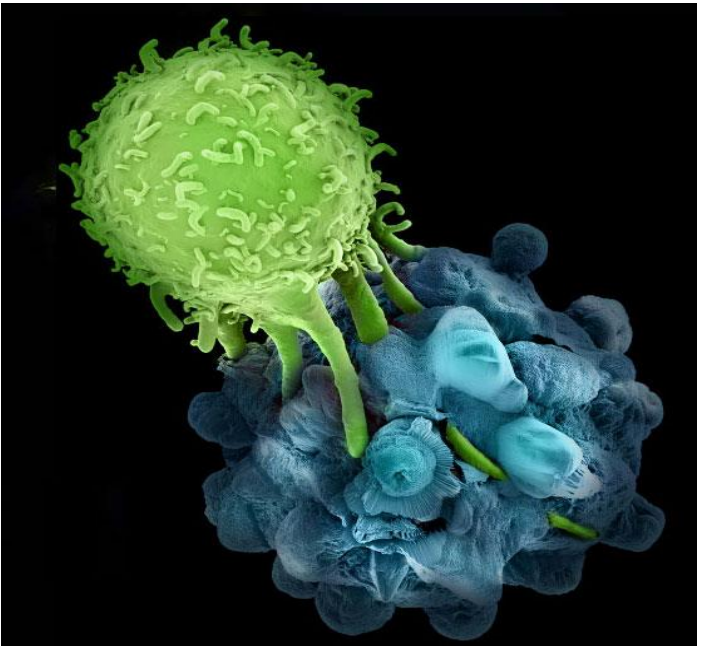
Immuno-Oncology Biomarkers: State of the Art (SITC)

Cancer Immunotherapy Trials Network (CITN): Data Management and Specimen Sharing

(May 17, 2018)



Martin A. “Mac” Cheever MD
PI: Cancer Immunotherapy Trials Network
Member: Fred Hutch
Professor: U of Washington
mcheever@fredhutch.org

Steven Fling PhD
Director: CITN Central Lab
Senior Staff Scientist: Fred Hutch
sfling@fredhutch.org

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Why are we all here?

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Dominance of Anti-PD1 & Anti-PD-L1

Profound responses in subsets of every type of malignancy

TIPPING POINT: (June 2012)

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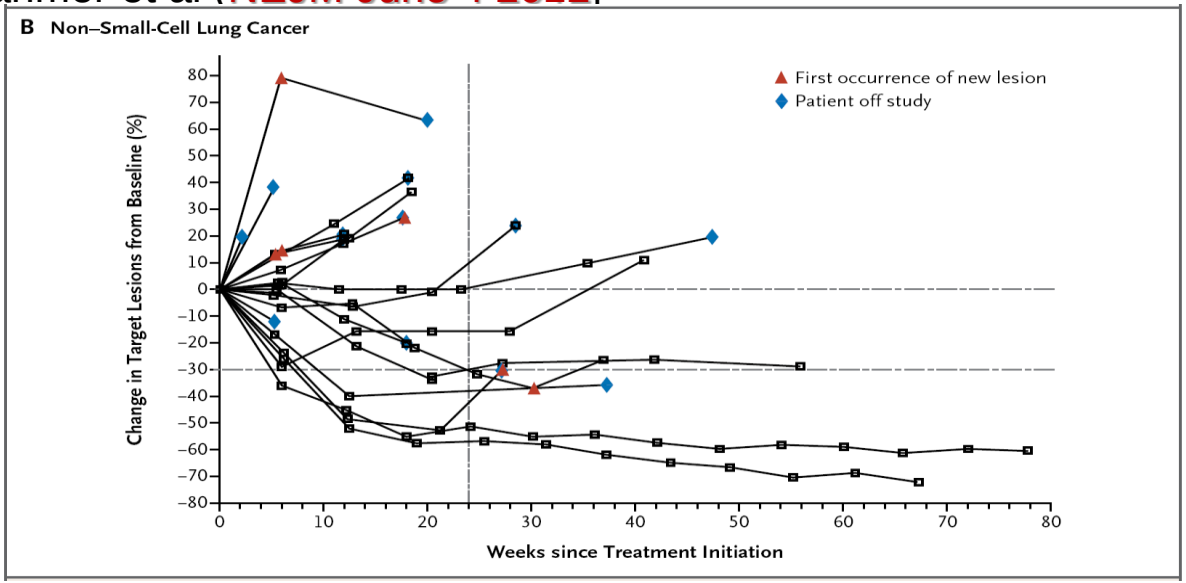
"Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer" [NSCLC: Partial Responses in 5 of 49]

[Brahmer et al (NEJM June 4 2012]



TIPPING POINT TO IMMUNE ONCOLOGY DOMINANCE

Anti-PD1

NSCLC: PR 14 of 76 (18%)

All patients: Objective Responses:

9 of 25 (36%) with PD-L1–positive tumors (P = 0.006)

0 of 17 (0%) with PD-L1–negative tumors

[Topalian et al NEJM June 4 2012]

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What's Happened in Six Years?

- 164 PD1 blocking drugs in development world wide
  - 50 in patient trials
- 1,502 clinical trials
  - 1,105 combination trials
- 5 FDA approved PD1 blocking drugs
  - Pembrolizumab (Keytruda)
  - Nivolumab (Opdivo)
  - Atezolizumab (Tecentriq)
  - Avelumab (Bavencio)
  - Durvalumab (Imfinzi)

[Tang, Shalabi & Hubbard-Lucey. Annals of Oncology 0: 1–8, 2017]

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Foreseeable Future?

