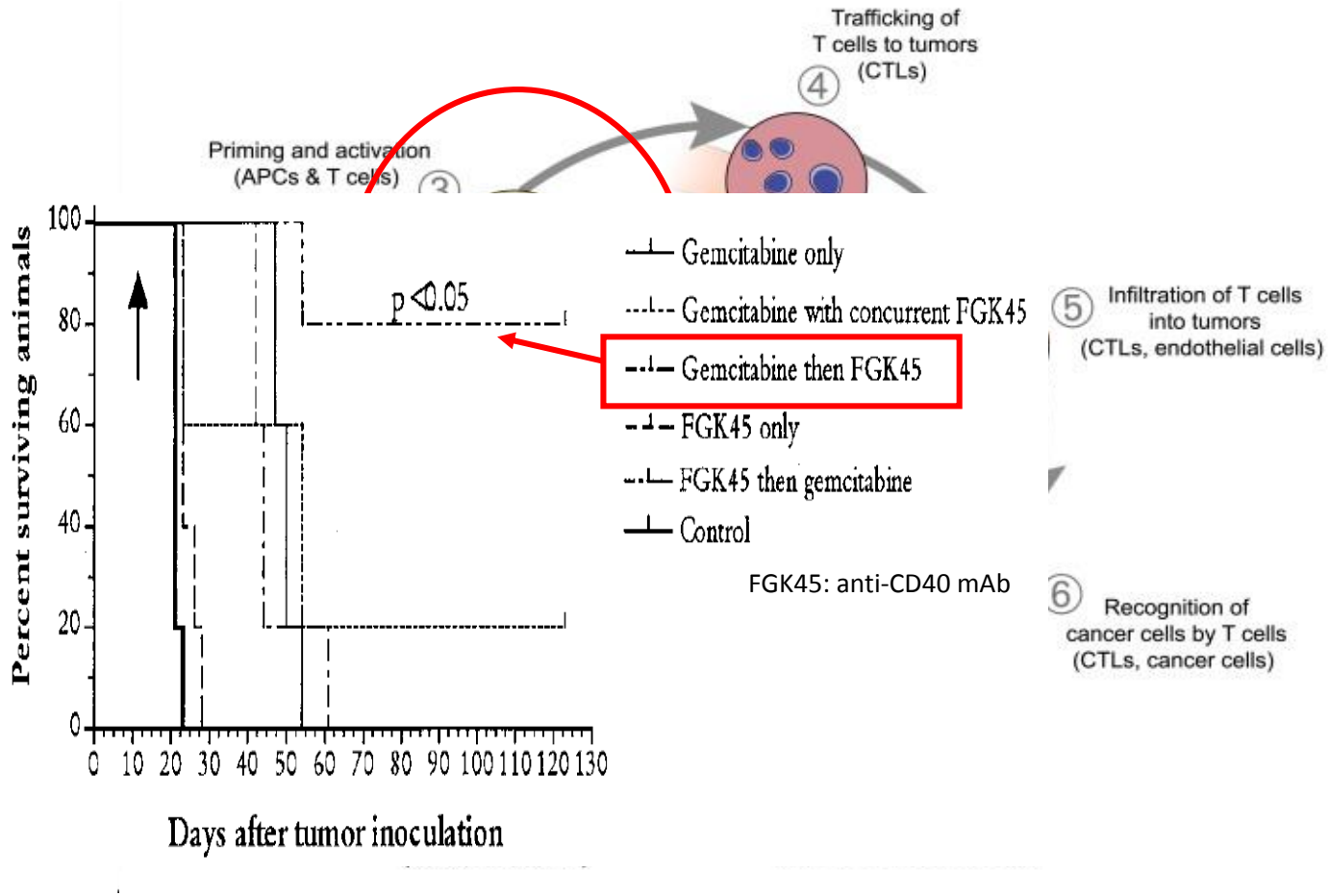
DC Licensing and Priming Antigen Specific T cell Responses



Adapted from Fu. Front Immunol. 2018.

Agonist Anti-CD40 mAbs Stimulate Anti-Tumor T cell Responses

- Agonist CD40 mAb promotes CD8+ T cell immunity in several cancer models independent of CD4+ T cell help [1,2]
- Augmented by agents that induce immunogenic cell death induced, such as chemotherapy or radiation[3,4]

