PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

The State-of-the-Art of PD-1/PD-L1 Development , Clinical Use & Outcomes

NATIONAL CANCER POLICY FORUM

Ramy Ibrahim, MD
Chief Medical Officer

Disclosure

- Scientific Advisory Board:

Arcus

Harpoon

ImaginAb

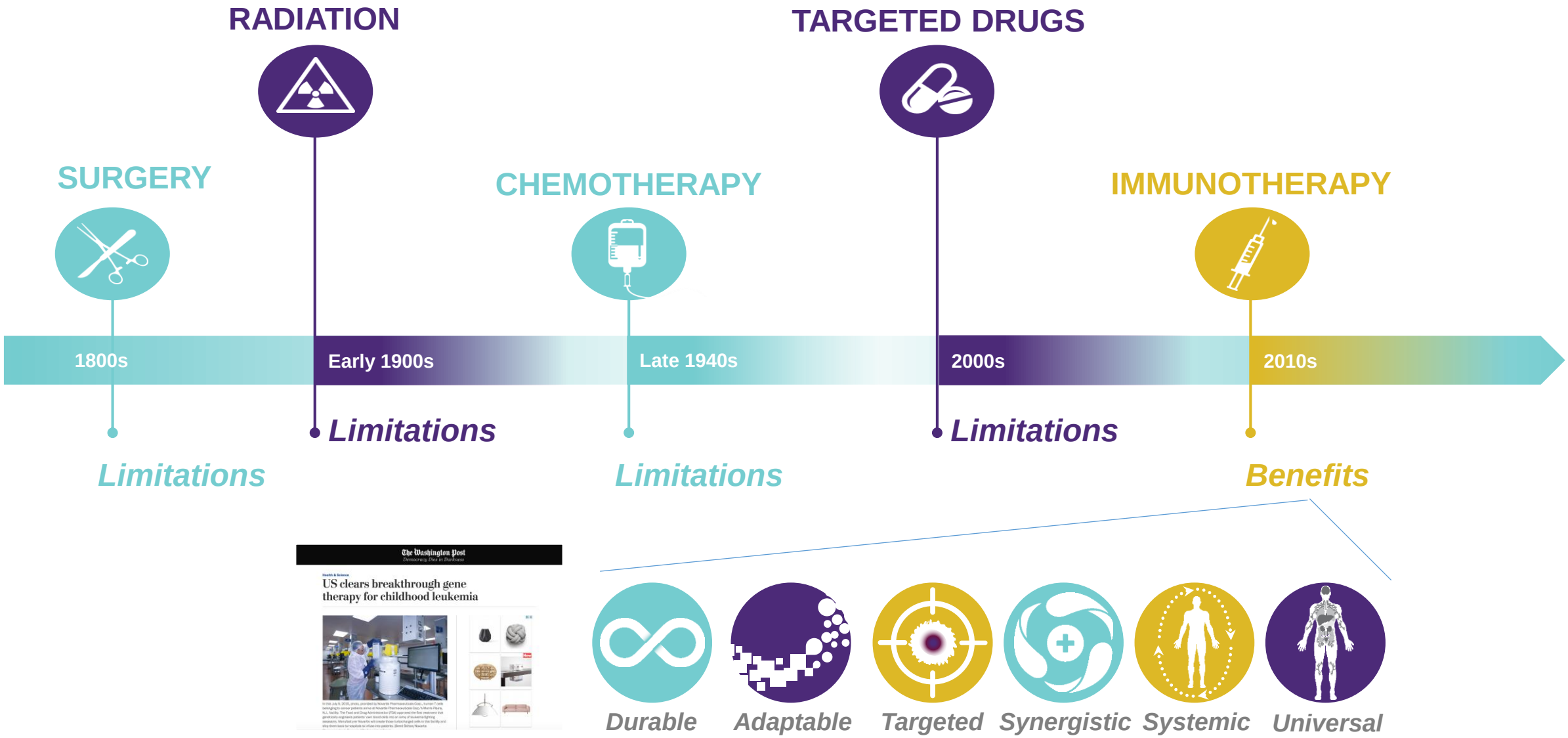
Immunovaccine

- Honoraria:

PER

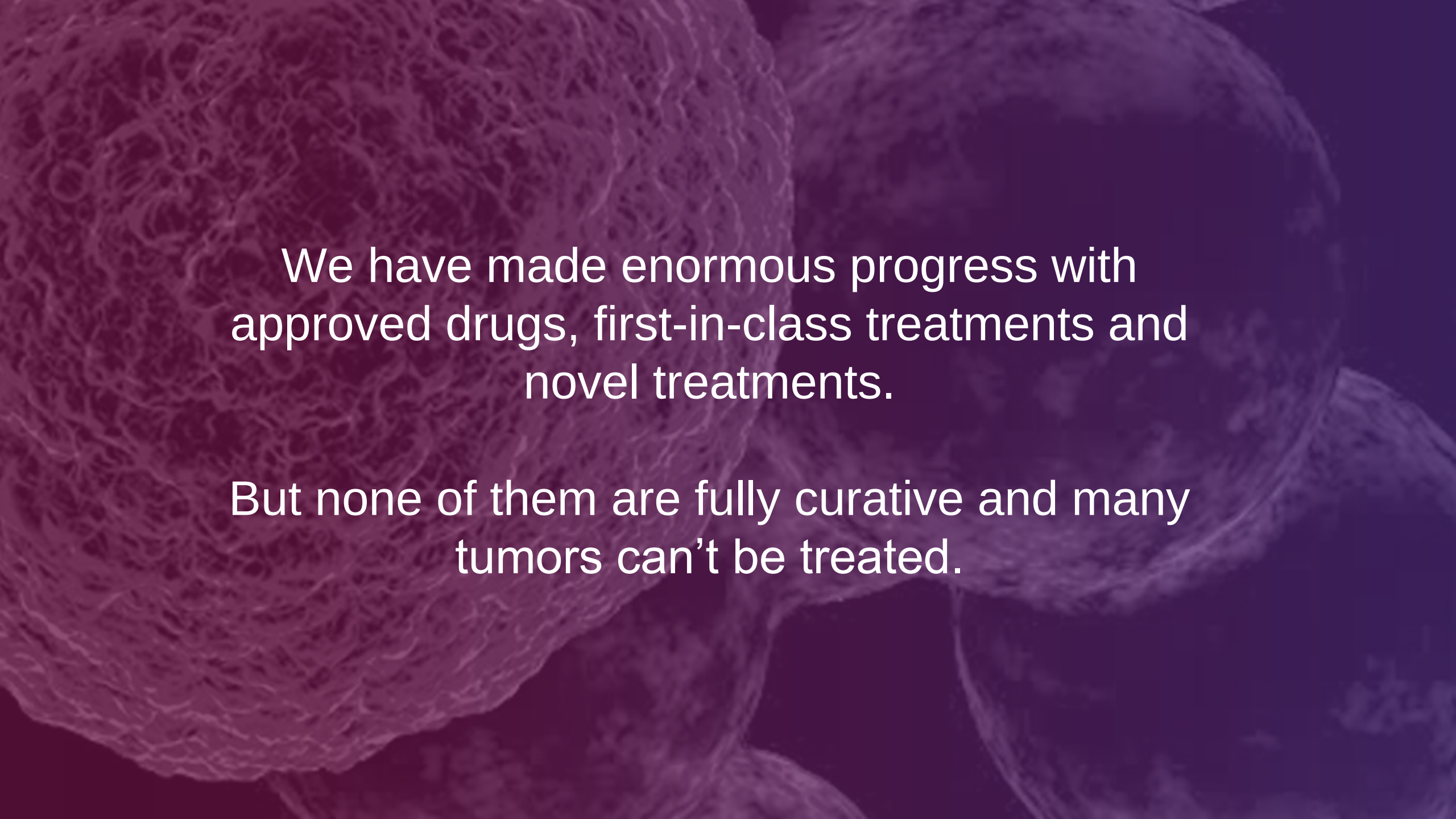
GLG

Cancer Immunotherapy has Arrived



The Washington Post
Democracy Dies in Darkness

US clears breakthrough gene therapy for childhood leukemia


We have made enormous progress with approved drugs, first-in-class treatments and novel treatments.
But none of them are fully curative and many tumors can’t be treated.

So what have we accomplished so far?

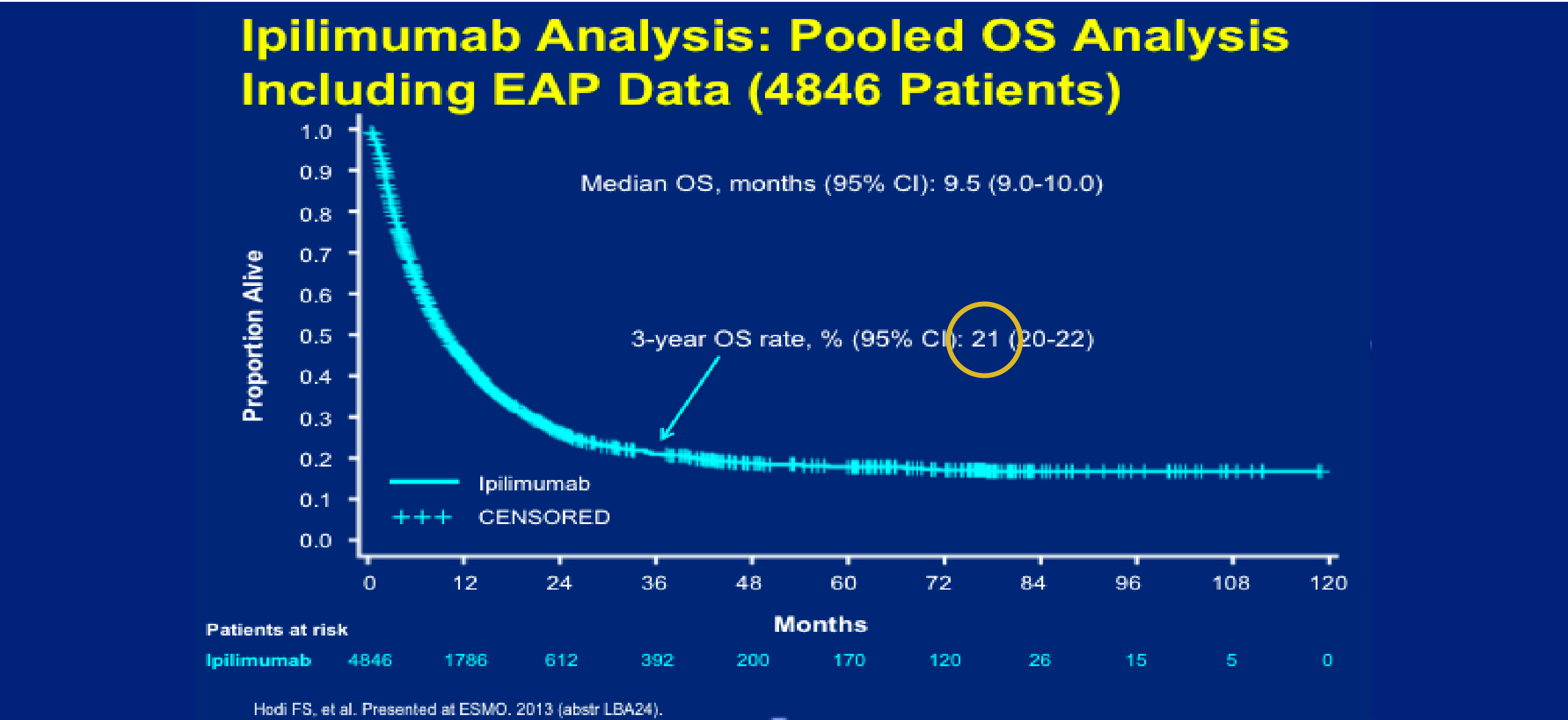
- ✓ Single agent CTLA4:
  - ✓ Long term OS benefit in a small subset of patients
  - ✓ Durable effect
  - ✓ Unique kinetics of response
  - ✓ irAEs that are mostly manageable and reversible with the use of toxicity management guidelines
  - ✓ No definitive biomarker
- ✓ Single agent PD(L)1:
  - ✓ Approvals based on survival benefit across multiple indications
  - ✓ Well established toxicity management guidelines
  - ✓ Benefit is no longer limited to “immunogenic” tumor types
  - ✓ Molecular based approvals rather than histology: MSI-H tissue agnostic
  - ✓ PDL1 expression can inform patient selection in certain settings
  - ✓ Unlikely to be the only biomarker. Need a composite biomarker
  - ✓ Synergy when combined with standard of care in some settings

