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APRIL 8-13, 2022 • #AACR22

7394/CT041. Monotherapy dose escalation of davoceticept (ALPN-202), a conditional CD28 costimulator and dual checkpoint inhibitor, in advanced malignancies (NEON-1)

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Session: Immunotherapy Combination Strategies in Clinical Trials, Tuesday Apr 12, 2022 2:30 PM - 4:30 PM

Disclosure Information

Diwakar Davar, MD

I have the following relevant financial relationships to disclose:

Grants/Research Support (Institutional): Arcus, BMS, Merck, Checkmate Pharmaceuticals, CellSight Technologies, Immunocore, Tesaro/GSK

Consultant: Checkmate Pharmaceuticals, Finch, Shionogi, Vedanta Biosciences

Intellectual Property:

US Patent 63/124,231, “Compositions and Methods for Treating Cancer”, Dec 11, 2020

US Patent 63/208,719, “Compositions and Methods For Determining Responsiveness to Immune Checkpoint Inhibitors (ICI), Increasing Effectiveness of ICI and Treating Cancer”, June 9, 2021

Davoceticept (ALPN-202):
A First-In-Class, PD-L1-Dependent CD28 Costimulator and Dual PD-L1/CTLA-4 Checkpoint Inhibitor

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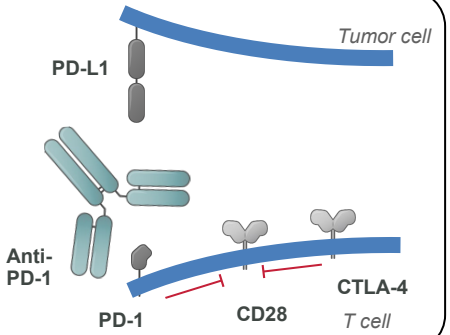
Background

- Inadequate CD28 costimulation may underlie T cell hyporesponsiveness during checkpoint inhibition, accounting for therapeutic resistance
- Davoceticept includes a variant CD80 domain, engineered to localize CD28 costimulation safely within the tumor microenvironment, while also inhibiting PD-L1 and CTLA-4
- Preclinical studies demonstrated favorable efficacy and safety compared to checkpoint inhibition

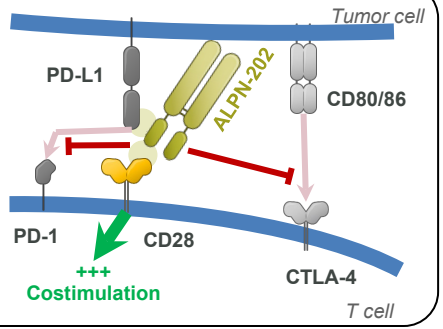
Checkpoint-Only Inhibition

- Inhibits PD-1/PD-L1
- Releases inhibition of, but does not activate, CD28



Davoceticept (ALPN-202)

- Inhibits PD-L1 and CTLA-4
- Mediates PD-L1-dependent CD28 costimulation



NEON-1 (NCT04186637):
A First-In-Human Dose Escalation and Expansion Study of ALPN-202 (Davoceticept) in Advanced Malignancies

