Limits of Monotherapy, and the State of PD-1 and PD-L1 Combination Therapies in Clinical Trials

National Academy of Medicine
July 16, 2018

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Director Immuno-Oncology Program (ad interim)

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Disclosures

Consulting

- AstraZeneca
- Eli Lilly
- Genentech/Roche
- Merck
- NextCure
- Novartis
- Pfizer

Research Support

- AstraZeneca
- Eli Lilly
- Merck
- Genentech

Plan for Discussion

1. Using NSCLC as an example, review both the promise and limitations of immunotherapy

2. Explore mechanisms of sensitivity and resistance to immunotherapy: Primary vs Acquired

3. Combination Immunotherapy: Principles and Practice

4. The Next step: Personalized Immunotherapy and rational Designs

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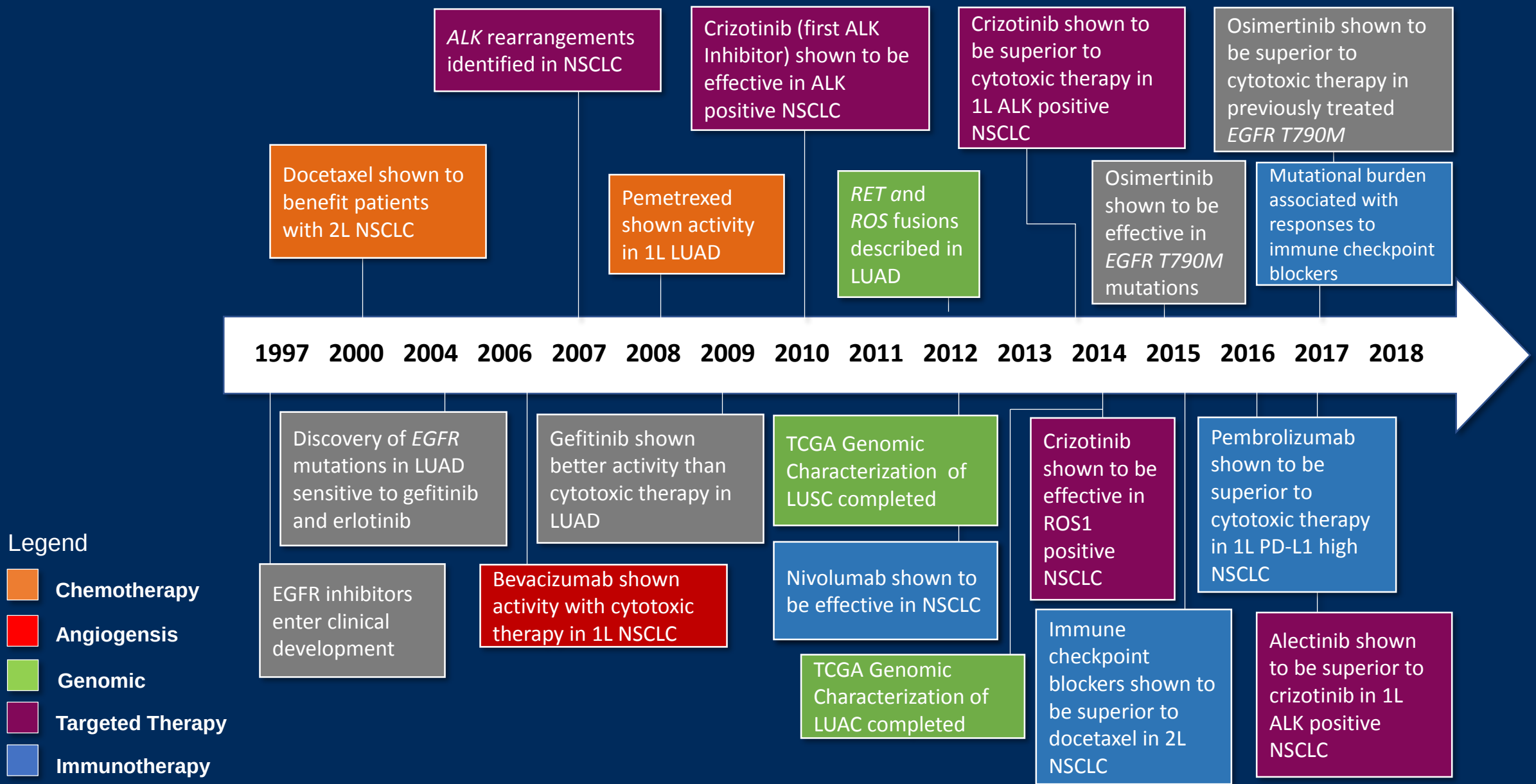
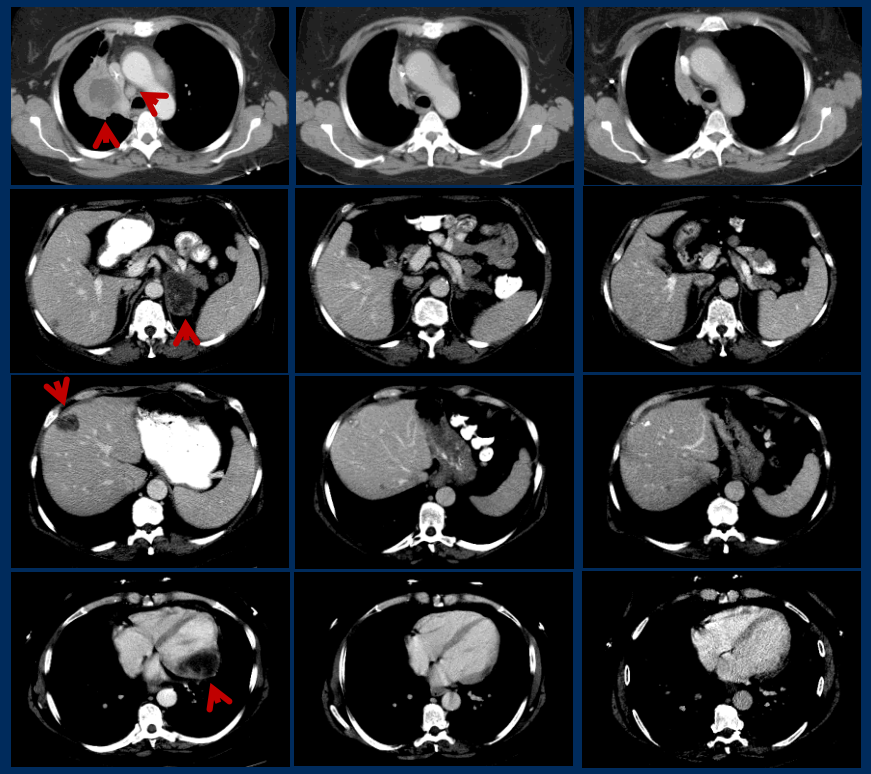
A New Era for NSCLC Treatment!



1L = First-line; 2L = Second Line

R S Herbst *et al. Nature* **553,** 446–454 (2018)

One of the very first lung patients on Nivolumab
Refractory Squamous Cell NSCLC, June 2010



Pre- Nivolumab | 2 Years on Nivolumab | year 6: > 4 Years off Nivolumab

Cure?

How Common is Maureen's Incredible Outcome

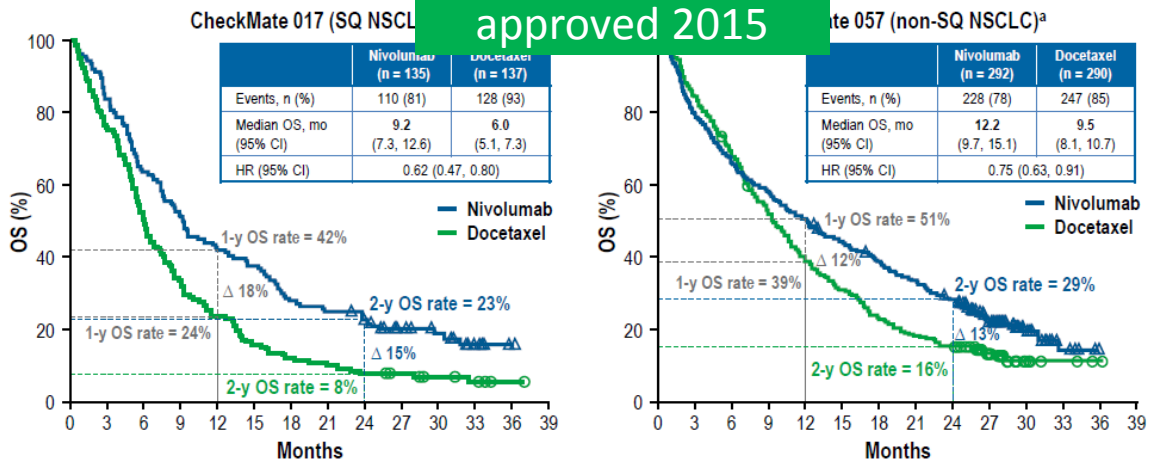
1. 10-15%
2. 15-30%
3. 30-50%
4. > 50%

Acquired Resistance > 50%

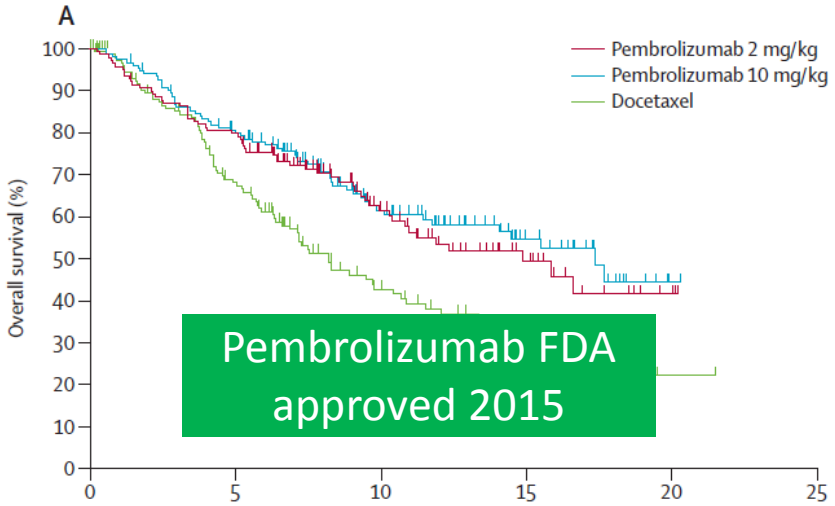
There is much more room for improvement!

PD-1, PDl-1 antibody Approvals in Refractory NCSLC

Nivolumab FDA approved 2015

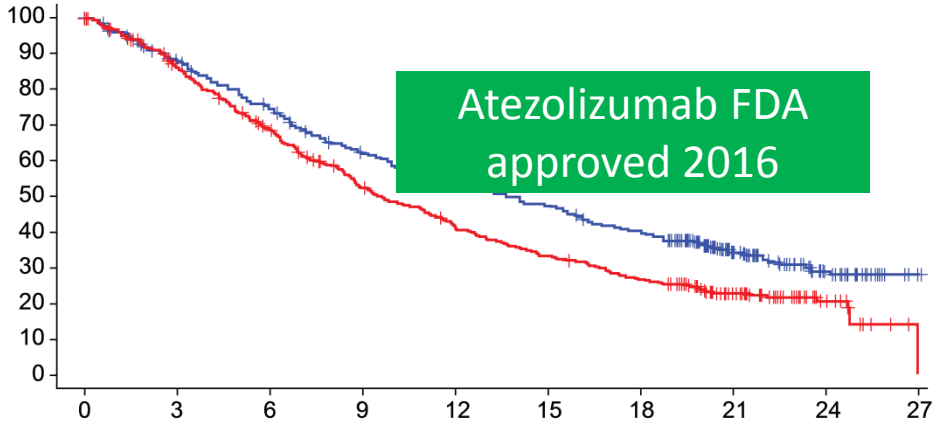


IO Grade ¾ toxicity is less than with chemotherapy- though significant Immune related adverse events can occur.