So what have we accomplished so far?

- ✓ Combinations:
  - ✓ When combined with right chemotherapy regimen, meaningful clinical benefit was reported (NSCLC)
  - ✓ Sequential therapy (Durvalumab Pacific study)
  - ✓ CTLA4+PD1 showed higher rate of adverse events in melanoma and risk:benefit is unclear when compared to PD1 monotherapy
  - ✓ TMB
  - ✓ Many combinations have been investigated in the PD1 resistant population and some results are disappointing
- ✓ CAR-T:
  - ✓ Impressive data in hematological malignancies (CD19)
  - ✓ Not ready for prime time in solid tumors
  - ✓ New enabling technologies are under development

Ten Years Follow Up: Long-Term Benefit

Only 1 in every 5 treated metastatic melanoma patients

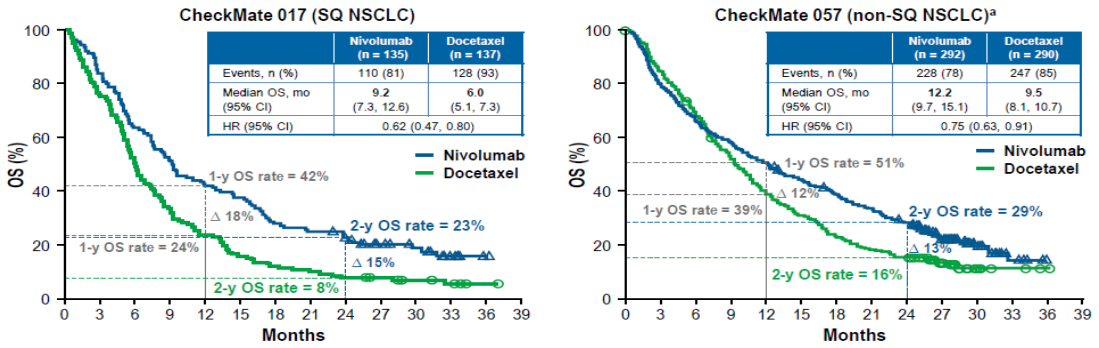


Hodi FS, et al. Presented at ESMO. 2013 (abstr LBA24).

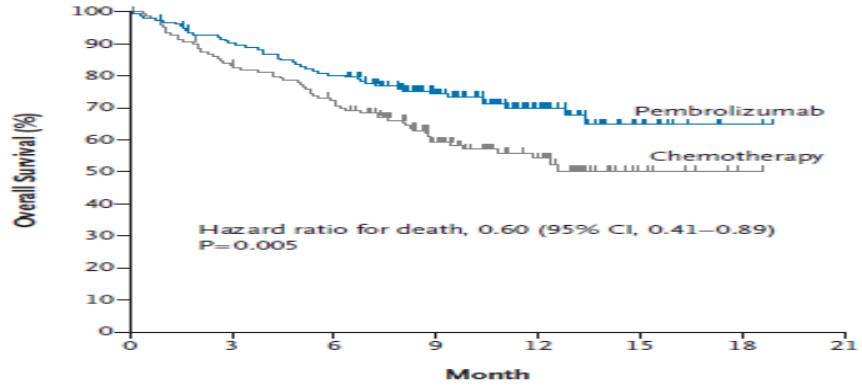
PD1 demonstrates superiority over chemotherapy (Melanoma and NSCLC)

Efforts to replace chemotherapy with many studies conducted with IO **vs** chemotherapy.