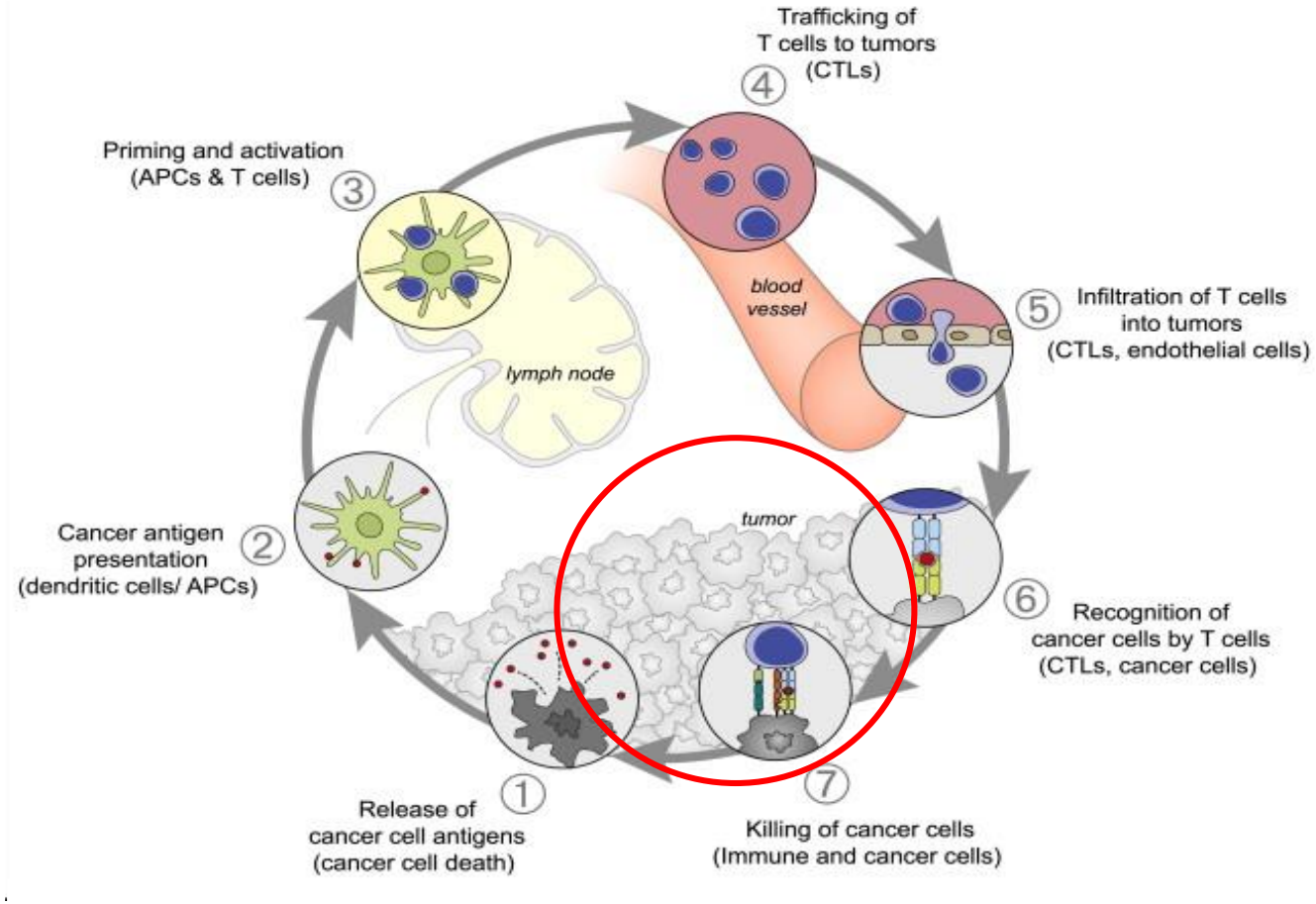


Adapted from Chen and Mellman. Immunity. 2013.

1. Diehl. Nat Med. 1999.
2. French. Nat Med. 1999.
3. Nowak. Cancer Res. 2003.
4. Kawashita. Radiat Res. 2014

CD40 Effects in the Tumor Microenvironment

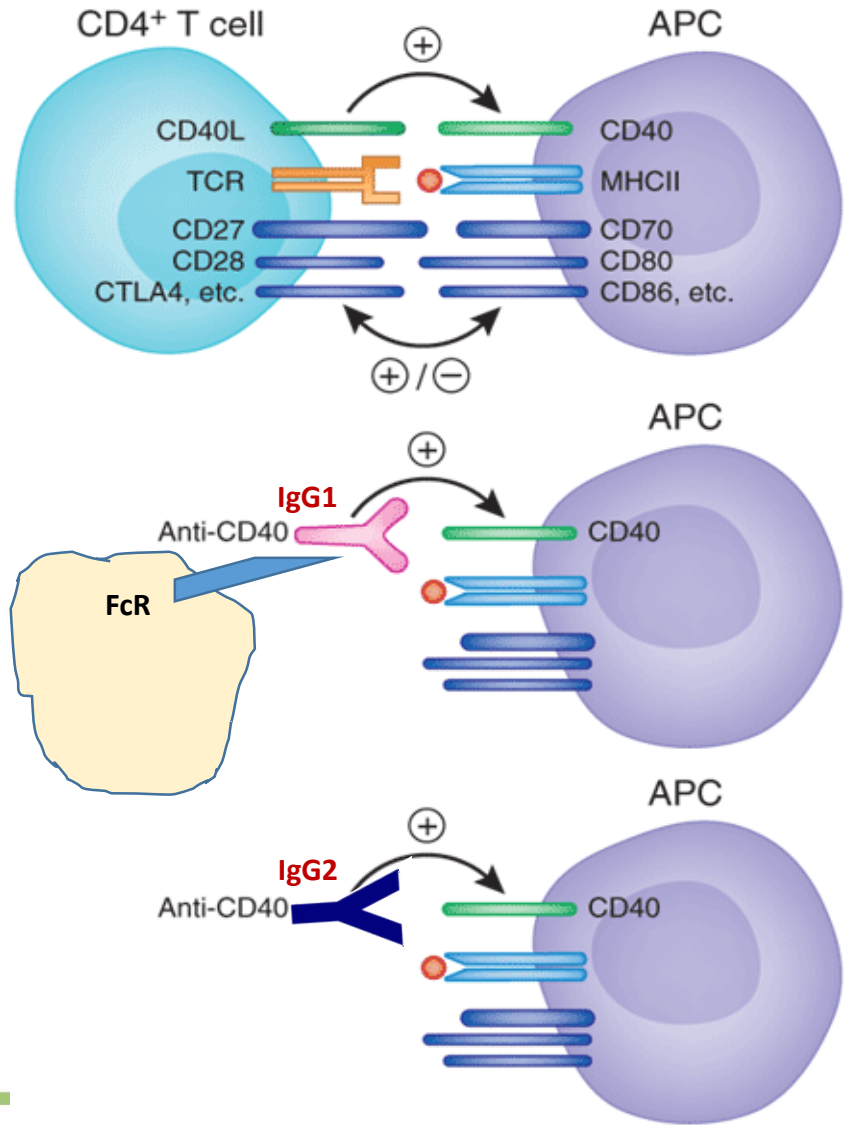
- Activates macrophage tumoricidal activity[1]
- Promotes secretion of pro-inflammatory cytokines and chemokines
- Remodeling of tumor stroma by matrix metalloproteinases[2]
- Promotes TAM M2 to M1 polarization[3]
- Mediates direct killing of CD40^{+} tumor cells[4]
- Agonist CD40 mAb reverses T cell exhaustion and reinvigorates anti-tumor immune response in an IL-12 dependent manner[5]
- Upregulates PD-L1 expression[6]



Adapted from Chen and Mellman. Immunity. 2013.

1. Lum. J Leuk Bio 2006.
2. Long. Cancer Discov. 2016.
3. Luheshi. OncoImmunol. 2014.
4. Eliopoulos. Mol Cell Bio. 2000.
5. Ngiow. Cancer Res. 2016.
6. Luheshi. Oncotarget. 2016.