- <u>Commonest single category of cancer patient will be patients on anti-PD1/PD-L1 combinations but progressing</u>

- Every patient will be considered for anti-PD1/PD-L1
  - Patients without correlates of response will be treated with anti-PD1/PD-L1 plus “X”
  - Patients with correlates of response will be treated with anti-PD1/PD-L1 alone or with “X”
- With >1,100 trials combining anti-PD1/PD-L1 plus “X”
  - Many “X”s will be effective
- There will never be a “standard” anti-PD1/PD-L1 therapy
  - East coast “X” will be different than West coast “X”
    - Like Tupac vs. Notorious B.I.G.

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With >1,500 trials,
how can academics remain relevant?

1. Initiate and accrue trials rapidly (nimble)
2. Identity actionable causes of anti-PD1/PD-L1 failure
3. Provide high quality biospecimens to CIMACs and other first-rate laboratories

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Sounds simple, but it's not!

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(1) Initiate Trials Rapidly (Nimble)

Operational Efficiency Working Group (OEWG) *"drop-dead" date*

	Absolute 2012-Present
Phase 1 and 2 LOIs	450 days
Phase 1/2 and 2 Concepts	450 days
Phase 3 Concepts	540 days

LOI submission to trial activation

[Report "OEWG Timeline Analysis for CTEP Trials 2017"]

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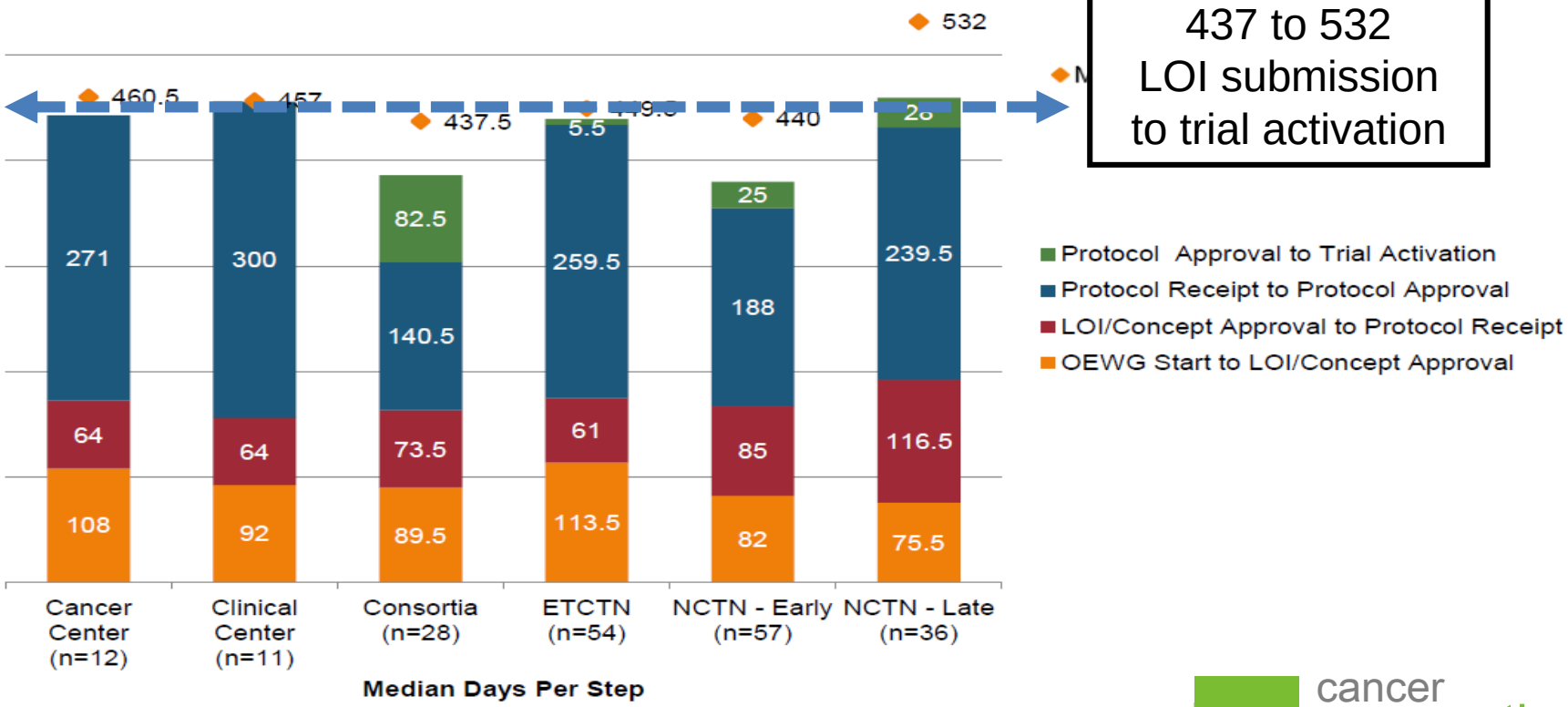
NCI Supported Trials



Median Total Days
437 to 532
LOI submission
to trial activation

[Report "OEWG Timeline Analysis for CTEP Trials 2017"]