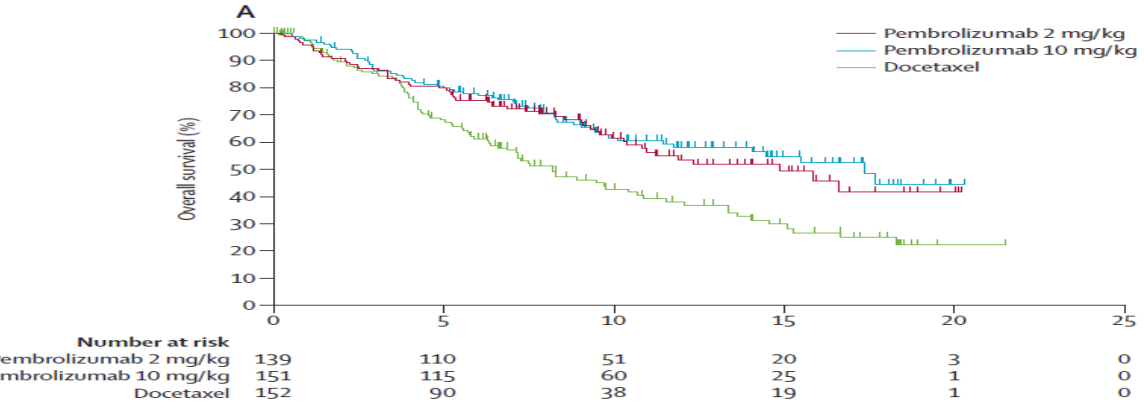
Nivolumab FDA approved 2015



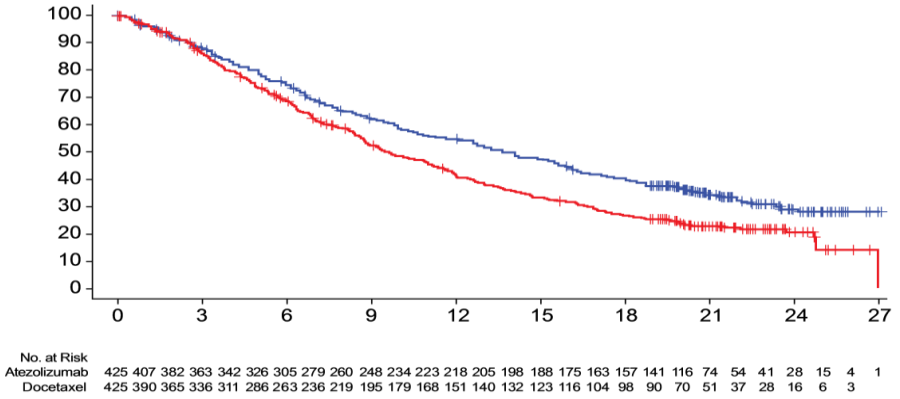
1st line pembro FDA approved 2016



Pembrolizumab FDA approved 2015



Atezolizumab FDA approved 2016

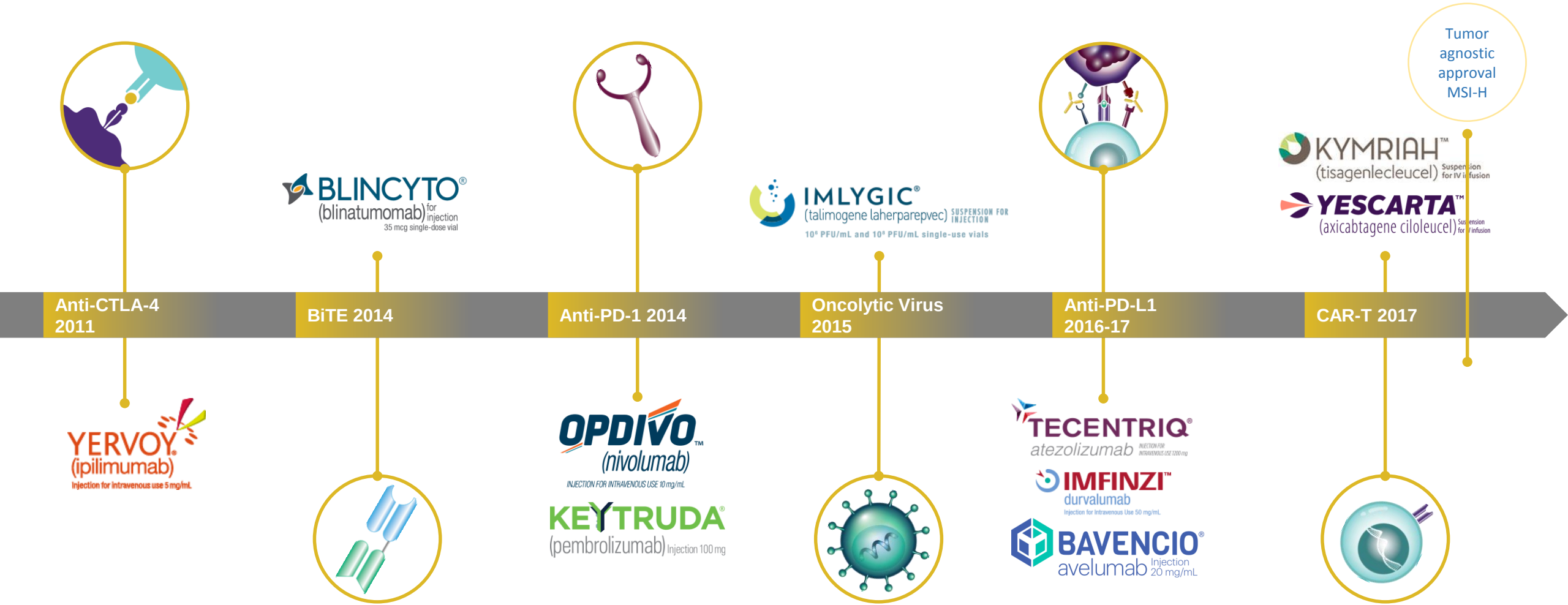


Borghaei and Brahmer, NEJM 2015
Herbst, Lancet 2016

Reck, NEJM 2016
Barlesi, ESMO 2016

Immunotherapy FDA Approvals

10 FDA immunotherapy approval milestones in 6 years



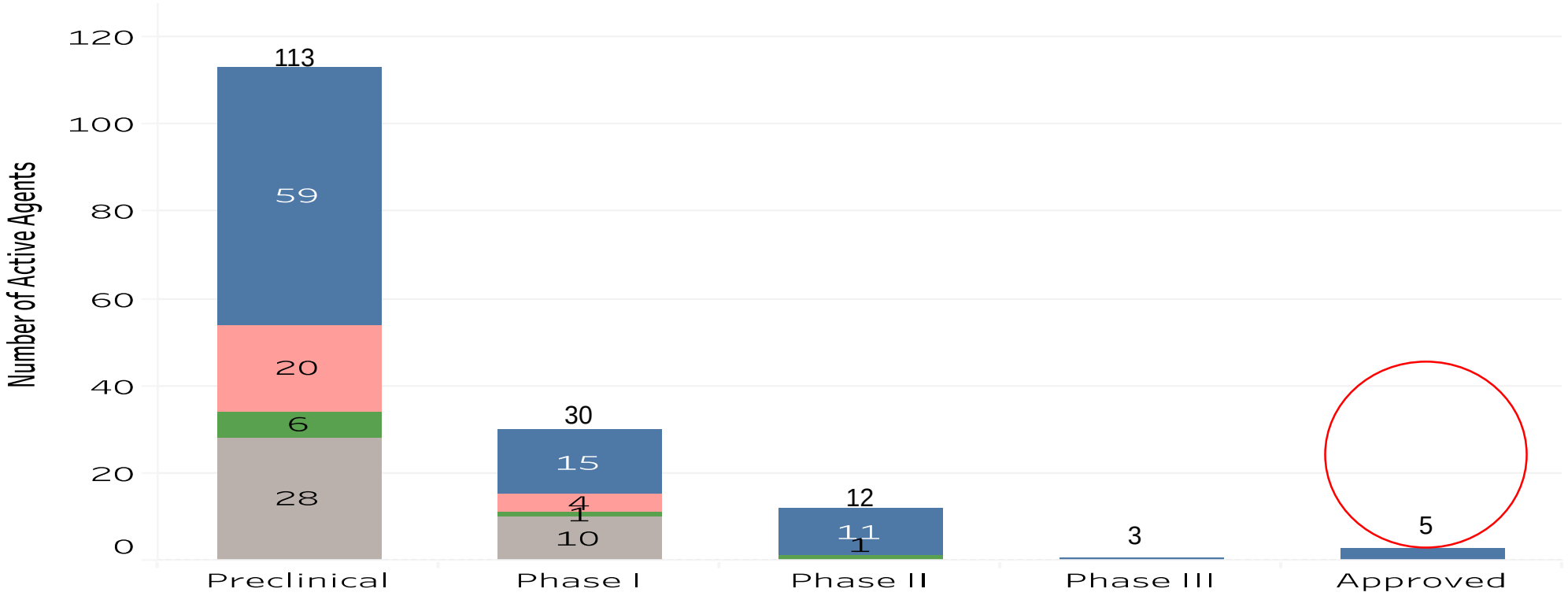
Cancer Immunotherapy Development and Approvals

1890	First vaccine developed			
1970	Discovery of dendritic cell (Steinman)	Tumor-specific monoclonal Abs	Immune component to spontaneous regressions in melanoma	
1980	1985 Adoptive T-cell immunotherapy	1986 IFN-α as adjuvant therapy for melanoma[2]		
1990	BCG approved for bladder cancer		Discovery of checkpoint inhibitors	1998 IL-2 approved for RCC and melanoma (US)
2010	First immunotherapy approved for prostate cancer (sipuleucel-T)	First checkpoint inhibitor (ipilimumab) approved for advanced melanoma		
2011				
2014	Pembrolizumab and nivolumab approved for advanced melanoma			
2015	Nivolumab approved for RCC	Nivolumab + ipilimumab approved for MM	Nivolumab approved for NSCLC	Pembrolizumab approved for PD-L1+ NSCLC
2016	Atezolizumab approved for urothelial carcinoma and NSCLC 2nd line	Nivolumab approved for cHL and SCCHN	Pembro SCCHN	Pembro, first line in PDL1 pos NSCLC
2017	Avelumab in Merkel cell carcinoma	Pembrolizumab for cHL and MSI H	Nivolumab approved Urethelial carcinoma and adjuvant melanoma	Durvalumab approved Urethelial carcinoma
2018	Keytruda primary mediastinal large B-cell lymphoma (PMBCL), Cervical and Gastric cancer	Durvalumab in stageIII NSCLC	Nivolumab, MSI-H, RCC,	

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.html

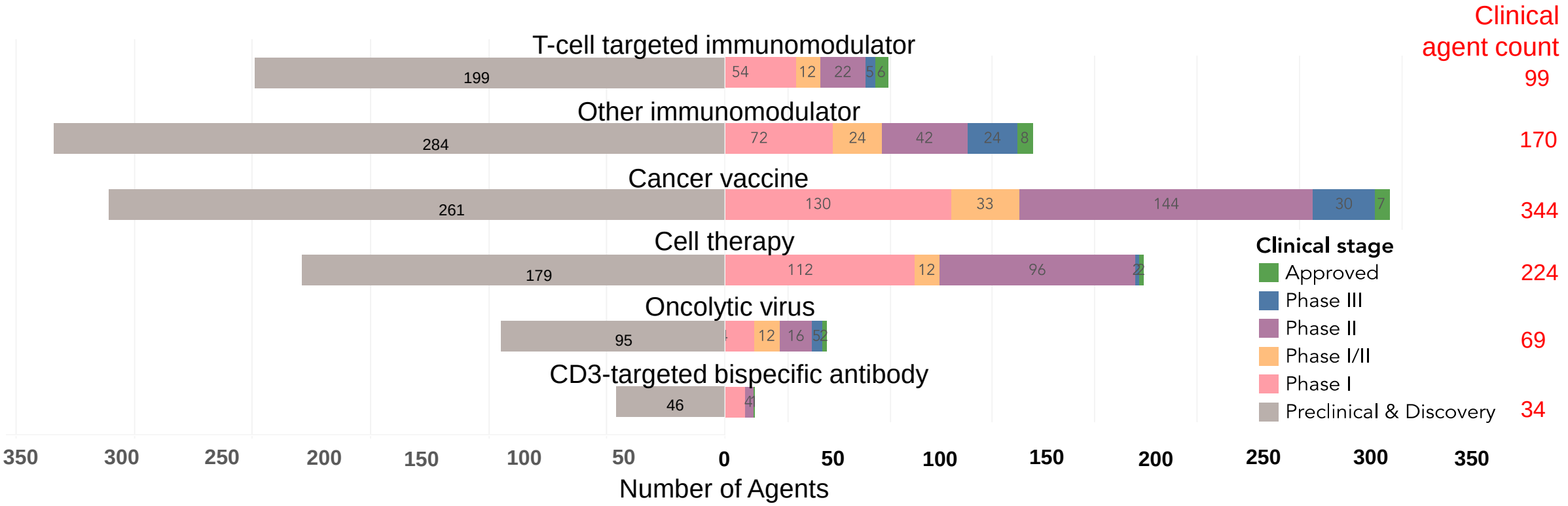
163 ACTIVE ANTI-PD-1/L1 AGENTS IN THE GLOBAL PIPELINE

By Sep 2017, 163 active agents with **50** in clinical phase



Tang, Shalabi, Lucey-Hubbard; *Ann Oncol;* 2017

Not just PD1 phenomenon…….
2,004 IO agents in development



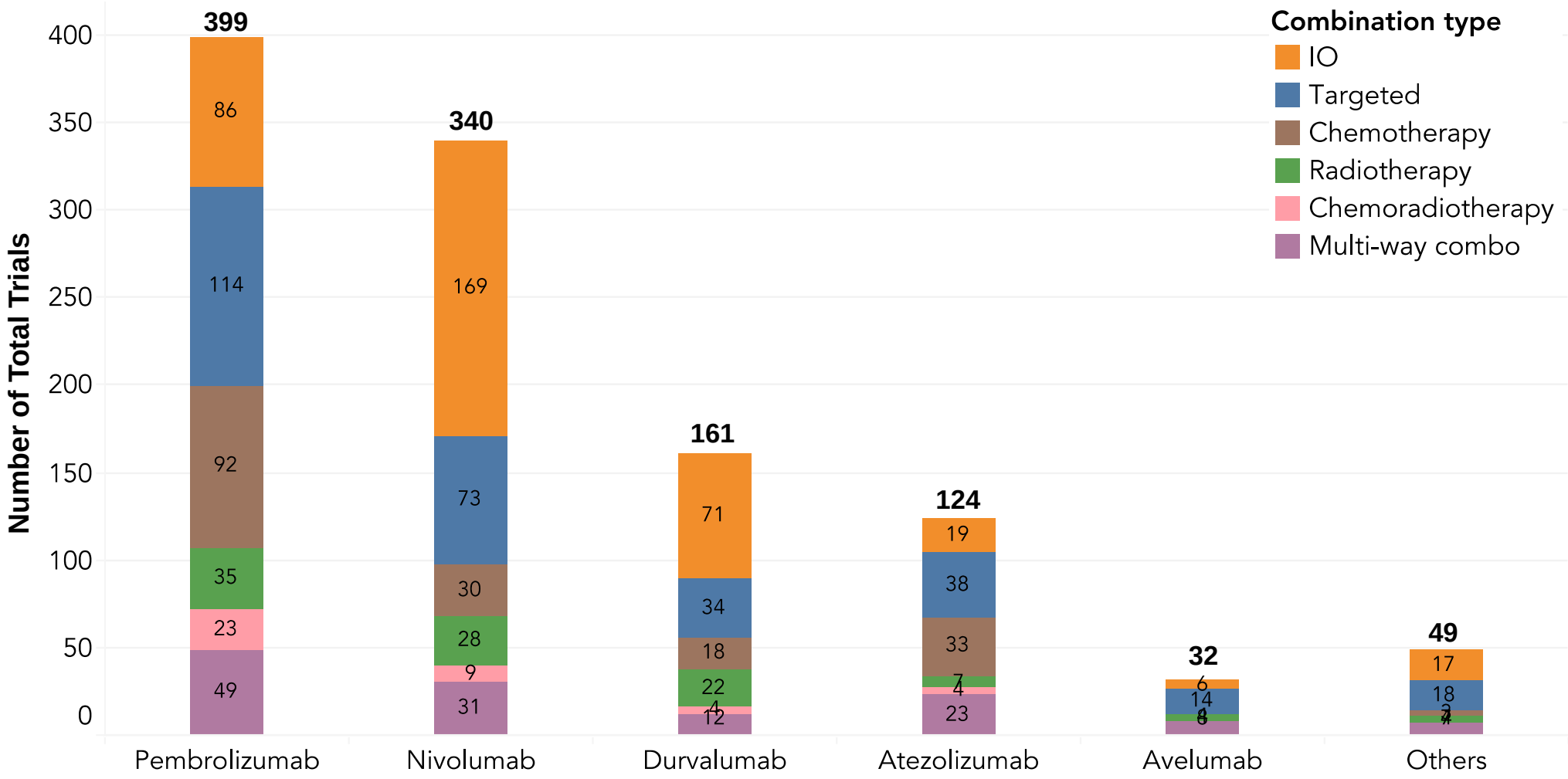
940 *AGENTS ARE IN CLINICAL STAGES, AND 1,064 IN PRECLINICAL OR DISCOVERY PHASES*

How to build on the monotherapy successes ?

