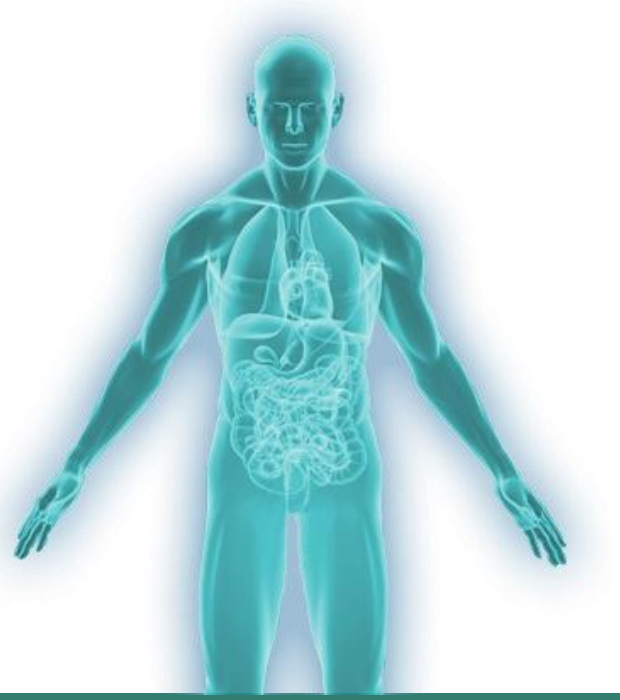
The Role of Immuno-Oncology Biomarkers in Lung Cancer

Vamsidhar Velcheti, MD, FACP
Staff Physician, Associate Director
Center for Immuno-Oncology Research
Taussig Cancer Institute | Cleveland Clinic



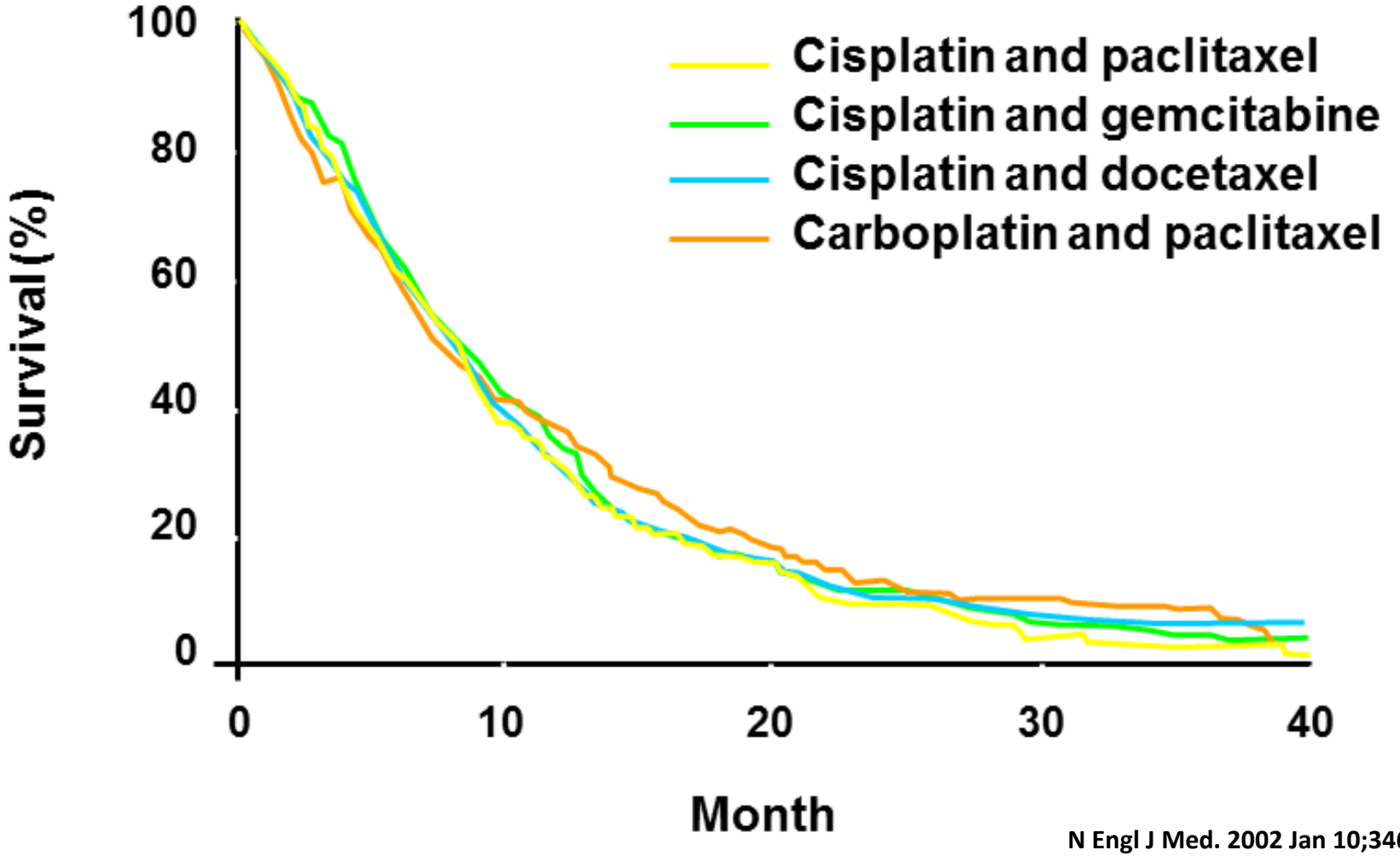
November 13, 2017

Disclosures

I will be discussing off-label indications and usage of drugs or biomarker assays that are currently FDA approved for other indications, or not FDA approved.

