SITC 2015

BIOMARKERS IN CANCER IMMUNOTHERAPY: OASIS OR MIRAGE?

Sunday November 8

Biomarkers in Cancer Immunotherapy: Overview

SITC 2015

9:30 a.m. – 9:45 a.m. **Welcome and The Science of Biomarkers**	**Daniel S. Chen, MD, PhD – Genentech**
9:45 a.m. – 10:15 a.m. **Biomarkers for Cancer Immunotherapy Debate**	**Moderator: Maria Karasarides, PhD – AstraZeneca** **Pro: Daniel S. Chen, MD, PhD – Genentech** **Con: Steve Averbuch, MD – Bristol-Myers Squibb**
10:15 a.m. – 11:05 a.m. **Panel Discussion with Open Audience Questions**	**Moderator: Maria Karasarides, PhD – AstraZeneca** **Steve Averbuch, MD – Bristol-Myers Squibb** **Daniel S. Chen, MD, PhD – Genentech** **Marc Theoret, MD – US Food and Drug Administration** **Thomas Gajewski, MD, PhD – University of Chicago** **Jeffrey Weber, MD, PhD – New York University**
11:05 a.m. – 11:35 a.m. **Other Topics in Biomarkers Discussion:** **Blood-Based Markers** **Tissue Markers**	**Moderator: Adrian Bot, MD, PhD – Kite Pharma, Inc.** **Michael D. Kalos, PhD – Eli Lilly and Company** **Naiyer Rizvi, MD – Columbia University Medical Center**
11:35 a.m. – 11:55 a.m. **Future Biomarkers Panel Discussion**	**Moderator: Adrian Bot, MD, PhD – Kite Pharma, Inc.** **Lisa H. Butterfield, PhD – University of Pittsburgh** **Suzanne L. Topalian, MD – Johns Hopkins University** **Michael D. Kalos, PhD – Eli Lilly and Company** **Naiyer Rizvi, MD – Columbia University Medical Center**
11:55 a.m. – Noon **Closing Remarks**	**Michelle Dawson, PhD – Bristol-Myers Squibb**

Biomarkers for Cancer Immunotherapy in 10 minutes.

SITC Annual Meeting 2015

Daniel S. Chen MD PhD |
Cancer Immunotherapy Franchise Head, Product Development, Genentech/Roche
Adjunct Clinical Faculty, Stanford University

CancerImmunology

Roche

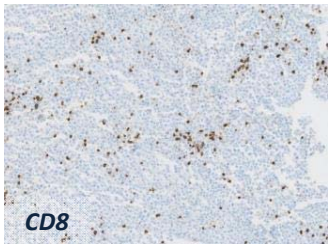
Genentech
A Member of the Roche Group

Objectives

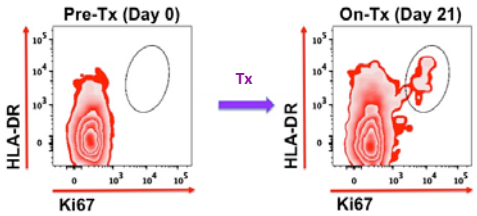
Cancer Immunotherapy Biomarker Efforts

- **Predictive-** *Identifying subsets of patients for whom a cancer immunotherapy is most likely to be effective*

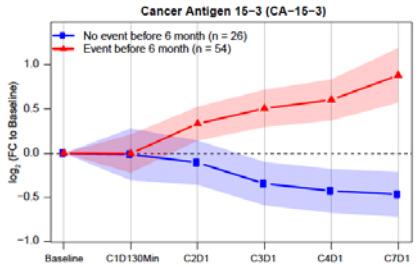
- **Prognostic-** *Identifying markers that are associated with a favorable or poor disease-related outcome*



- **Pharmcodynamic-** *mechanism related biomarkers modulated by a therapeutic intervention*



- **On-treatment marker of efficacy-** biomarkers that are measured during or after a therapeutic intervention that are associated with biologic activity and clinical efficacy