COMBINATION STUDIES

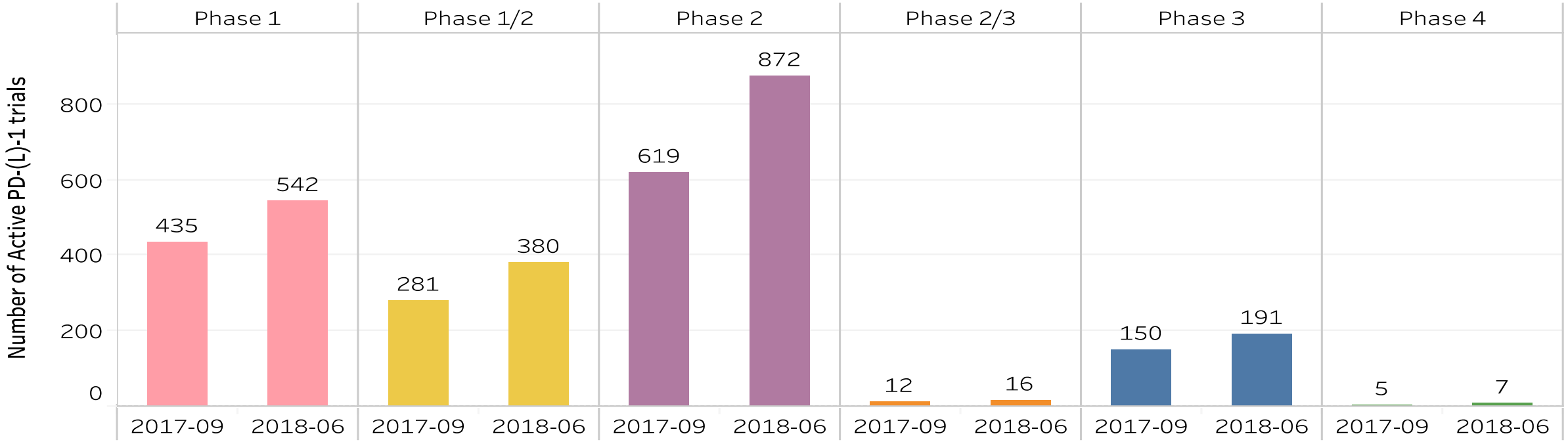
THE LANDSCAPE OF COMBO TRIAL TYPE

COMBINATION WITH OTHER IO AGENTS IS THE MOST COMMON APPROACH



Tang, J, Shalabi A, Hubbard-Lucey VM
Ann Oncol. December 07, 2017.

506 more new PDx trials since Sep 2017



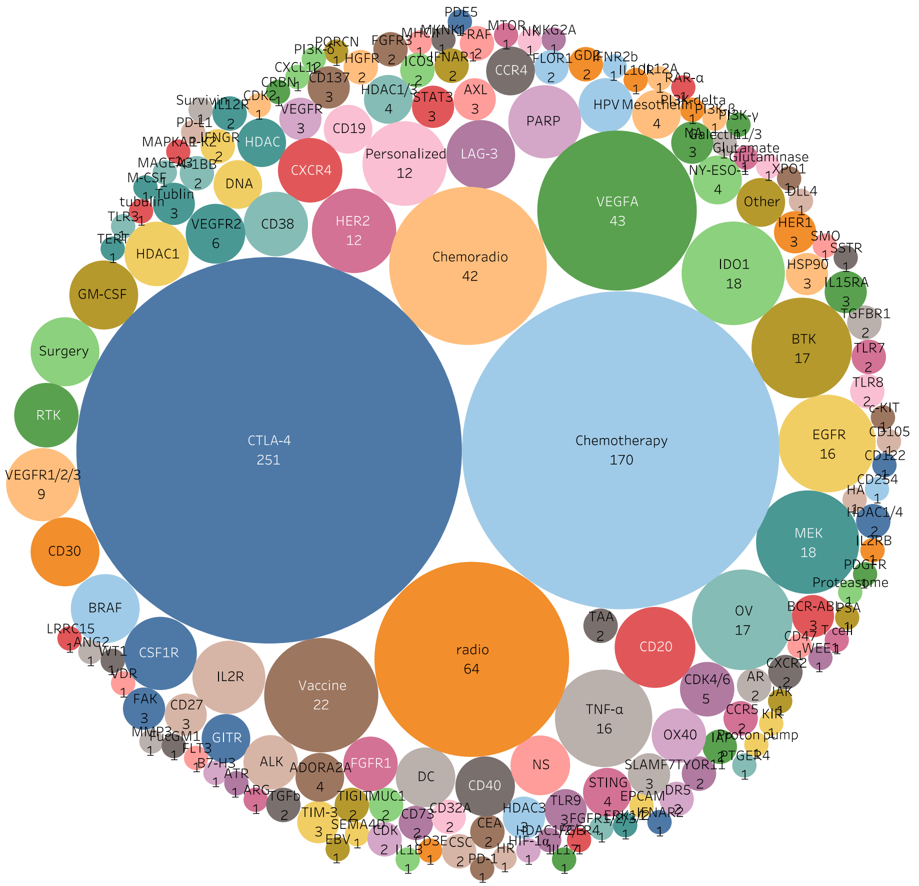
10. Phases (group)

- Phase 1
- Phase 1/2
- Phase 2
- Phase 2/3
- Phase 3
- Phase 4

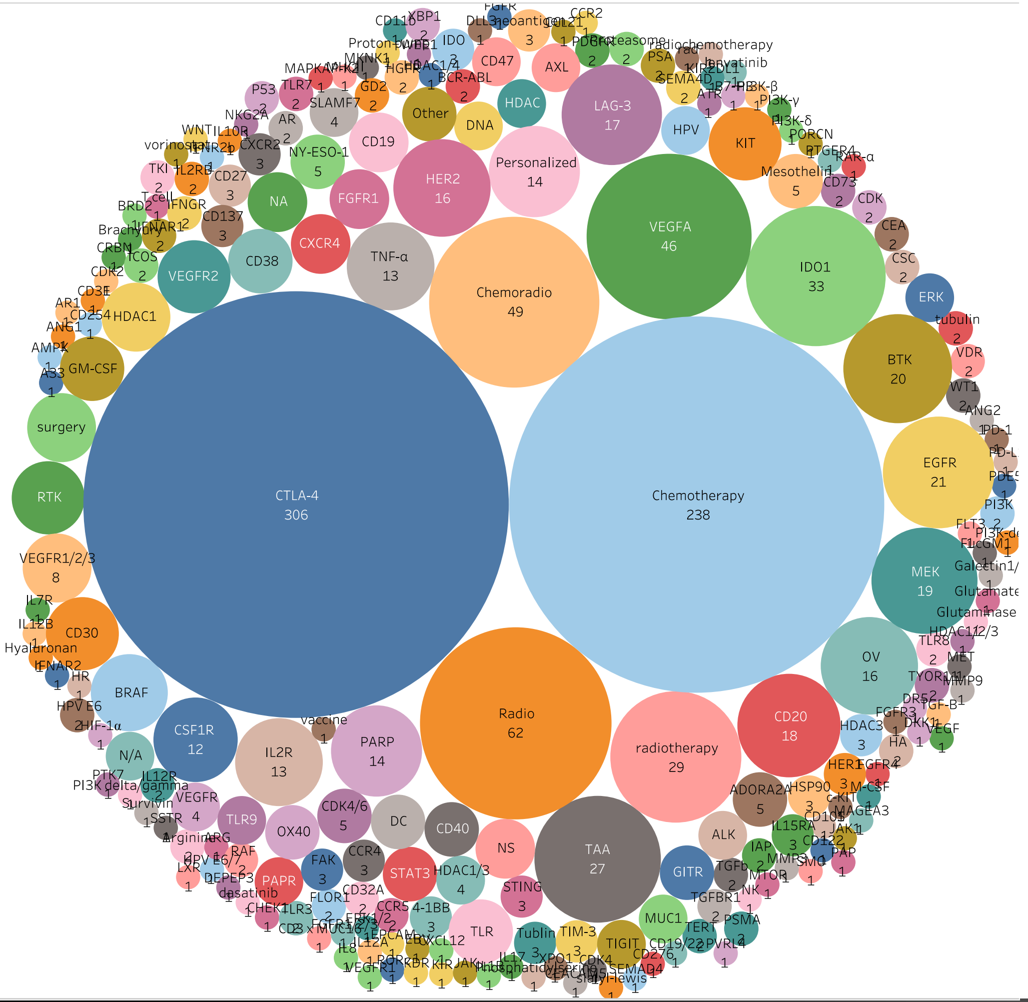
- **1502** active anti-PDx trials as of Sep 2017.
- **2008** active anti-PDx trials as of Jun 2017, 508 new trials.