Pembrolizumab FDA approved 2015

Borghaei and Brahmer, NEJM 2015
Herbst, Lancet 2016

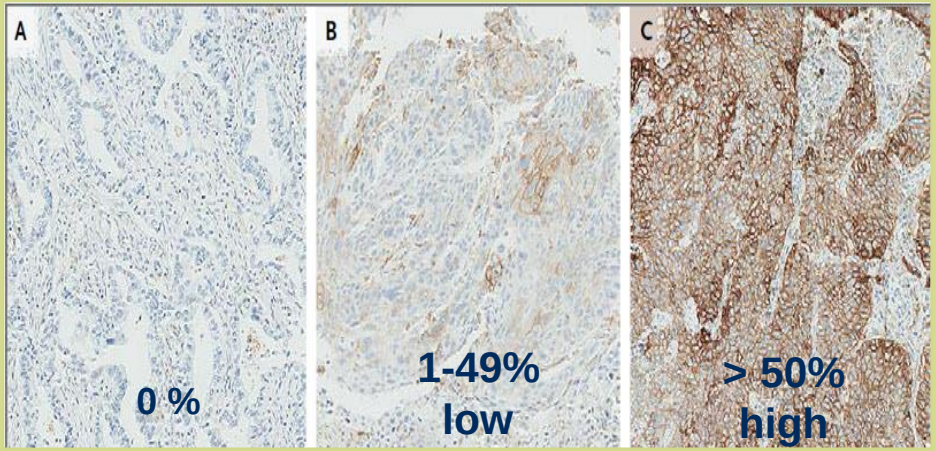


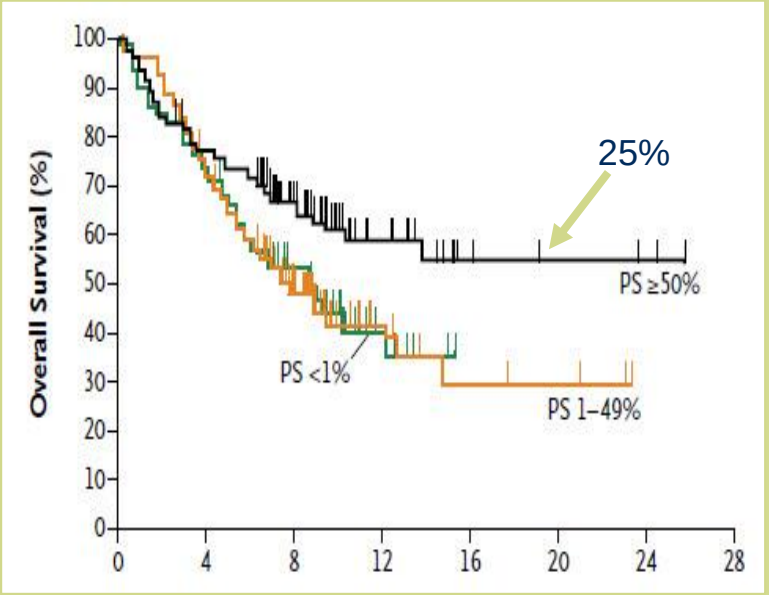
Atezolizumab FDA approved 2016

Reck, NEJM 2016
Barlesi, ESMO 2016

Pembrolizumab Biomarker Development

Pembrolizumab DAKO-22c3 Ab

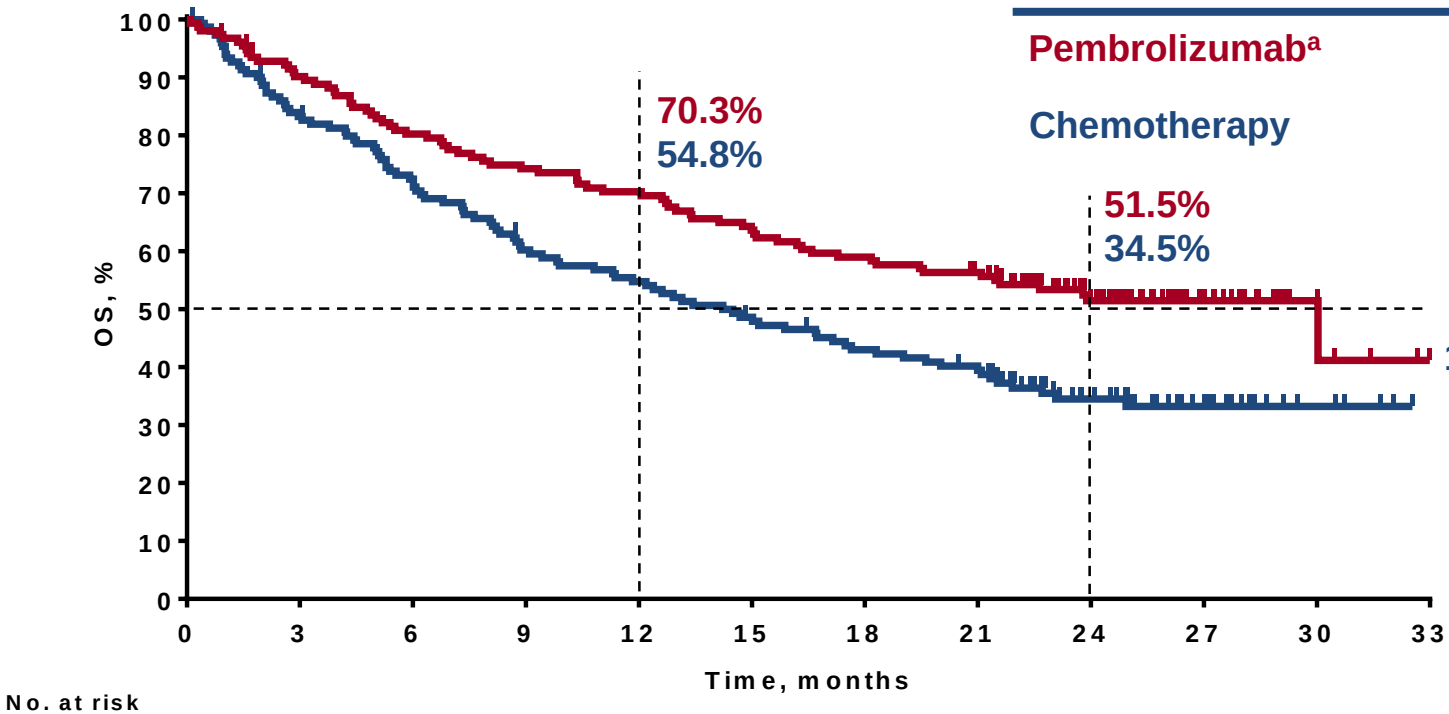




Garon EB et al. *N Engl J Med* 2015 372:2018-2028

Overall Survival: Pembrolizumab PDL-1 High (>50%)

KEYNOTE 024



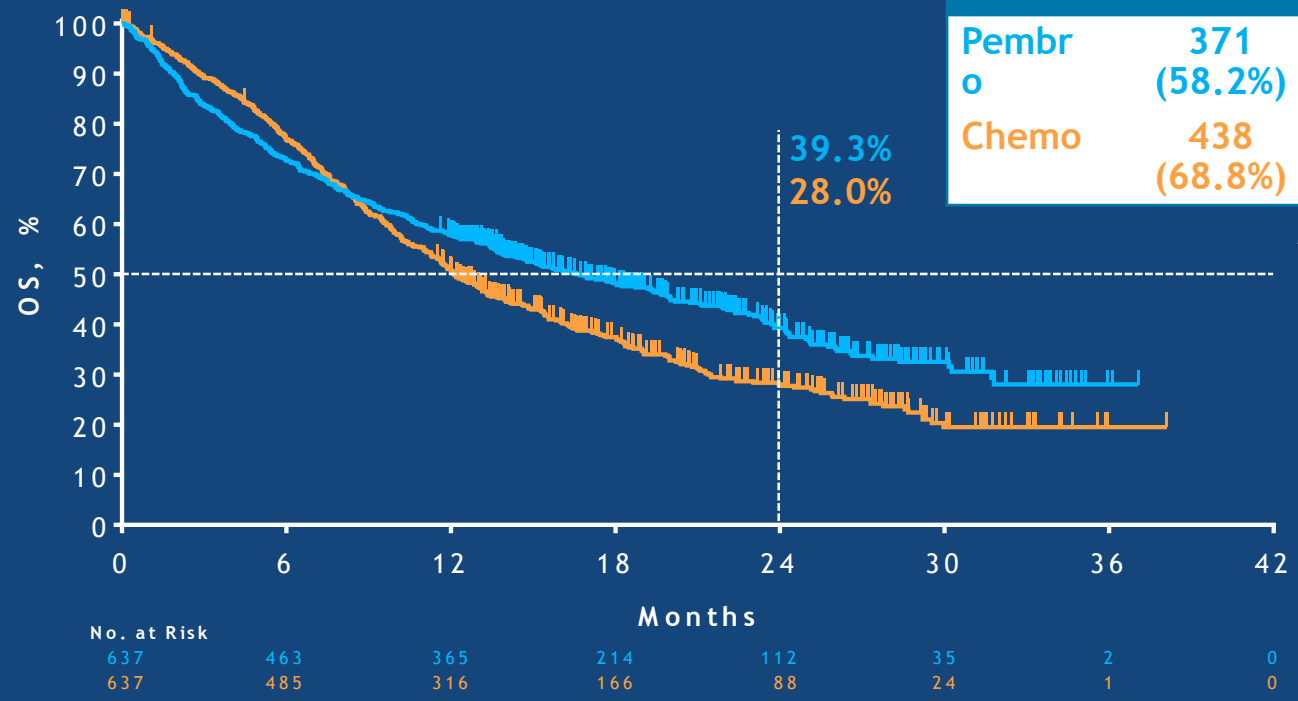
	Events, n	HR (95% CI)
Pembrolizumab[a]	73	0.63 (0.47–0.86) *P* = 0.002[b]
Chemotherapy	96	

Median (95% CI)

30.0 mo (18.3 mo–NR)

14.2 mo (9.8 mo–19.0 mo)

Overall Survival: PD-L1 ≥1%



	Events	HR (95% CI)	*P*
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		

Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)

Data cutoff date: Feb 26, 2018.

Gilberto Lopes

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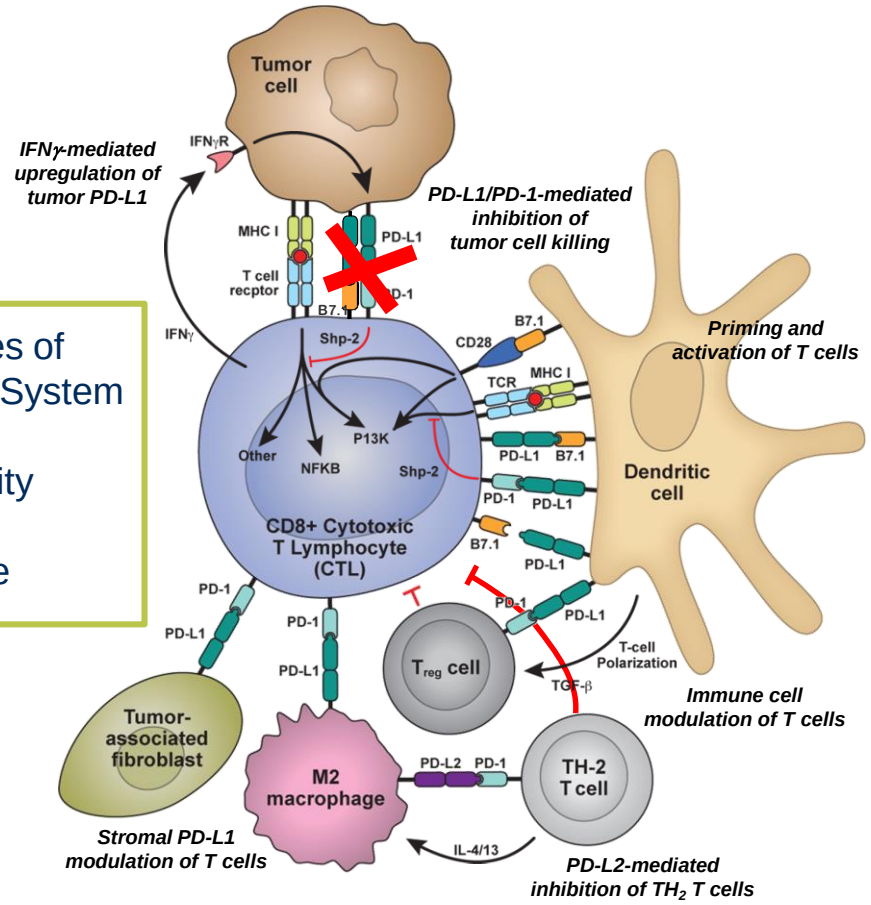
Mechanism of Immune Checkpoint Inhibitors

Key Attributes of the Immune System

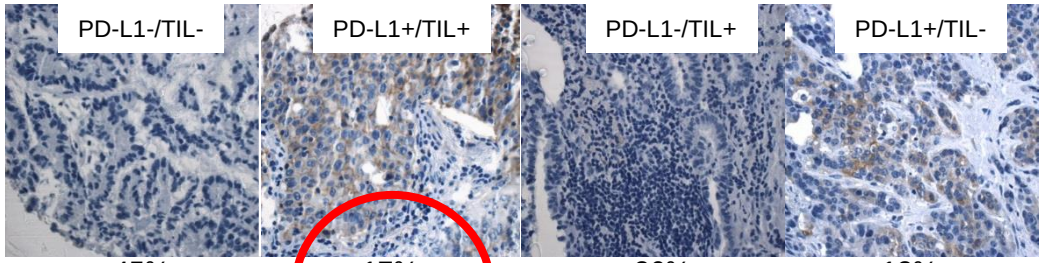
- Specificity
- Memory
- Adaptive



- Cancer cells develop many mutations that can make them appear foreign to the immune system
- T cells can recognize, attack and kill these “foreign” cancer cells
- Cancer cells can evade immune attack by expressing PD-L1
- Adaptive tumor expression of PD-L1 turns the immune system OFF
- Clinically, we want to block PD-1 or PD-L1 to <u>reactivate</u> the immune system
- PD-L1 plays an important role in dampening the anti-tumor immune response

Herbst RS et al. *J Clin Oncol* . 2013;31(suppl; abstr 3000)

Four Categories of Tumors
Based on Presence of PD-L1 and TILS



PD-L1 = B7- H1

Proposed mechanisms associated with NSCLC resistance to anti-PD-1/B7-H1 therapy

Subgroup		Type	Tumor Distribution	Possible Resistance Mechanism(s)	Analysis
B7-H1	TIL				
-	-	I	45%	Poor priming of general T cell responses	Peripheral CD4+ and CD8+ T cell responses to autologous tumor cells
				Lack of inflammatory cell recruitment	Chemokine expression in biopsy or FFPE samples
+	+	II	17%	Incomplete PD-1/B7-H1 pathway blockade and activation of alternate immune suppressive pathways	CD80 expression on TILs, expression of alternate suppressive pathways in TME
-	+	III	26%	Alternate immune suppressive pathways	Expression of select molecules in pathways with roles in evasion of NSCLC immunity
+	-	IV	12%	Intrinsic induction of B7-H1 by oncogenes	Expression of molecules triggering aberrant signaling events