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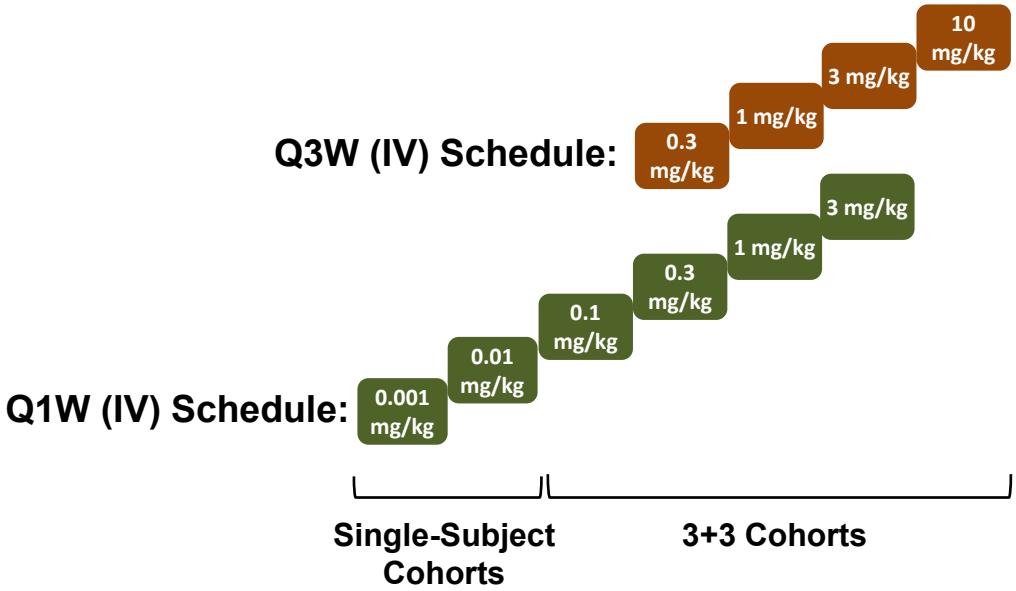
Dose Escalation (Part A)



NEON-1 Demographics

Characteristic	Total (N=58)
Age (yr, median, range)	**60 (36-79)**
Male/Female (n, %)	**33/25 (57%/43%)**
Race	
Caucasian	46 (79%)
Asian, Hawaiian or Other Pacific Islander	5 (9%)
Black or African American	3 (5%)
Not Reported, Unknown or Other	4 (7%)
Prior Lines of Therapy (median, range)	**4.0 (1-9)**
Prior I/O Therapy / PD-(L)1 Inhibitor	24 (41%) / 17 (29%)
Archival PD-L1 Expression (22C3)	
CPS 0-10 / >10	34/51 (67%) / 17/51 (33%)
Tumor Type	
Colorectal*	14 (24%)
Pancreatic	11 (19%)
Esophageal	5 (9%)
Mesothelioma	4 (7%)
Cholangio, Renal Cell, Non-Melanoma Skin	3 (5%) each
Head & Neck, Neuroendocrine, Ovarian/Fallopian, Uterine, Uveal Melanoma	2 (3%) each
Adenoid Cystic, Cervical, Melanoma, Prostate, Thymoma	1 (2%) each

Data Extract: 21MAR2022

*100% (of 12/12 available) were pMMR/MSS

NEON-1 Participant Disposition, All Cohorts

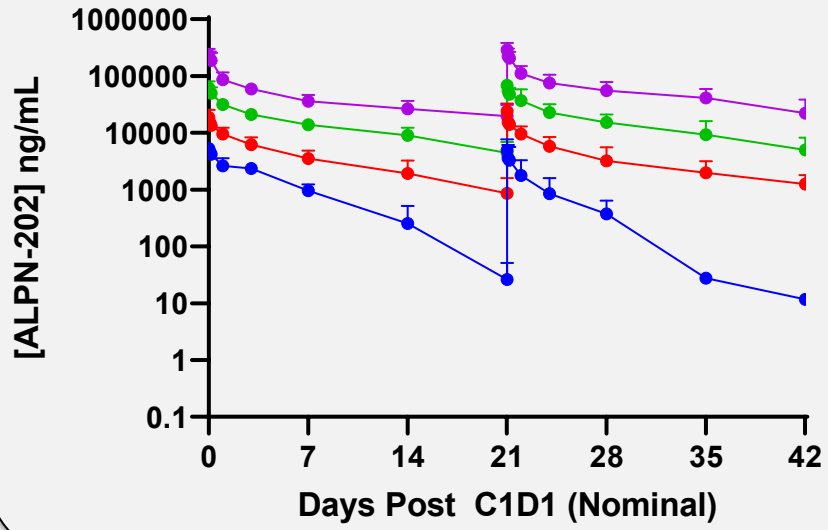
Subjects Treated	Total (N=58)
Ongoing	**3 (5%)**
Discontinued	**55 (95%)**
Disease Progression (Radiographic or Clinical)	43 (78%)
Subject, Investigator, or Sponsor Decision	6 (11%)
Adverse Event Study Drug-Related[1] Study Drug-Unrelated[2]	4 (7%) 3 (5%) 1 (2%)
Death[2] Study Drug-Related	2 (4%) 0