334 new PDx Combo trials have started in 9 months

1105 combo trials as of Sep 2017

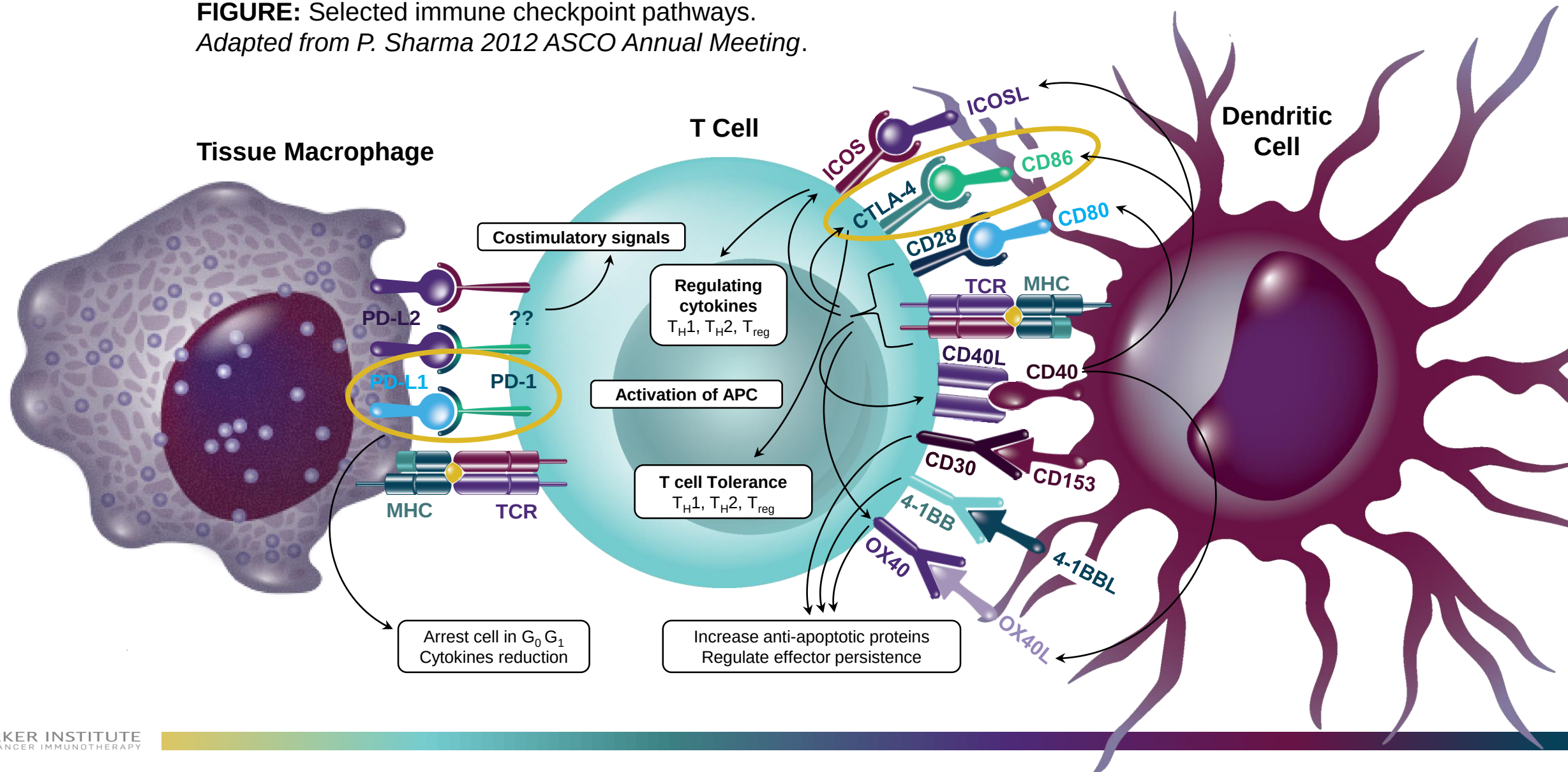


1449 combo trials as of Jun 2018



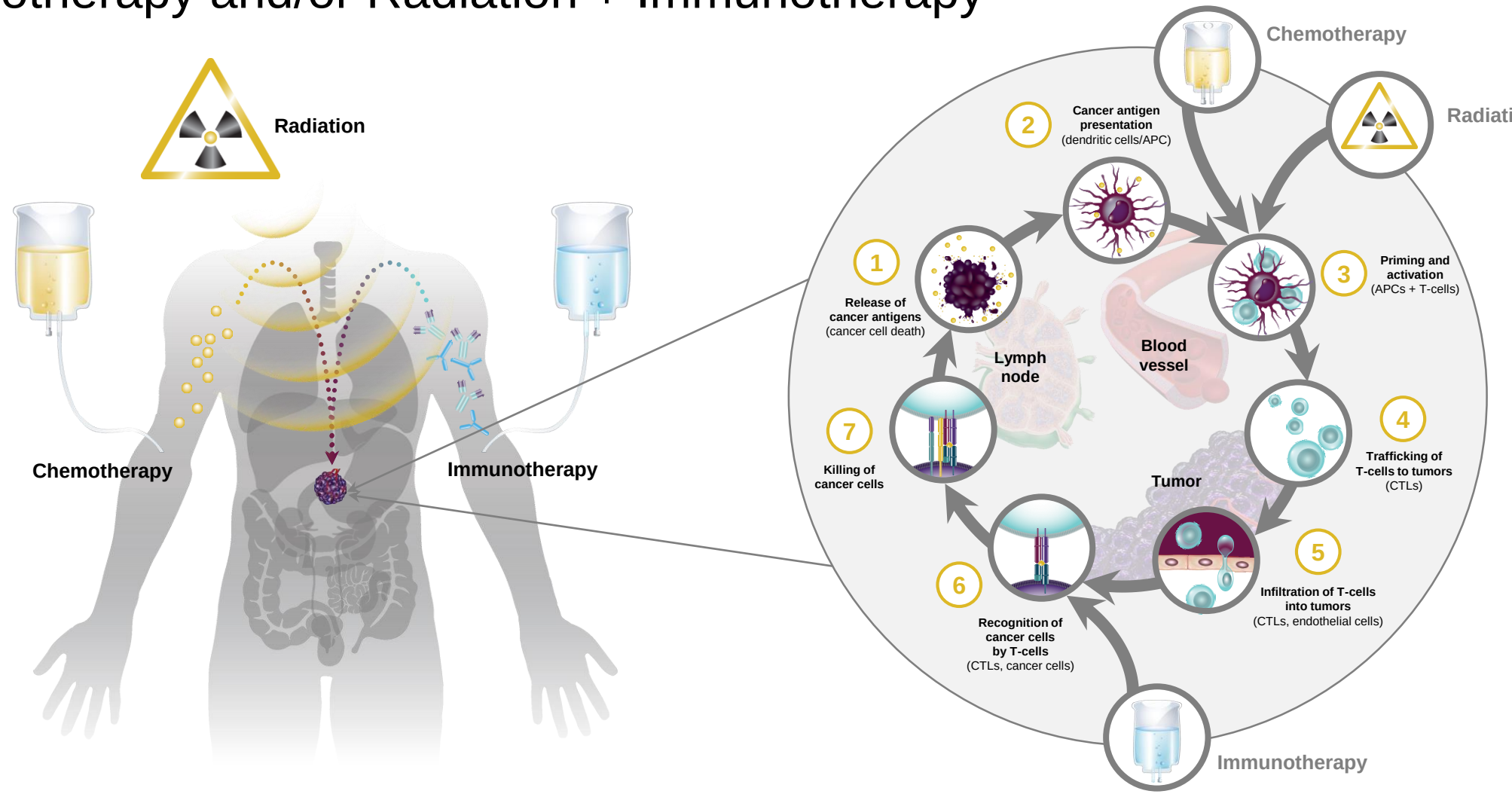
Synergy: 1+1=3 if we target different IO pathways?

FIGURE: Selected immune checkpoint pathways.
Adapted from P. Sharma 2012 ASCO Annual Meeting.



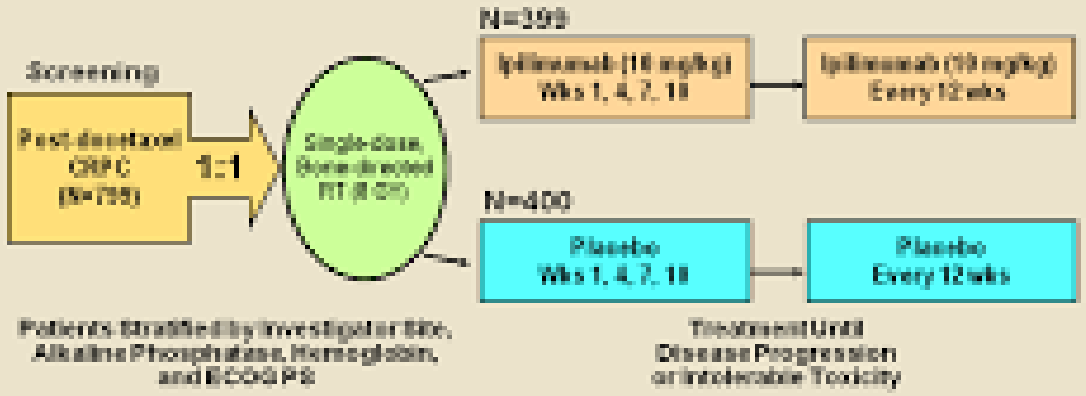
Exploring Combinations for Cancer Treatments

Chemotherapy and/or Radiation + Immunotherapy



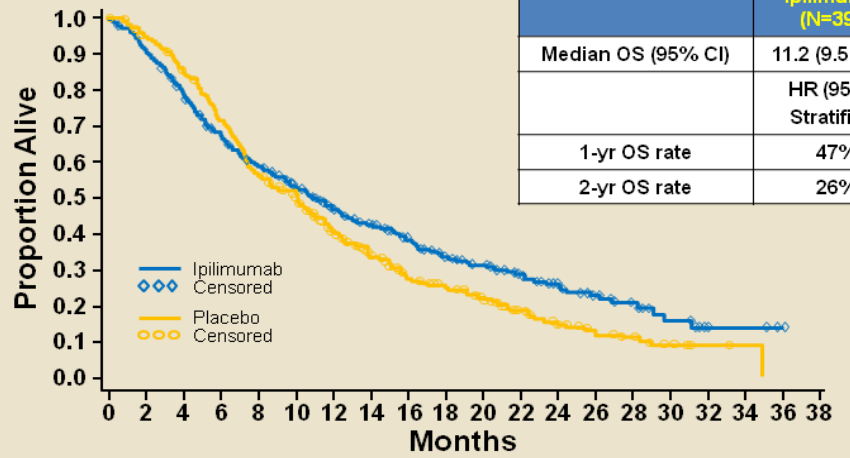
Sound scientific rational but not the desired clinical outcome: ipilimumab + radiation in castrate resistant prostate cancer

CA184-043: Ipilimumab in Post Docetaxel mCRPC



- Primary endpoint: overall survival (OS)
- Secondary endpoints: progression-free survival, safety
- Exploratory endpoint: PSA response rate

Overall Survival: ITT Population



	Ipilimumab (N=399)	Placebo (N=400)
Median OS (95% CI)	11.2 (9.5-12.7)	10.0 (8.3-11.0)
	HR (95% CI): 0.85 (0.72-1.00) Stratified log-rank P=0.0530	
1-yr OS rate	47%	40%
2-yr OS rate	26%	15%