Velcheti (Rimm) et al. *Lab Invest*. 2014 Jan;94(1):107-16.; Chen L. Unpublished

450 samples analyzed

Trends in Immunology

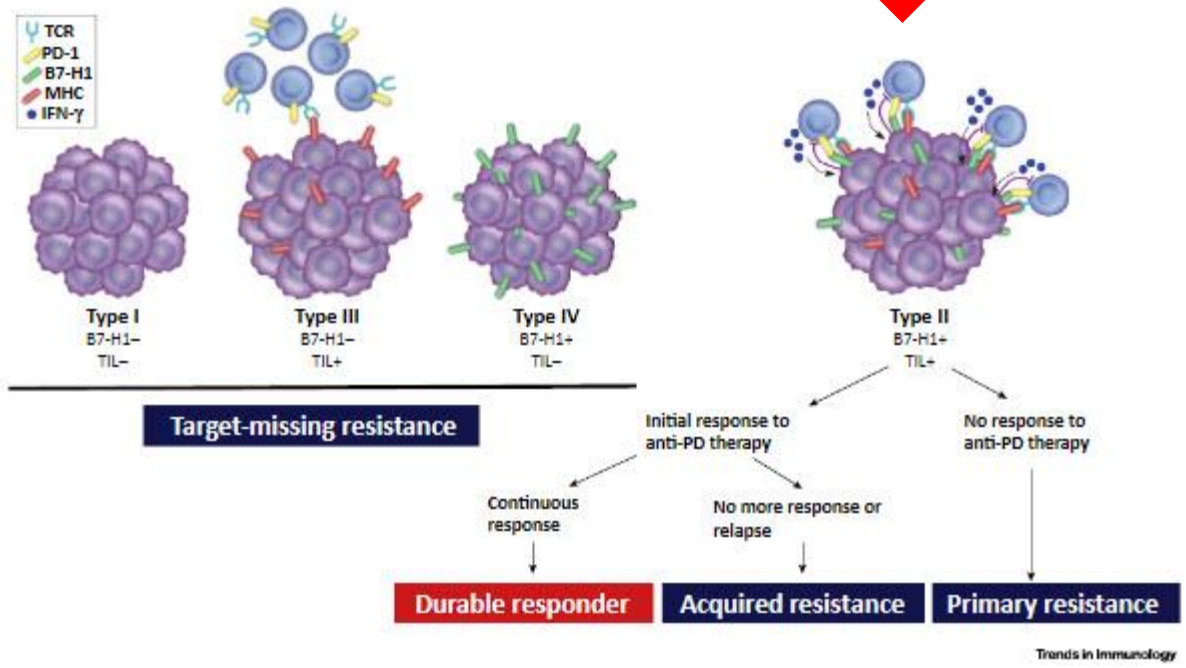
CellPress
REVIEWS

Review

Defining and Understanding Adaptive Resistance in Cancer Immunotherapy

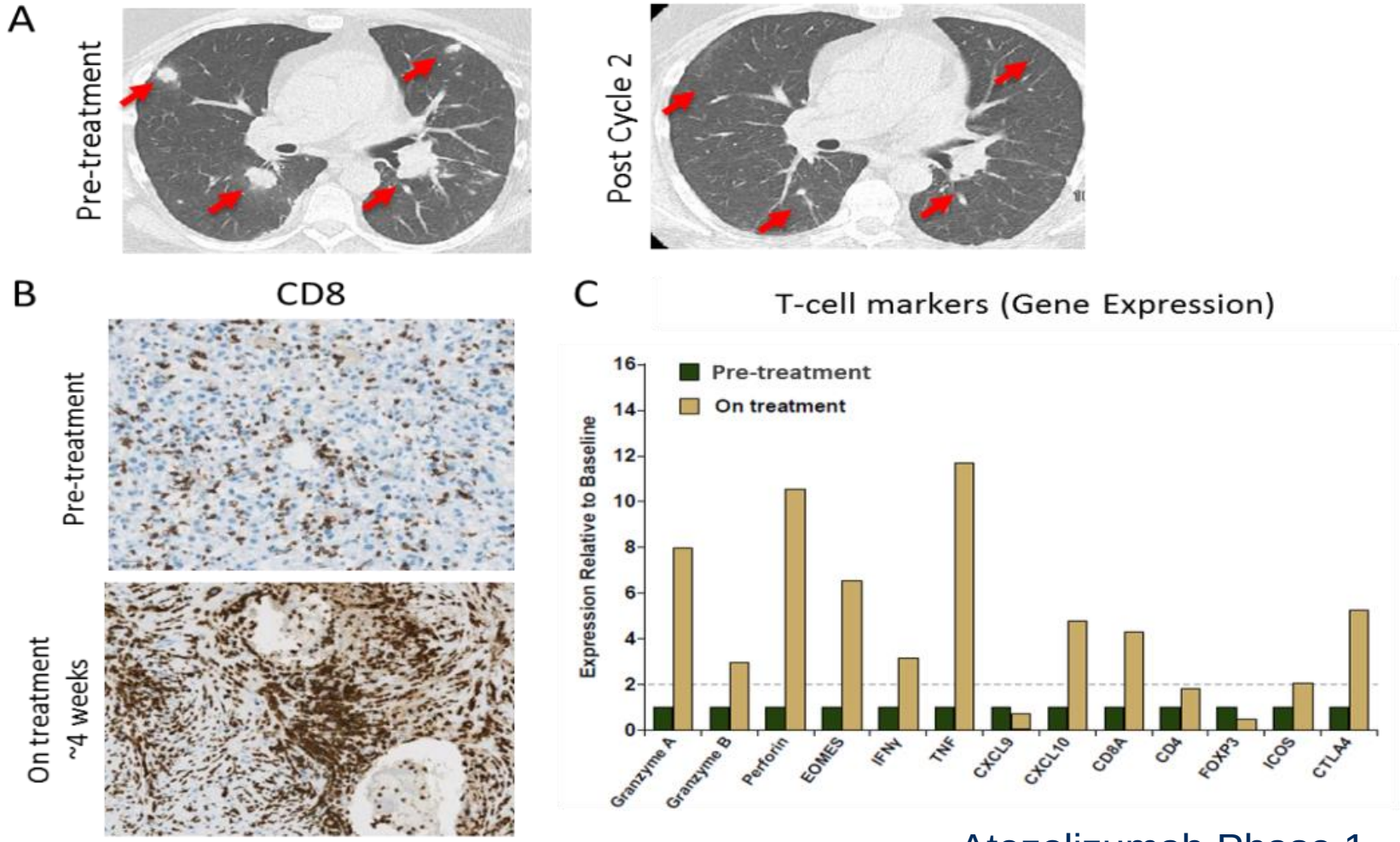
Tae Kon Kim,[1] Roy S. Herbst,[2] and Lieping Chen[2,3,*]

On Target Resistance



Biomarker Analyses for PD-L1 Treatment

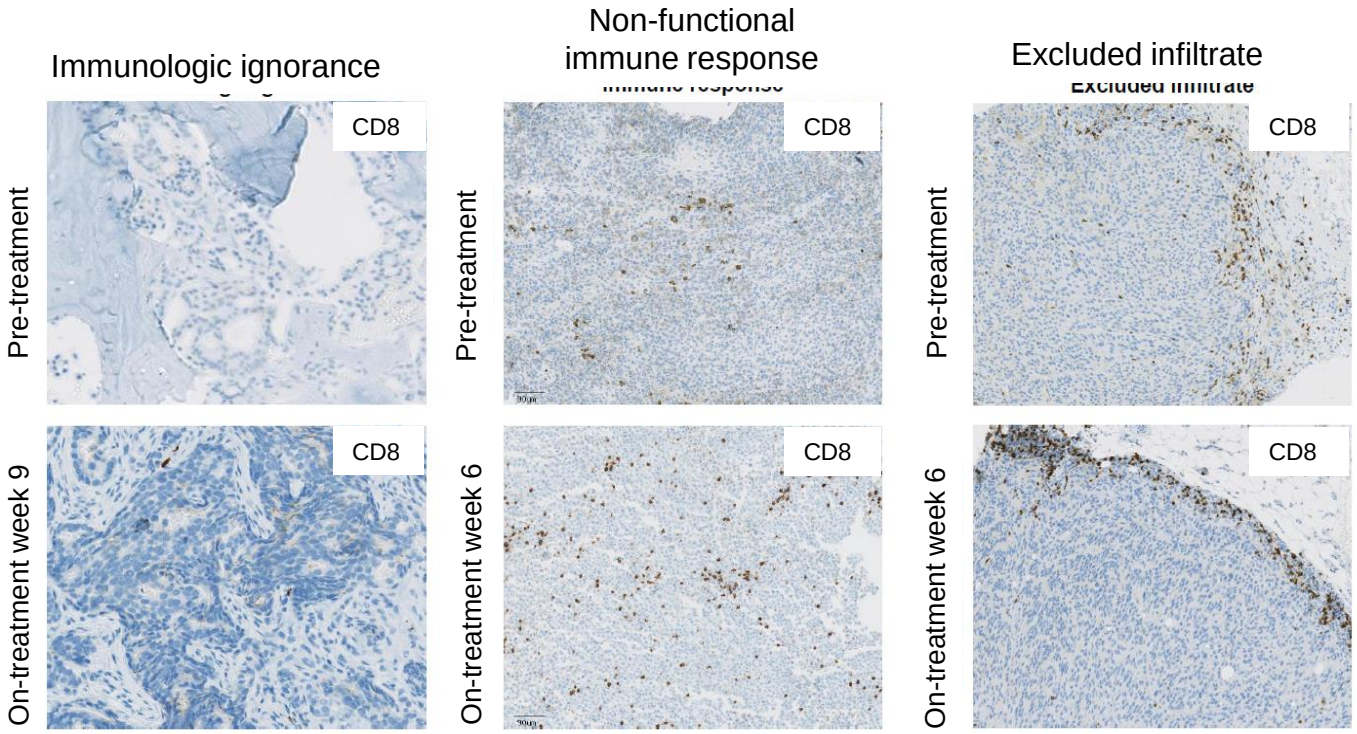
Mechanistic studies using pre and post biopsies



Atezolizumab Phase 1

Herbst RS et al. *Nature* 2014;515: 563-567;

Biomarker Analyses
Defining the Profile of Non-responders

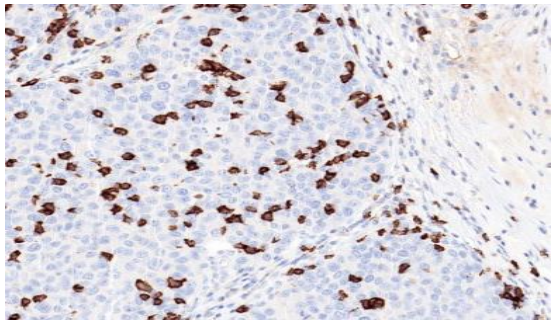
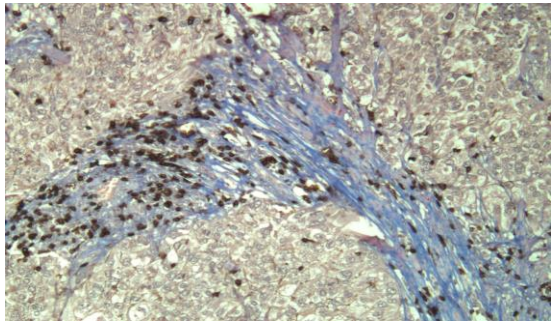
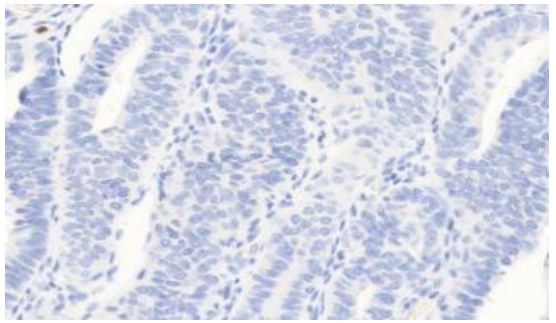


- Three distinct patterns of nonresponse were observed
- Most patients who progressed failed to show up-regulation of PD-L1 or evidence of activated T cells
- These results provide evidence for the “inflamed tumor” hypothesis

Herbst RS et al. *Nature* 2014;515: 563-567;

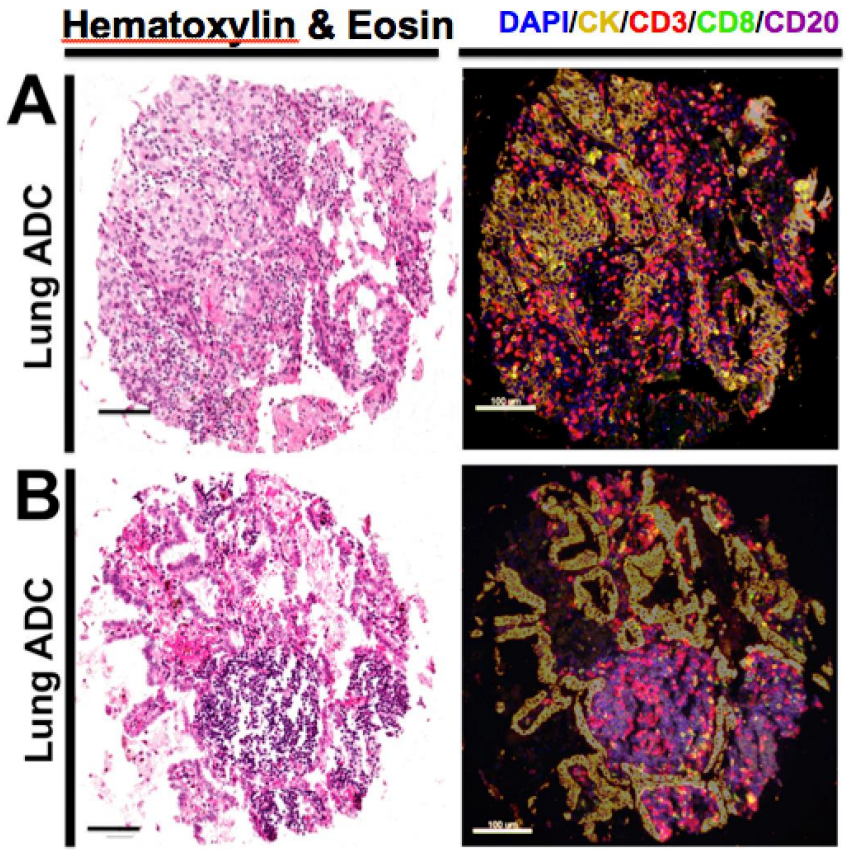
The next frontier: utilising immune profiling for a patient-driven approach

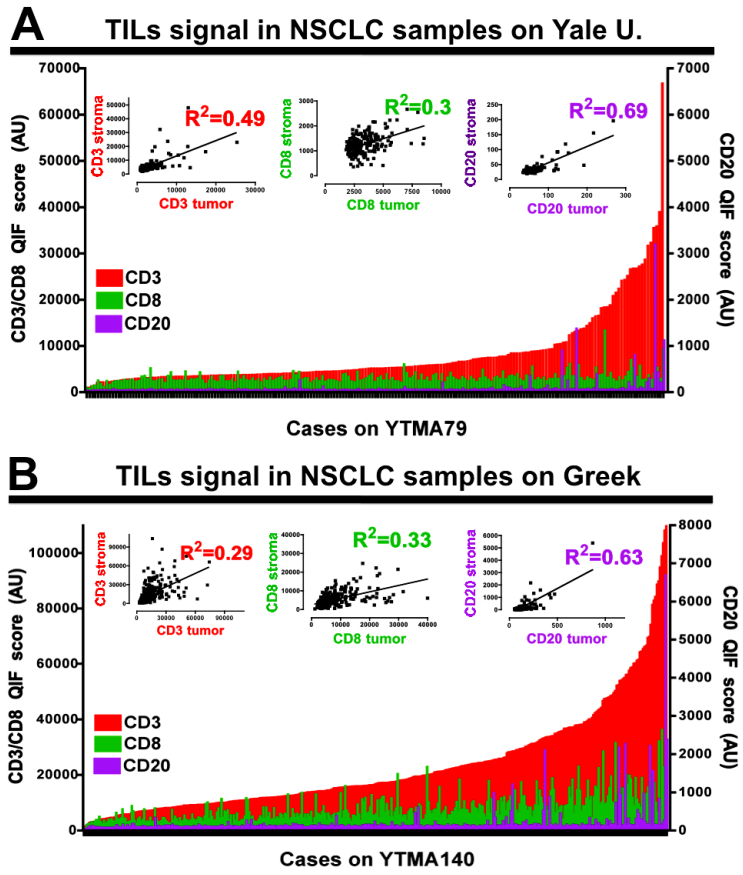
Each immune phenotype requires a **personalized immunotherapy approach** to initiate/re-initiate the antitumor immune response

INFLAMED	IMMUNE EXCLUDED	IMMUNE DESERT
		
Essential T cell activity required		
KILL tumour	**INFILTRATE** tumour	**GENERATE** active, tumour-directed T cells

Adapted from Chen and Mellman. Immunity 2013; Hegde, et al. Clin Cancer Res 2016; Kim and Chen. Ann Oncol 2016; Chen, Herbst et al Nature 2014, and Mellman. Nature 2017