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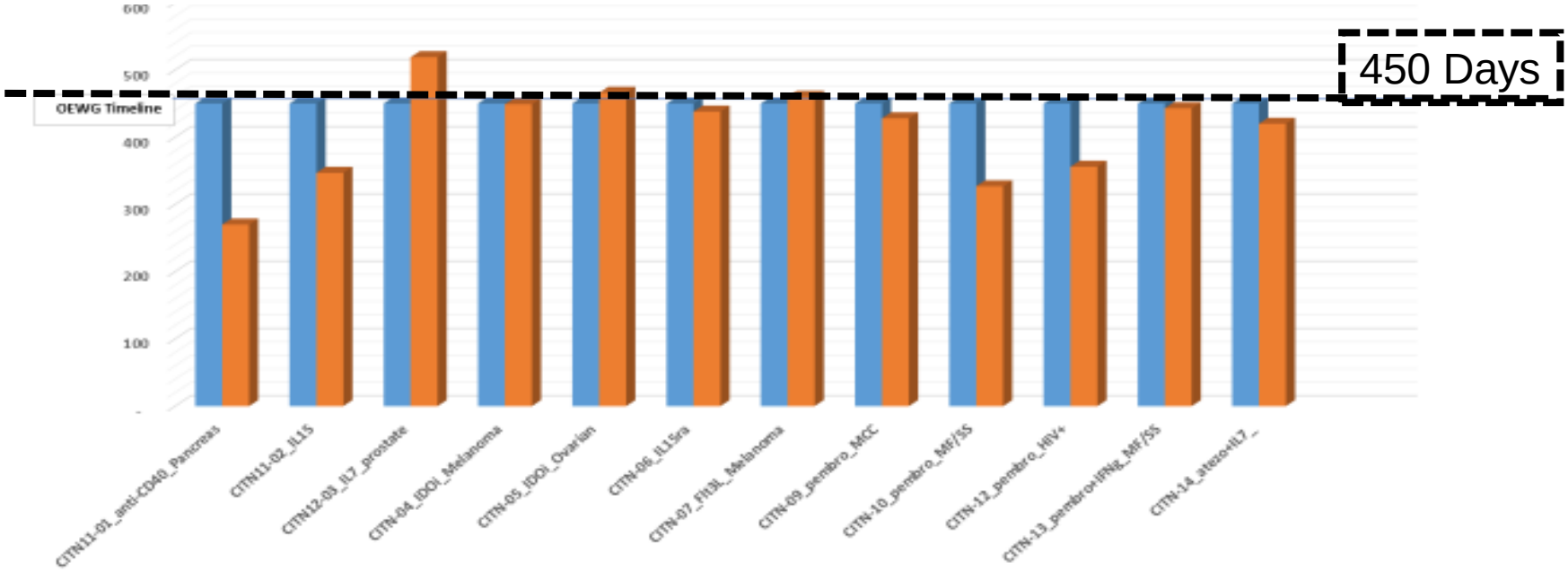
CITN: OEWG vs Actual Activation Timeline

Operational Efficiency Working Group (OEWG) *"drop-dead" date*



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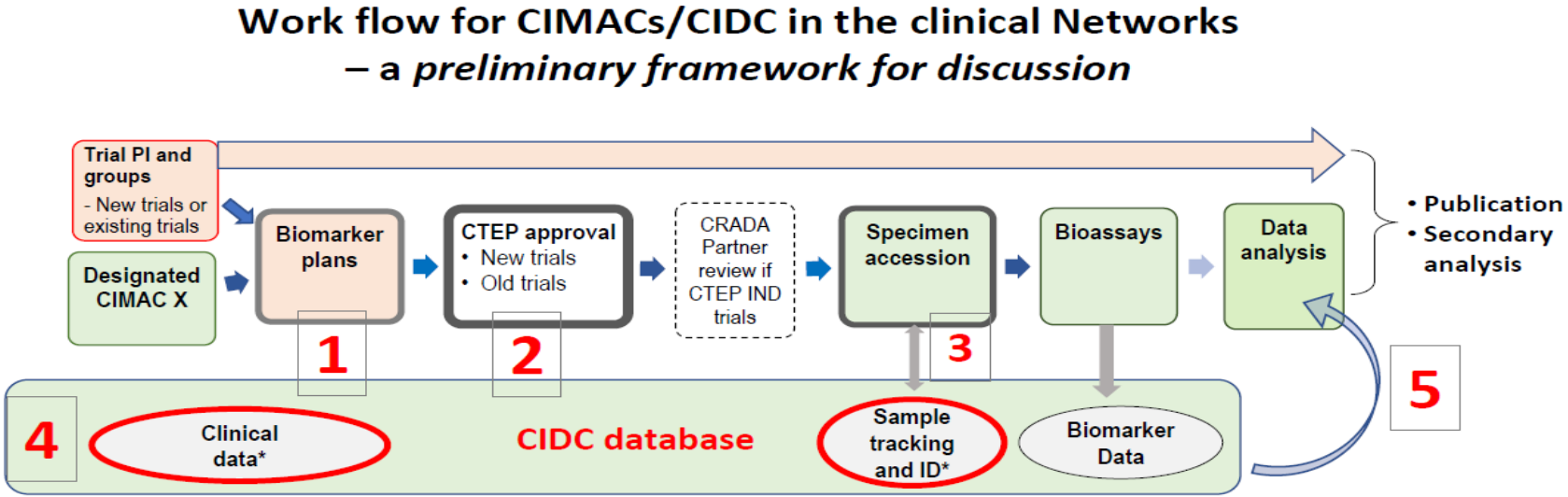
Relevance to CIMAC/CIDC Work Flow?