CD40 Agonist Antibodies



FcR dependent:

- APX005M (Apexigen; Fc mutated humanized IgG1)
- ABBV-927 (Abbvie; Fc mutated humanized IgG1)
- ADC-1013 (Alligator; fully human IgG1)
- SEA-CD40 (Seattle Genetics; non-fucosylated humanized IgG1)

FcR independent:

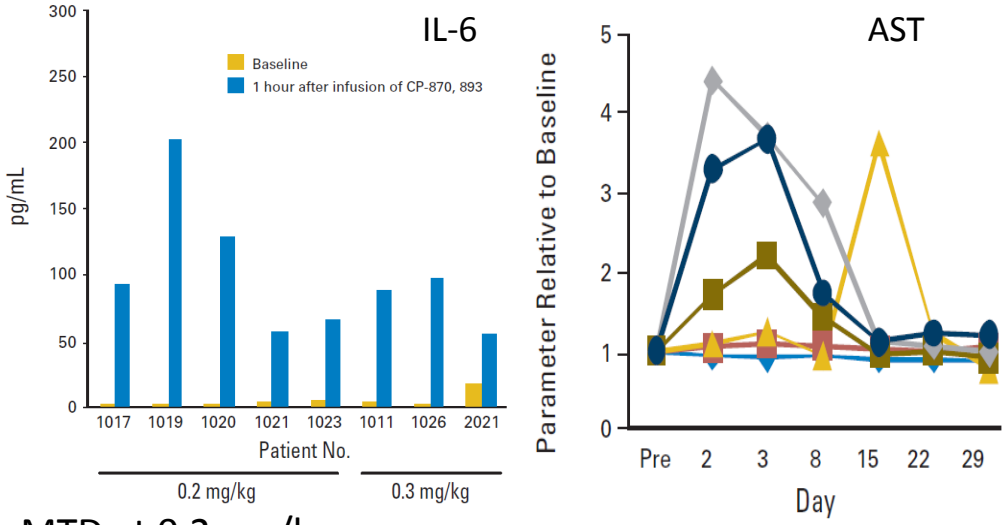
- Selicrelumab (Roche [RO7009789/CP-870,893]; fully human IgG2)
- CDX-1140 (Celldex; fully human IgG2)

Clinical Activity and Immune Modulation in Cancer Patients Treated With CP-870,893, a Novel CD40 Agonist Monoclonal Antibody

Robert H. Vonderheide, Keith T. Flaherty, Magi Khalil, Molly S. Stumacher, David L. Bajor, Natalie A. Hutnick, Patricia Sullivan, J. Joseph Mahany, Maryann Gallagher, Amy Kramer, Stephanie J. Green, Peter J. O'Dwyer, Kelli L. Running, Richard D. Huhn, and Scott J. Antonia

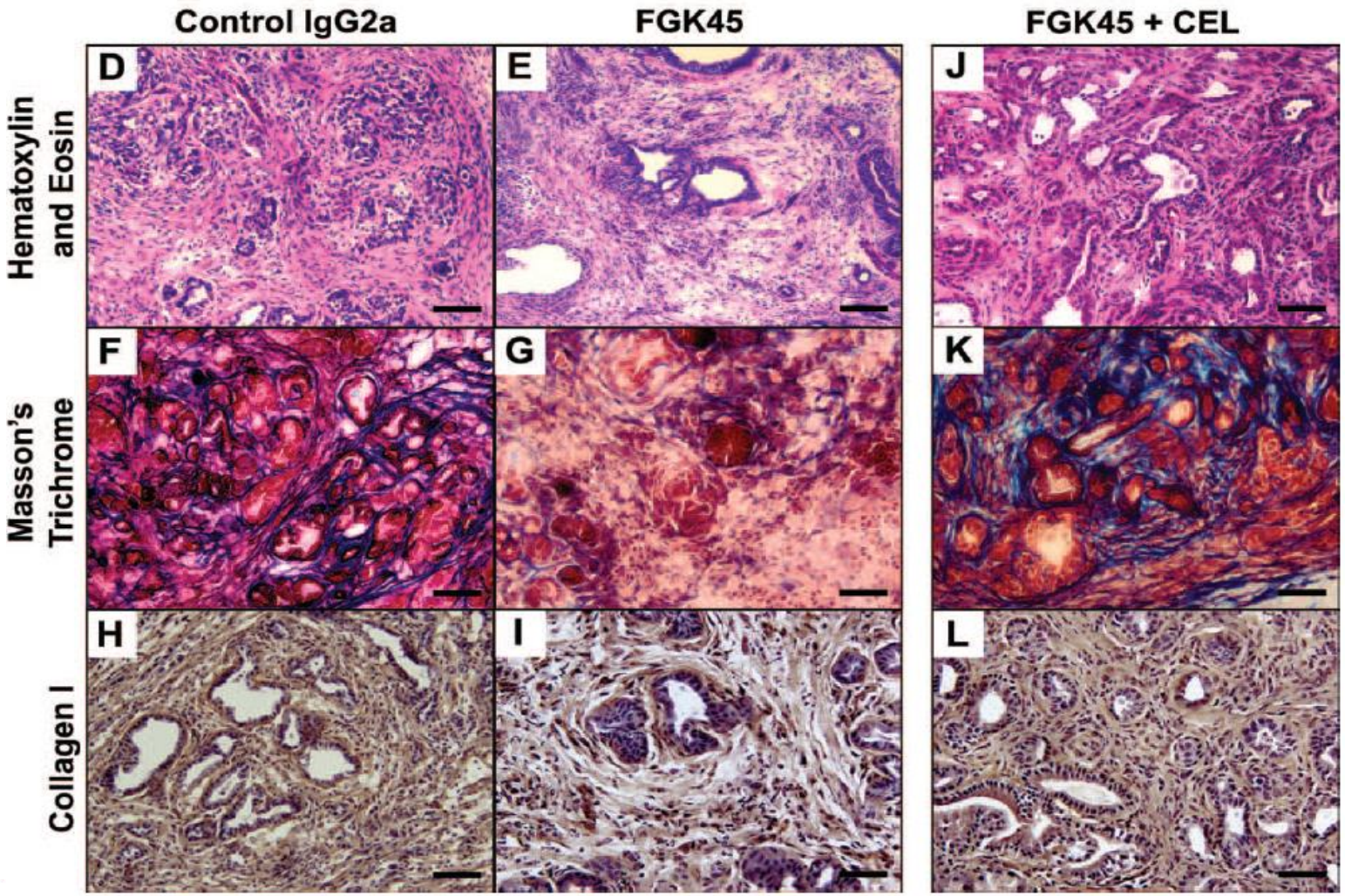
JCO. 2007
ClinicalTrials.gov Identifier NCT02225002

- Enrolled patients with solid tumors (n=29)
- Dose escalation of CP-870,893 IV as single dose
- Drug related toxicity included CRS and transient increased liver function tests



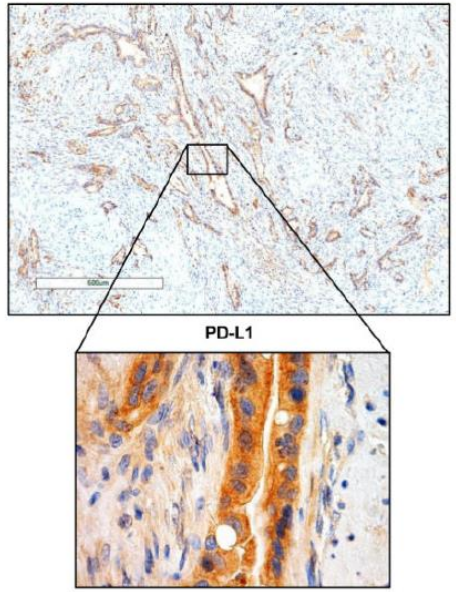
- MTD at 0.2 mg/kg
  - DLTs of thrombosis and headache at 0.3 mg/kg
- PR in 4/15 (27%) of patients with melanoma (3 at 0.2 mg/kg and 1 at 0.3 mg/kg)