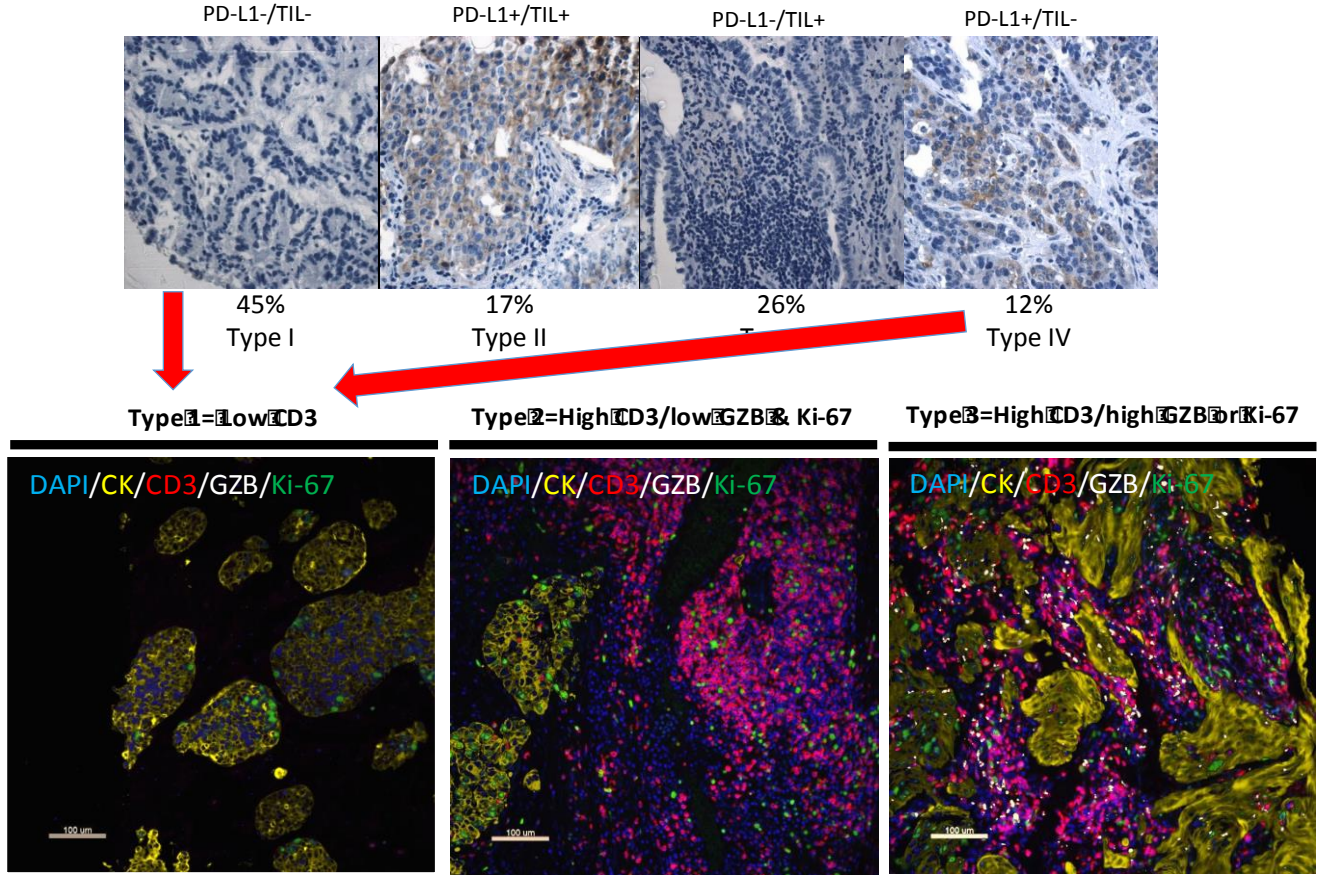
TIL subtype quantification in FFPE defines the “Inflamed” phenotype in NSCLC





Schalper et al., 2015, JNCI, 107(3)

Converting the Lung Tumor Subclasses to T-cell Activation Subclasses



Kurt Schalper et al, Nat Comm In Press

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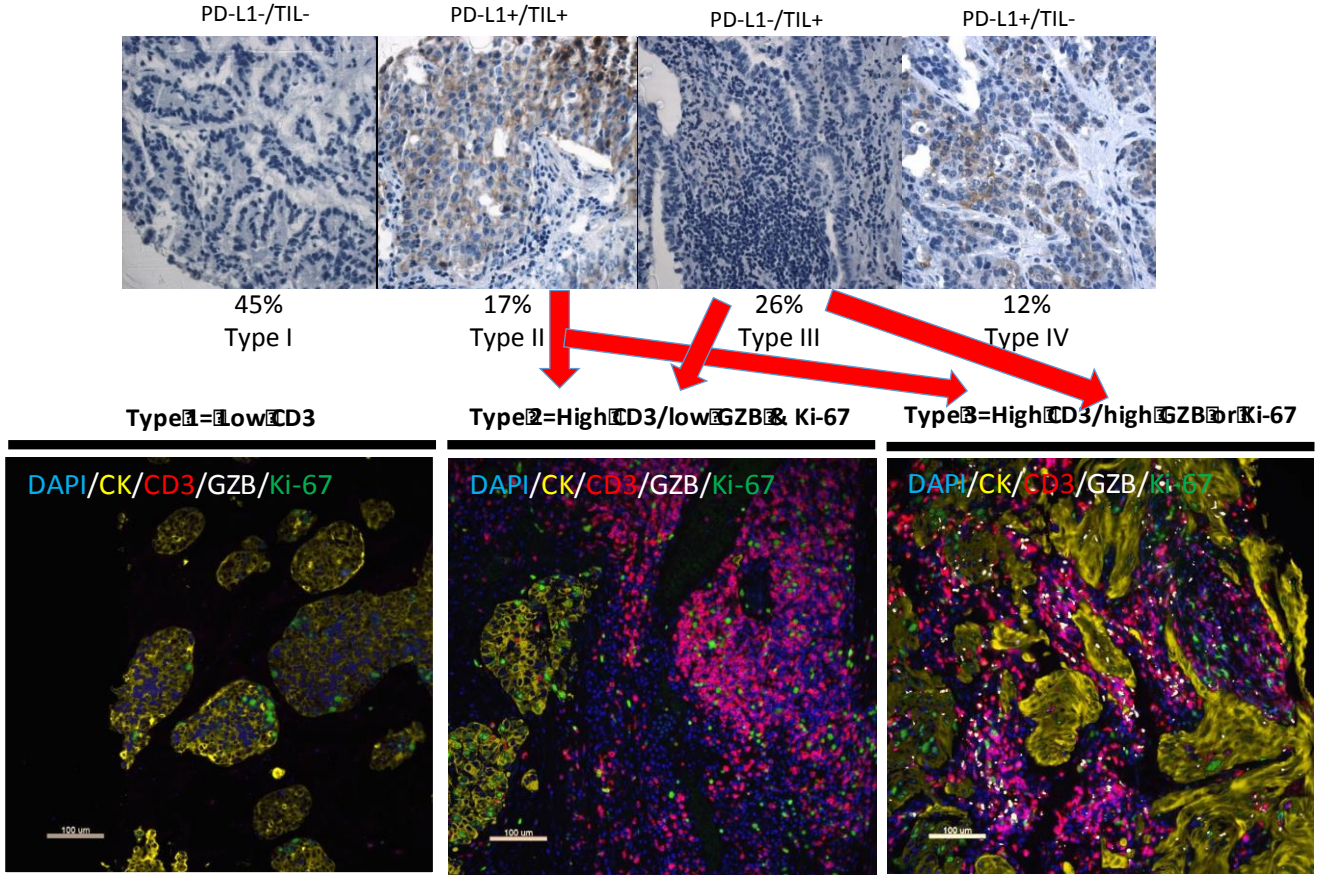
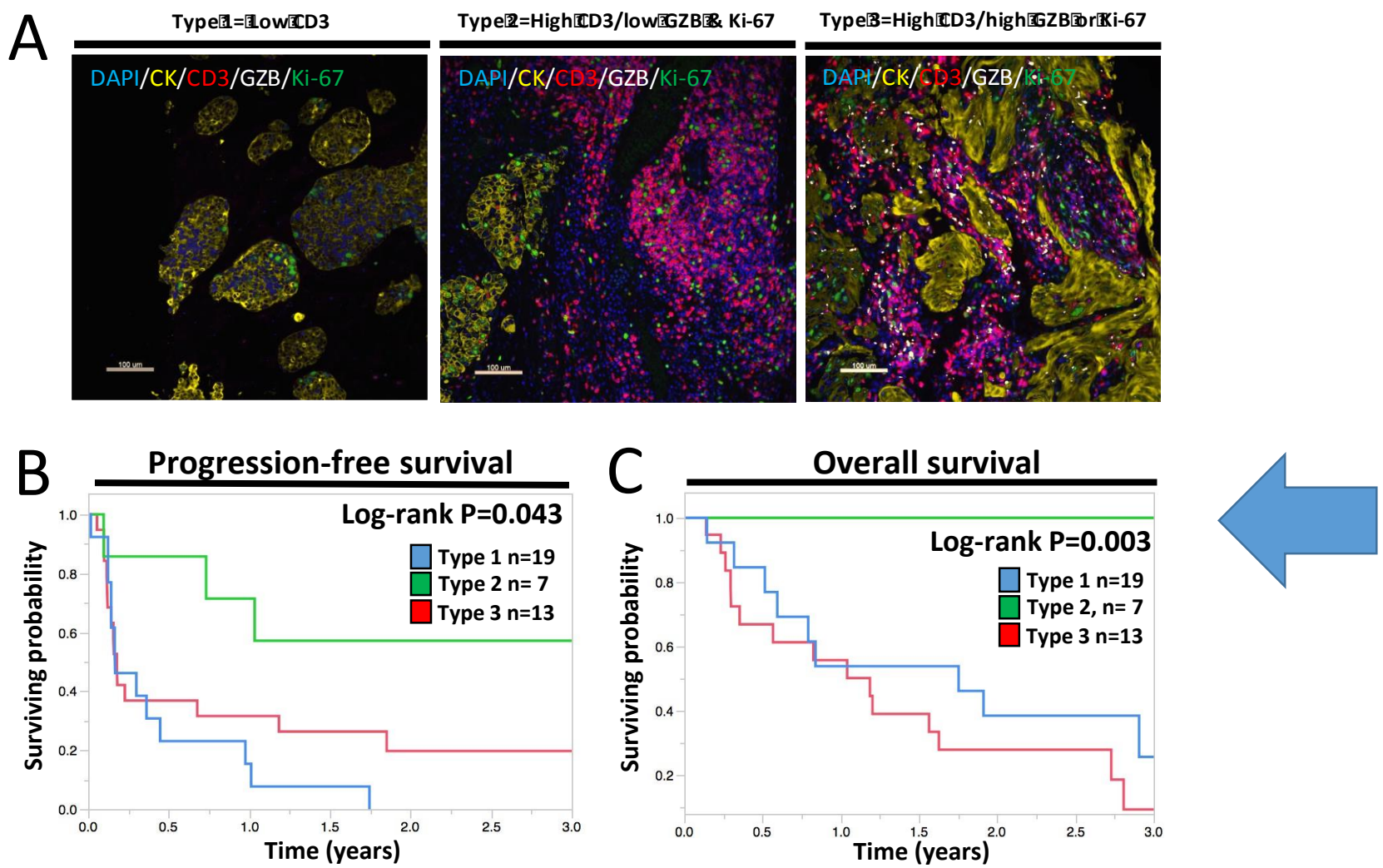


Type 1- Absent

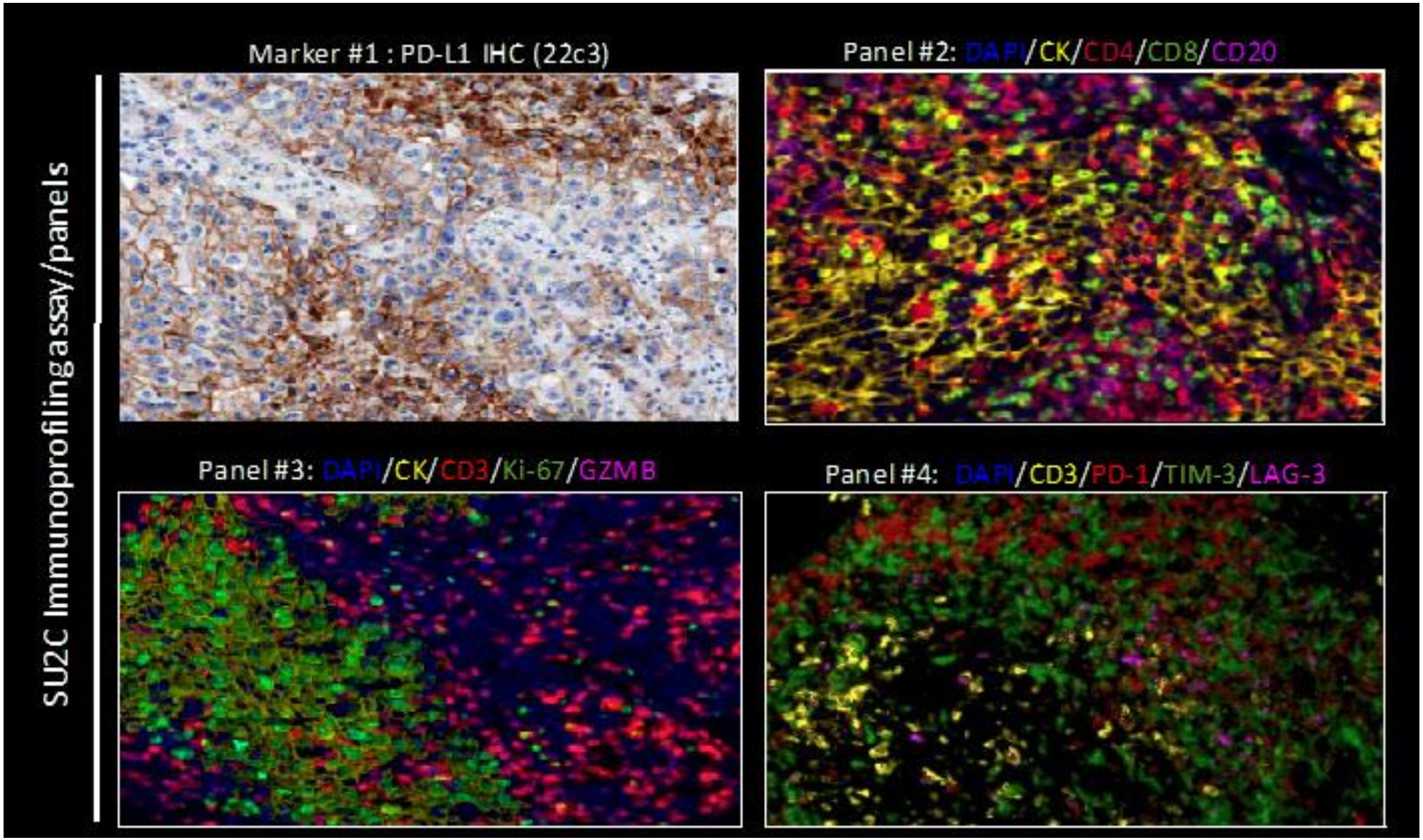
Type 2- Dormant?