At least 3 additional levels of review!



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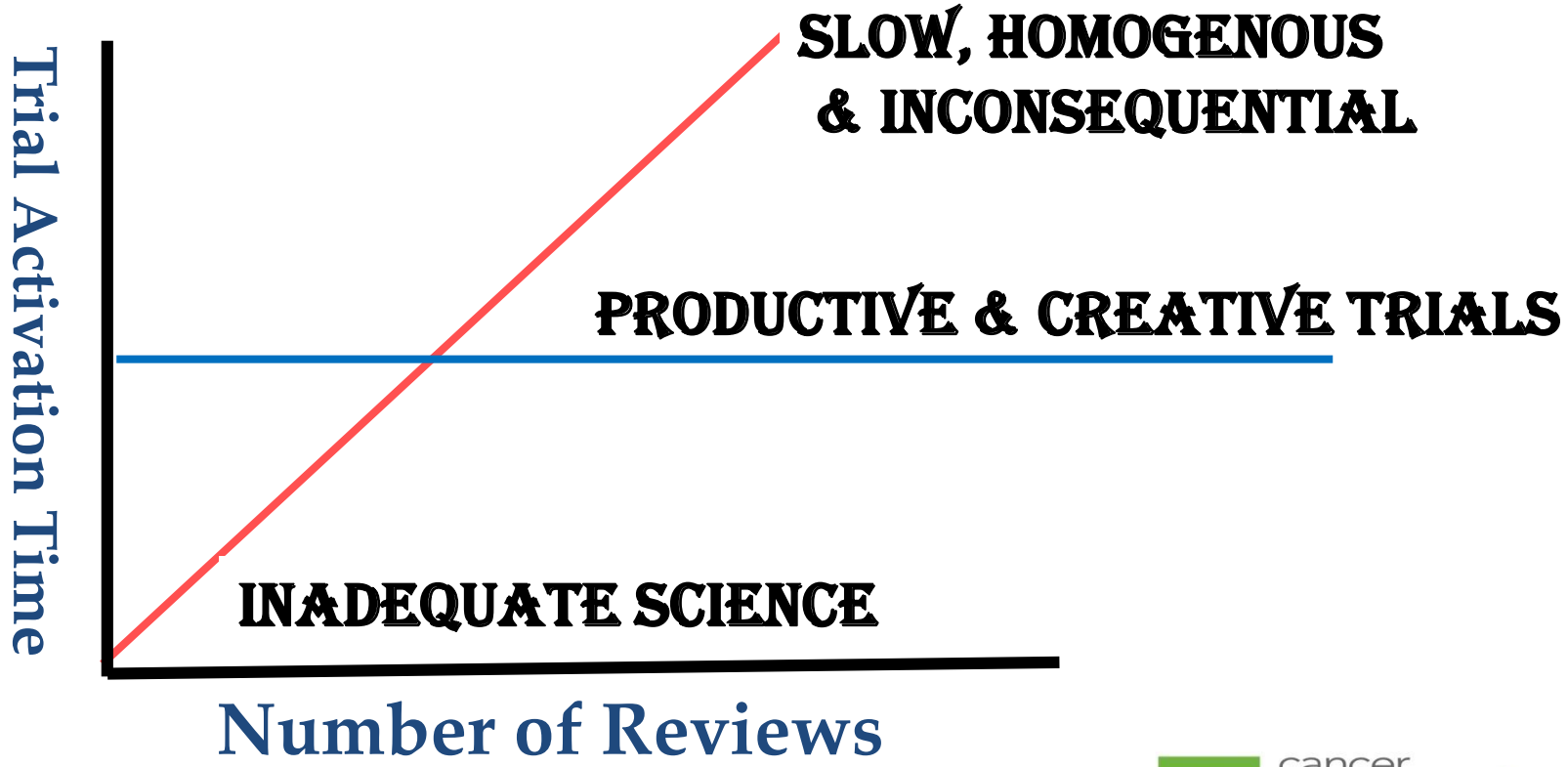
How many reviews are helpful?



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(2) Identify Actionable Causes of anti-PD1/PD-L1 Failure:

Available Agents

- **(1) Release of cancer antigens**
  - Chemotherapy
  - Radiation
  - Targeted therapy
  - Chemoembolization
  - Oncolytic viruses
  - Cryotherapy
- **(3) Priming & Activation**
  - T cell stimulators
    - Anti-CD137
    - Anti-OX40
    - Anti-CD27
  - Checkpoint inhibitors
    - Anti-PD1/PD-L1
    - Anti-TIM-1
    - Anti-CTLA4
    - Anti-GITR
- **(2) Cancer antigen presentation**
  - DC activator
    - Anti-CD40
  - DC growth factor
    - Flt3L
  - Vaccines
  - Vaccine adjuvants
    - TLR agonists (systemic and intratumor injection)
    - CpG
    - Imiquimod
    - MPL/ GLA
    - Poly ICLC
    - Venti (TLR 8 agonist)
    - BCG
  - IFN and IFN stimulator (IL-12)