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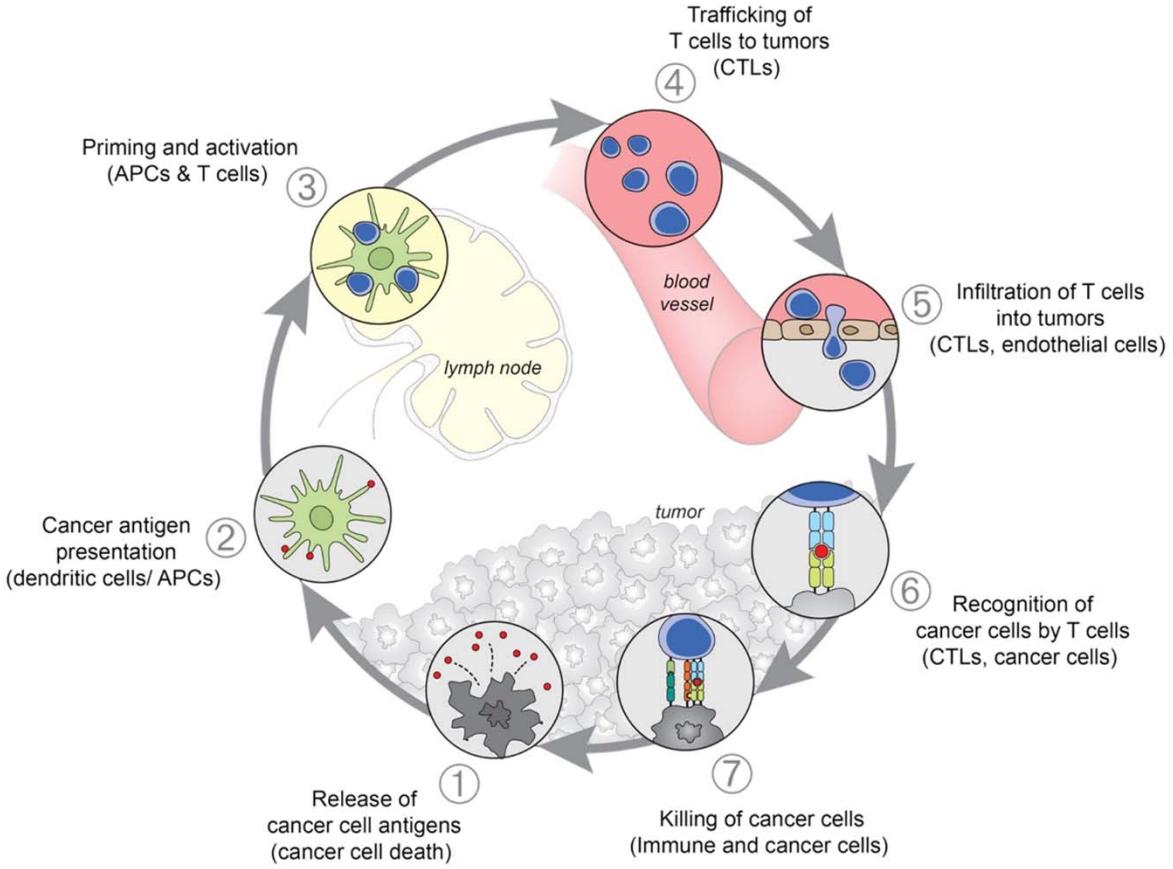
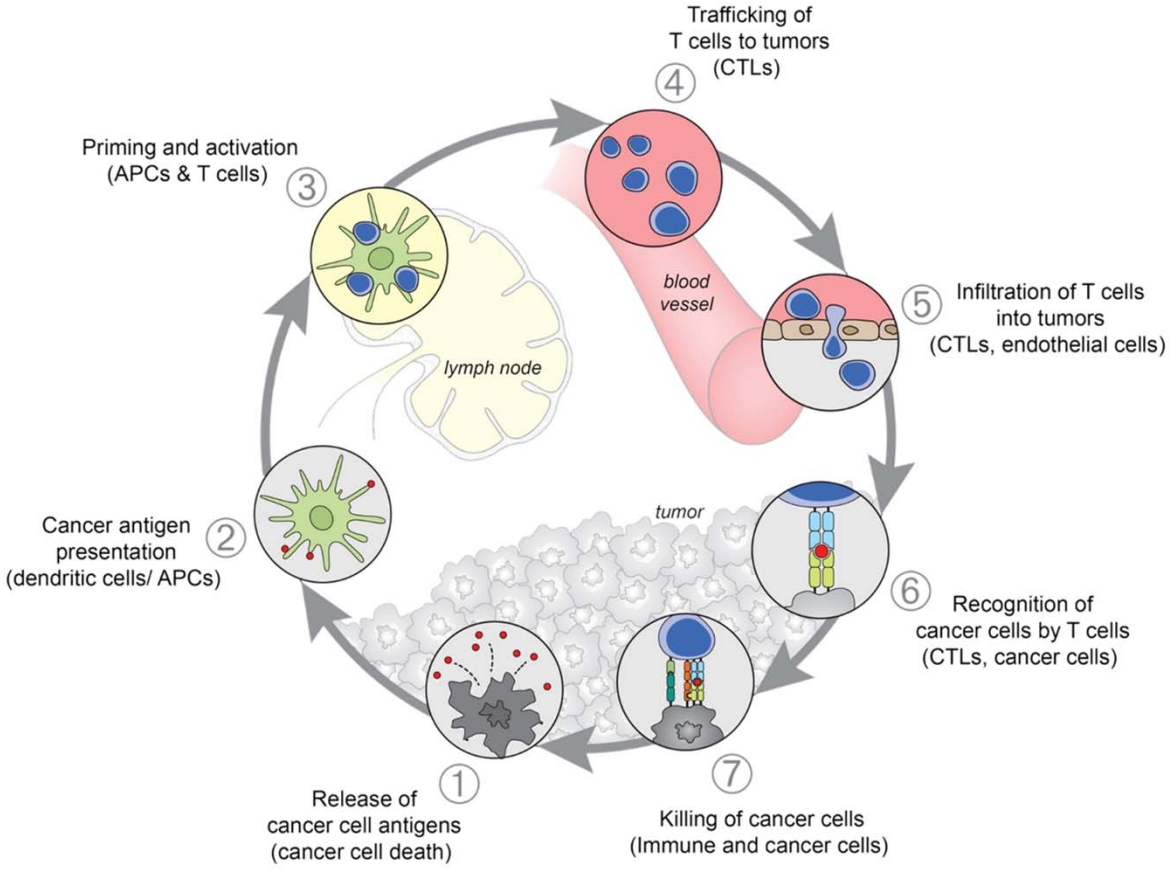
Start with the Biology: The Cancer-Immunity Cycle



