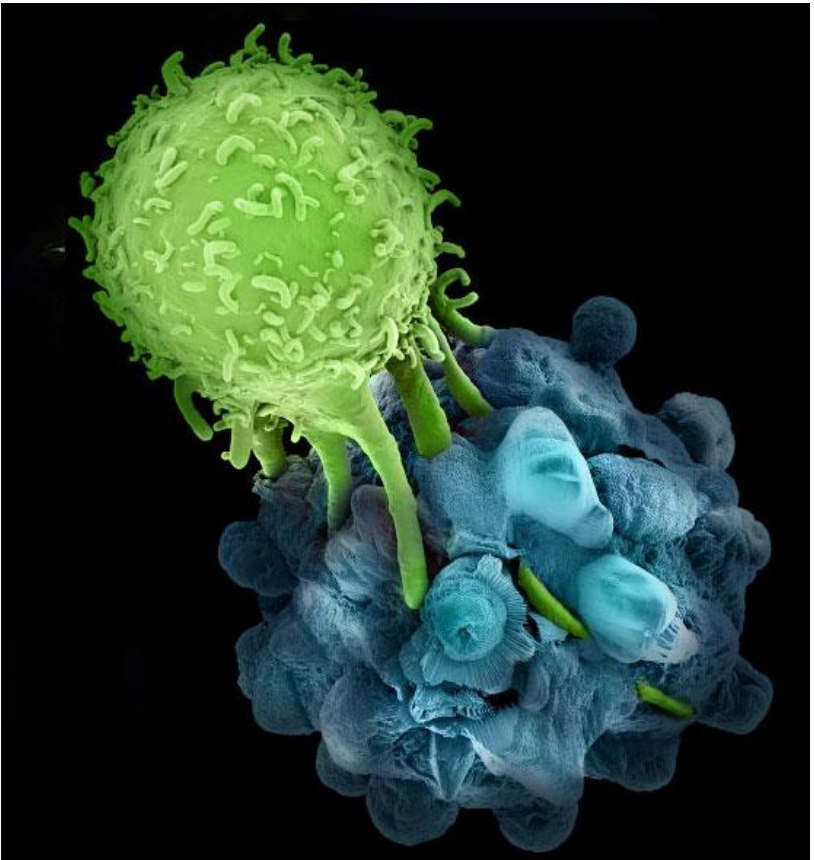
Cancer Immunotherapy Trials Network

"Update: 2019"

(November 8, 2019)



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CITN: Origin

- **AAI/AACR Extramural Immunology Expert Steering Committee**
  - Worked with NCI to query: **"Why have basic scientists invented so many potentially effective immunotherapy agents that are not being tested in patients?"**
    - Jim Allison, Mac Cheever, Olivera Finn, Ira Melman, Drew Pardoll, Ralph Steinman

- **NCI Immunotherapy Workshop (2007)**
  - Prioritized: **Agents that could cure cancer patients if we (the field) could get our hands on the agents to learn how to use them!**

- **CITN formed** to bring together foremost immunotherapists **to bring an essential focus on the high priority agents.**

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Focus on High Priority Agents Central to Effective Immune Responses

- Dendritic cell growth factor (Flt3L)
- Dendritic & APC activator (anti-CD40)
- Dendritic & APC activator (poly ICLC)
- Innate immune response activator (IFN-gamma)
- Homeostatic T-cell growth factor (IL-7)
- T-cell and NK cell activator & growth factor (IL-15)
- Checkpoint inhibitor (anti-PD1)
- Agent to inhibit suppressive enzymes (IDO inhibitor)

"Building Blocks for Constructing Effective Immune Responses"

Remarkably few academic initiated trials except anti-PD1/PD-L1

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Progress: CITN Trials with 8 Core Agents

- **Changed standard of care with anti- PD1 (4 diseases)**
  - Merkel Cell carcinoma
  - Mycosis fungoides/Sezary Syndrome
  - Advanced cancer with HIV
  - Pancreas cancer (by extrapolation)