[1] Acute kidney injury, gastritis, and colitis leading to protocol-disallowed dose delay
[2] Seizure
[3] Pneumonia (due to underlying disease), sudden death (due to opiate overdose)

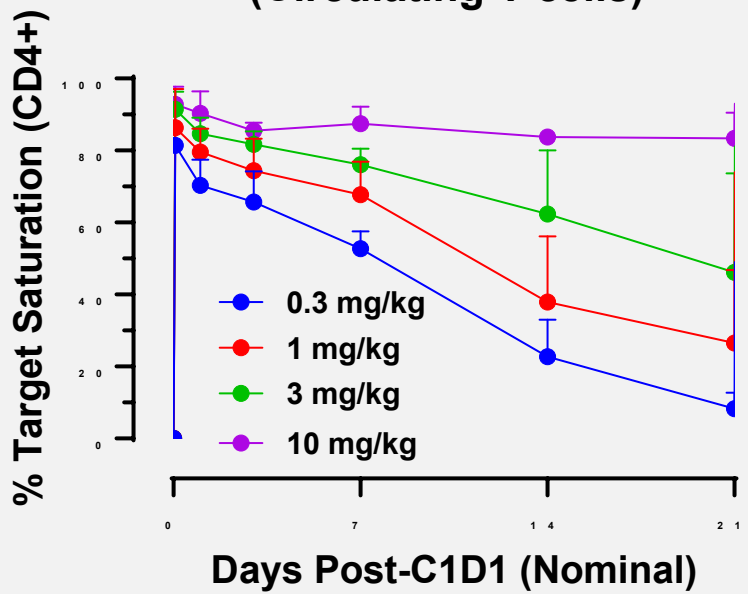
Data Extract: 21MAR2022

Davoceticept Demonstrates Dose-Dependent PK/PD

Pharmacokinetics



Target Saturation (Circulating T cells)



Q3W Schedule (Q1W not shown)

Davoceticept Monotherapy Preliminary Safety:
Well-Tolerated to 10 mg/kg; Most Notable Events are irAEs

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Adverse Event (AE) Summary

Characteristic	Subjects (N=58)
Treatment-Related (TR) AE Gr 3+	**7 (12%)**
TR-Serious AE (SAE) / Gr 3+	**3 (5%) / 3 (5%)**
AE of Interest (AEI) Immune-related AE (irAE) / Gr 3+ Infusion-Related Reaction (IRR) / Gr 3+ Cytokine Release Syndrome	**25 (43%)** 19 (33%) / 3 (5%) 9 (16%) / 0 0
Dose-Limiting Toxicities	**1 (2%)**

Participants with Grade 3 TR-AEs

Dose	Adverse Event(s)	SAE	irAE	DLT
3Q3W	Gastritis	X	X	X
0.1Q1W	Acute Kidney Injury Testicular Pain	X	X	
3Q3W	Dehydration	X		
10Q3W	Urticaria		X	
0.1Q1W	ALT Increased			
3Q3W	Anaemia Lipase Increased			
3Q3W	Diarrhoea Oedema Peripheral			
3Q3W	Hypokalemia			