Chen DS, Mellman I. *Immunity*. 2013.

Consider the Sample



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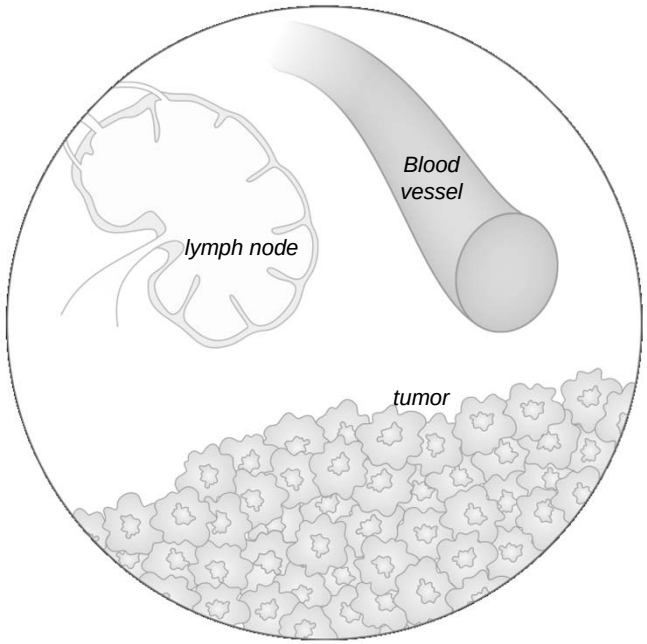