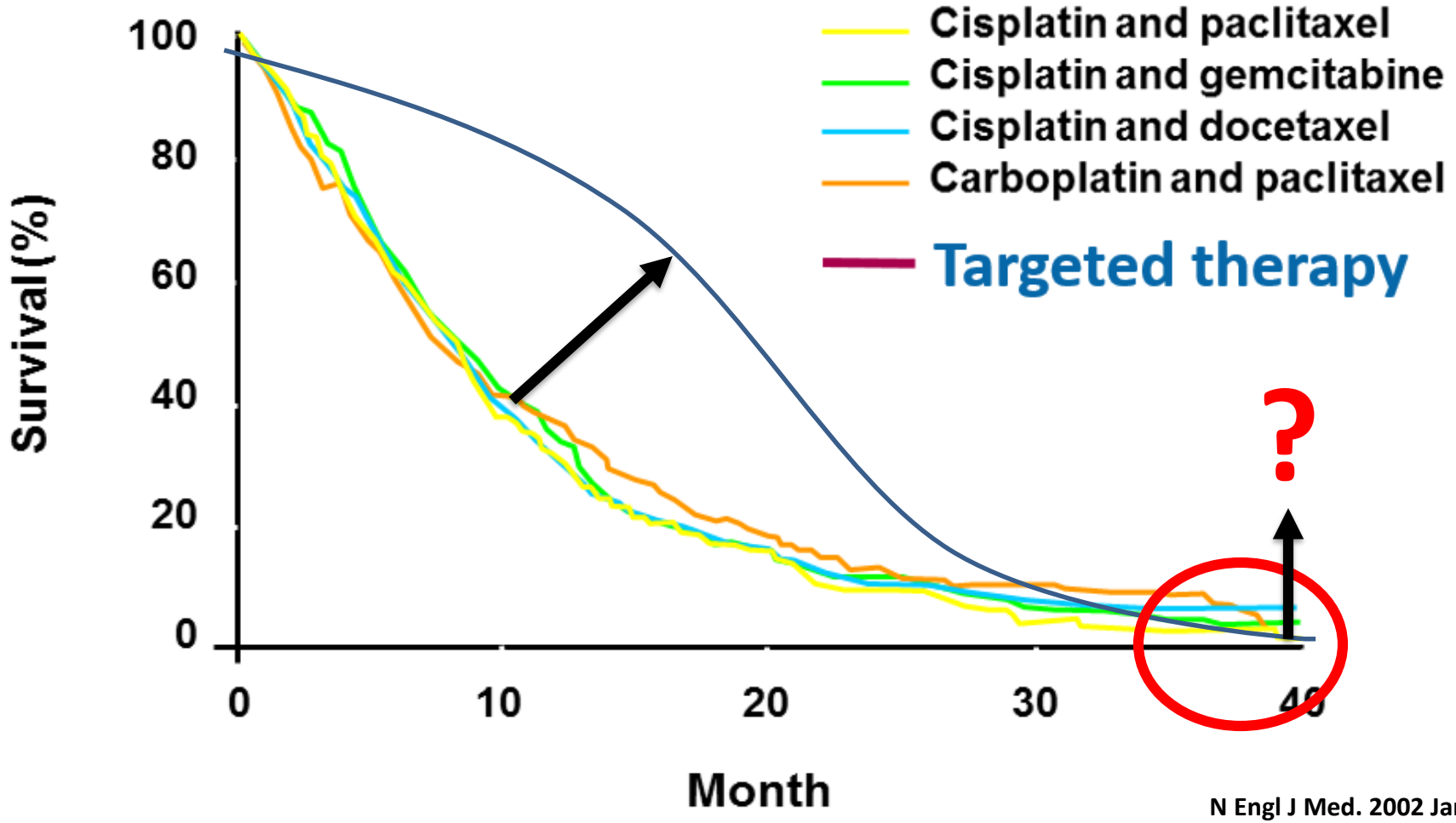
- Consultant/Advisory Board
  - Merck
  - Bristol-Myers Squibb
  - Genentech
  - Celgene
  - AstraZeneca
  - Navigate BioPharma
  - Foundation Medicine
  - Takeda Oncology
  - Fulgent Genetics

Treatment of Advanced Stage Non-small Cell Lung Cancer



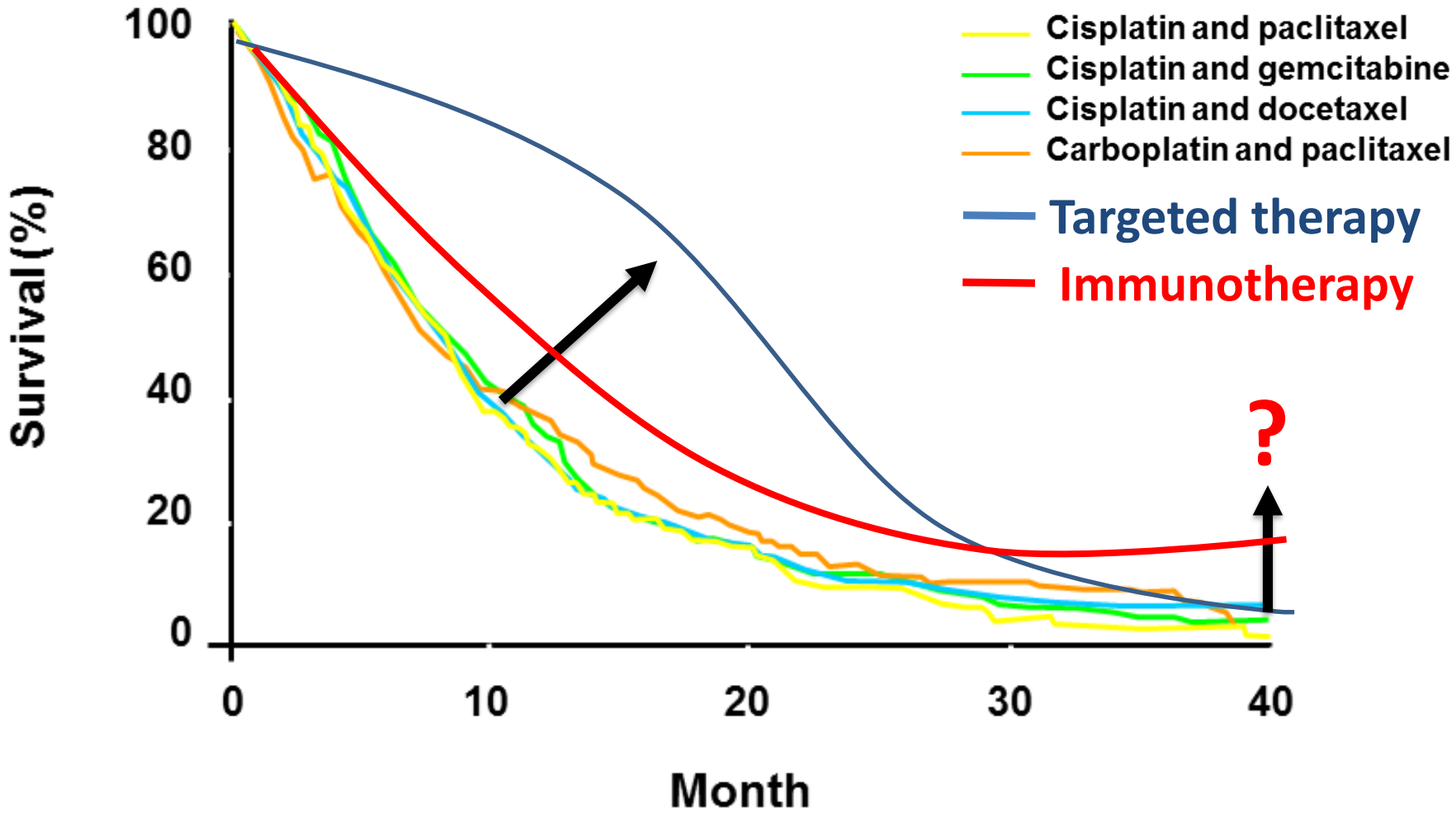
N Engl J Med. 2002 Jan 10;346(2):92-8.