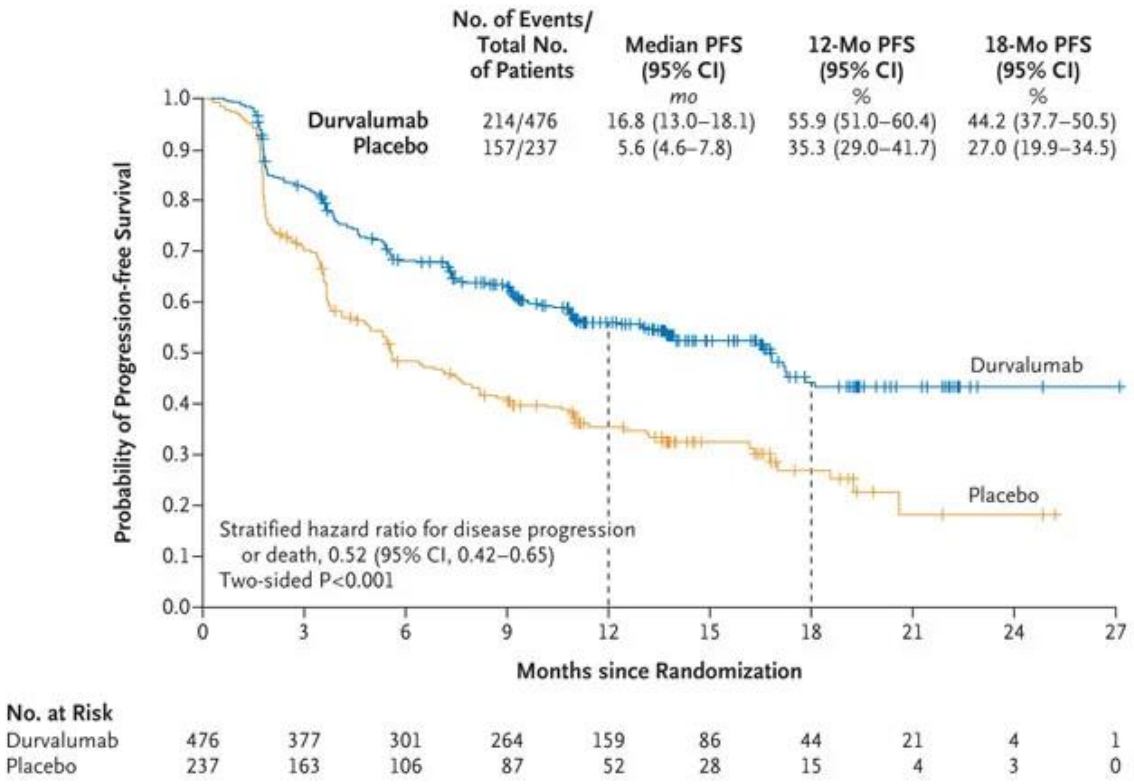
Patients at Risk

Ipilimumab	399	362	306	260	228	195	155	131	106	85	69	52	37	24	15	9	4	3	1	0
Placebo	400	376	332	281	222	184	138	106	77	65	47	36	26	16	12	6	2	1	0	0

ITT, intention-to-treat

PD(L)1 can be combined or sequenced with Standard of care

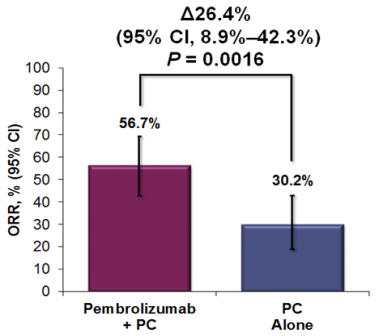
Pacific study:
unresectable stage III NSCLC durvalumab following chemo-rad

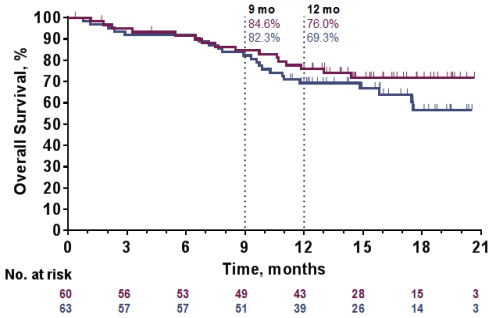


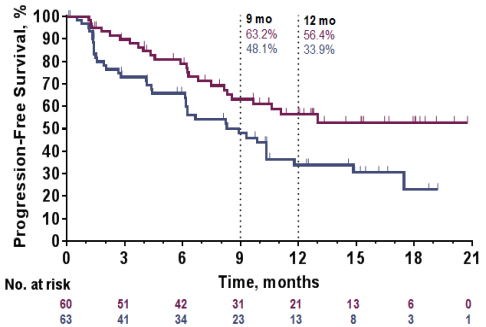
Antonia et al, NEJM 2017

1L NSCLC: Combination with Carboplatin and Pemetrexed (KN021G)

Approved in the US





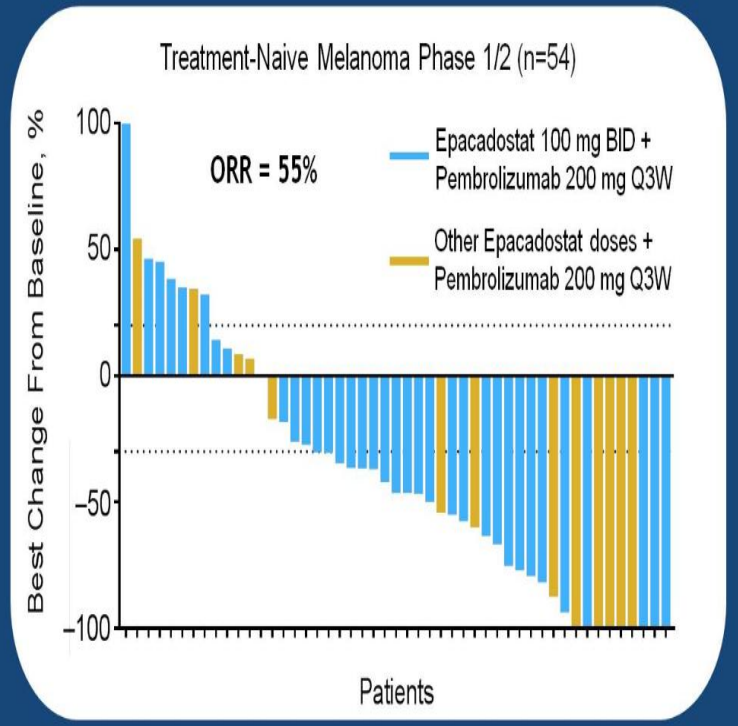


- Approved based on significant improvement in ORR and PFS
- Trend toward OS benefit is emerging despite the high rate of crossover (75%)

Papadimitrakopoulou V, Gadgeel SM, Borghaei H, et al. First-line carboplatin and pemetrexed (CP) with or without pembrolizumab (pembro) for advanced nonsquamous NSCLC: Updated results of KEYNOTE-021 cohort G. *J Clin Oncol*. 2017;35 (suppl; abstr 9094).

Early signal of activity doesn't always translate to definitive clinical benefit in phase 3

Background: Rationale for Combination and Dosing



ECHO-202 / KEYNOTE-037

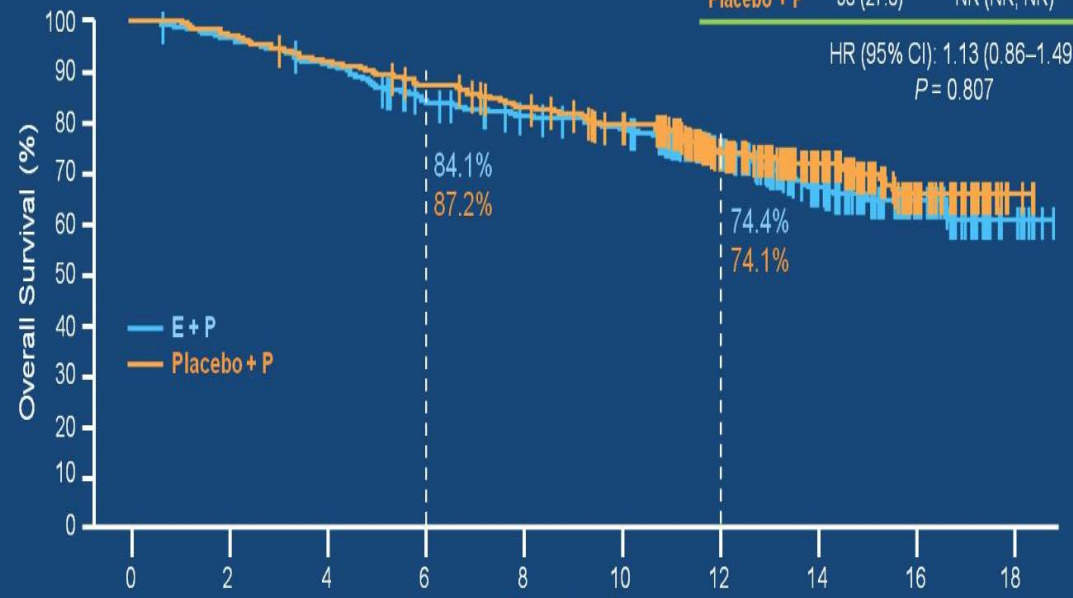
- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
- Phase 1/2 efficacy in treatment-naive melanoma:
  - ORR = 55%
  - Median PFS = 22.8 mo (12.4 mo all melanoma)

BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Hamid O, et al. *Ann Oncol.* 2017;28(suppl 5):1214O.

Overall Survival

	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807



Number at risk

E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.

Is this the best approach for combinations?

Clinical Data Deconvolution is Needed

It is not a matter of generating more data but it is important to learn from existing data

There is an overwhelming amount of data

- Pharma and academia
- To make sense of this data and harness it to inform the next generation of trials and therapies, we must develop novel methods to explore and analyze big biological data.

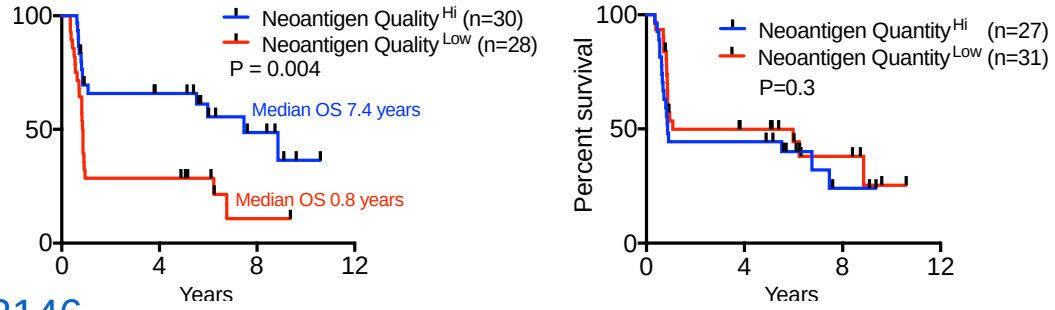
TRIAL DATA ⟩⟩⟩⟩⟩⟩ **COMBINE WITH OTHER RELEVANT DATASETS (Public data, other published clinical trials)** ⟩⟩⟩⟩⟩⟩ **AUTOMATED PIPELINES**

PICI Informatics is building infrastructure to do cloud-based data analytics using pipelines that are **rapid and reproducible.**

This lets scientists spend less time crunching data, and more time asking questions and discovering treatments..