Anti-CD40 Modulation of Macrophage and T Cell Responses in Pancreatic Cancer

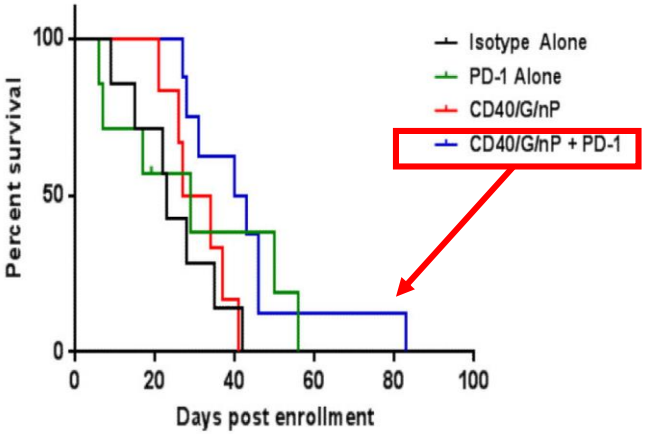


Beatty. Science. 2011.
ClinicalTrials.gov Identifier NCT00711191

FGK45: anti-CD40 mAb
CEL: clodronate encapsulated liposome

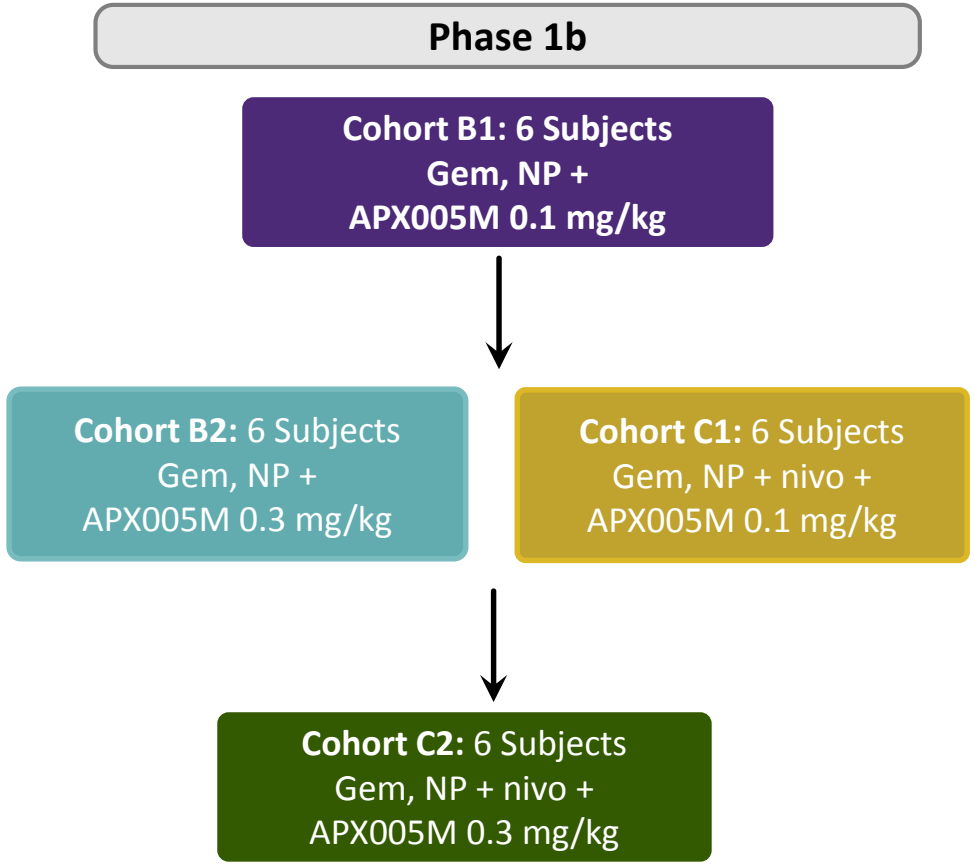


PD-L1+ pancreatic cancer[2]



Winograd. Cancer Immunol Res. 2015.

A Phase 1b Study of CD40 Agonistic Monoclonal Antibody APX005M Together with Gemcitabine and nab-Paclitaxel with or without Nivolumab in Untreated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) Patients
PICI0002 (PRINCE)