Treatment of Advanced Stage Non-small Cell Lung Cancer



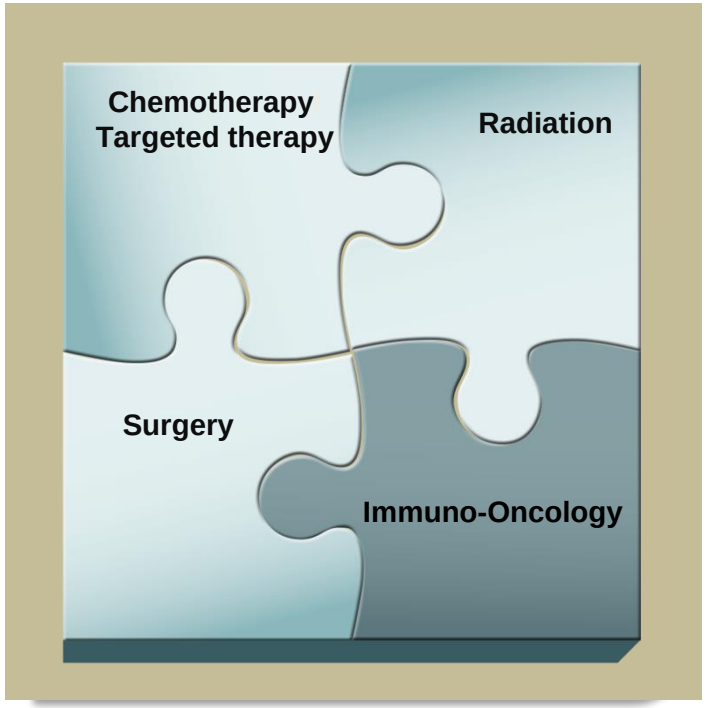
N Engl J Med. 2002 Jan 10;346(2):92-8.

Treatment of Advanced Stage Non-small Cell Lung Cancer



I-O: Evolving Cancer Treatment Modality

- I-O is a fundamentally different approach to fighting cancer that harnesses the body's own immune system[1]

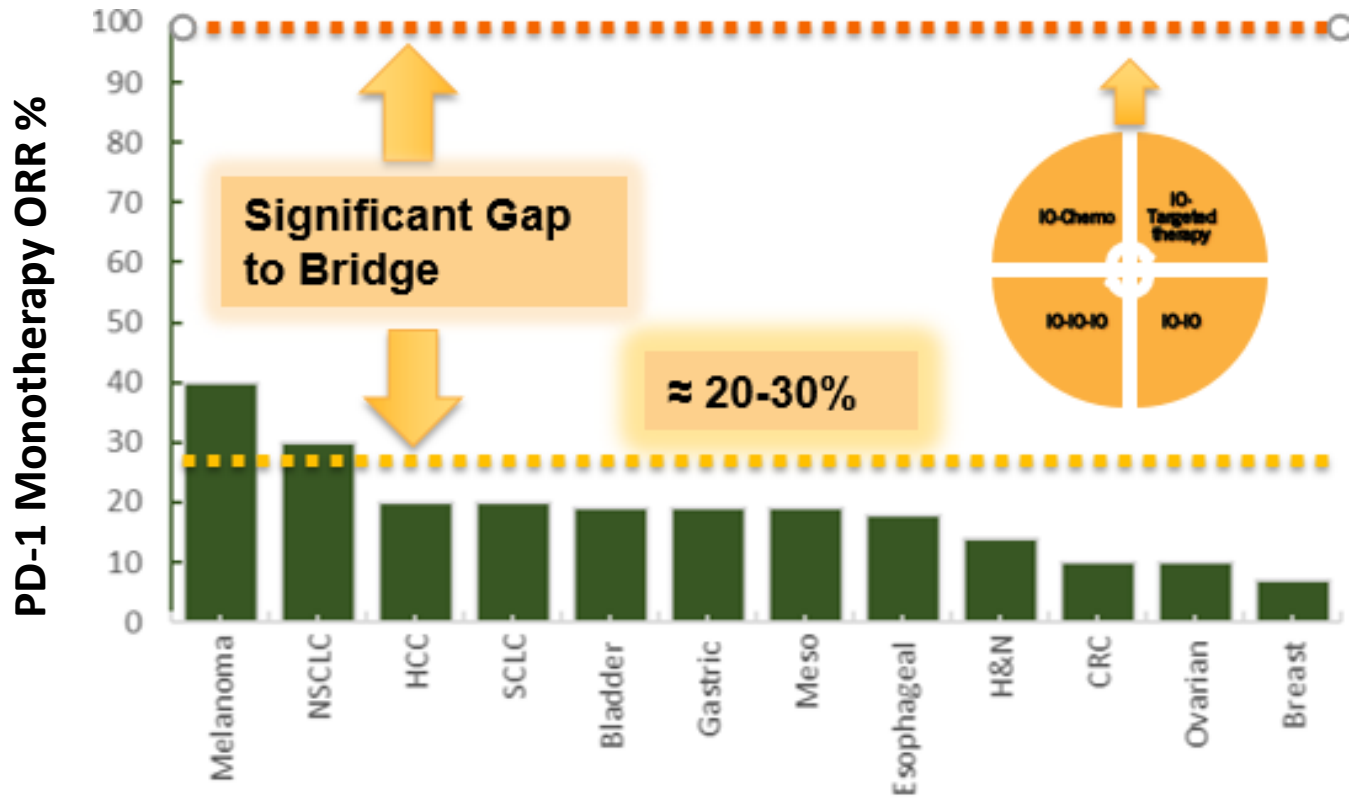


I-O, immuno-oncology.

1. Murphy JF. *Oncology*. 2010;4:67-80.
2. Kirkwood JM et al. *CA Cancer J Clin*. 2012;62(5):309-335.
3. Borghaei H et al. *Eur J Pharmacol*. 2009;625(1-3):41-54.