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(2) Identify Actionable Causes of anti-PD1/PD-L1 Failure:
Available Agents

(4) Trafficking of T cells to tumors

- Chemokines
  - CCL21
- T cell growth factors
  - IL7
  - IL15
  - IL21

(6) Recognition of cancer cells by T cells

- T cells
  - CARS
  - Recombinant TCR
  - Tumor Infiltrating T cells
- Increase HLA
  - IFN-gamma
  - Demethylation agents

(5) Infiltration of T cells into tumors

- Anti-VEGF
- Hyaluronidase

(7) Killing of cancer cells

- Checkpoint inhibitors
  - Anti-PD1
  - Anti-PD-L1
  - Anti-Vista
  - Anti-LAG3
  - Anti-TIM3
- IDO inhibitor
- Cytokine neutralizers
  - Anti-IL10
  - Anti-TGF-beta
  - Anti-CSFR1

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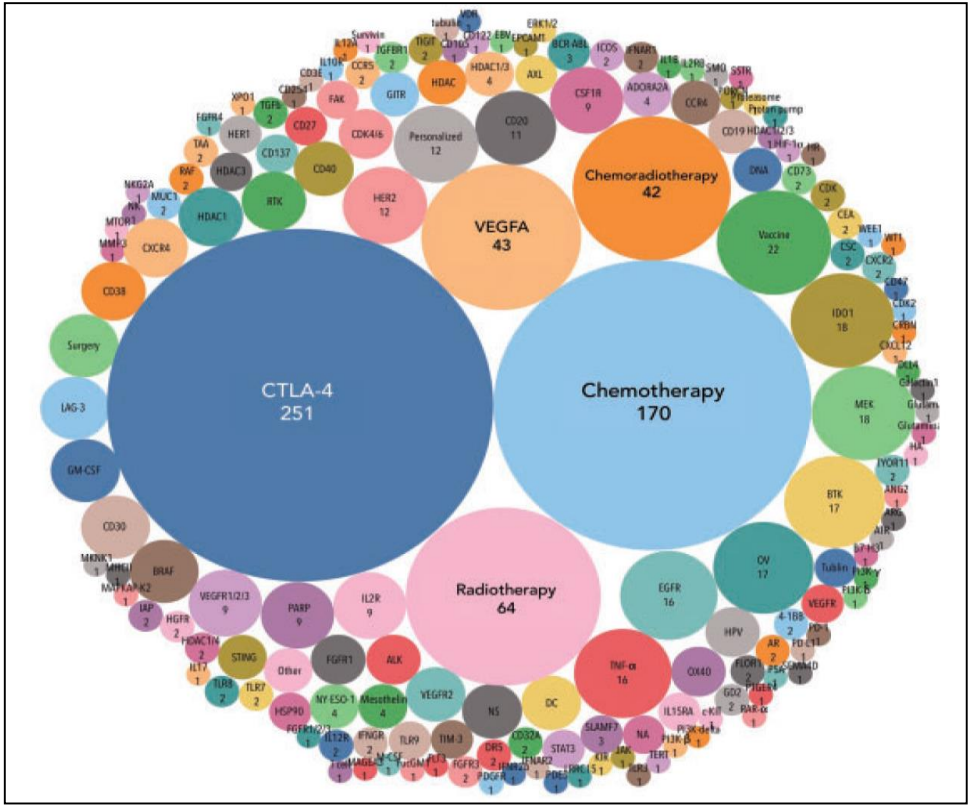
Landscape analysis available agents for anti-PD-1/L1 combination trials. Size of the bubble correlates to the number of trials



Number of combo trials	
Anti-CTLA-4	251
Chemotherapy	170
Radiation	64
Anti-VEGF	43
Chemoradiotx	42
Other	535
TOTAL	1,105

[Tang, Shalabi, Hubbard-Lucey Annals of Oncology 0: 1–8, 2017]