- **Established doses for taking forward in combination regimens (6 agents)**
  - IL-7
  - IL-15
  - IL-15:IL-15Ra-Fc
  - Flt3L
  - Anti-CD40
  - IFN-gamma

- **Established or confirmed pharmacodynamics (5 agents)**
  - IL-7
  - IL15
  - IL15:IL15Ra-Fc
  - Flt3L
  - IDO inhibitor

- **Motivated several companies to develop agents (3 agents)**
  - IL-7
  - IL-15
  - Flt3-L

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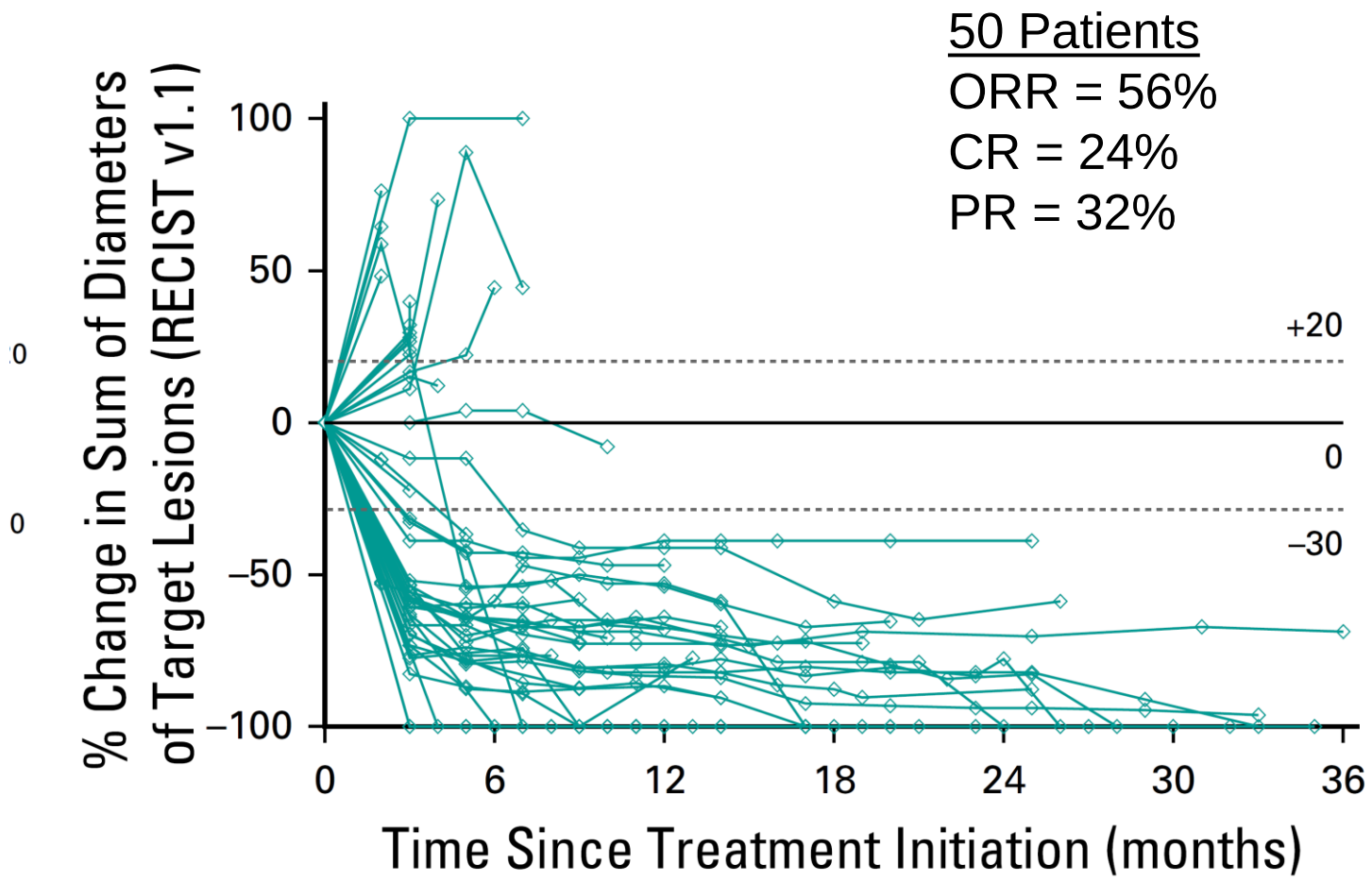
CITN-09: Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy



[Nghiem et a, JCO Feb 2019]

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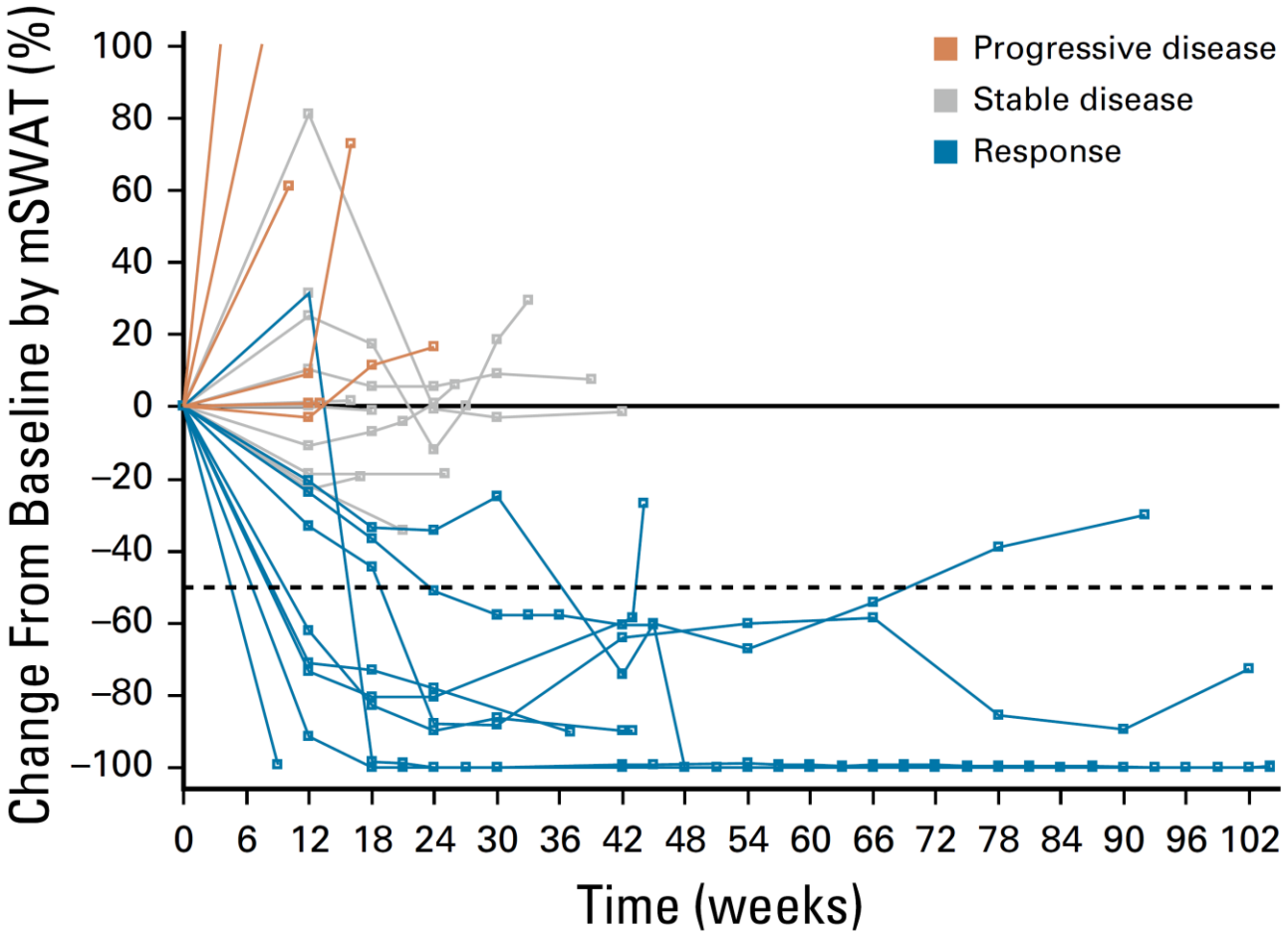
CITN-10: Pembrolizumab in Relapsed & Refractory Mycosis Fungoides and Sézary Syndrome