Type 3- Active

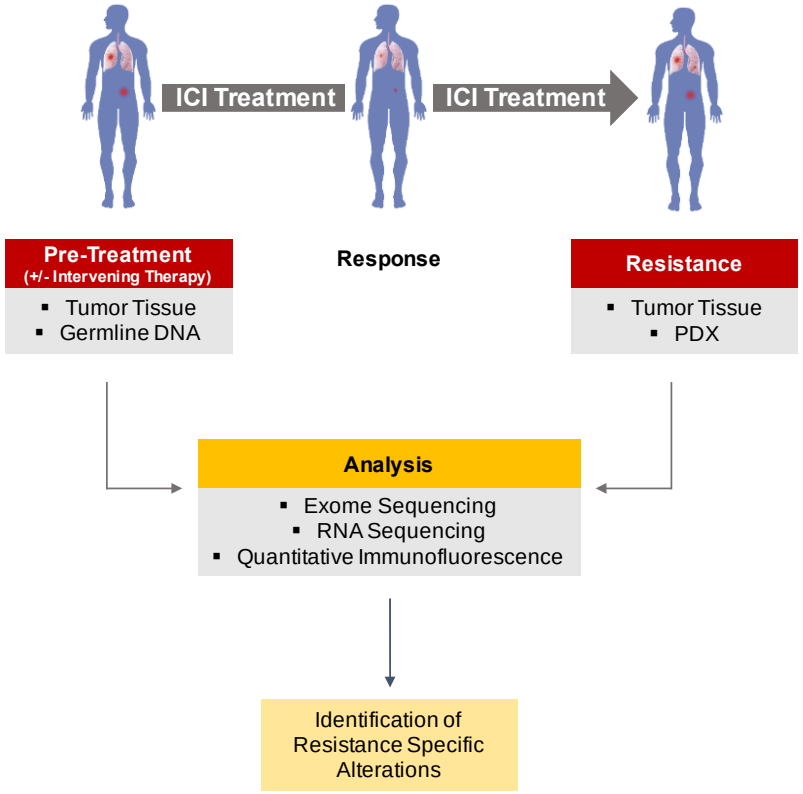
Kurt Schalper et al, In Press Nature COmmunications

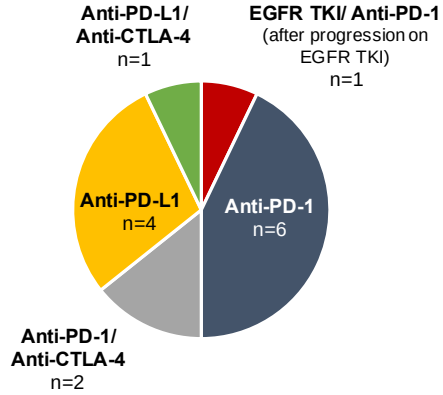

A
Type 1=Low CD3
Type 2=High CD3/low GZB & Ki-67
Type 3=High CD3/high GZB or Ki-67
DAPI/CK/CD3/GZB/Ki-67
DAPI/CK/CD3/GZB/Ki-67
DAPI/CK/CD3/GZB/Ki-67
100 um
100 um
100 um
B
Progression-free survival
Log-rank P=0.043
Type 1 n=19
Type 2 n= 7
Type 3 n=13
Surviving probability
Time (years)
C
Overall survival
Log-rank P=0.003
Type 1 n=19
Type 2, n= 7
Type 3 n=13
Surviving probability
Time (years)

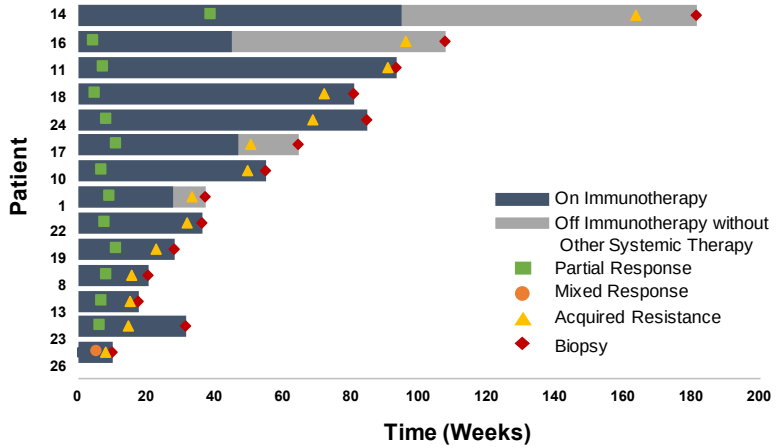
Validation will Require Collaboration!



Yale Cohort of Patients with Acquired Resistance to Immune Checkpoint Inhibitors

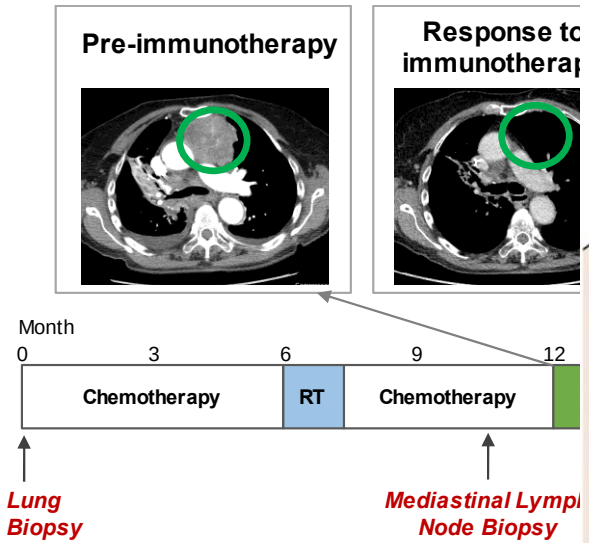


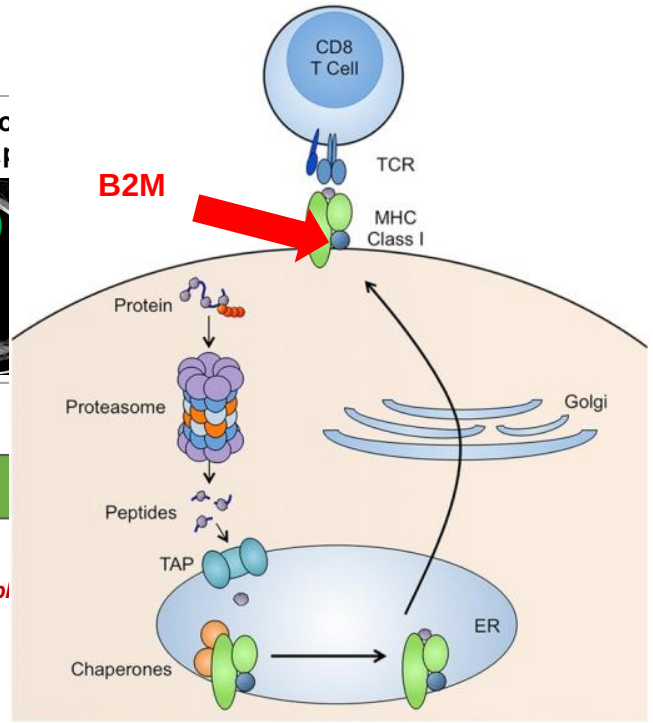




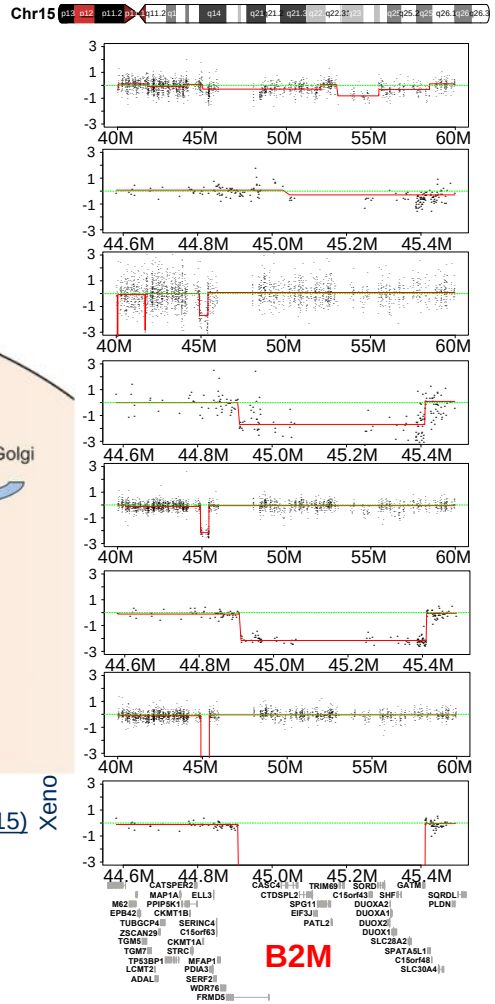
Gettinger, Choi, Hastings, Truini, Datar, Politi et al., Cancer Disc. 2017

Acquired Resistance to Anti-PD-L1 plus Anti-CTLA4





McCarthy MK, Weinberg JB Front Microbiol (2015)



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Jungmin Choi, Anna Wurtz, Scott Gettinger

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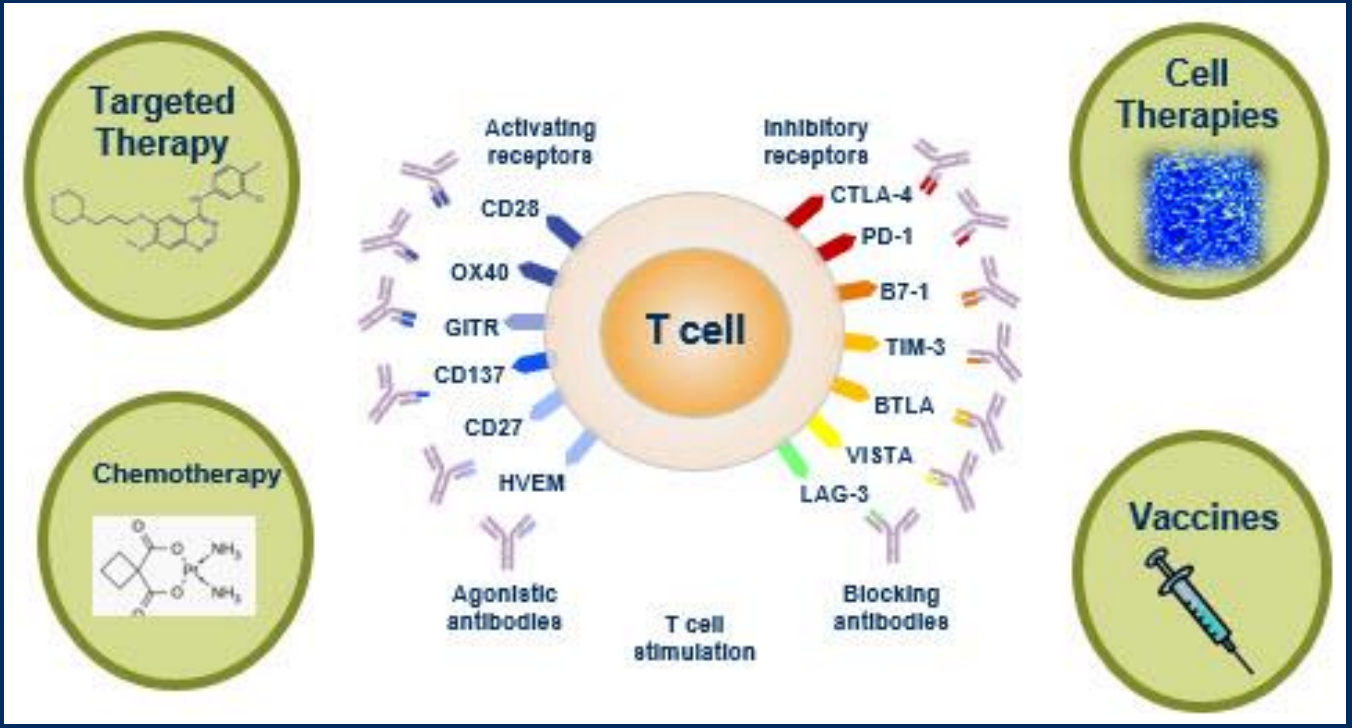
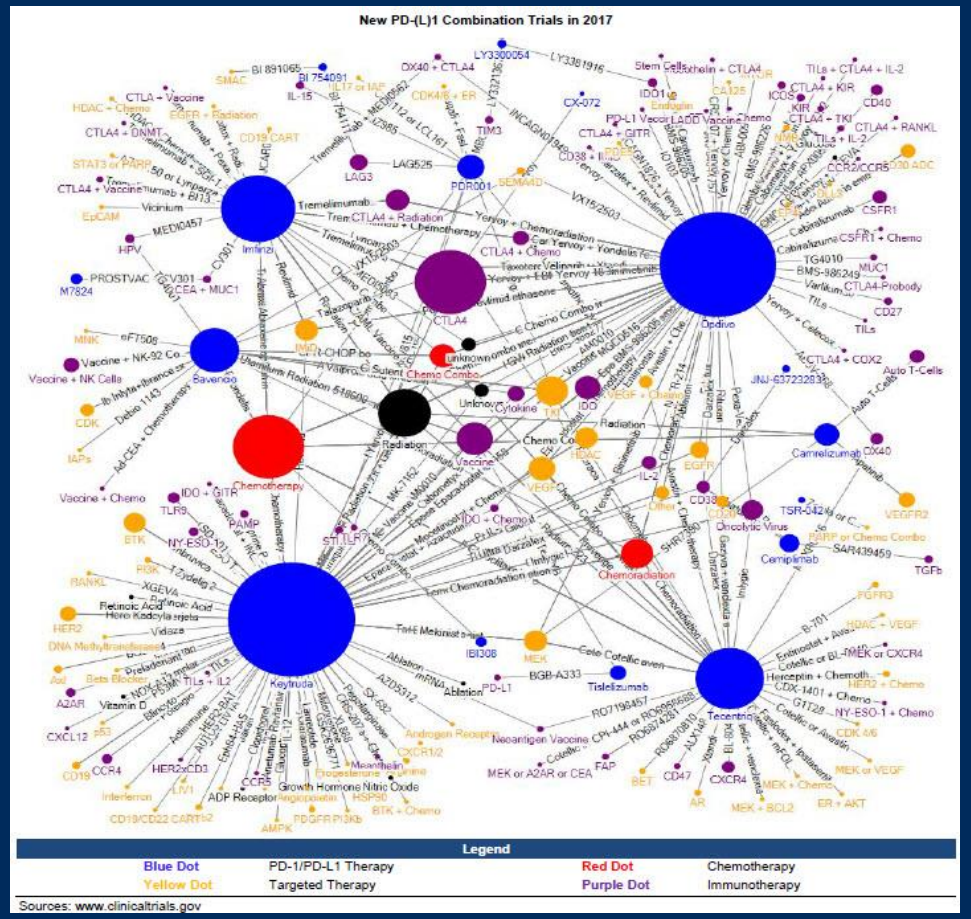
And Certainly The Search for New Combinations and Personalized Immunotherapy Must Continue





Mellman I et al. *Nature* 2011 Dec 21;480(7378):480-9.
M. Philips, Equity Research 2018

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Anti-PD1/PDL1 as backbone to lung combination treatment?