O'Hara. AACR. 2019

Grade 3/4 Treatment-Related AEs

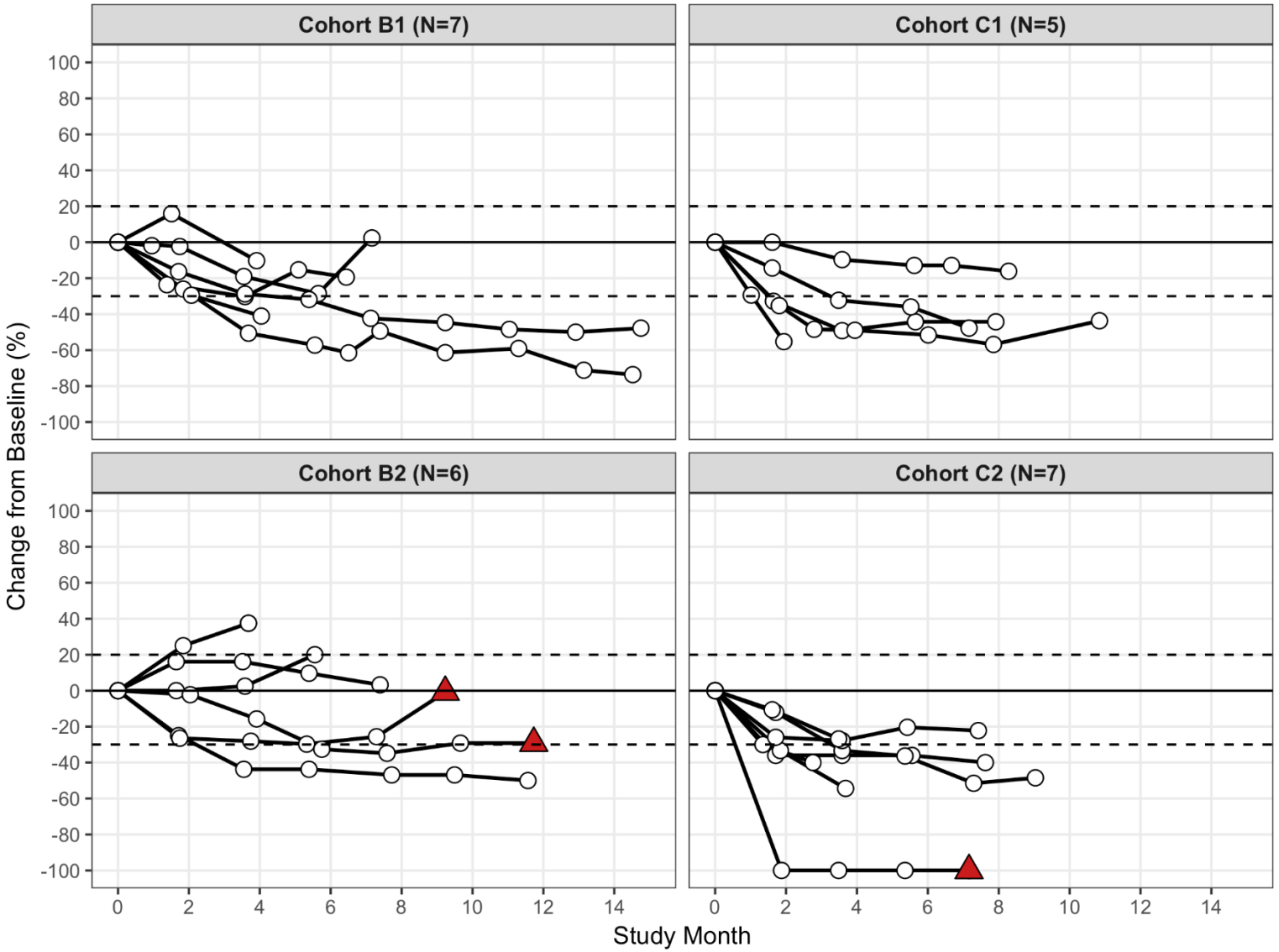
Occurring in ≥ 20% of N=30 Subjects

MedDRA Preferred Term	Cohort B1 Gem/NP/ APX005M 0.1 mg/kg (N=7)	Cohort B2 Gem/NP/ APX005M 0.3 mg/kg (N=7)	Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=8)	Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=8)	Total (N=30)
Lymphocyte count decreased	5 (71.4%)	6 (85.7%)	5 (62.5%)	4 (50.0%)	20 (66.7%)
Neutropenia	3 (42.9%)	5 (71.4%)	1 (12.5%)	3 (37.5%)	12 (40.0%)
Anemia	2 (28.6%)	3 (42.9%)	4 (50.0%)	1 (12.5%)	10 (33.3%)
Fatigue	3 (42.9%)	2 (28.6%)	3 (37.5%)	0	8 (26.7%)
Aspartate aminotransferase increased	0	4 (57.1%)	0	3 (37.5%)	7 (23.3%)
Leukopenia	0	4 (57.1%)	1 (12.5%)	1 (12.5%)	6 (20.0%)

- No grade 3/4 cytokine release syndrome was noted
- 2 DLTs (febrile neutropenia, unrelated to APX005M or nivolumab)

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Encouraging Clinical Activity in Pancreatic Cancer



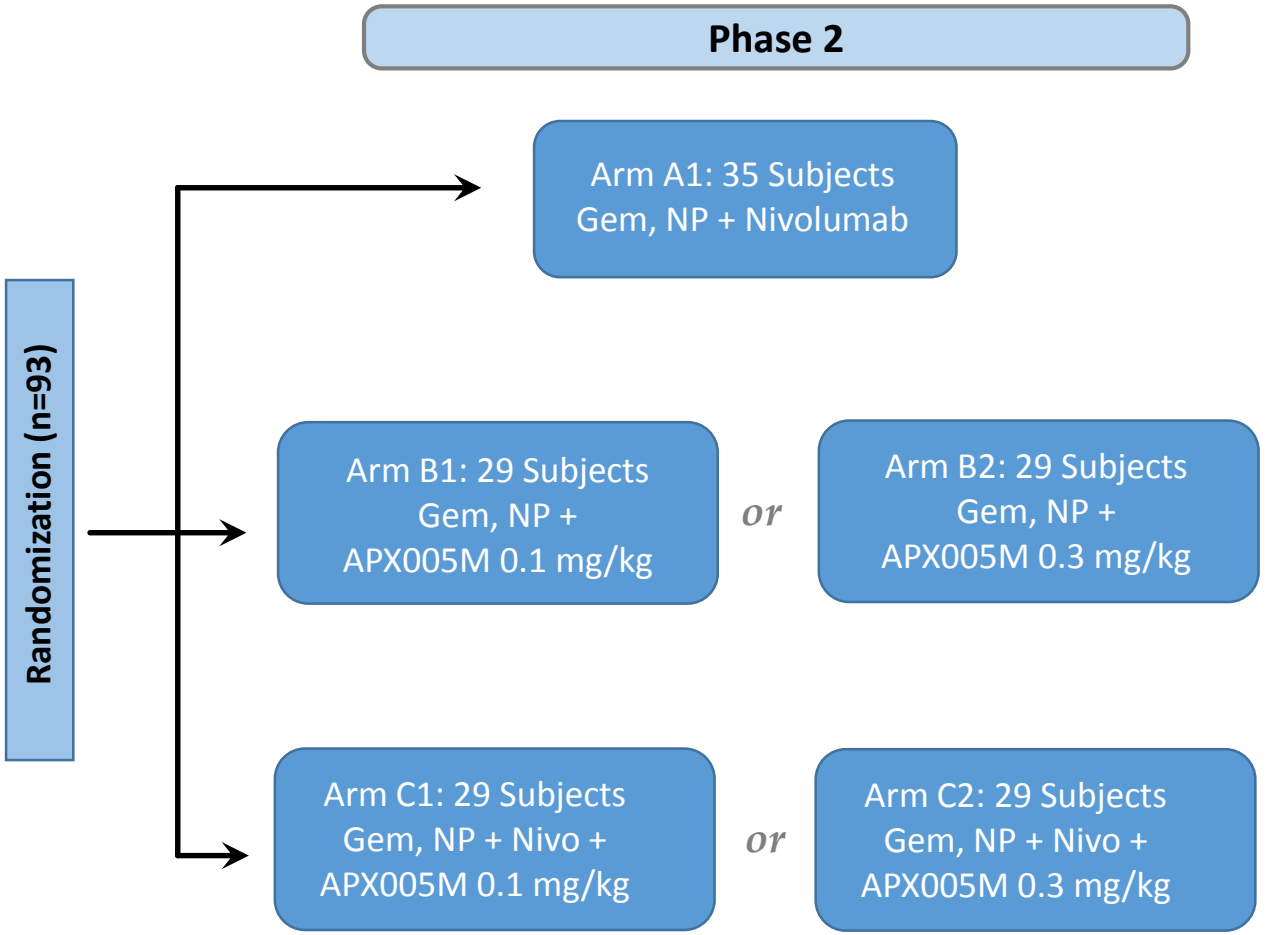
Cohort B1: Gem/NP/APX005M 0.1 mg/kg
Cohort B2: Gem/NP/APX005M 0.3 mg/kg
Cohort C1: Gem/NP/APX005M 0.1 mg/kg + nivo
Cohort C2: Gem/NP/APX005M 0.3 mg/kg + nivo