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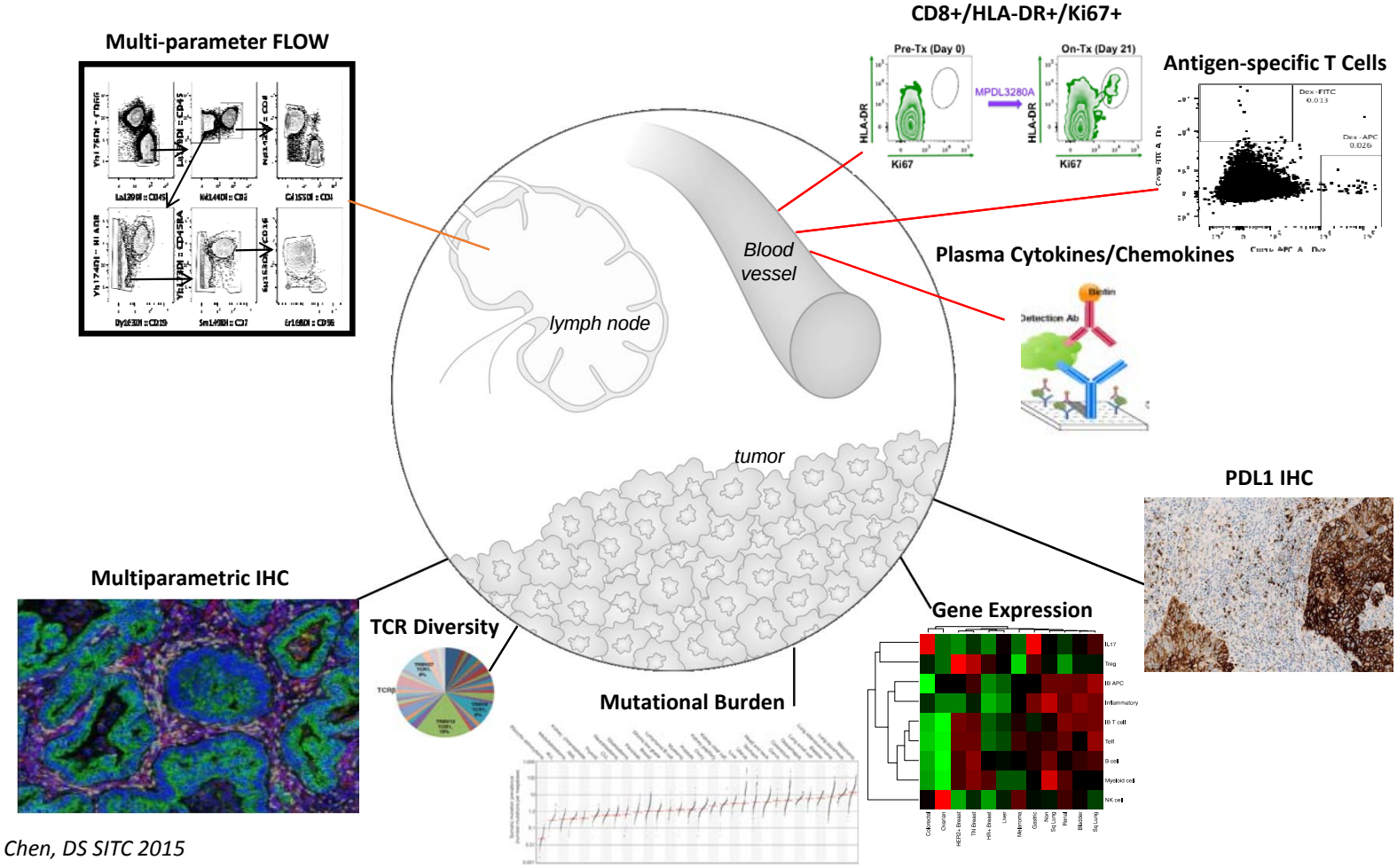

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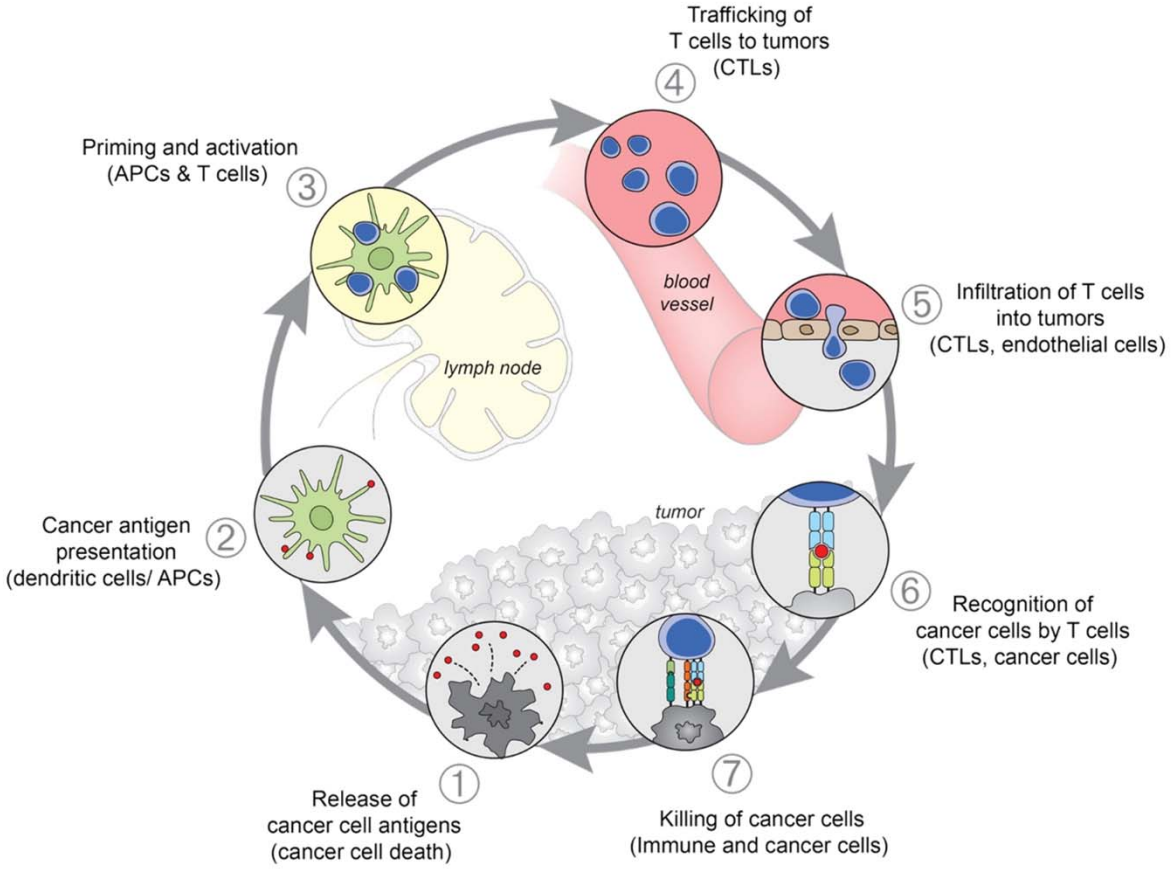