Nivolumab

- Chemotherapy
- Radiation/Ablation
- EGFR/ALK TKI

- Gene therapy
- IL15 agonist
- PEG IL10
- TGFβR1 inhibitor
- Anti-CD27
- Ant-CXCR4
- Anti-CSF-1R
- IDO-1 inhibitor
- Anti-CTLA4
- Anti-LAG
- Anti-TIM-3
- Anti-KIR

Pembrolizumab

- Chemotherapy
- Radiation
- EGFR/ALK TKI

- CRM1 Inhibitor
- FAK Inhibitor
- Anti-EGFR
- Anti-CEACAM1
- PEG hyaluronidase
- Vaccine
- Oncolytic
- PEG IL10
- Anti-CSF-1
- IDO1 Inhibitor
- Anti-CTLA4
- Anti-B7-H3

Atezolizumab

- Chemotherapy
- Radiation
- EGFR/ALK TKI

- Anti-CSF-1
- Adenosine A2A Inhibitor
- IDO-1 Inhibitor
- Anti-CTLA4
- Anti-TIGIT

Avelumab

- ALK inhibitor (crizotinib and lorlatinib)
- Anti-41BB
- Anti-OX40

Durvalumab

- Chemotherapy
- Radiation
- EGFR/ALK TKI

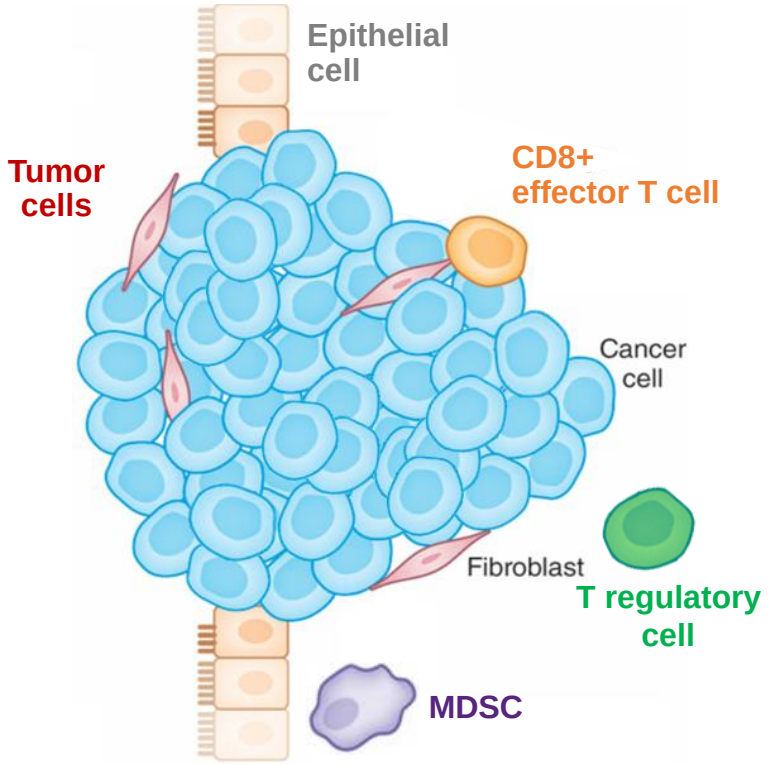
- CSF
- Anti-CD73
- Anti-CCR4
- Anti-CSF1R
- Anti-NKG2A
- Adenosine A2a Inhibitor
- IDO1 Inhibitor
- Anti-CTLA4
- Anti-PD1

HEALTH

A Cancer Conundrum: Too Many Drug Trials, Too Few Patients

By GINA KOLATA AUG. 12, 2017

Immuno-Oncology
Multiple Immune Mechanisms for Resistance



Checkpoint Inhibitors
- Anti-PD-L1
- Anti-PD-1

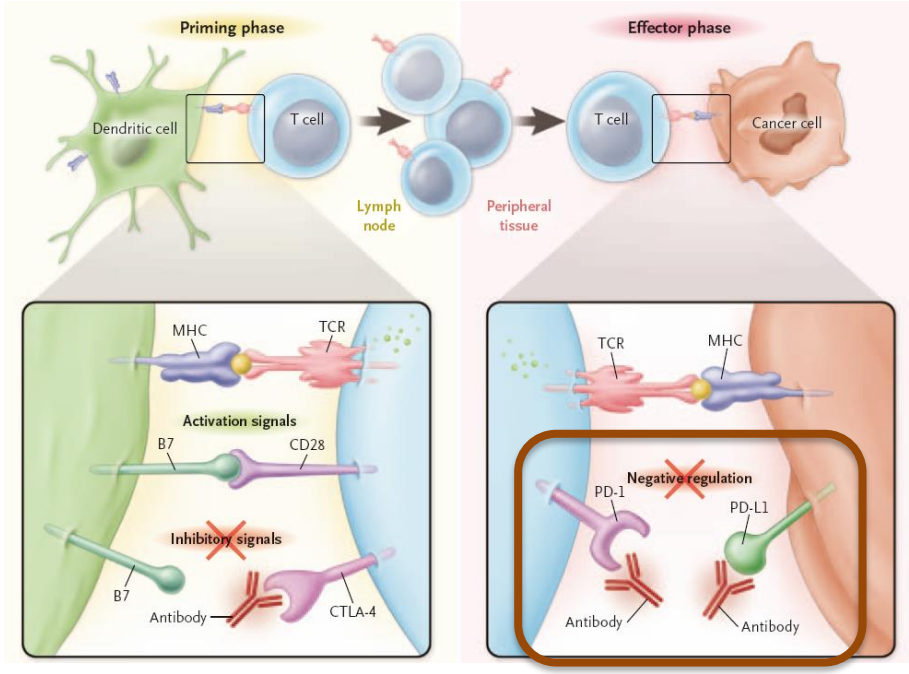
Activate T Cells
- CD137/4-1BB
- OX-40 agonist antibody

Abrogate Suppression from Macrophages & MDSCs
- M-CSF
- IDO1 inhibitor

Transfer Engineered T Cells
- CAR-T

Vaccines, Oncolytic Viruses, Bispecific

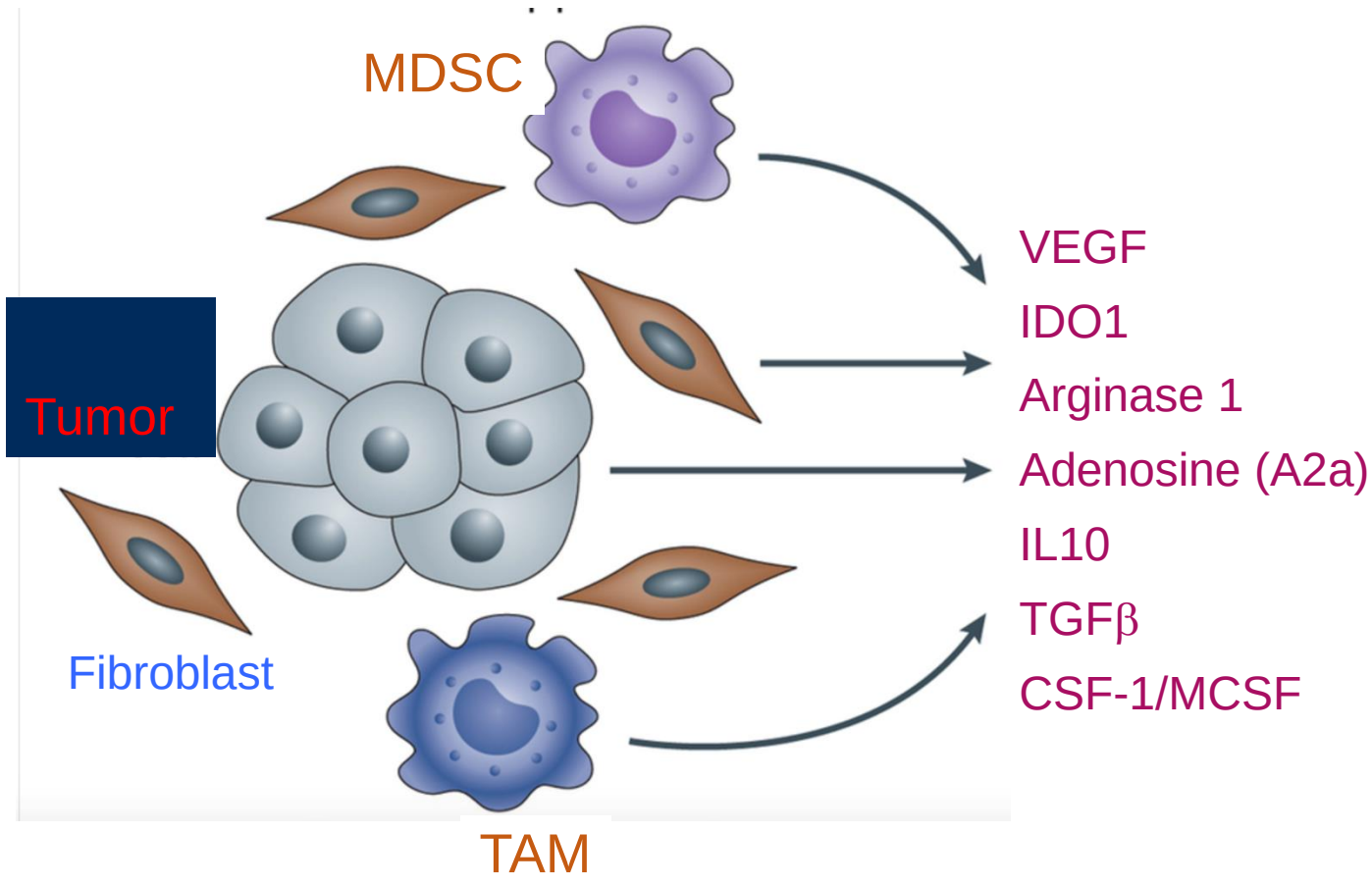
Dual Checkpoint Blockade PD1/PDL-1 and CTLA-4



Early Evidence Suggests Tumor Mutational Burden (TMB) as a Biomarker

Ribas A et al NEJM 2012

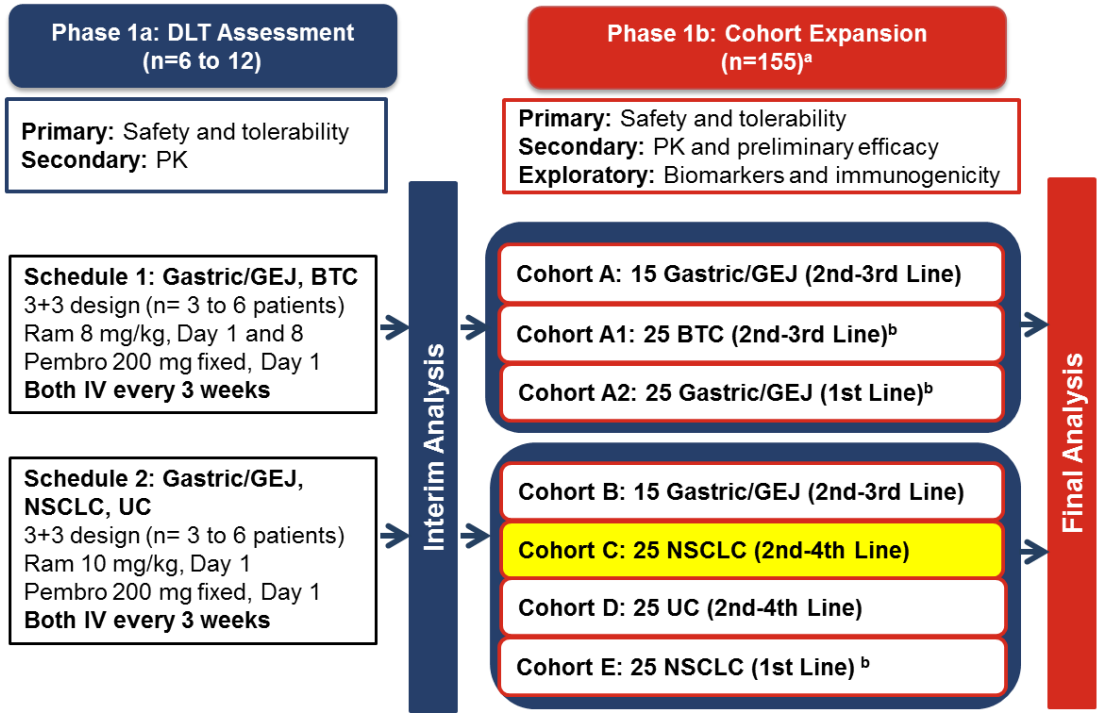
Targeting the Immunosuppressive Microenvironment



Many Ongoing Early Studies- What Will Rise to the Top?

PD1 + VEGF Inhibition: Pembrolizumab plus Ramacirumab

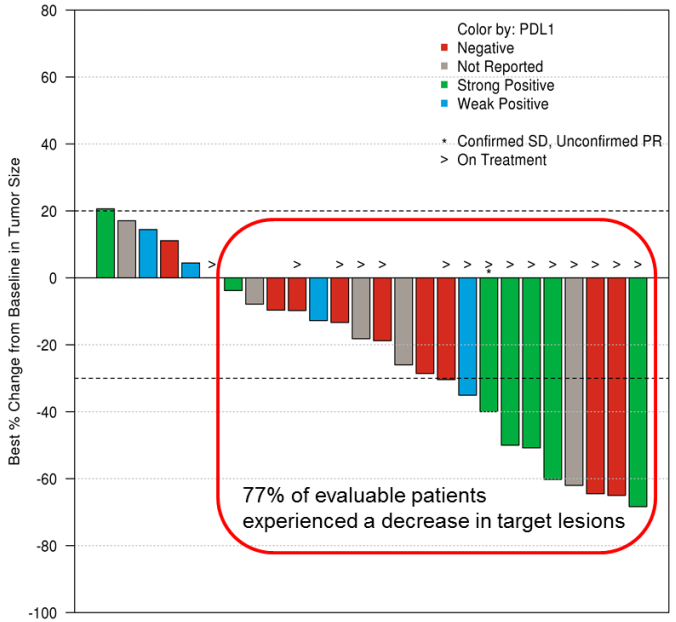
STUDY JVDF (NCT02443324) PHASE 1A/B STUDY DESIGN



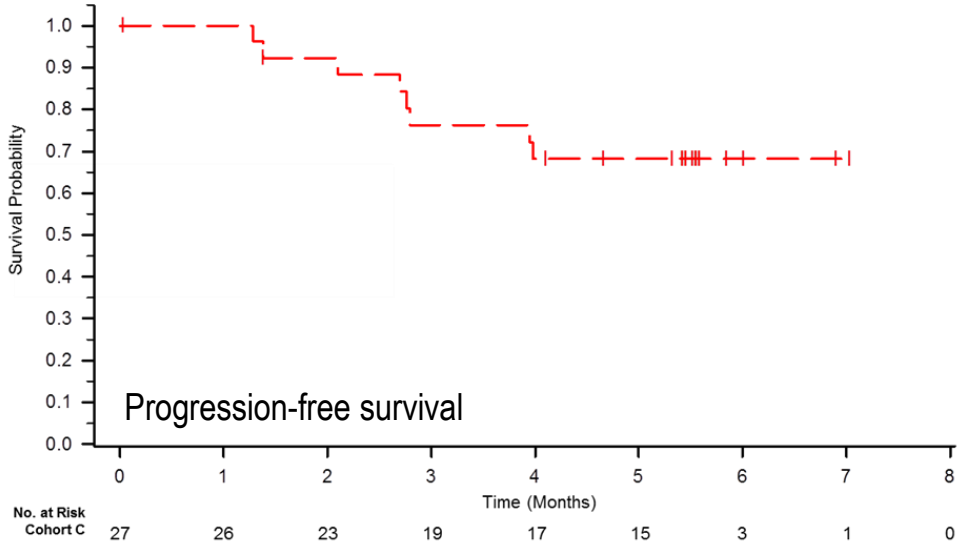
[a]Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason. [b]Protocol was recently amended to add cohorts A1, A2 and E; cohorts are currently enrolling. DLT dose-limiting toxicity; PK pharmacokinetics; Ram ramucirumab; Pembro pembrolizumab

Phase 1 Study Using VEGF Inhibitors to Enhance T Cell Activity

COHORT C: INTERIM CLINICAL ACTIVITY RAMUCIRUMAB + PEMBROLIZUMAB



ITT Population	Cohort C NSCLC (n=27)
Objective response rate, n (%)	8 (30%)
Disease control rate, n (%)	23 (85%)