▲ = New lesion

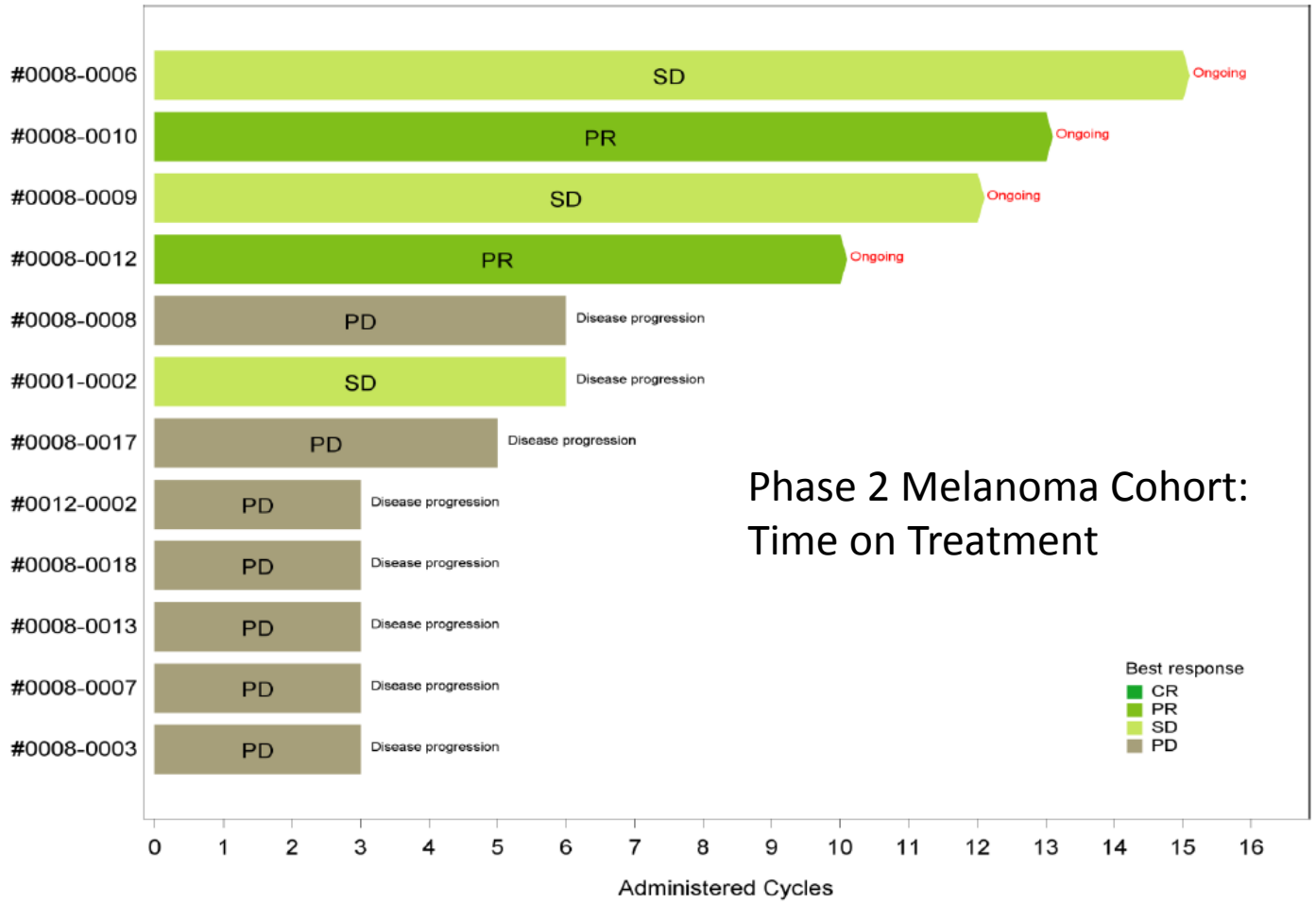
- **ORR = 46.7% (14/30) (95% exact CI: 28.3 – 65.7)**
- **DCR = 80%**

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Randomized Phase 2 Study



Phase 1b/2 Study of CD40 Agonistic Antibody APX005M in Combination with Nivolumab in Subjects with Metastatic Melanoma and Subjects with Non-small Cell Lung Cancer