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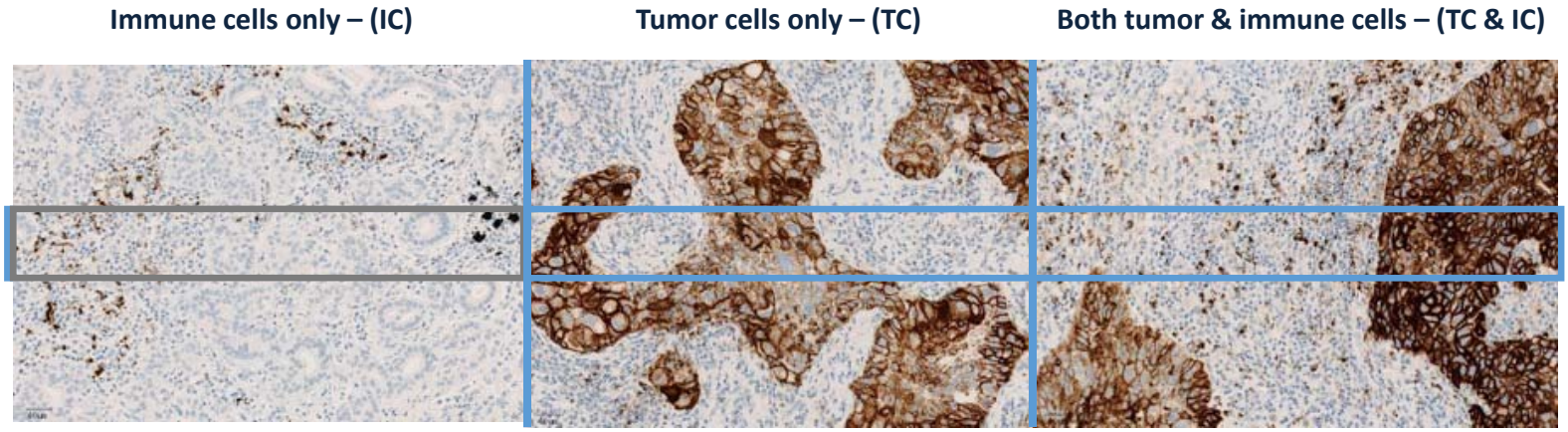
PD-L1 is a Critical Source of Immune Suppression in Cancer



Predictive of benefit in bladder cancer (ORR/OS)[1]

Predictive of benefit in lung cancer (ORR/PFS/OS)[2]

WCLC 2015

[1]IMvigor 210 ECC 2015, [2]POPLAR ECC 2015

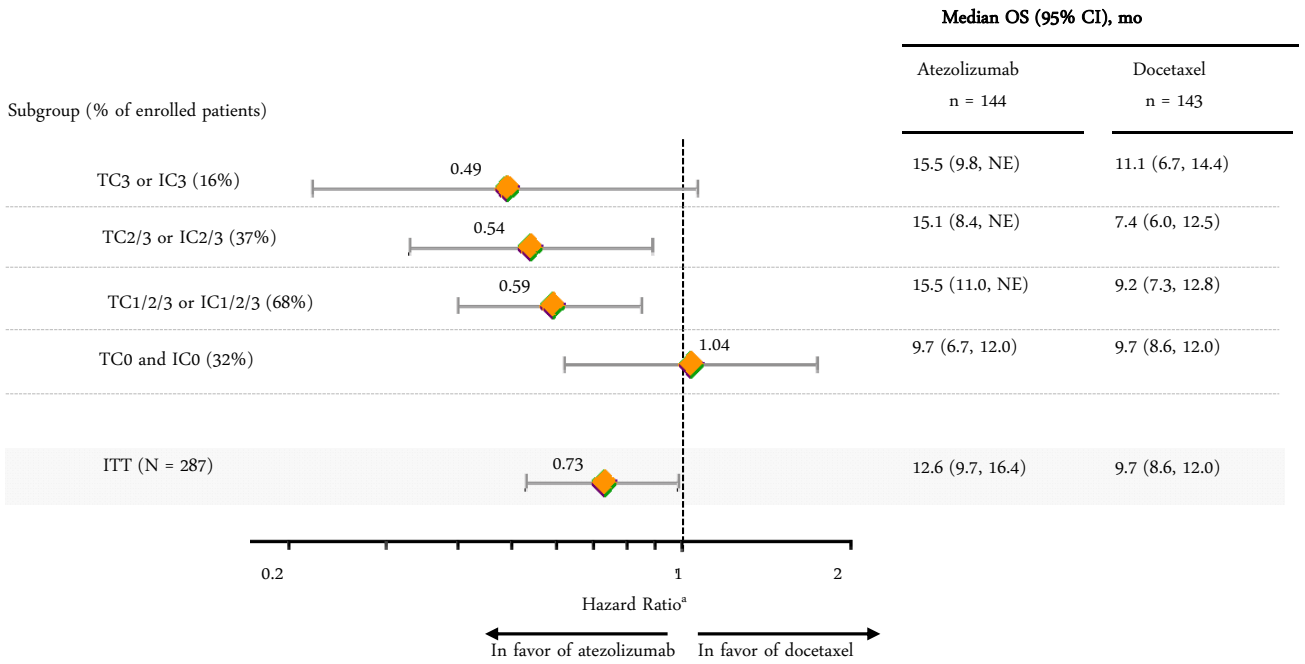
Interpreting PD-L1 IHC Biomarker Data: *a Checklist*