Through I-O research, therapies are being investigated in an attempt to utilize the body's own immune system to fight cancer[1-3]

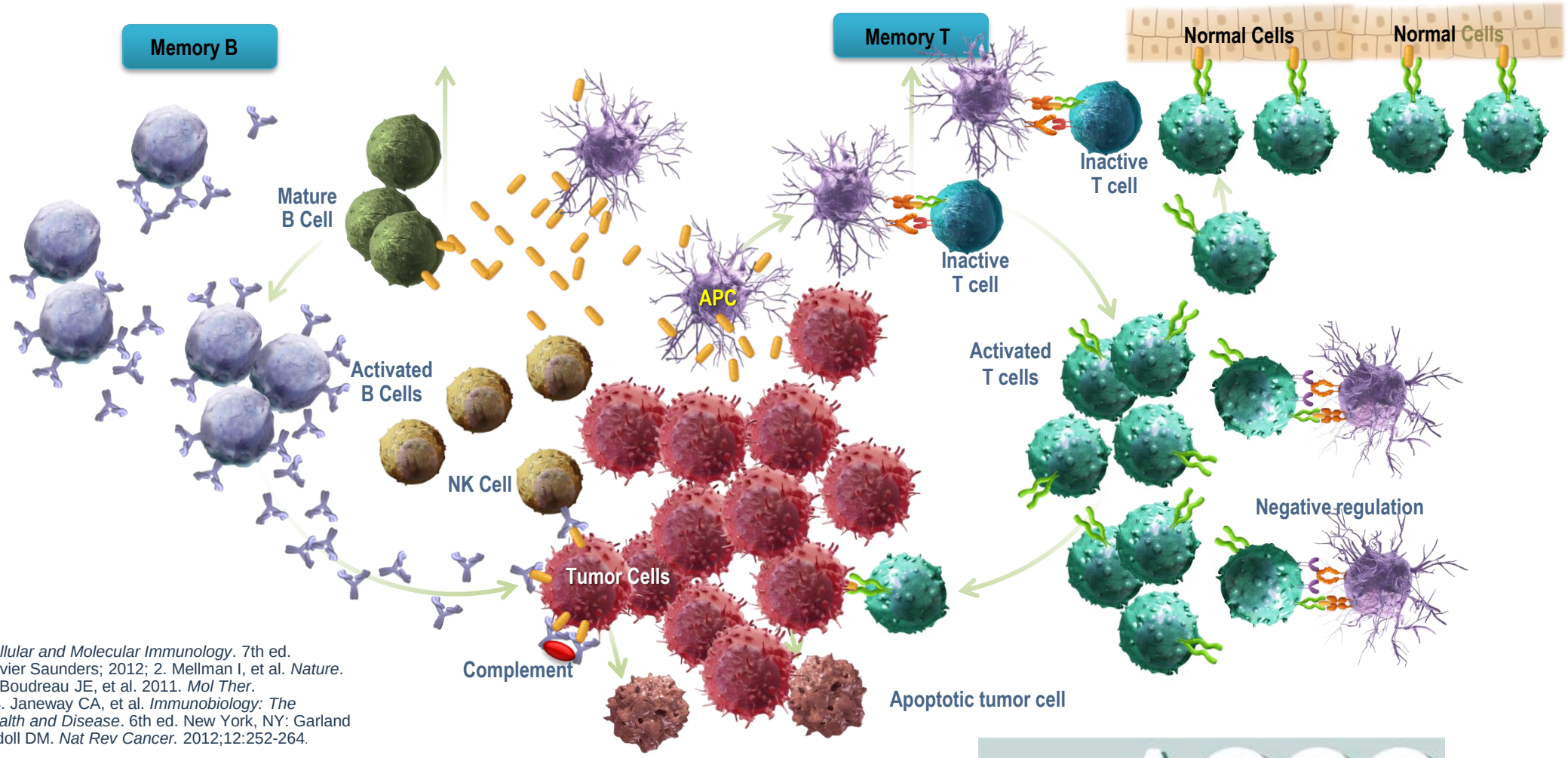
Emerging Challenge in Cancer Immunotherapy



"Bridging the Gap" Requires

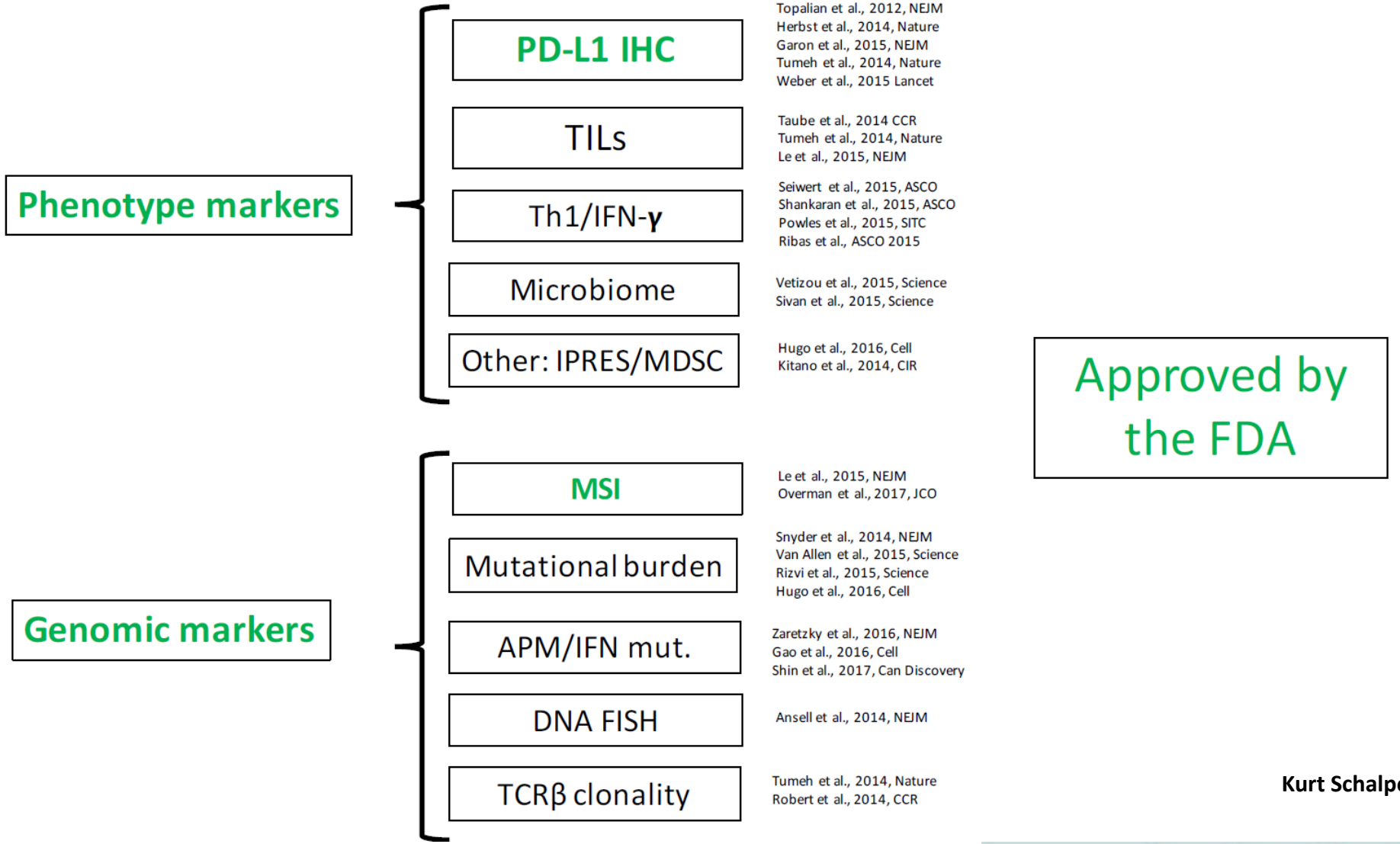
- ❑ Identifying patients that would benefit the most from immunotherapy
- ❑ Identifying patients at high risk for serious irAEs
- ❑ Rational combinations based on sound mechanistic principles