PICI Informatics Examples

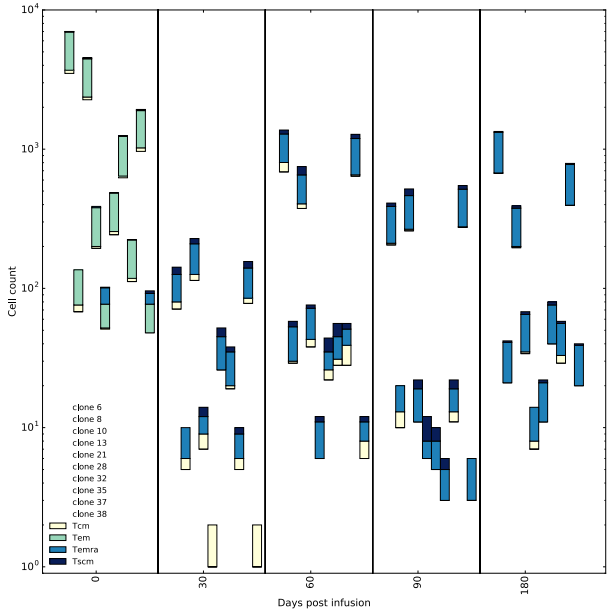
PICI worked with **MSKCC** to identify neoantigens predictive of surviving Pancreatic Cancer (PDAC)



(Balachandran et al., Nature 2017)
https://www.ncbi.nlm.nih.gov/pubmed/29132146

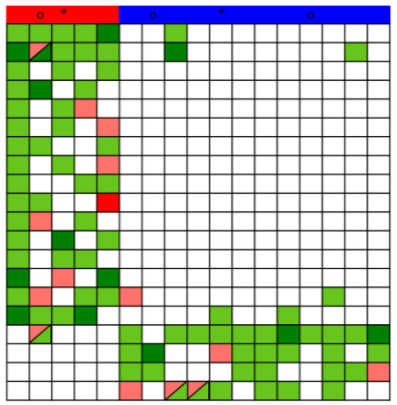
PICI worked with **Stanford** to track long-lived clones following engineered T cell therapy in a "super-responder" patient.

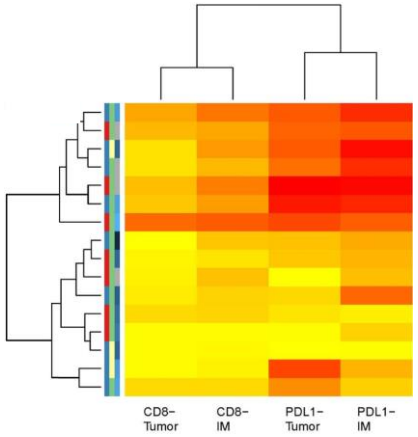
(Provisionally accepted, Cancer Discovery)



PICI Informatics Examples

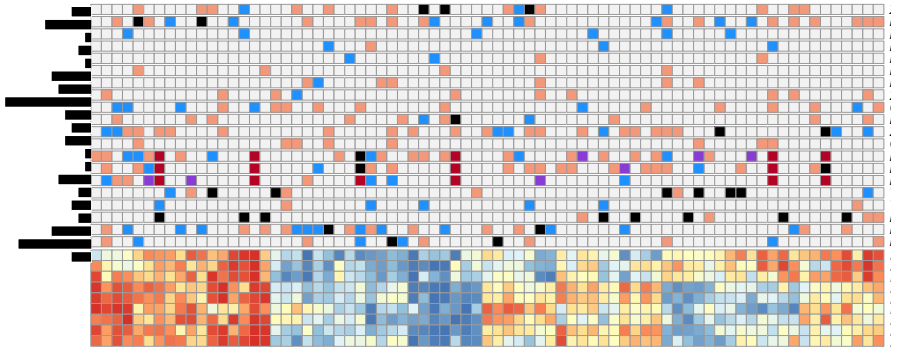
PICI worked with **UCLA** to show a high response rate to PD-1 blockade in patients with demoplastic melanoma.





(Eroglu et al., Nature 2017)
https://www.ncbi.nlm.nih.gov/pubmed/29320474

PICI worked with **UCLA & DFCI** on an analysis of colorectal cancer and identified mutations contributing to immune evasion suggesting a path for immunotherapy treatment.



(Grasso et al., Cancer Discovery, 2018)
https://www.ncbi.nlm.nih.gov/pubmed/29510987

Non-profit organizations

Role of philanthropic funding

A New Network

7 *Research Institutions*

350+ *Nation's Top Researchers*

65+ *Laboratories*

40+ *Industry & Non-profit Partners*

April, 2016: Billionaire tech entrepreneur Sean Parker announced a $250 million donation to establish the Parker Institute for Cancer Immunotherapy to speed research into innovative cancer treatments.

FORTUNE | Health

PICI Connects Academia, Industry, Nonprofit

Comprehensive Resources and Tools

Best and the Brightest Researchers and Ideas

Centralized IP Infrastructure

Dedicated IO Research Team

Clinical Trials Management Team

Enabling Broad and Specific Collaborations

Menu of Access to Therapeutics

Bioinformatics Team: Data Analysis

Core Research Infrastructure

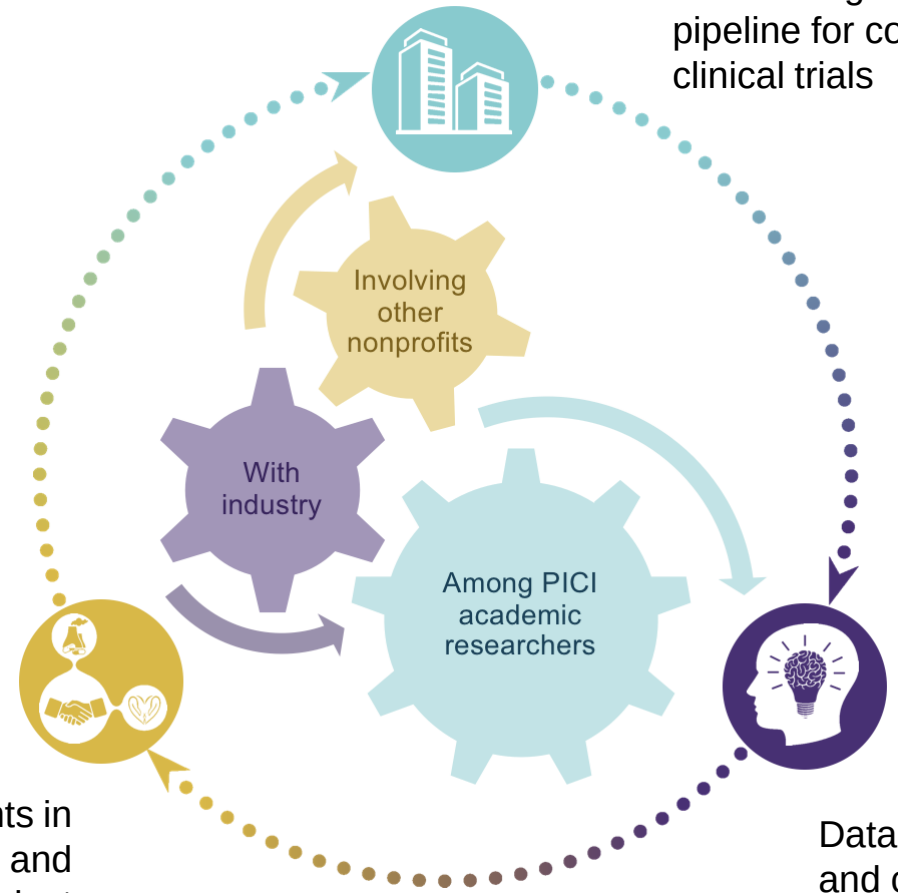
Biorepository and Standardized SOPs

A comprehensive organization to accelerate science and research

Clinical Trials Management

Bioinformatics

Technology Development



Access to global pipeline for combination clinical trials

Investments in startups and product development

Data sharing and centralized IP management

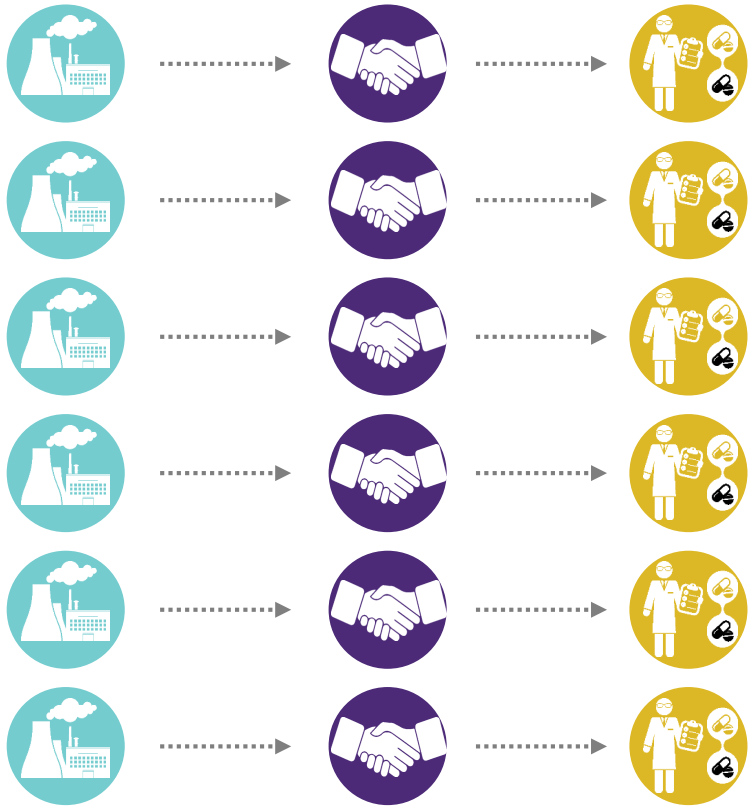
Shared Research Tools & Infrastructure

Strategic Partnerships

Data Sharing & Collaboration Platform

Single Exploratory Studies with Predefined Drugs and Arms

1,105 PD(L)-1 combos (60% in academia)