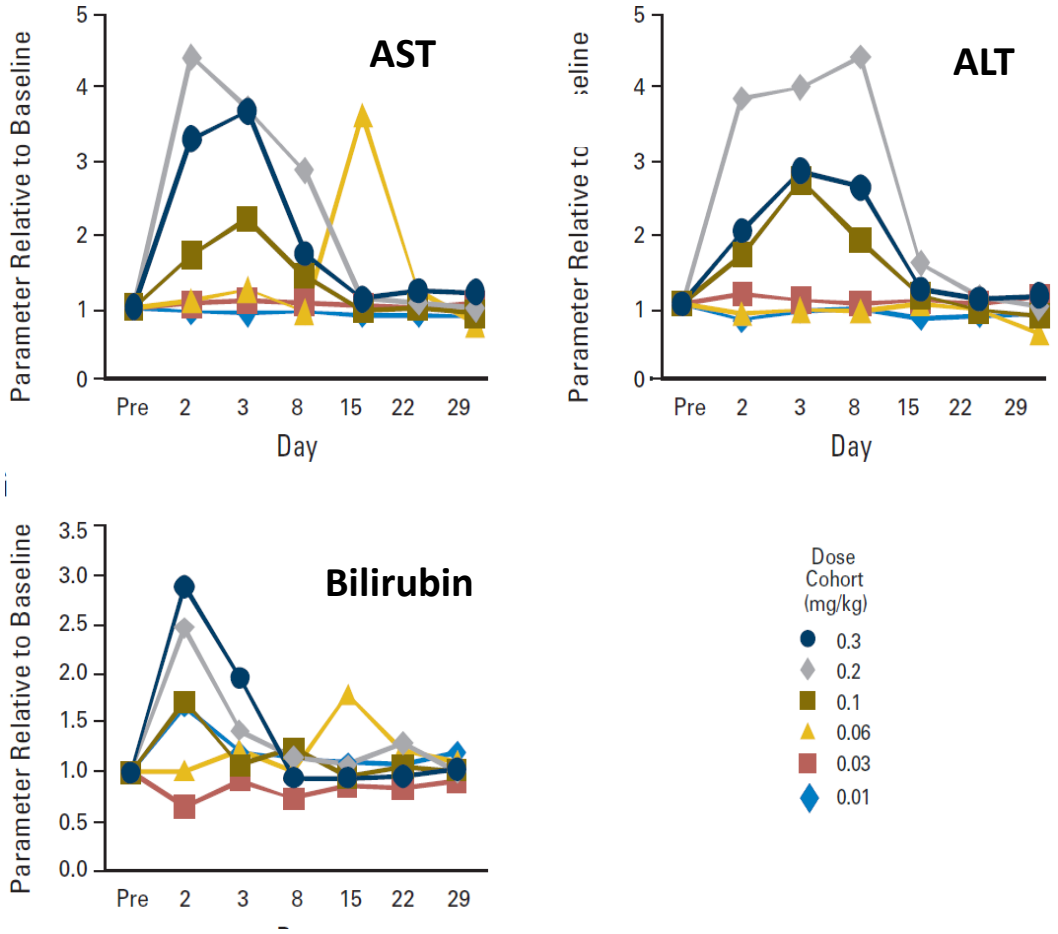


Phase 2 Melanoma Cohort:
Time on Treatment

Kluger and Weiss. AACR. 2019
ClinicalTrials.gov Identifier NCT03123783

Systemic Agonist Anti-CD40 Toxicities

- Cytokine release syndrome[1]
  - Fever, rigors, chills, nausea, vomiting, hypotension, hypoxia
  - Dose limiting
- Hepatotoxicity[1]
  - Transient transaminase and bilirubin elevations
- MTD or recommended phase 2 dose of agonist anti-CD40 mAbs has been in the range of ≤ 0.3 mg/kg



Vonderheide. JCO 2007

1. Vonderheide. Clin Cancer Res. 2013.
2. Byrne. J Immunol. 2016.

Strategies to Mitigate Systemic Adverse Events

- Pre-infusion corticosteroid administration[1]
  - Phase 1 dose escalation study of ADC-1013 ± pre-infusion corticosteroids
    - Steroid cohort dosed up to 2 mg/kg and steroids had decrease incidence of infusion related reactions
    - Impact on pharmacodynamics and clinical activity not reported
- Intratumoral administration[2] ClinicalTrials.gov Identifier NCT02379741
  - Phase 1 dose escalation study of intratumoral ADC-1013
    - ADC-1013 22.5 – 400 μg/kg q2 weeks x 4
    - Superficial (LN/skin) vs. deep (hepatic) lesions
    - 15 of 18 had drug related AEs
    - Liver intratumoral injections associated with CRS symptoms
    - Deep lesions had systemic exposure at higher doses and pharmacodynamic activity at all dose levels
- Phase 1 dose escalation study of intratumoral APX005M with systemic pembrolizumab[3] ClinicalTrials.gov Identifier NCT02706353
  - Treatment naïve melanoma
  - APX005M 0.1 mg – 10 mg (n=14)
  - Well tolerated; low grade AEs; no DLTs
  - Increase in innate and adaptive immune response gene signature in a responding patient as determined by NanoString gene analysis
  - 1 CR, 6 PR (ORR 50%), 2SD, 5 PD

ADC-1013 Intratumoral Administration

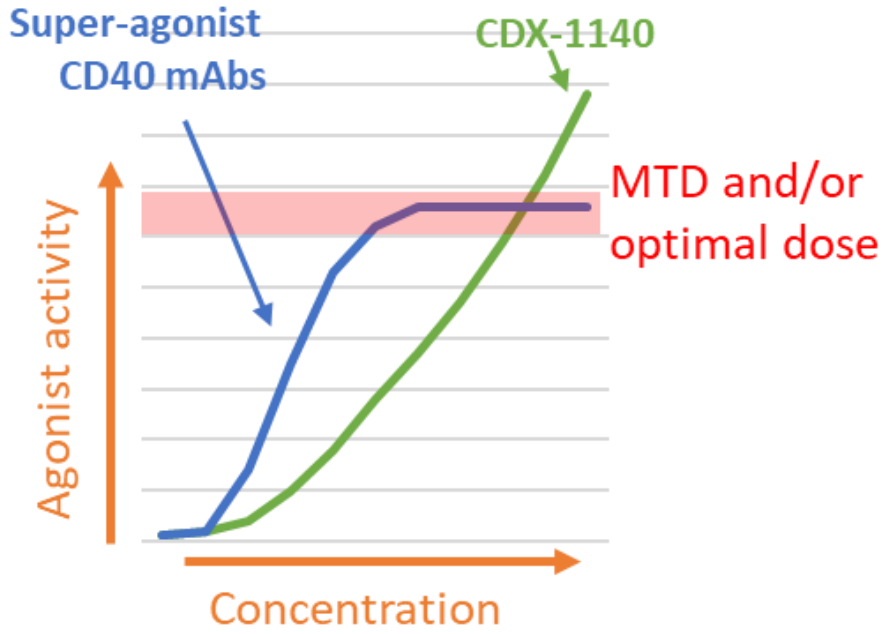
Adverse event	Pat no	Dosage (μg/kg)	Grade	Dose limiting toxicity
Chills	9	200	3	No
Hypotension	11	400	3	No
Cholecystitis	14	400	3	Yes
Shiverings[1]	16	400	3	No
Abdominal pain			3	Yes

[1]Occurred on two separate occasions.