The Immune Response to Cancer: Very Complex Balance Between Continuous Activation and Suppression



1. Abbas AK, et al. *Cellular and Molecular Immunology*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2012; 2. Mellman I, et al. *Nature*. 2011;480:480-489; 3. Boudreau JE, et al. 2011. *Mol Ther*. 2011;19(5):841-853; 4. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease*. 6th ed. New York, NY: Garland Science; 2004; 5. Pardoll DM. *Nat Rev Cancer.* 2012;12:252-264.

Approved Biomarkers for Immuno-oncology Diagnostics



Kurt Schalper ASCO 2017

Current FDA-approved PD-1 Inhibitors and Diagnostic Biomarkers in Lung Cancer

Drug	FDA Approval	Indication	Companion Diagnostic	Complementary Diagnostic
Nivolumab	March 2015	2nd Line advanced stage NSCLC (Squamous Cell Carcinoma)	None required	DAKO- 28.8 PD-L1 IHC (1%, 5% and 10%)
Nivolumab	October 2015	2nd Line advanced stage NSCLC (Non-Squamous Cell Carcinoma)	None required	DAKO- 28.8 PD-L1 IHC (1%, 5% and 10%)
Pembrolizumab	October 2015	2nd Line advanced stage NSCLC	DAKO- 22C3 PD-L1 IHC >1% TPS, 1-49%	
Atezolizumab	April 2016	2nd Line advanced stage NSCLC	None required	Ventana- SP142, TC=Tumor cell IC = Immune cell Combine both Percentage and Subjective intensity++
Pembrolizumab	October 2016	1st Line advanced stage NSCLC	DAKO-22C3 PD-L1 IHC >50% TPS*	
Pembrolizumab with Carboplatin/Pemetrexed	May 2017	1st Line advanced stage NSCLC (Non-Squamous Cell Carcinoma)	None required	
Durvalumab		Stage III Non-small cell lung cancer maintenance	none	Ventana- SP263, TC=Tumor cell Membrane staining

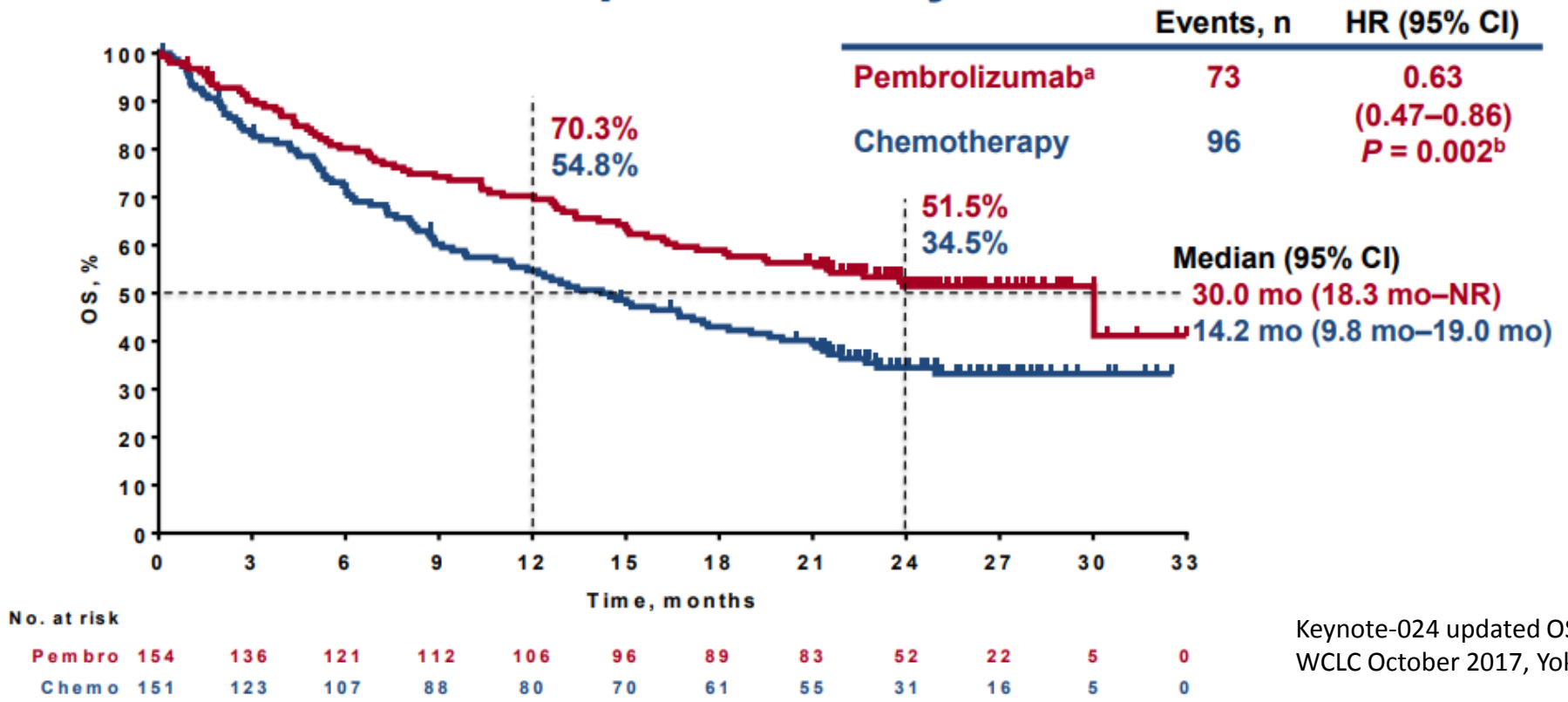
++
TC3=TC>50%
IC3= IC>10%
TC2/IC2=TC or IC>5%
TC1/IC1=TC or IC>1%

*
Tumor proportion score

Current Biomarker Approach for Selecting Patients for Immunotherapy

KEYNOTE-24 : I-L Metastatic NSCLC w/ PDL-1 IHC > 50% TPS (Dako 22C3)

Overall Survival: Updated Analysis



Keynote-024 updated OS analysis: Brahmer J, et al. WCLC October 2017, Yokohoma Japan