24 patients
ORR 38%
2 CR
7 PR

[Khodadoust et al JCO Sept 2019]

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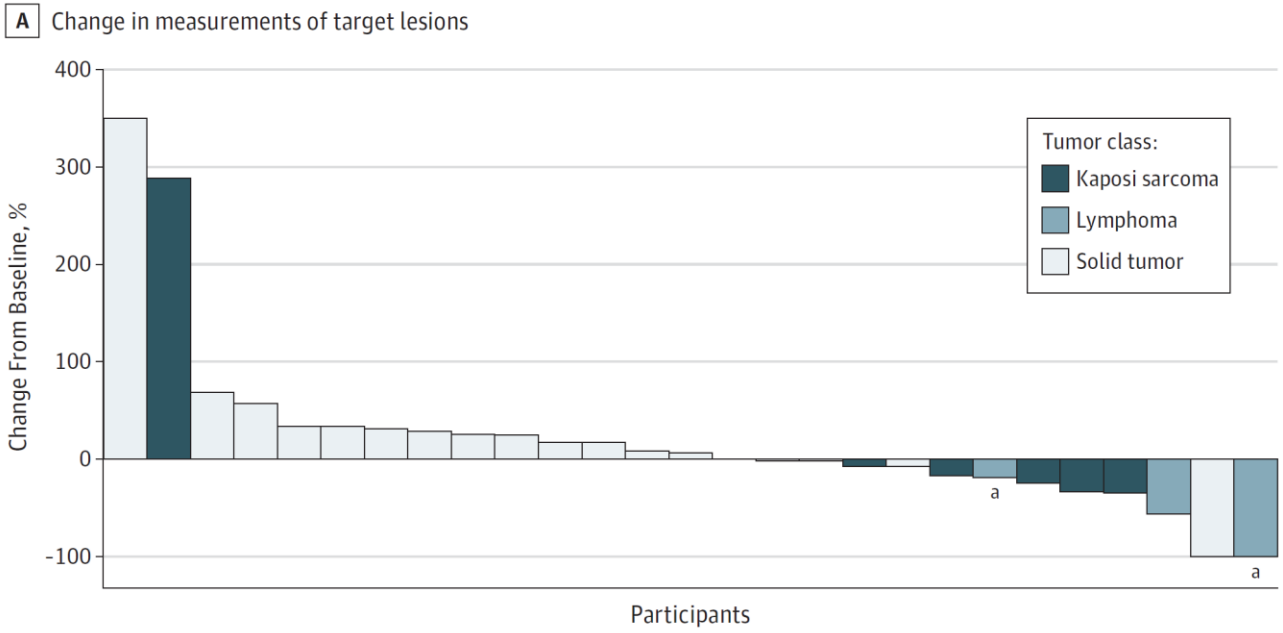
CITN-12: Assessment of the Safety of Pembrolizumab in Patients With HIV & Advanced Cancer

30 Patients (3 CD4 level cohorts)
6 Kaposi sarcoma (KS),
5 non-Hodgkin lymphoma (NHL)
9 non−AIDS-defining cancers.

Safety was observed over 183 cycles of pembrolizumab

One participant with pretreatment KS herpesvirus (KSHV) viremia developed polyclonal KSHV-associated B-cell lymphoproliferation & died.