1. Calvo. ASCO. 2019
2. Irenaeus. IJC. 2019.
3. Bentebibel. CICON. 2019.

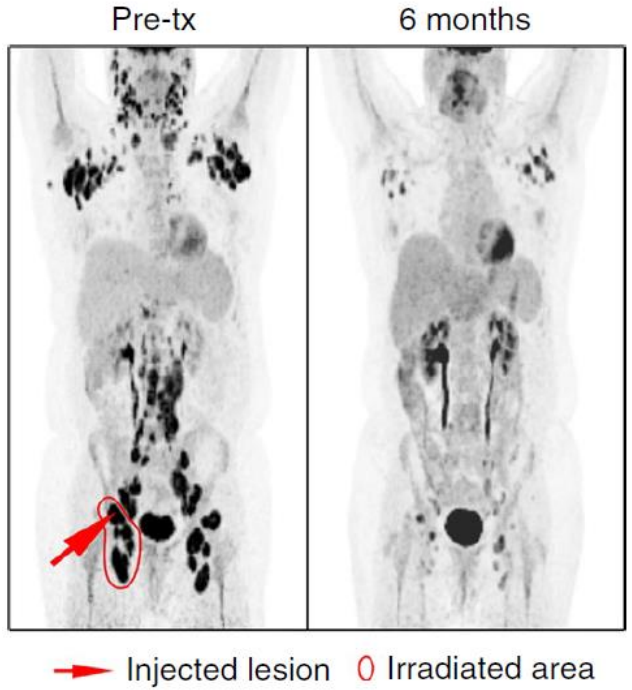
CDX-1140: CD40 Agonist Antibody

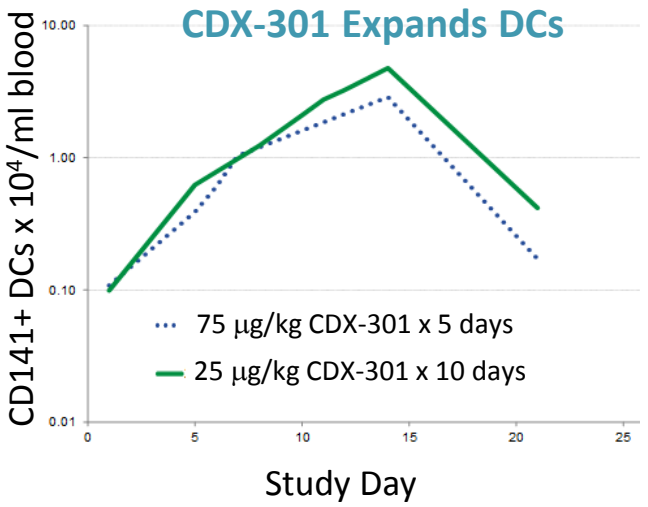
- Less steep dose-response curve
- FcR independent agonist activity
  - Fully human IgG_2 monoclonal antibody
  - Potentially more consistent and better controlled agonist activity
  - Minimal effector function
- Systemic delivery
  - Side effect profile that allows sufficiently high doses for good tissue/tumor penetration
- Synergy with CD40 ligand-mediated activation
  - May synergize locally with CD40L-expressing cells
- Phase 1 dose-escalation study of CDX-1140 monotherapy and in combination with CDX-301 (FLT3L)

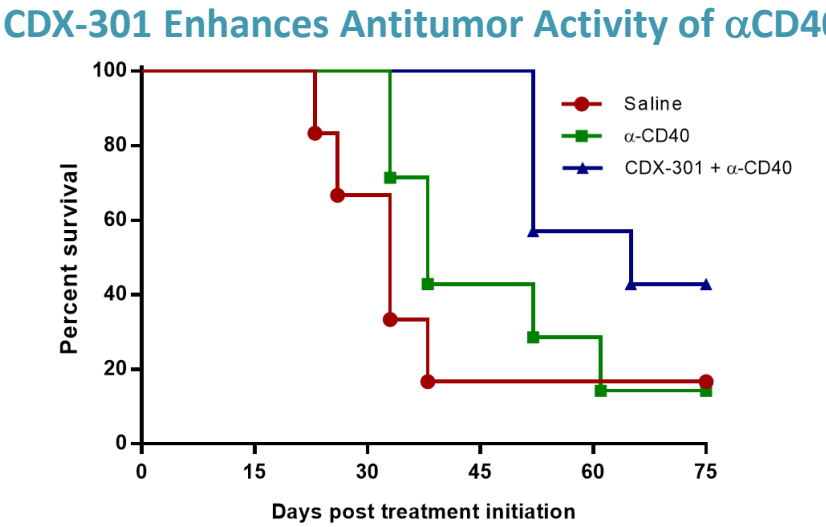


CDX-301 (Flt3 ligand)

- Hematopoietic growth factor that uniquely induces proliferation and expansion of dendritic cells
- Enhanced kinetics, magnitude, and percentage responding to cancer vaccine (Bhardwaj, submitted) ClinicalTrials.gov Identifier NCT02129075
- Phase 2 study of CDX-301 + RT + TLR3a showed promising results in FL (Hammerich, Nature Medicine. 2019) ClinicalTrials.gov Identifier NCT01976585
- Phase 2 study of CDX-301 + SBRT showing promising early results in CPI refractory NSCLC (Ohri, AACR 2018) ClinicalTrials.gov Identifier NCT02839265
- Combination with CD40 agonist mAb is effective in preclinical models







CDX-1140 Phase 1 FIH Study in Patients with Advanced Solid Tumors and Lymphomas

CDX-1140 Monotherapy Arm

Study Portion	Cohort	CDX-1140 Dose Level (mg/kg q4w)	Patients (n)
Dose-Escalation	1*	0.01	2
	2*	0.03	1
	3*	0.09	3
	4*[1]	0.18	7
	5*	0.36	3
	6*	0.72	3
	7*	1.5	3
	8	3.0	3-6
Expansion Cohorts		TBD	Up to 15 per cohort

CDX-1140 + CDX-301 Combination Arm

Study Portion	Cohort	CDX-1140 Dose Level (mg/kg q4w)	CDX-301 75 µg/kg	Patients (n)
Dose-Escalation	3A*	0.09	X	5
	4A*	0.18	X	3
	5A	0.36	X	3-6
	6A	0.72	X	3-6
	7A	1.5	X	3-6
	8A	3.0	X	3-6
Expansion Cohorts		TBD	X	Approx. 12 per cohort

ClinicalTrials.gov Identifier NCT03329950

*Presented at 2019 AACR meeting by Rachel Sanborn, MD
1. DLT (pneumonitis)

CDX-1140 Induces DC Activation and Cytokine Secretion

Study update to be presented by Rachel Sanborn Friday (Abstract P827)

Conclusions

- CD40 is expressed on DCs, macrophages, other cell types…….and tumor cells
- CD40 plays key roles in cellular and humoral immune responses
  - CD40 dependent signaling can enhance anti-tumor adaptive and innate cellular immune responses
  - CD40 dependent signaling has the potential to bypass tumor immune escape mechanisms
  - CD40 expressed on tumor cells is a direct target for anti-CD40 based therapy
- Systemic agonist CD40 targeted therapy can modify the tumor microenvironment via multiple mechanisms
- Systemic agonist anti-CD40 mAb therapy has been generally well tolerated
  - Associated with cytokine release syndrome and transient transaminitis
- Greatest potential for anti-tumor immunotherapy is a combinatorial approach targeting multiple points of the cancer immune cycle
  - Agonist anti-CD40 therapy has demonstrated modest evidence of clinical benefit in clinical studies to date
  - Encouraging emerging data in combination with checkpoint blockade and chemotherapy