Study 1

Study 2

Study 3

Study 4

Study 5

Study 6

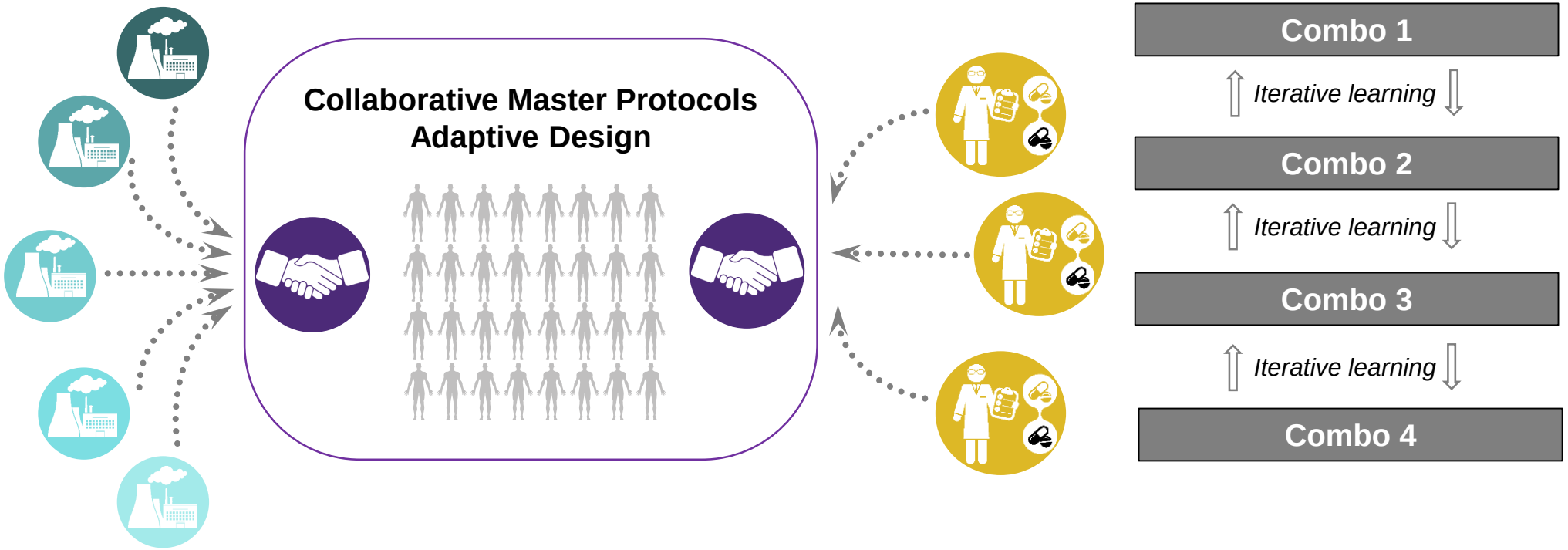
Single company, single institute and limited resources

- Inconsistencies
- Uncoordinated
- Duplication
- Inefficient
- Data quality

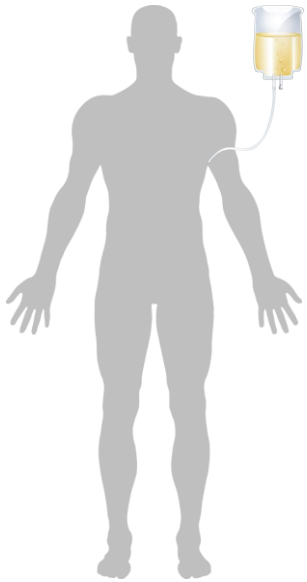
Where Will We Go From Here?
PICI Clinical Trial Platform 2.0

Multiple companies
Combinations not restricted to one portfolio/pipeline
Combinations based on a strong hypothesis or existing data

Ideas coming from scientists
Multiple institutes to participate
Data monitoring
eCRF library
PICI – IND sponsor



IO Master Neoadjuvant Protocol to generate mechanistic data



Patient(s)

Monotherapy Arm

Combo 1

MOA data inform future selection

Combo 2

Combo 3

Signal seen › expanded cohort

Combo 4

TIME: Trial Start

Diagnostic bx

Dose 1

Dose 2

Dose 3

Surgical resection specimen

8-12 weeks

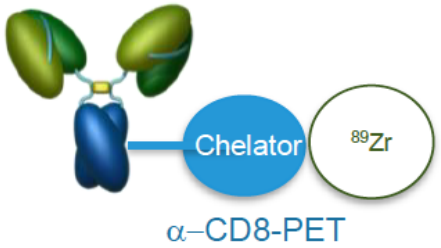
depending on the indication

Developing new technologies

ImaginAB

T-Cell Response Predicts Benefit of Immunotherapy “Replacing the Need for a Biopsy with a Scan”

ImaginAb Disruptive Solution:

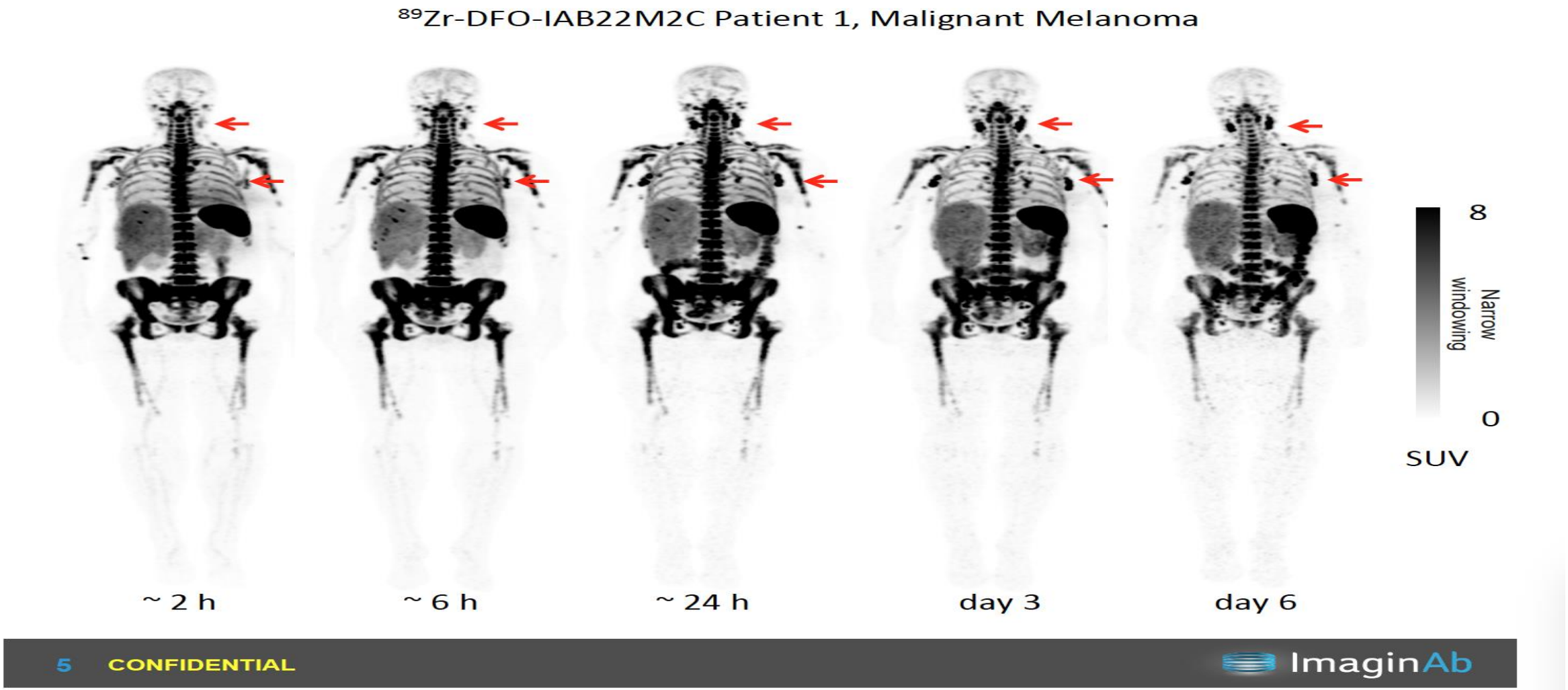


Non-invasive imaging of CD8⁺ T cells to see whether checkpoint inhibitors and other immuno-modulators are working

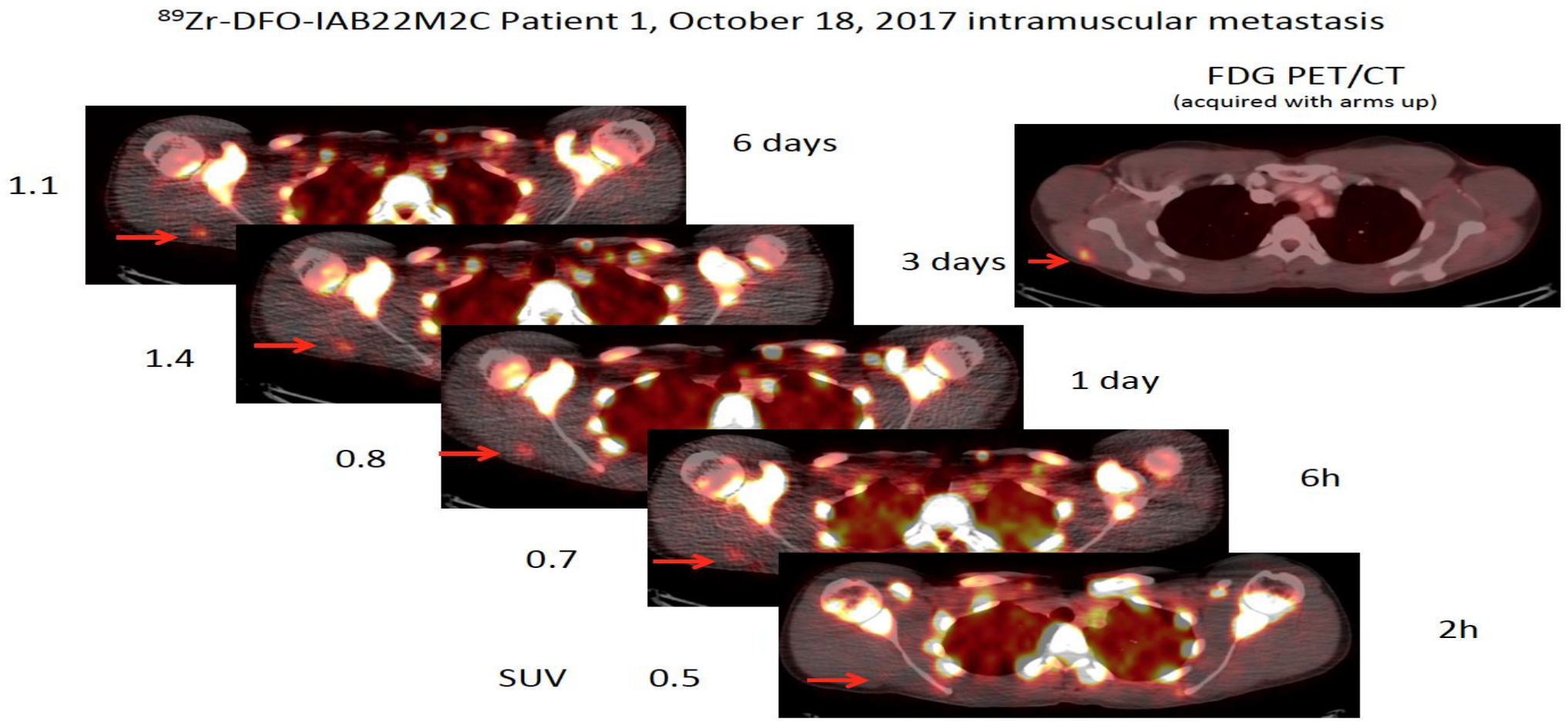
Compelling Value Proposition:

- Track CD8⁺ T cells before, during and after treatment for patient selection and treatment monitoring
- Early detection of response to therapy (weeks vs months)
- Utility in many mono- or combination- immunotherapies
- Expedite the clinical development and market launch of immunotherapy drugs

Patient 1: Lowest Dose Level



CD8 positive tumor

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