Current Biomarker Approach for Selecting Patients for Immunotherapy

Challenges with clinical PD-L1 biomarker evaluation

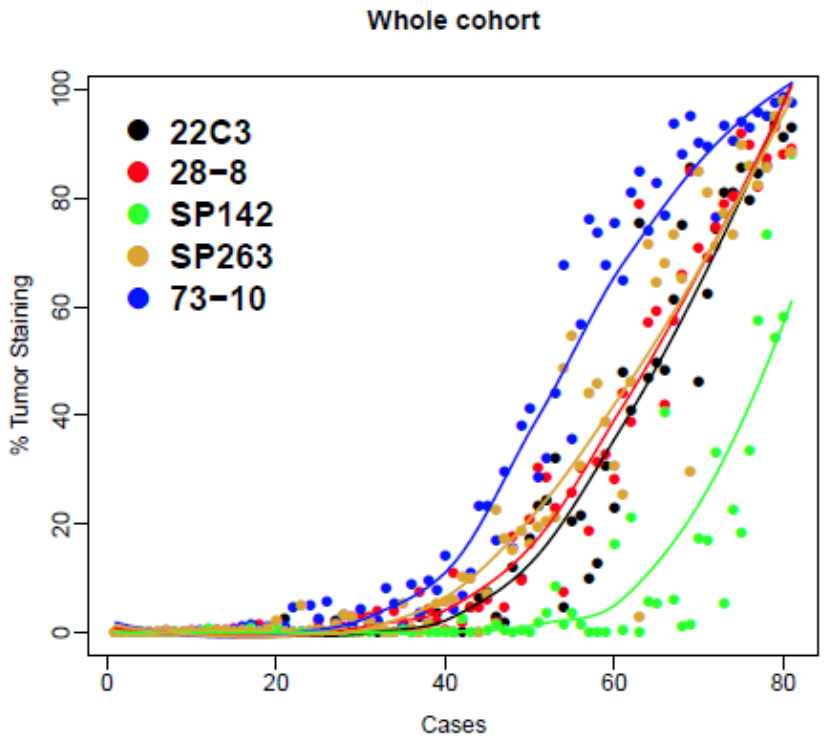
1. How different are these PD-L1 IHC assays when compared to each other, in terms of their staining characteristics
2. Can these assays be interchanged when used to determine the PD-L1 status of patient's tumor
3. Is PD-1 status reproducible, i.e., spatial and temporal heterogeneity

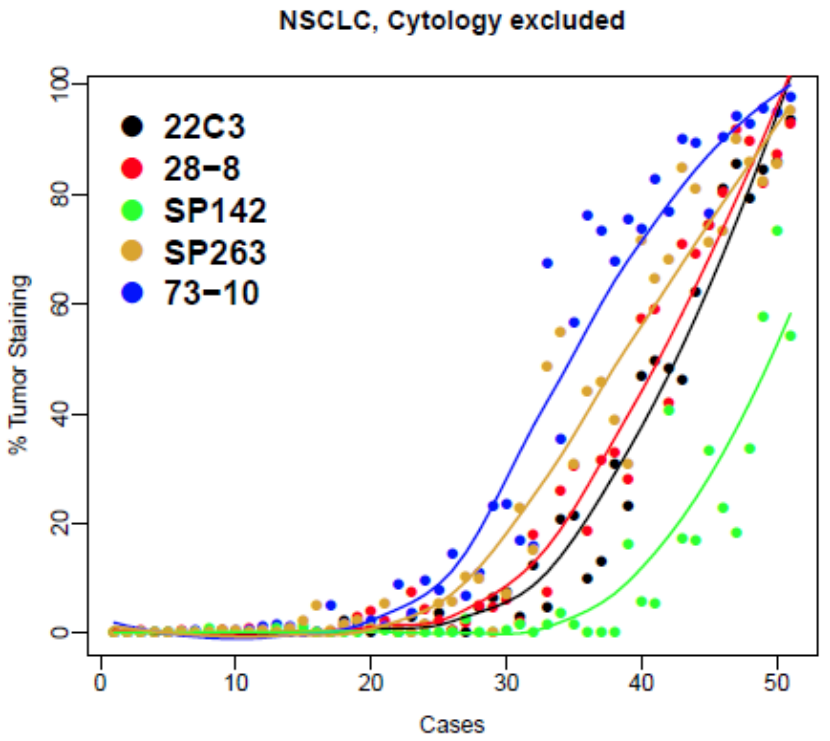
Current Biomarker Approach for Selecting Patients for Immunotherapy

Challenges with clinical PD-L1 biomarker evaluation

1. How different are these PD-L1 IHC assays when compared to each other, in terms of their staining characteristics
2. Can these assays be interchanged when used to determine the PD-L1 status of patient's tumor
3. Is PD-1 status reproducible, i.e., spatial and temporal heterogeneity

Comparability among Five PD-L1 IHC Assays Based on Tumor Cell Staining





Each circle represents the mean of all scores (glass slide & digital combined)

Blueprint phase-2 study: M.S. Tsao. et al. WCLC October 2017, Yokohoma Japan

Real-world Distribution of PD-L1 Tumor Expression by Assay Type

PD-L1 biomarker IHC assay results (N=1728*)

PD-L1 tumor expression, categorized †	FDA-approved IHC assay, n (%)			Laboratory-developed tests, n (%) (N=323)
	Dako 22C3 (N=1335)	Dako 28-8 (N=90)	Ventana SP142 (N=75) ‡	
<1%	478 (35.8)	37 (41.1)	46 (61.3)	127 (39.3)
1–49%	376 (28.2)	25 (27.8)	16 (21.3)	107 (33.1)
≥50%	481 (36.0)	28 (31.1)	13 (17.3)	89 (27.6)

*Some patients had >1 test and are represented in >1 column

†**p<0.0001** for χ^2 test comparing results across the 4 assay types, and **p=0.053** for χ^2 test comparing results across 3 assay types, excluding the Ventana SP142