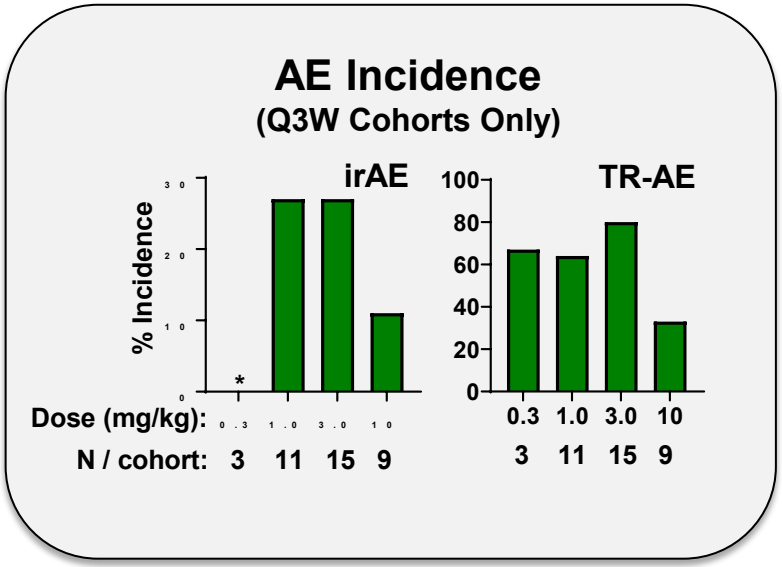
All Cohorts (Q1W + Q3W)

Data Extract: 21MAR2022

Immune-Related Adverse Events with Davoceticept

Skin, Thyroid and GI Most Common, Especially at Mid-Range Doses

irAEs, All Cohorts	Subjects (N=58)
Skin and Subcutaneous Tissue • Rash Maculo-Papular • Rash Macular • Pruritus, Urticaria • Night Sweats, Rash Papular, Rosacea	**14 (24%)** • 7 (12%) • 5 (9%) • 2 (3%) each • 1 (2%) each
Endocrine • Hypothyroidism • Hyperthyroidism	**5 (9%)** • 5 (9%) • 2 (3%)
Gastrointestinal • Colitis, Gastritis, Terminal Ileitis	**3 (5%)** • 1 (2%) each
Musculoskeletal/Connective Tissue • Arthralgia, Arthritis, Myalgia	**2 (3%)** • 1 (2%) each
Other • Acute Kidney Injury, ALT Increased, Chills, Testicular Pain	• 1 (2%) each