- What IHC antibody is being used? In what disease?
- Does this IHC antibody reliably stain human FFPE tumor tissue?
- Can appropriately trained pathologists provide concordant scoring of stained tissue?
- What tissue is being used to assess PD-L1 by IHC?
- What is the definition of PD-L1+ with this assay?
  - Cutoffs?
  - PD-L1 on immune cells or tumor cells or both or neither?

What is treatment effect on PD-L1+ vs PD-L1- from randomized studies on PFS and OS? Activity can be seen by ORR, but to define benefit generally requires PFS, OS (unless ORR is very high)

Atezolizumab: PDL1 biomarker and OS

POPLAR: 2L+ NSCLC



Atezolizumab: Doubled likelihood of survival in PD-L1-high tumors (IC2/3 or TC2/3)

Vansteenkiste et. al. ECC 2015

Nivolumab and Pembrolizumab: PDL1 biomarker and OS

Checkmate-057 and Checkmate-017: 2L+ NSq and 2L Sq NSCLC

Nivolumab efficacy (at 3mg/kg Q2W) in 2L+ NSq[1] and Sq[2] NSCLC

	ORR (%)*		mPFS (mos)		mOS (mos)		
	NSq	Sq	NSq	Sq	NSq	Sq	
All patients	19	20	2.3	3.5	**12.2**	**9.2**	← All Patients
≥1%	31	18	n/a	n/a	17.7	9.3	
≥5%	36	21	n/a	n/a	19.4	10	
≥10%	37	19	n/a	n/a	**19.9**	**11**	← PDL1 High

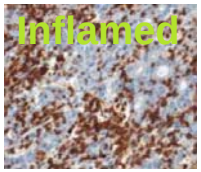
Keynote-001: 2L+ NSq and Sq NSCLC

Pembrolizumab efficacy (at 10mg/kg Q2W or Q3W) in 2L+ NSCLC (both histology)[3]

	ORR (%)[4]	mPFS (mos)	mOS (mos)	
All patients	18	3.0	**11.3**	← All Patients
TPS ≥1%	9	2.1	8.6	
TPS 1-49%	15	2.3	7.8	
TPS ≥50%	41	5.8	**15.5**	← PDL1 High

[1] Paz-Ares et al., ASCO 2015; [2] Spigel et al., ASCO 2015; [3] Soria et al., ECC 2015; [4] Rivzi et al., NEJM 2015