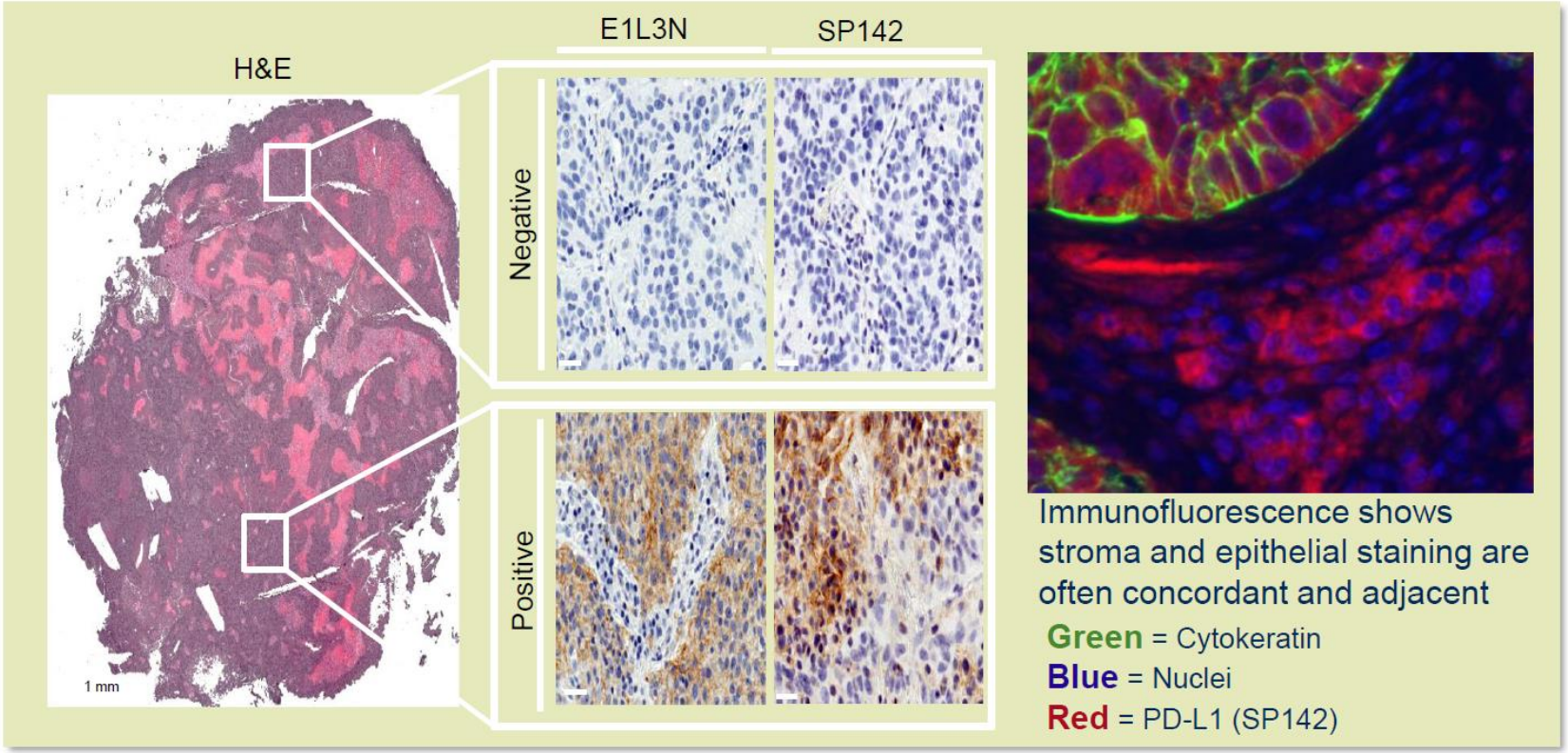
Velcheti et al. WCLC October 2017, Yokohoma Japan

Current Biomarker Approach for Selecting Patients for Immunotherapy

Challenges with clinical PD-L1 biomarker evaluation

1. How different are these PD-L1 IHC assays when compared to each other, in terms of their staining characteristics
2. Can these assays be interchanged when used to determine the PD-L1 status of patient's tumor
3. Is PD-1 status reproducible, i.e., spatial and temporal heterogeneity

Tumor PD-L1 Heterogeneity

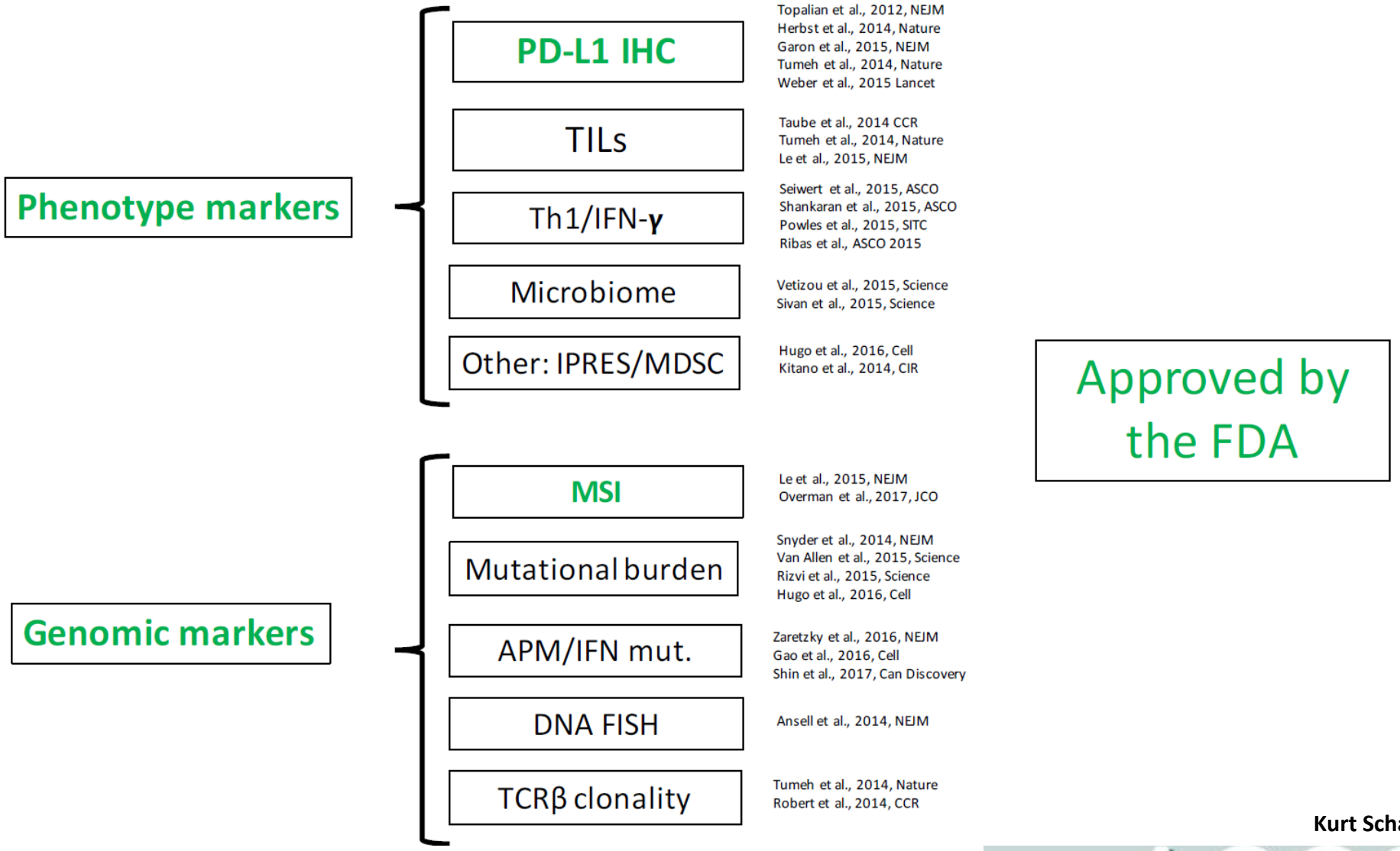


- Heterogeneity – multiple tumors and multiple passes within a tumor
- Interval between biopsy and treatment
- Primary versus metastatic disease
- Antibody and staining conditions