Data Extract: 21MAR2022

Davoceticept Promotes T cell Activation

Engages CD28, Modulates ICOS, T_{CM}, T_{reg}, Especially at Mid-Range Doses

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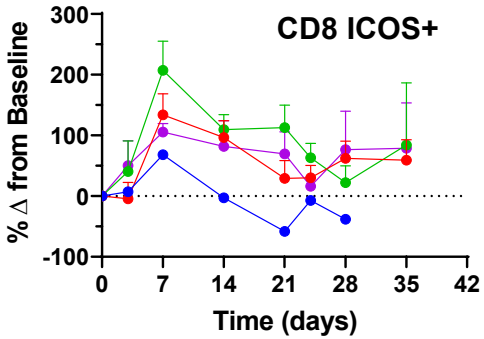
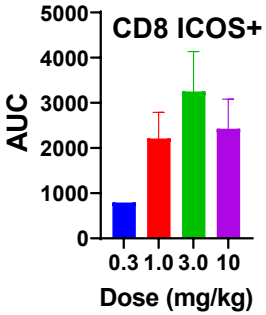
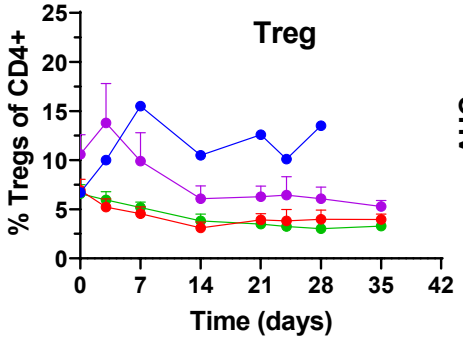
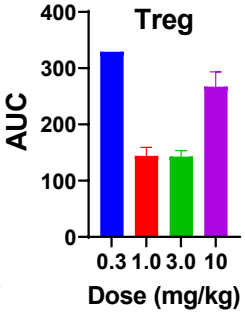
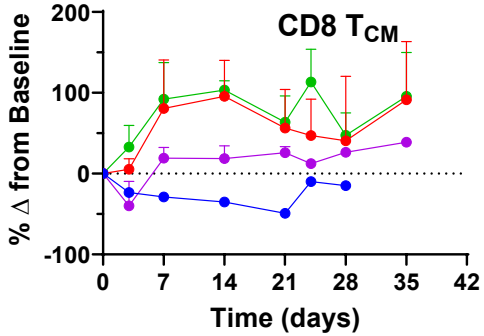
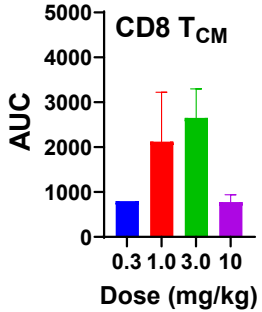






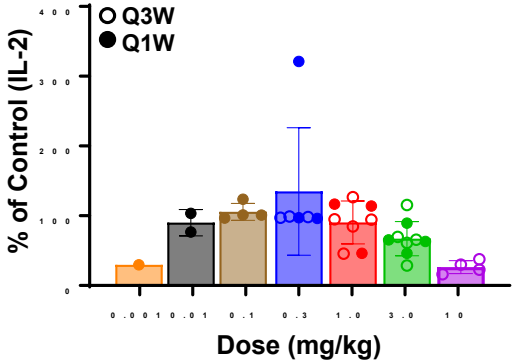






*Q3W Schedule Only (Q1W not shown)

CD28 Costimulation (End-of-Infusion)