Responses at all CD4 levels

[Uldrick et al. JAMA Oncol. Sept 2019]

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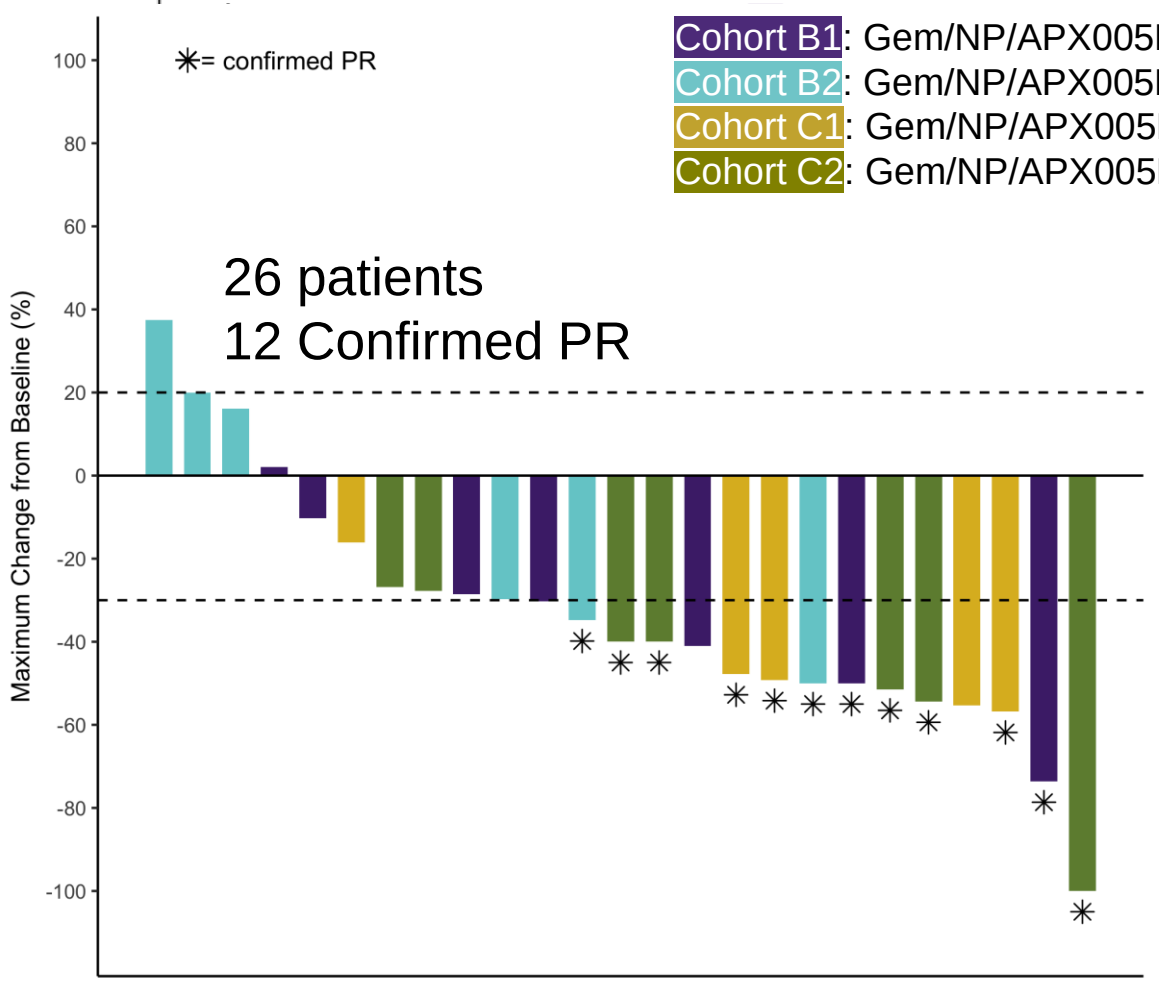
Parker Institute Trial:

Vonderheide/CITN/SU2C Regimen (anti-CD40 + Gemcitabine + nab-Paclitaxel) with or without Nivolumab for Untreated Metastatic Pancreatic Ductal Adenocarcinoma

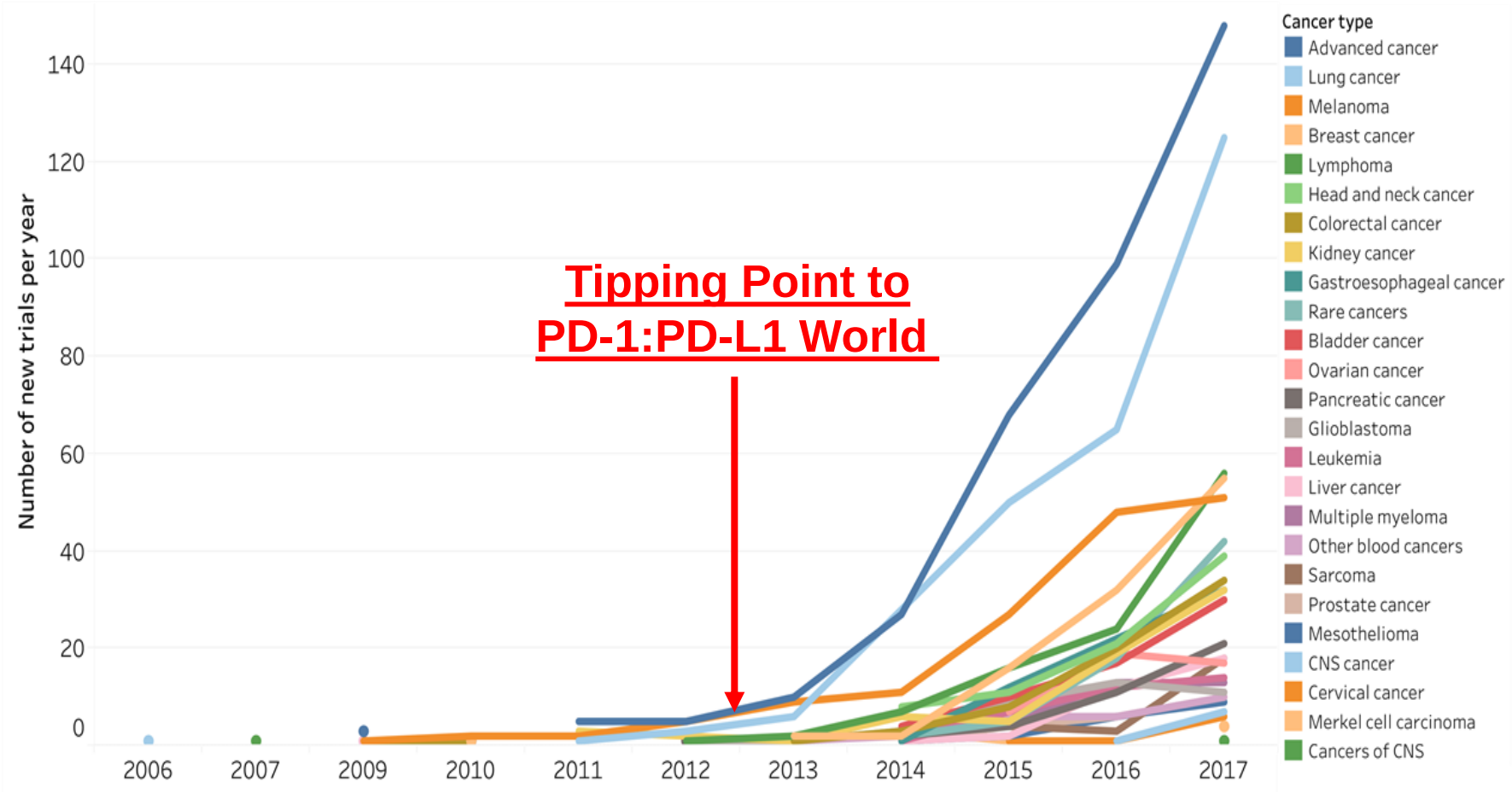
Percent Change in Sum of Target Lesions (Best Response)