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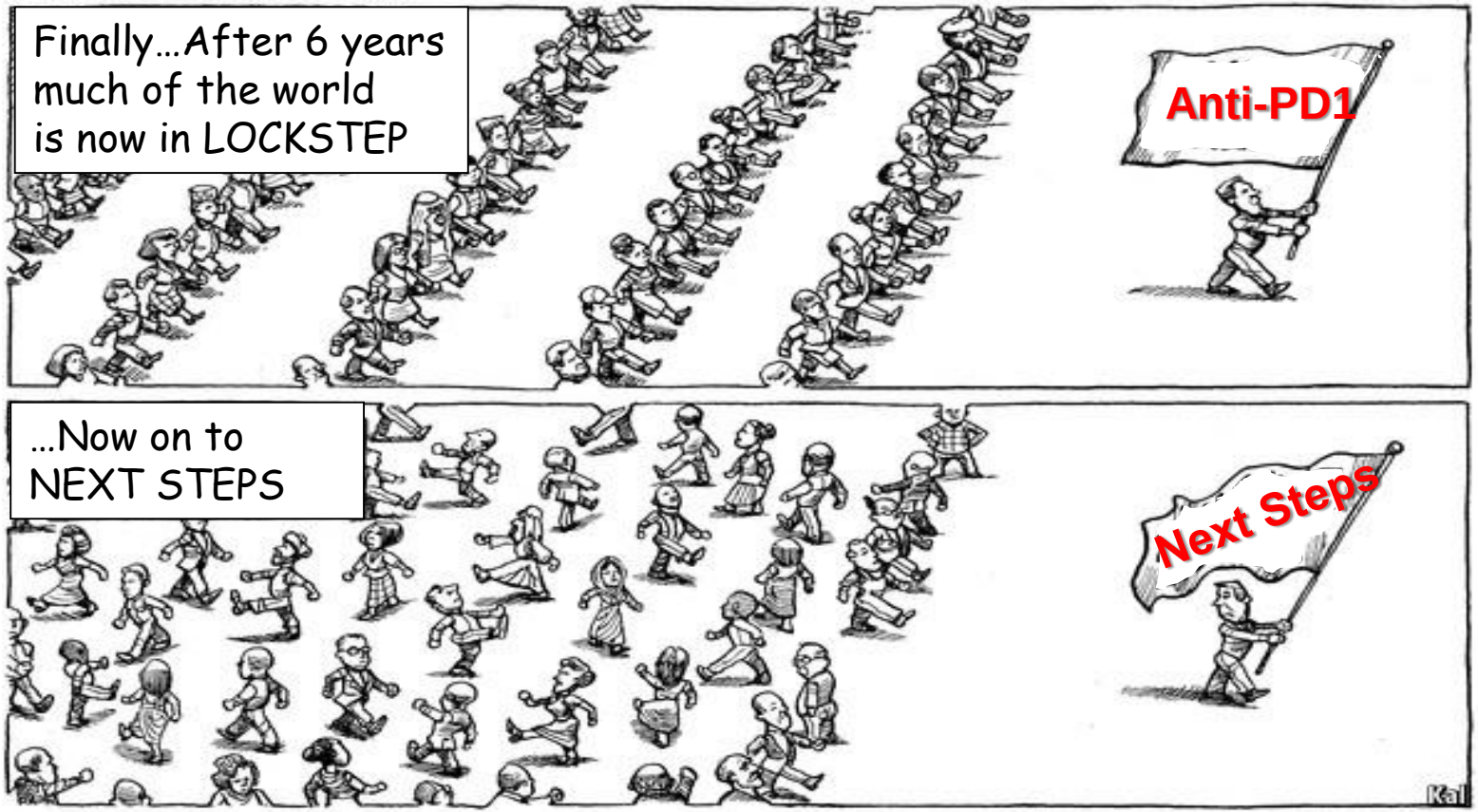
With >1,100 Combination Trials, what are the next steps ?



[With apologies to Climate Change & the Economist]

How to Prioritize Immunotherapy Regimens?

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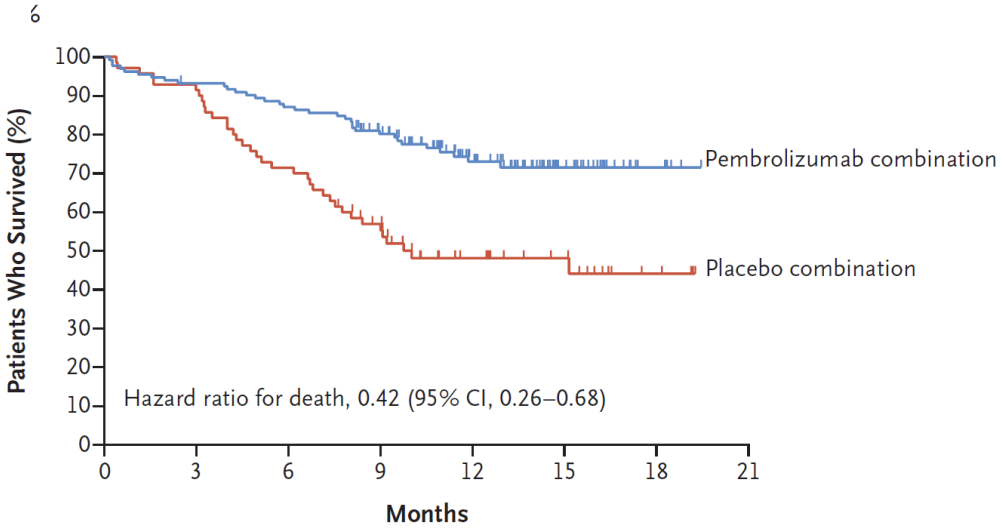
Throw it against the wall to see what sticks?

Huge Opportunity for Academic Biomarker Trials to Select "Rescue" Therapies

Pembrolizumab **plus** Chemotherapy (premetrexed + platinum) in Metastatic Non–Small-Cell Lung Cancer

PD-L1 ≥50%



No. at Risk								
Pembrolizumab combination	132	122	114	96	56	25	6	0
Placebo combination	70	64	50	35	19	13	4	0

[Gandhi et al NEJM May 8, 2018]