Anti-Tumor Activity with Davoceticept Monotherapy

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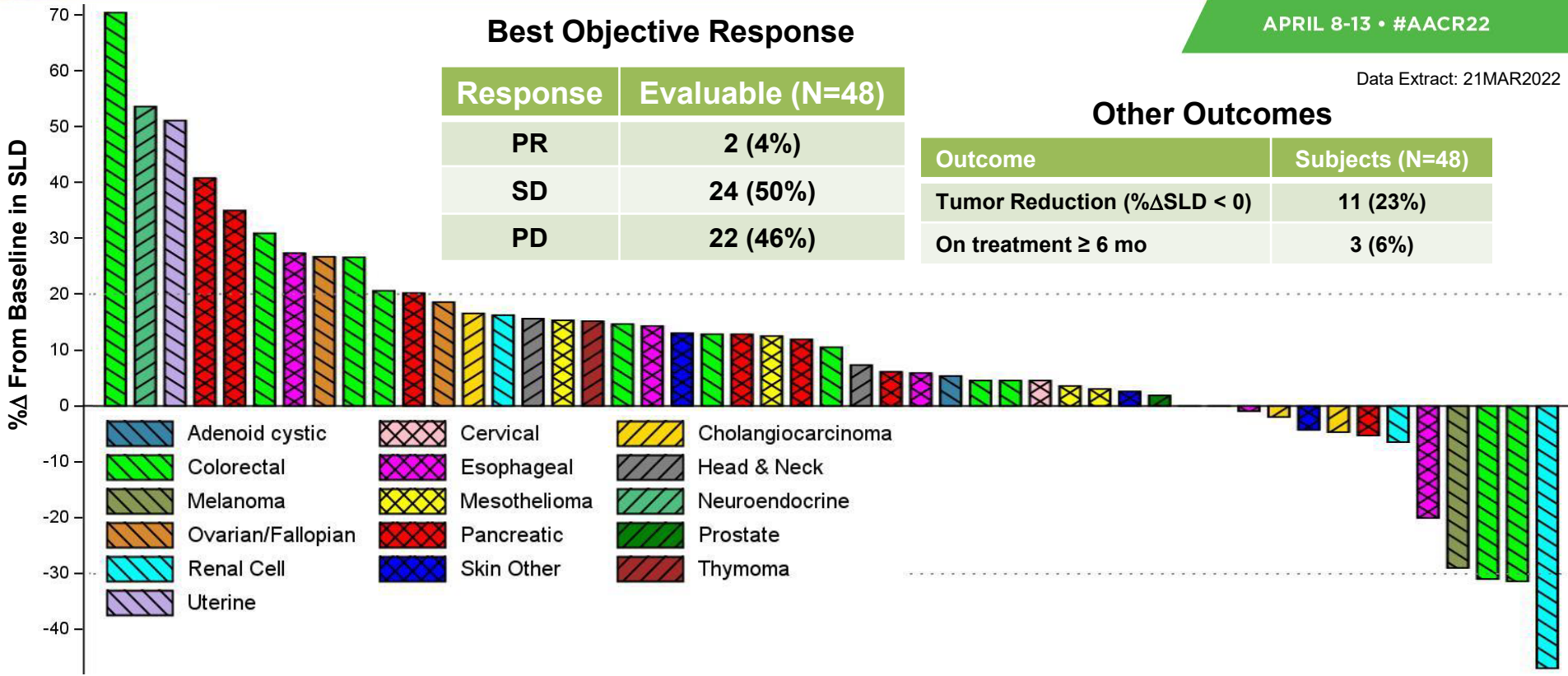
Best Objective Response

Response	Evaluable (N=48)
PR	2 (4%)
SD	24 (50%)
PD	22 (46%)