Immune Biology and Biomarker Associations are Strong



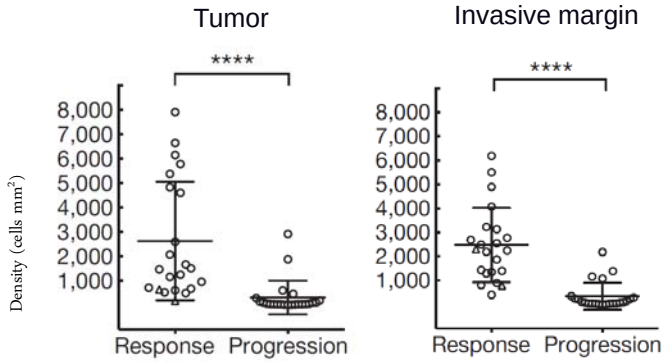
PD-L1 expression

IFN-γ producing CD8+ T cells

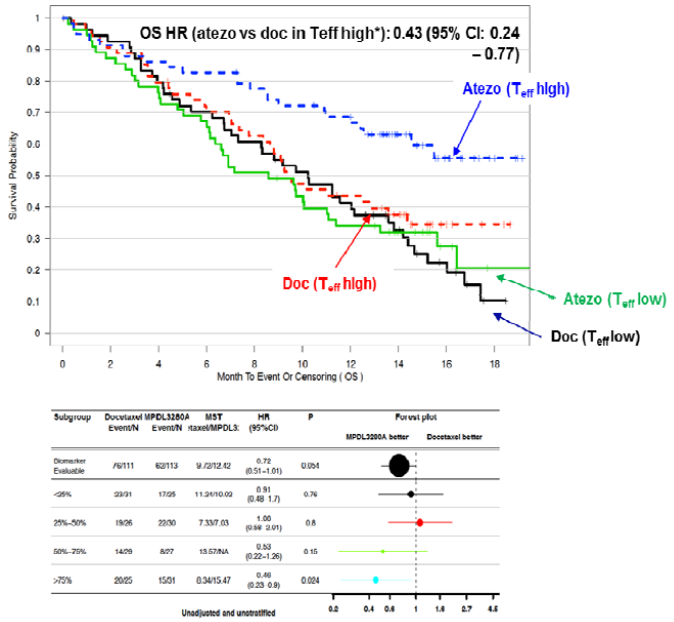
Genomic instability

Pre-existing immunity

CD8+ T cell density associated with response to pembrolizumab in melanoma[1]

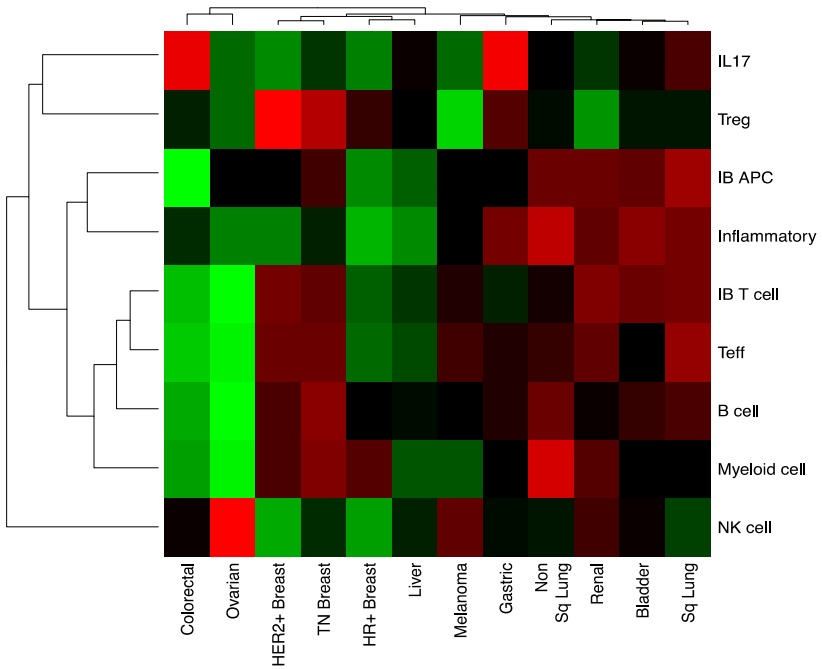


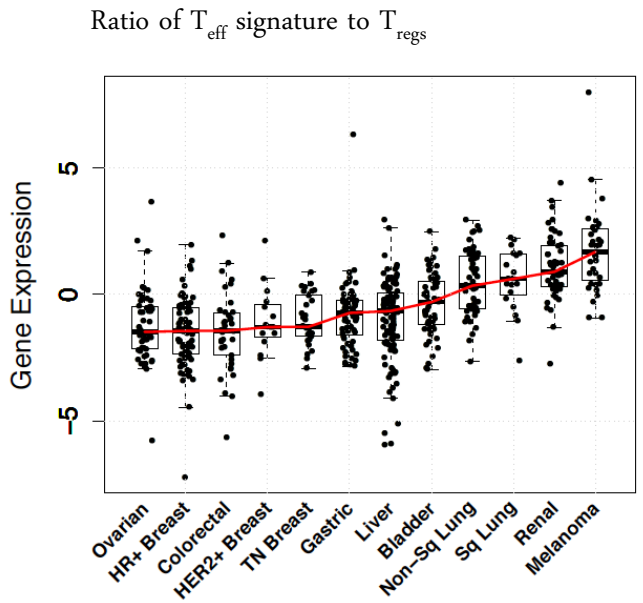
Tumor T_{eff} gene signature associated with OS with atezolizumab in NSCLC[2]