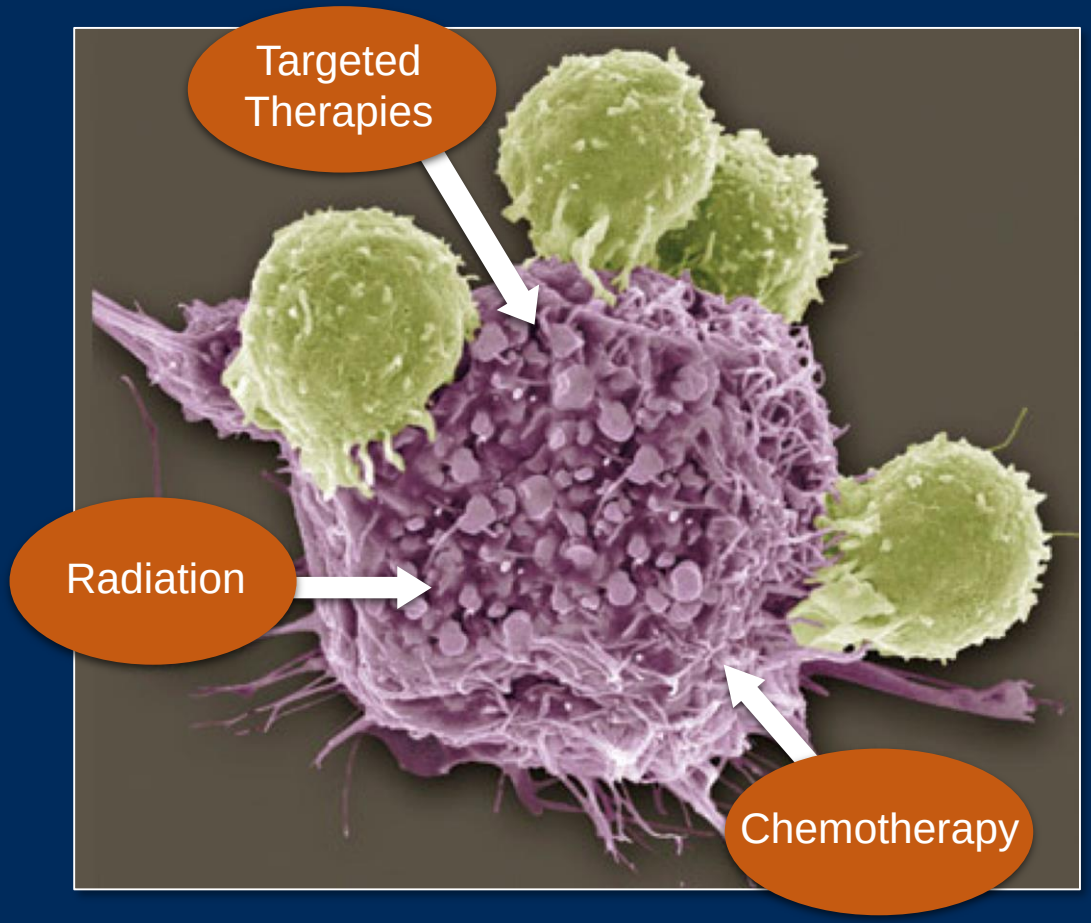


PD-L1 Status	Patients	Events	Median PFS, Mo (95% CI)
All Patients	27	8	NR (3.98, --)
Negative	10	2	NR
Weak positive	4	2	3.98 (2.76, --)
Strong positive	7	2	NR
Not reported	6	2	NR

Herbst et al, 2016 ESMO

Needs Phase II Confirmation and Biopsy Studies re Mechanism!

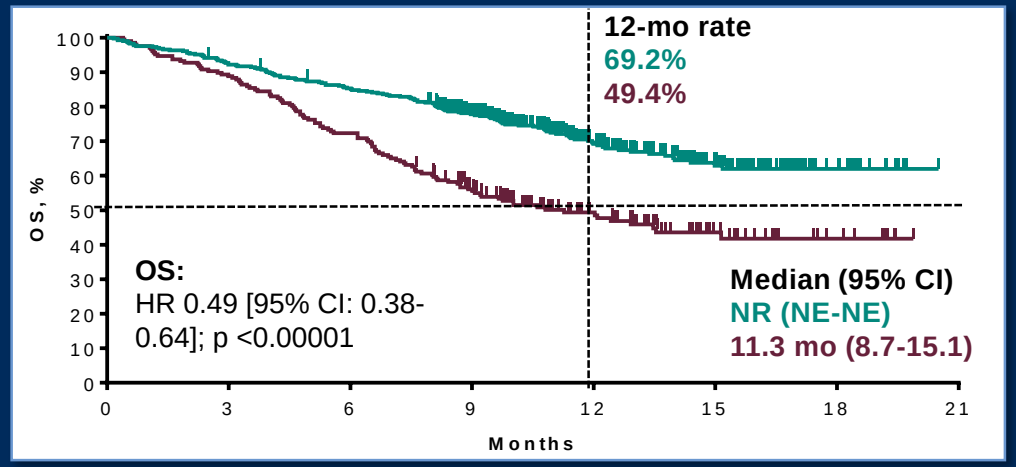
Rationale for Combination Therapy

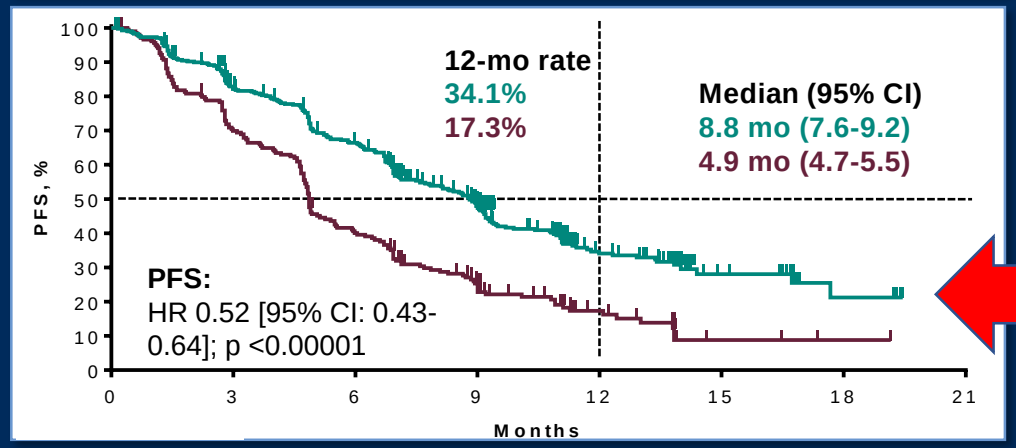


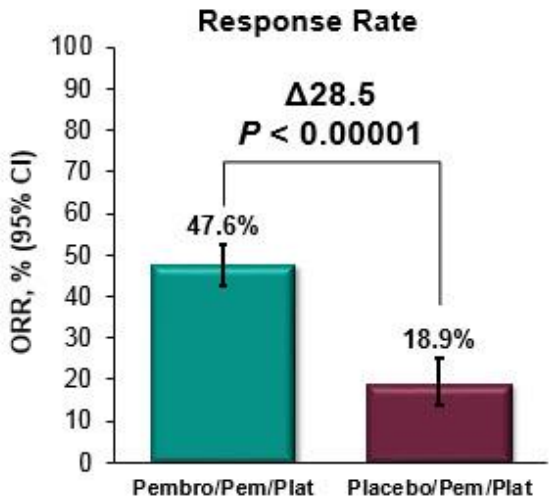
- Reduces tumor bulk – Improves T-cell: tumor target ratio
  - Theoretical concerns exist regarding side effects of cytotoxic chemotherapy on proliferation of T-cells
  - Long term data needed to truly understand the combinatorial effect
- Kills tumor cells in a manner that increases their recognition by T-cells and APC (vaccination)
- Alters T-cell signaling/gene expression to produce T-cell attractants

Adapted from M. Sznol, Yale Cancer Center

Keynote 189: Pembrolizumab (PD1 plus Chemotherapy) Met All Primary Endpoints







Subgroup Analyses

OS: Positive across all subgroups

PFS: Positive across all subgroups except for PD-L1 TPS <1%

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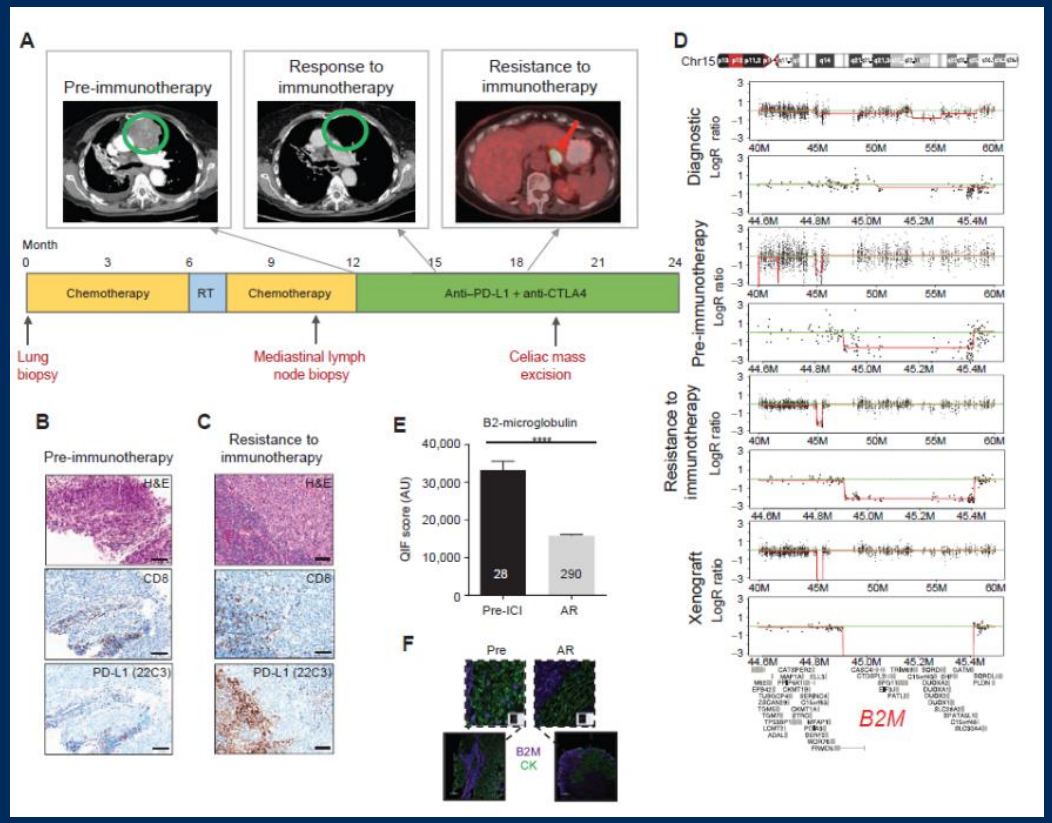
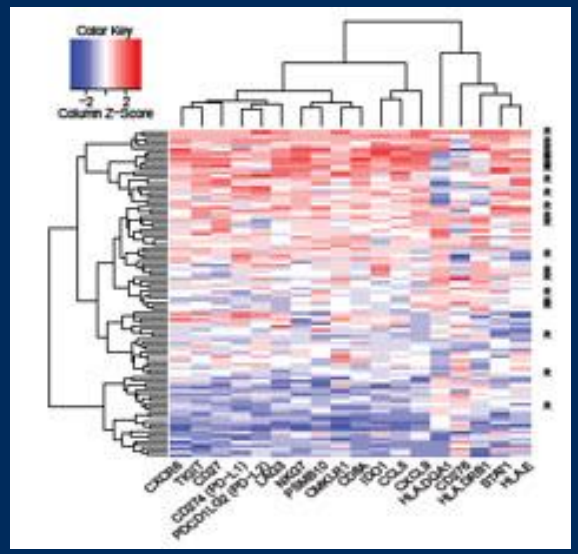
Gandhi et al, NEJM 2018

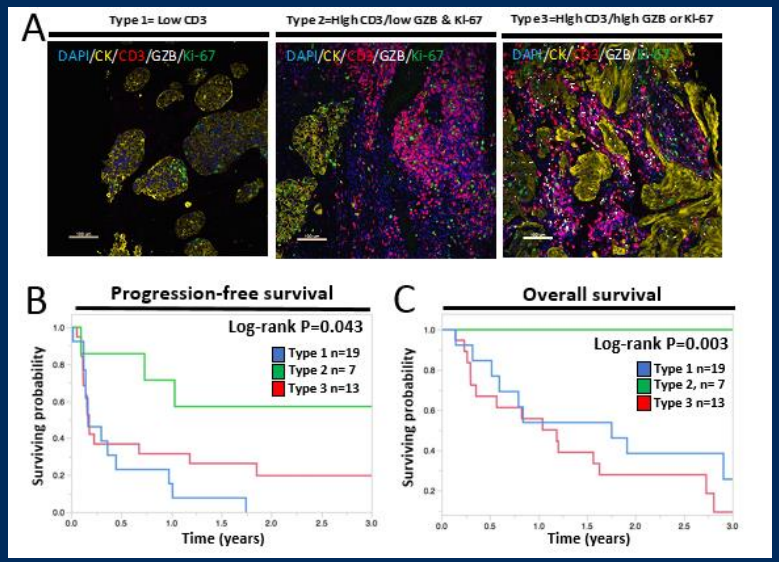
Plan for Discussion

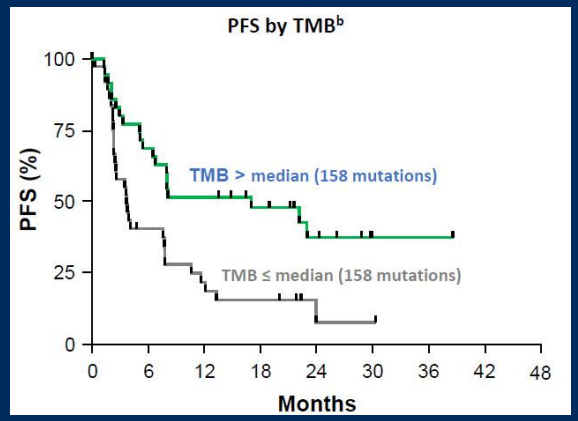
1. Using NSCLC as an example, review both the promise and limitations of immunotherapy
2. Explore the sensitivity and resistance to immunotherapy: Primary vs Acquired
3. Combination Immunotherapy: Principles and Practice
4. The Next step: Personalized Immunotherapy and rational Designs

We need to consider evolving biomarkers (including TMB, Liquid Biopsies, microbiome and Imaging)