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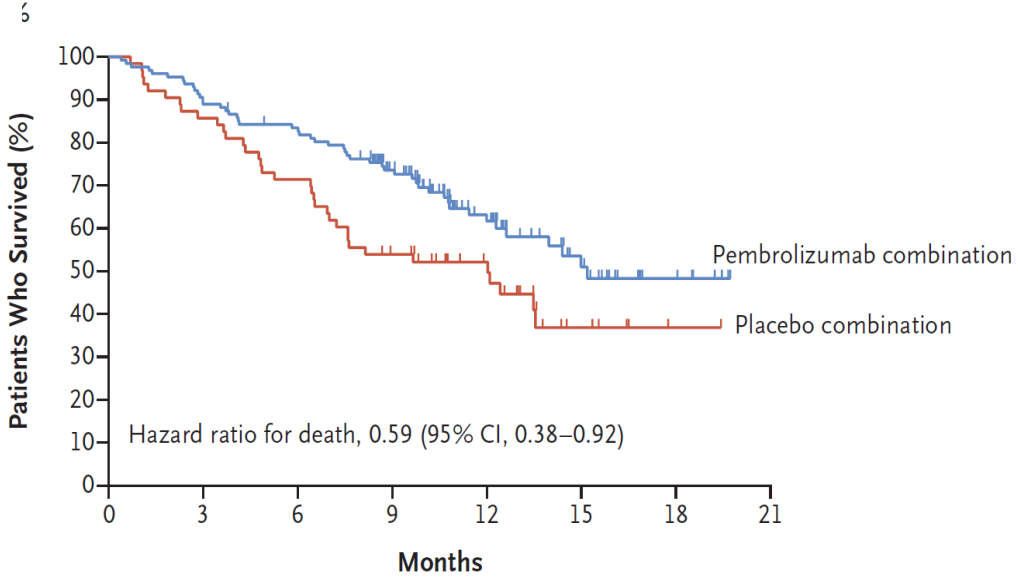
Pembrolizumab **plus** Chemotherapy (premetrexed + platinum) in Metastatic Non–Small-Cell Lung Cancer

PD-L1 <1%



No. at Risk								
Pembrolizumab combination	127	113	104	79	42	20	6	0
Placebo combination	63	54	45	32	21	6	1	0

[Gandhi et al NEJM May 8, 2018]

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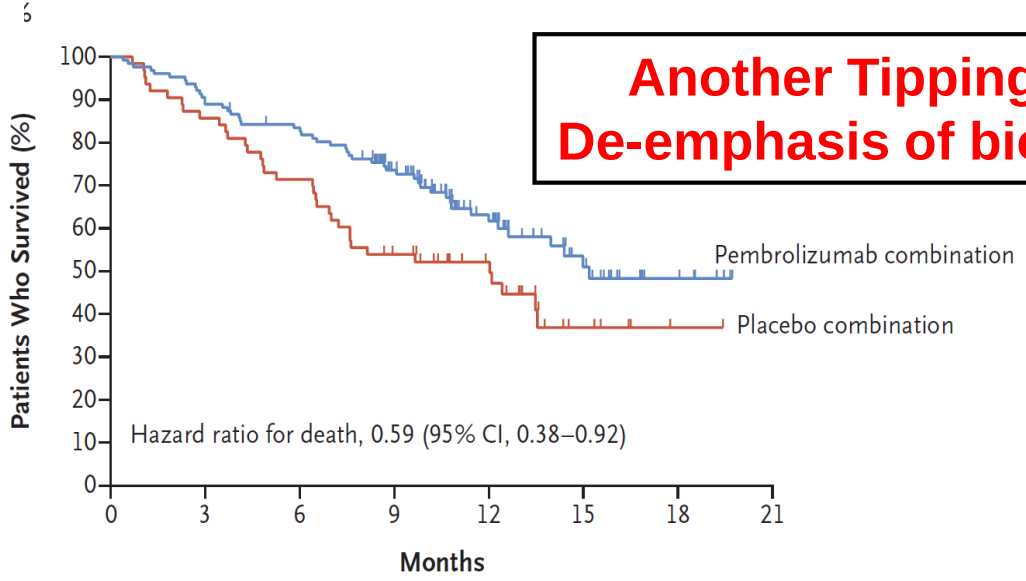
Pembrolizumab **plus** Chemotherapy (premetrexed + platinum) in Metastatic Non–Small-Cell Lung Cancer

PD-L1 <1%



No. at Risk								
Pembrolizumab combination	127	113	104	79	42	20	6	0
Placebo combination	63	54	45	32	21	6	1	0

Another Tipping Point?
De-emphasis of biomarkers?

[Gandhi et al NEJM May 8, 2018]