- 1. Tumeh, et al. Nature 2014
- 2. Schmid, et al. ECC 2015

Diversity in the tumor immunome

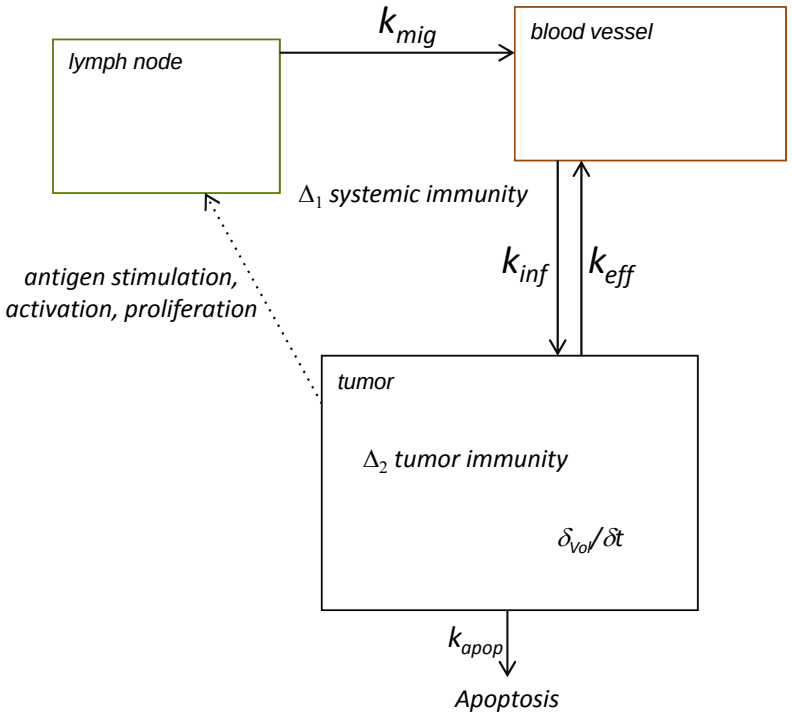




Hegde PS TAT 2015

So What's the Problem?

A Complex System



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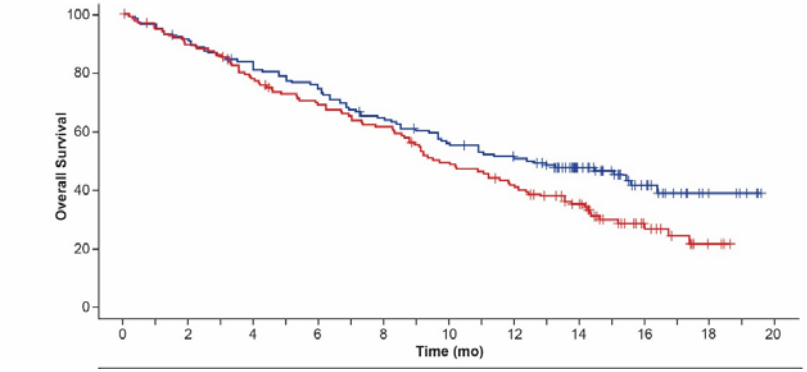
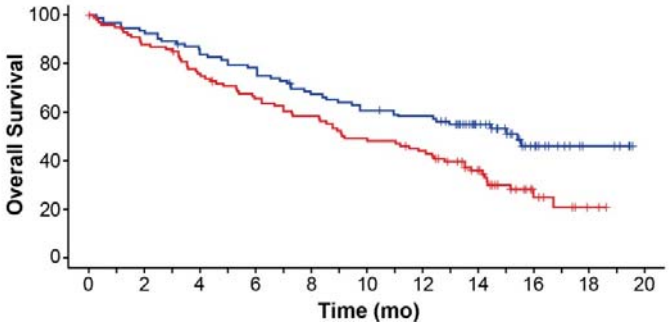
So What's the Problem?

Some Biomarker Negative Patients will Benefit with Durable Responses

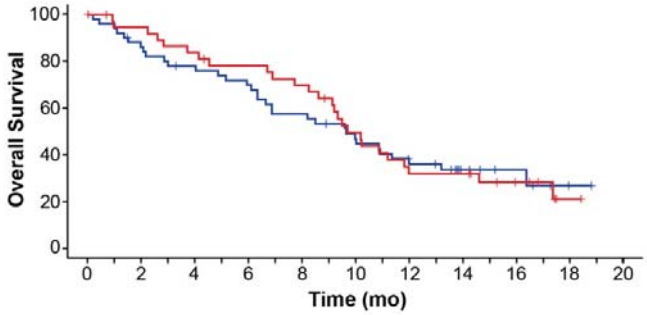
Unselected Patients



Biomarker+ Patients



Biomarker- Patients



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