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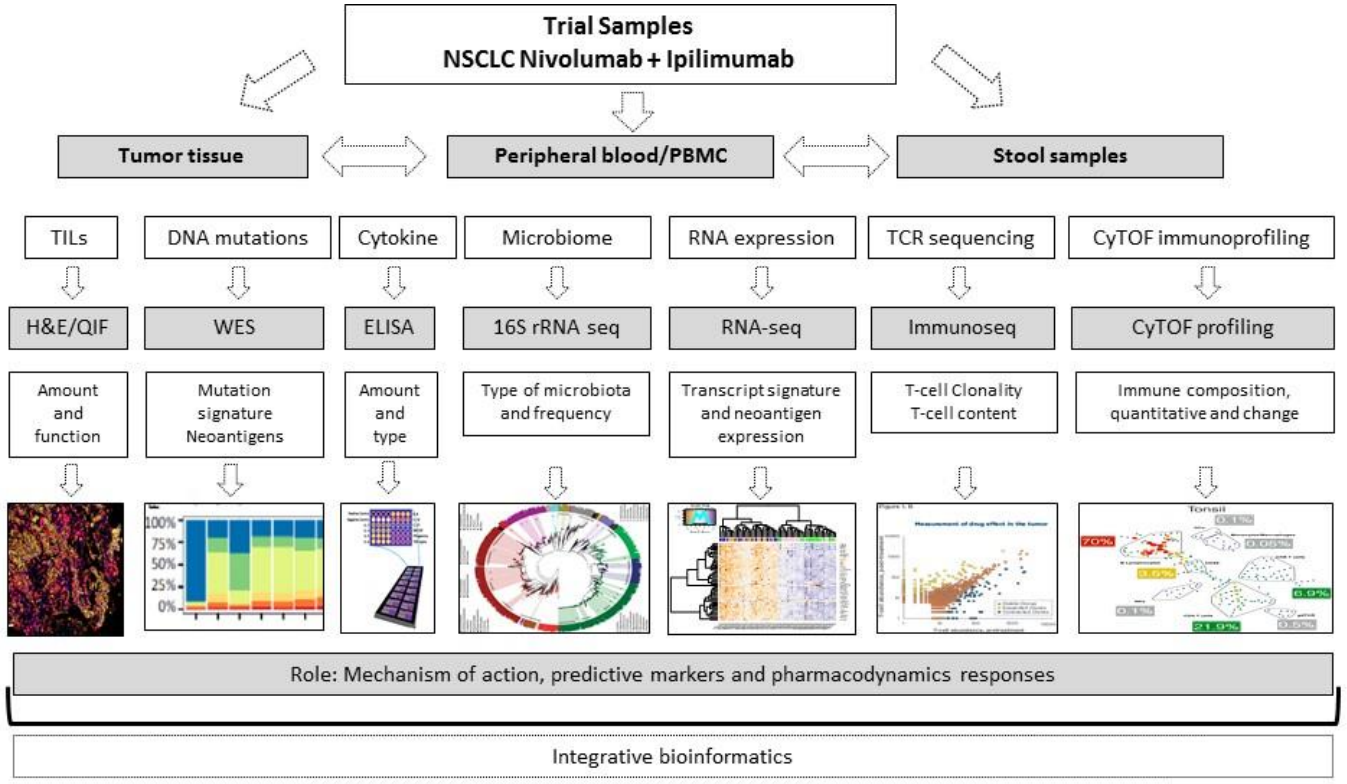
S. Ramalingam AACR 2018 CT 078, K. Schalper et al. Manuscript Accepted; Gettinger et al. Cancer Discovery 2017:7(12):1420-35)

Novel Clinical Trials:

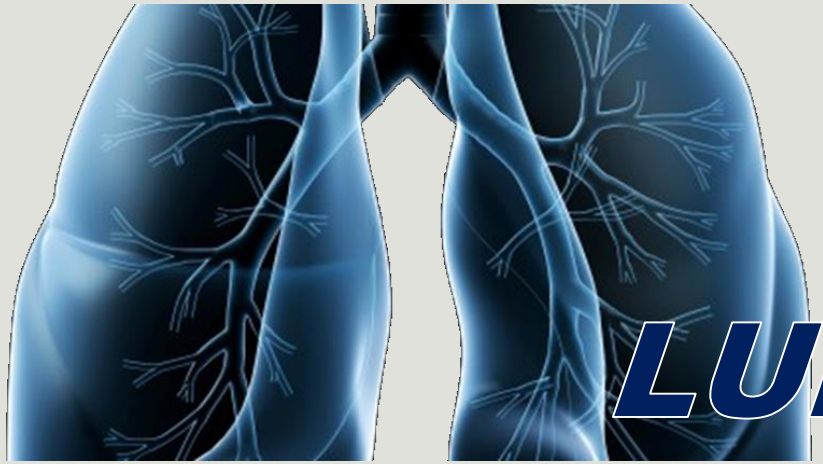
A multi-disciplinary approach to understand response and resistance



PD-L1 PET Imaging

Multi-site trial led by Scott Gettinger
Translational Collaborators:
Richard Flavell
David Hafler
Kurt Schalper
Katie Politi

Imaging Collaborator:
Richard Carson



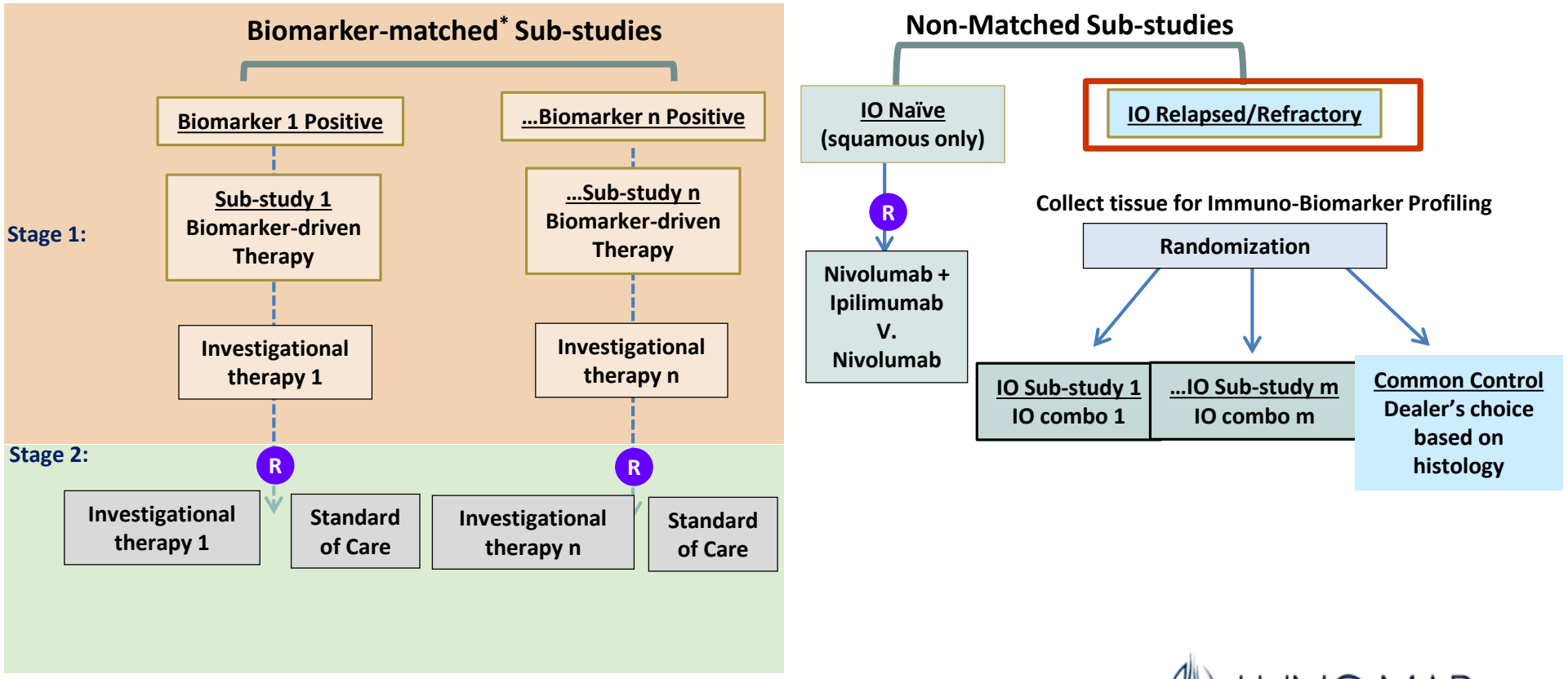
LUNG-MAP

S1400 LUNG MASTER PROTOCOL

LUNG-MAP (S1400): Ongoing Current Amendments

Previously-treated Stage IV or Recurrent Non-Small Cell Lung Cancer (all histologies) Immunotherapy or Chemotherapy Relapsed/Refractory Patients

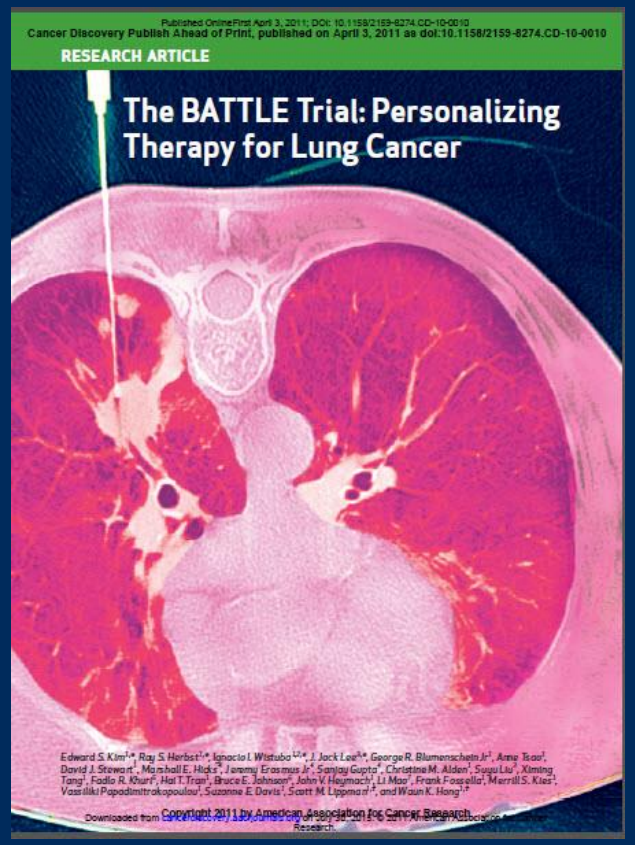
800 US Sites
Over 1700 Patients Enrolled!



LUNG-MAP

Progress in Lung Cancer

The Journey From Targeted Therapy to Immunotherapy for Lung Cancer



Biomarkers don't just involve the tumor anymore!

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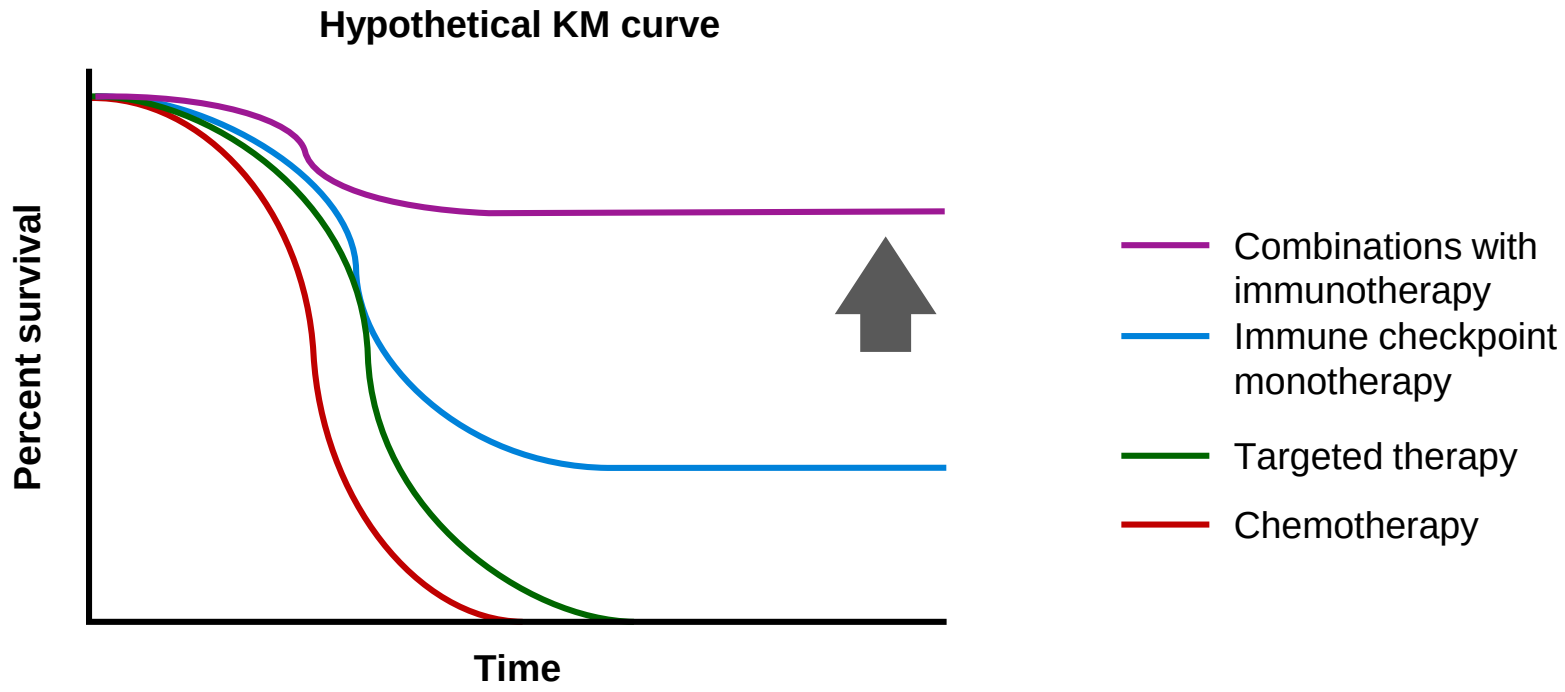
We have spent over 20 years developing personalized mechanisms for administering targteted agents: now the same must be done for IO (with even additional complexity)

To Raise the Tail!!!!



Thank You

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Acknowledgements

The Schalper lab@Yale
Nikita Mani
Ila Datar, PhD
Franz Villarroel, PhD
Micaela Morgado, PhD
Rasikh Tuktamyshov, MD
Matthew Ribeiro
Jacob Usadi
Bailey Hughes (admin)

Yale University
Mario Sznol MD
Lieping Chen, MD, Ph.D.
Miguel Sanmamed MD, PhD
David Hafler, MD
Patricia LoRusso, DO

YPTS & STS lab
Lori Charrette
Joe Salemme
Sudha Kumar
Yalai Bai MD
Veronique Neumeister, MD
John McGuire

The Rimm lab@Yale
Daniel Carvajal, MD
Mehmet Altan MD
Vasso Pelekanou, MD/PhD
Maria Toki, MD
Patricia Gaule, PhD
Lauren Moore
Yuting Liu
James Smithy

Immunosequencing
Roy Herbst, MD, PhD.
Edward Kaftan PhD
Scott Gettinger, MD
Katie Politi PhD
Rick Lifton MD,PhD
Jungmin Choi PhD
Hongyu Zhao, PhD
Xiaoqing Yu, PhD
Susan Kaech, PhD
Paula Kavathas, PhD

SU2C Lung CancerDream Team:
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Justin Gainor, MD
Matt Hellmann, MD

Funding:
Stand Up to Cancer-Dream Team
Yale SPORE in Lung Cancer
Lung Cancer Research Foundation
NIH
DOD LCRP
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