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

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Evolution of PD-1/PD-L1 trials by different cancer type



[*Tang et al.* Nat Rev Drug Discov. Nov 28;17(12) 2018]

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Anti-PD1 & anti-PD-L1: The Core of Cancer Immunotherapy as single agents

- Objective tumor regressions (single agent):
  - Hodgkin lymphoma (65-87%)
  - Merkel cell Ca (32-64%)
  - Melanoma (17-50%)
  - Lung cancer (10-30%)
  - Kidney cancer (12-29%)
  - Bladder cancer (15-30%)
  - Head & neck cancer (20-25%)
  - Colon with many mutations (~50%)
  - Liver Ca (~15%)
  - Gastric Ca (~15%)
  - Ovarian cancer, nasopharyngeal Ca, TNBC, mesothelioma, ...

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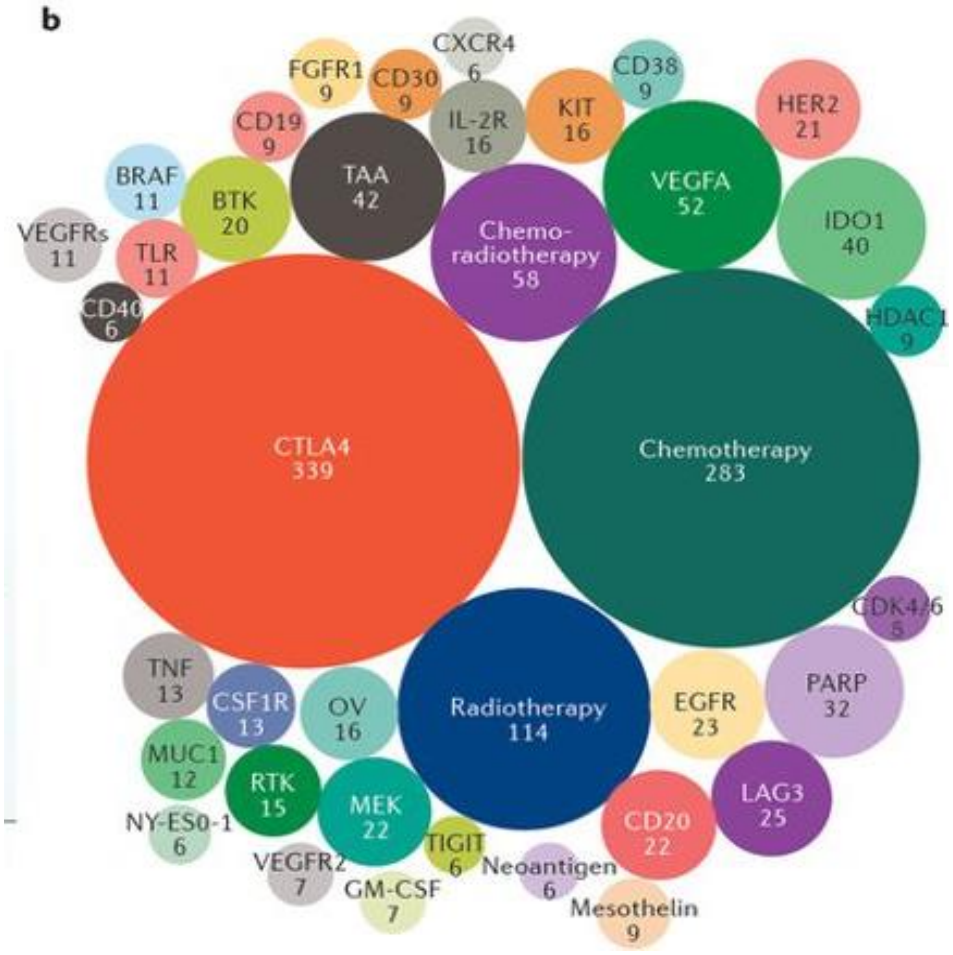
Original AAI/AACR Extramural Immunology Expert Steering Committee Question Leading to CITN - **RESOLVED**