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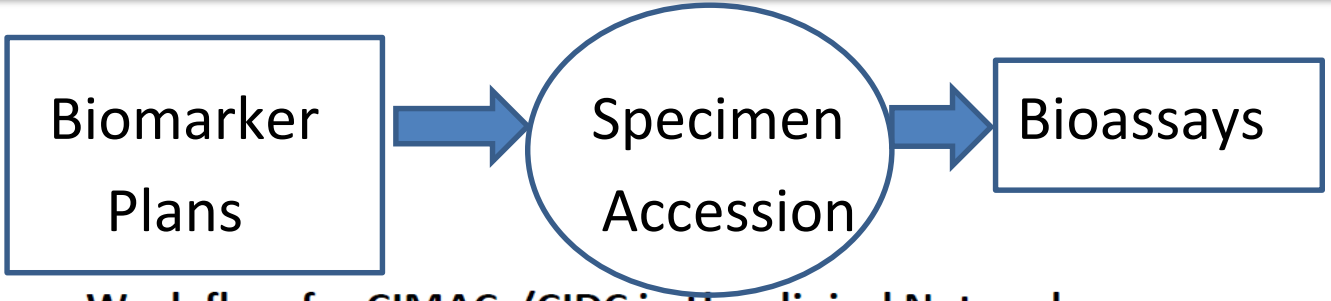
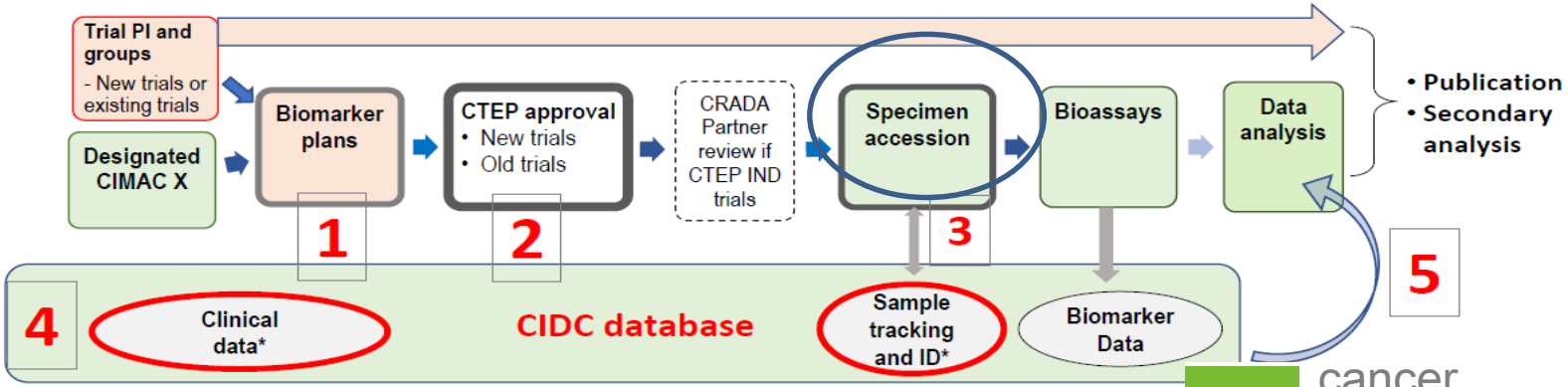
(3) Provide high quality, annotated biospecimens to CIMACs and other high quality laboratories



Work flow for CIMACs/CIDC in the clinical Networks
– a preliminary framework for discussion



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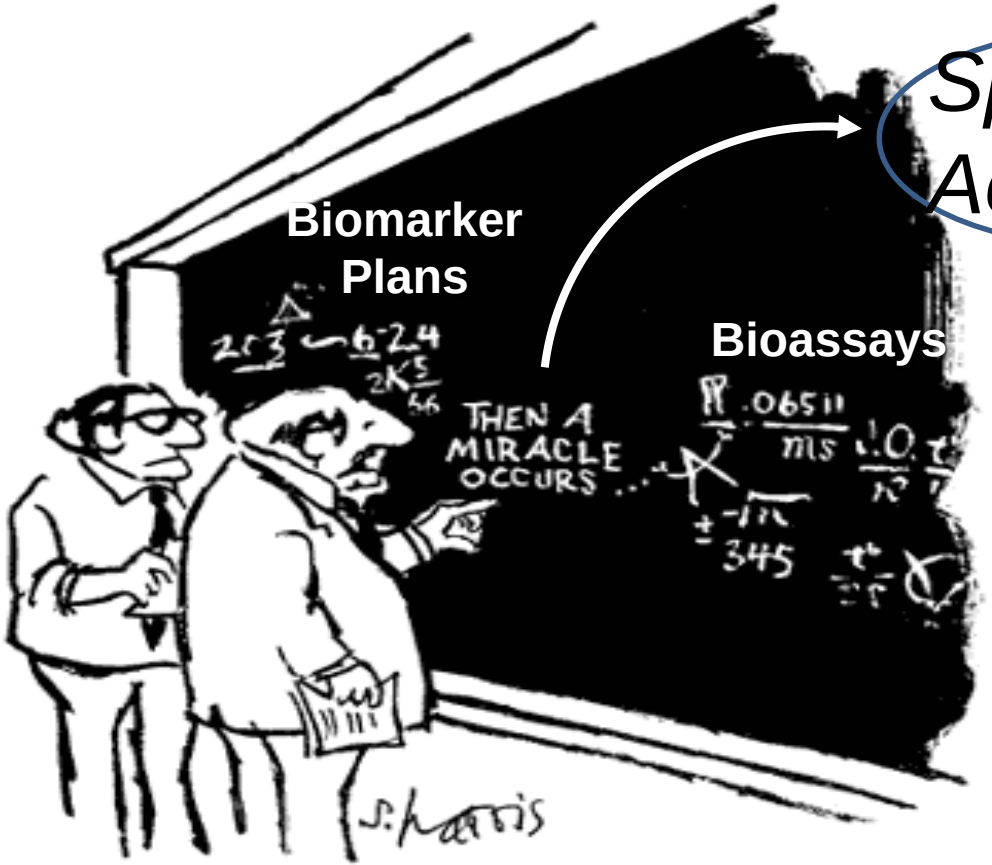

"I think you should be more explicit here in step two."

With Apologies to Sydney Harris

UWIML

Nora Disis

Chihiro Morishima

CITN Central Lab

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CITN Central Lab

Without quality specimens…there is no quality science!

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