Data Extract: 21MAR2022

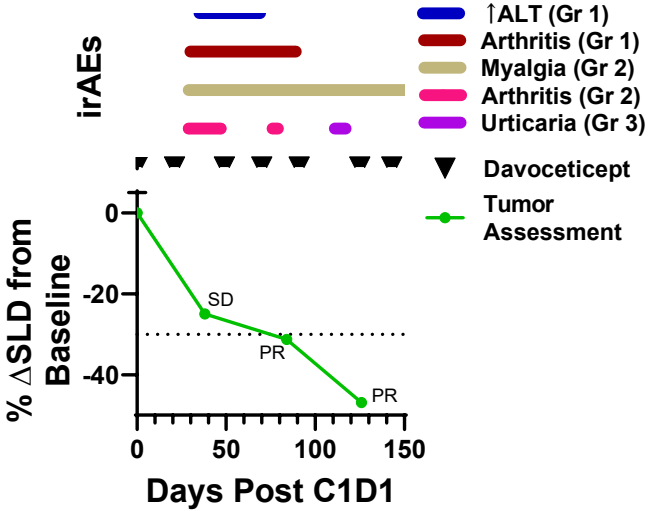
Other Outcomes

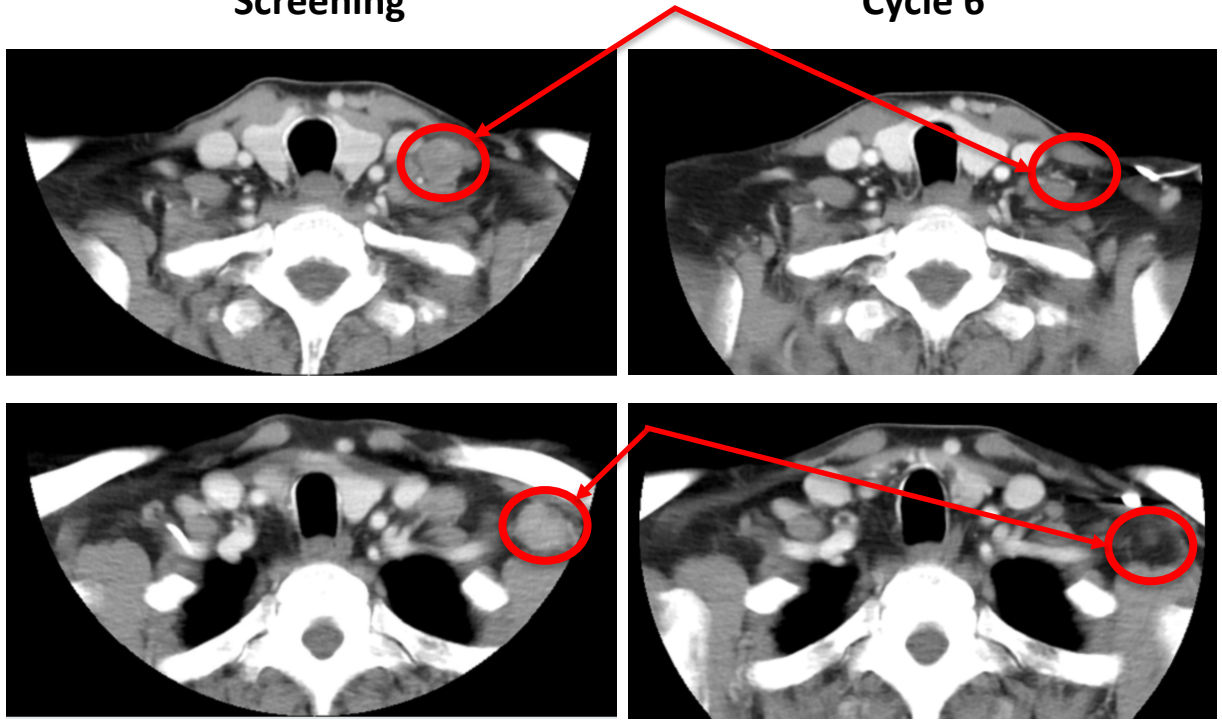
Outcome	Subjects (N=48)
Tumor Reduction (%ΔSLD < 0)	11 (23%)
On treatment ≥ 6 mo	3 (6%)



Participant 20404: 68M Papillary Renal Cell

- Diagnosed 10/2020
- Liebovich score 8, MSKCC poor risk
- Nephrectomy (pT3a N1) 11/2020
- Metastatic disease 7/2021
- PD-L1 CPS <1, TPS 0





Conclusions: Monotherapy Dose Escalation

- Davoceticept is a first-in-class variant CD80 Fc fusion designed to overcome CPI resistance by focusing CD28 costimulation to the TME, while inhibiting PD-L1 and CTLA-4.
- In advanced tumors, davoceticept has been well-tolerated, with dose-dependent PK/PD, including relevant immune activation such as ↑ICOS, ↑T_{CM} and ↓Treg. The 1 and 3 mg/kg dose levels appear to result in optimal immunomodulation.
- Early clinical benefit is suggested in some cancers not traditionally responsive to CPIs.
- Ongoing development of davoceticept continues to be warranted.
  - Expansions planned: melanoma, renal cell and PD-L1+ tumors, 1 & 3 mg/kg Q3W
  - A study of combination with pembrolizumab has been initiated (NEON-2; NCT04920383) (Additional tumor types and/or combos, e.g., chemotherapy, are under consideration[1])
  - Preclinical background now published:

nature COMMUNICATIONS

https://doi.org/10.1038/s41467-022-29286-5 OPEN

The engineered CD80 variant fusion therapeutic davoceticept combines checkpoint antagonism with conditional CD28 co-stimulation for anti-tumor immunity

[1]Lewis *et al.* (2019) J Immunother Cancer 7(S1): P467