- Why have basic scientists invented so many potentially effective immunotherapy agents that are not being tested in patients"
- **240 agents in 1,716 PD-1 combination trials (2018)**



Number of clinical trials are indicated by size of bubble

[Tang et al. Nat Rev Drug Discov. Nov 28;17(12) 2018]

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Targets in ≥6 PD-1 combination trials

339 CTLA4
283 Chemotherapy
114 Radiotherapy
58 Chemo-radiotherapy
52 VEGFA
42 TAA
40 IDO
32 PARP
23 EGFR
25 LAG3
22 CD20
22 MEK
21 HER2
20 BTK
16 KIT
16 IL-2R
16 OV
15 RTK
13 CSF1R
13 TNF
12 MUC1
11 BRAF
11 TLR
11 VEGFRs
9 CD19
9 CD30
9 CD38
9 FGFR1
9 HDAC1
9 Mesothelin
8 CDK4/6
7 GM-CSF
7 VEGFR2
6 CD40
6 CXCR4
6 Neoantigen
6 NY-ES)-1
6 TIGIT

CITN Trial Agents

1 IL-7 (CITN)
3 IL-15 (2 at NCI)
0 Flt3-L (1 pending)
0 CD47
3 TGFbi (1 recruiting)

[From: Tang et al. Nat Rev Drug Discov. & clinictrials.gov]

Despite Responses with Anti-PD-1 Single Agents & Combinations, Most Don't Respond or Relapse

[teepublic.com]

- Patients on anti-PD-1 combinations with growing tumors are likely the commonest single category of patient

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CITN Goals: (1) Identify Actionable Causes of PD1 Failure, (2) Develop Panel of Agents Effective for Specific Causes of Failure

- **CITN "Template" trial sequence**
  1. Biopsy to assess possible actionable causes of failure
  2. Continue anti-PD1/PD-L1
  3. Administer putative "rescue" agent(s)
  4. Timed biopsy to assess agent biological activity
  5. Follow clinical response to determine whether changes in tumor result in patient benefit

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- **Initial "Rescue" Agent Trials (to begin accrual momentarily)**

Agent	Putative Role
– IL-7	Tumors with too few T cells
– IL-2/IL-15	Tumors with too few activated T cells
– TGFb inhibitor	Tumors with TGFb signature

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  - **237 other agent possibilities with CITN prioritization based on functions central to effective immune response**

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Three Pediatric Trials in Development

- **Checkpoint inhibition**
  - Identify children with anti-PD1 responsive cancers
    - Anti-PD1 Combination Immunotherapy in Children, Adolescent and Young Adult Patients with Relapsed/Refractory Hypermutant Cancers
- **Synthetic immunity**
  - GD2-CAR T Cells for sarcoma and neuroblastoma
  - Anti-CD47 plus anti-GD2 in Children with Relapsed and Refractory Neuroblastoma and Osteosarcoma to facilitate infiltrating macrophage function

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Foreseeable Future

- Majority of patients with advanced cancer will be treated with combinations of current standard of care plus anti-PD1/PD-L1
- Combinations will increase responses & survival, but most will relapse
  - **Development of regimens to rescue failures is perhaps the greatest opportunity for academic trials to contribute substantively to patient benefit**

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Thanks!!!

- Patients – Past, current & future!
- CITN Site PIs & Investigators
- SITC Presidents
  - Bernie Fox
  - Tom Gajewski
  - Franco Marincola
  - Howard Kaufman
  - Lisa Butterfield
  - Mario Sznol
  - Tara Withington - Executive Director
- CTEP
  - William Merritt – ex Project Officer
  - Percy Ivy - Project Officer
  - Malcolm Smith – Project Officer
  - Howard Streicher - Senior Investigator
  - Elad Sharon – Senior Investigator