- Defining a positive result (cut-offs):
  - Cell type expressing PD-L1 (immune cell versus tumor or both)
  - Location of expression – cell surface versus intracellular versus stromal
  - Intensity, percent of cells 'positive'
  - Distribution - patchy versus diffuse, intratumoral versus peripheral

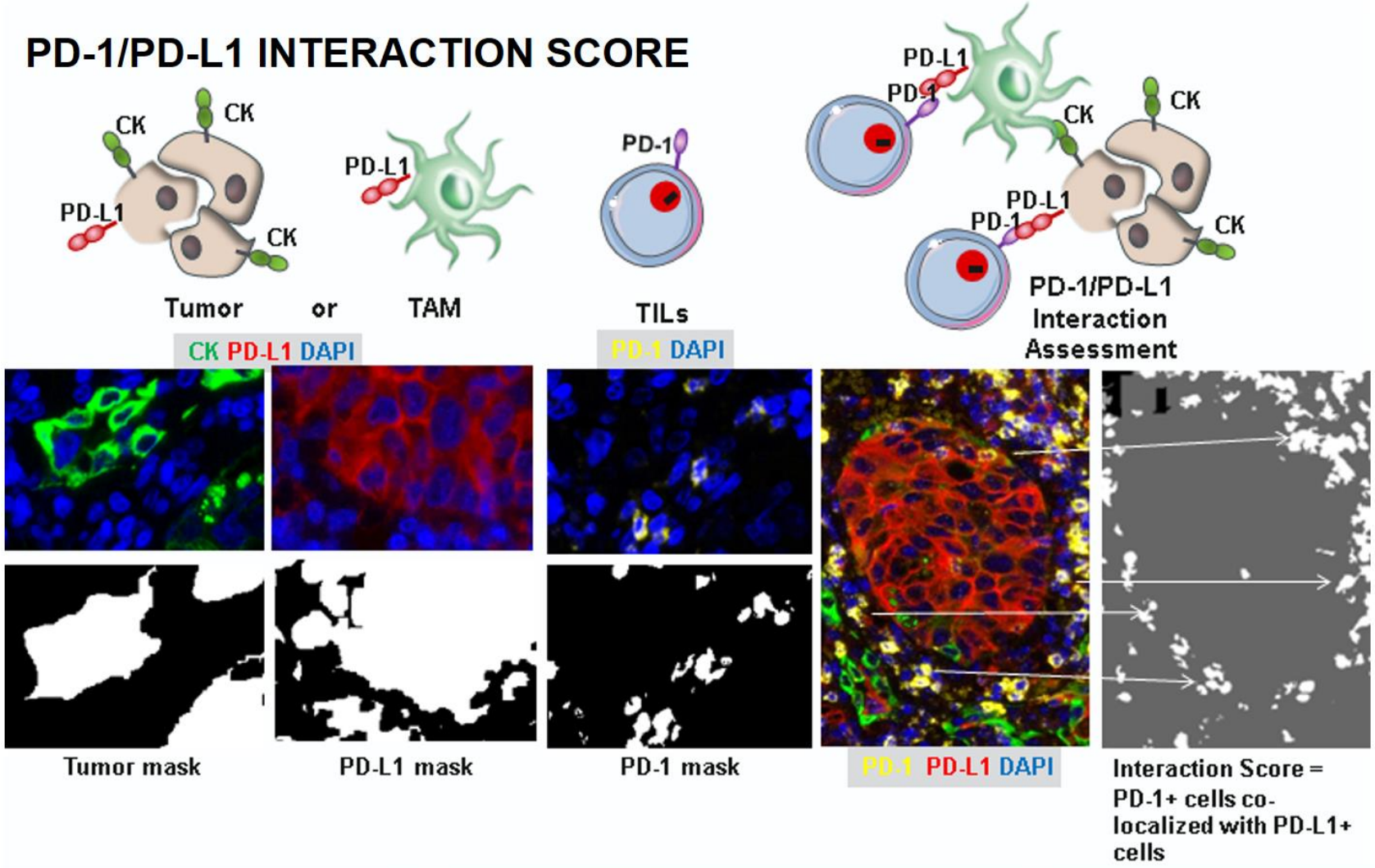
McLaughlin J et a JAMA Oncol 2016

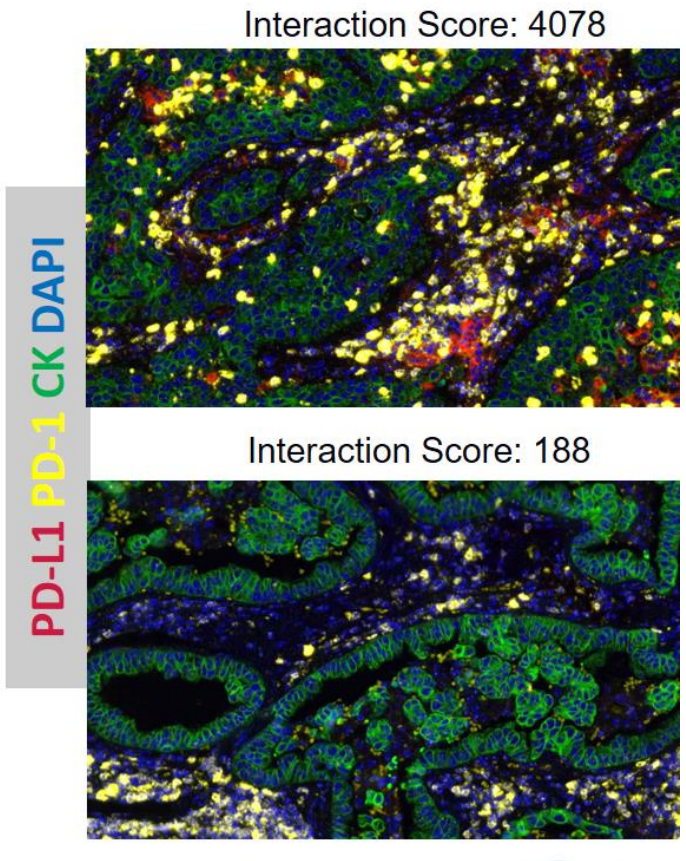
Approved Biomarkers for Immuno-oncology Diagnostics



Kurt Schalper ASCO 2017

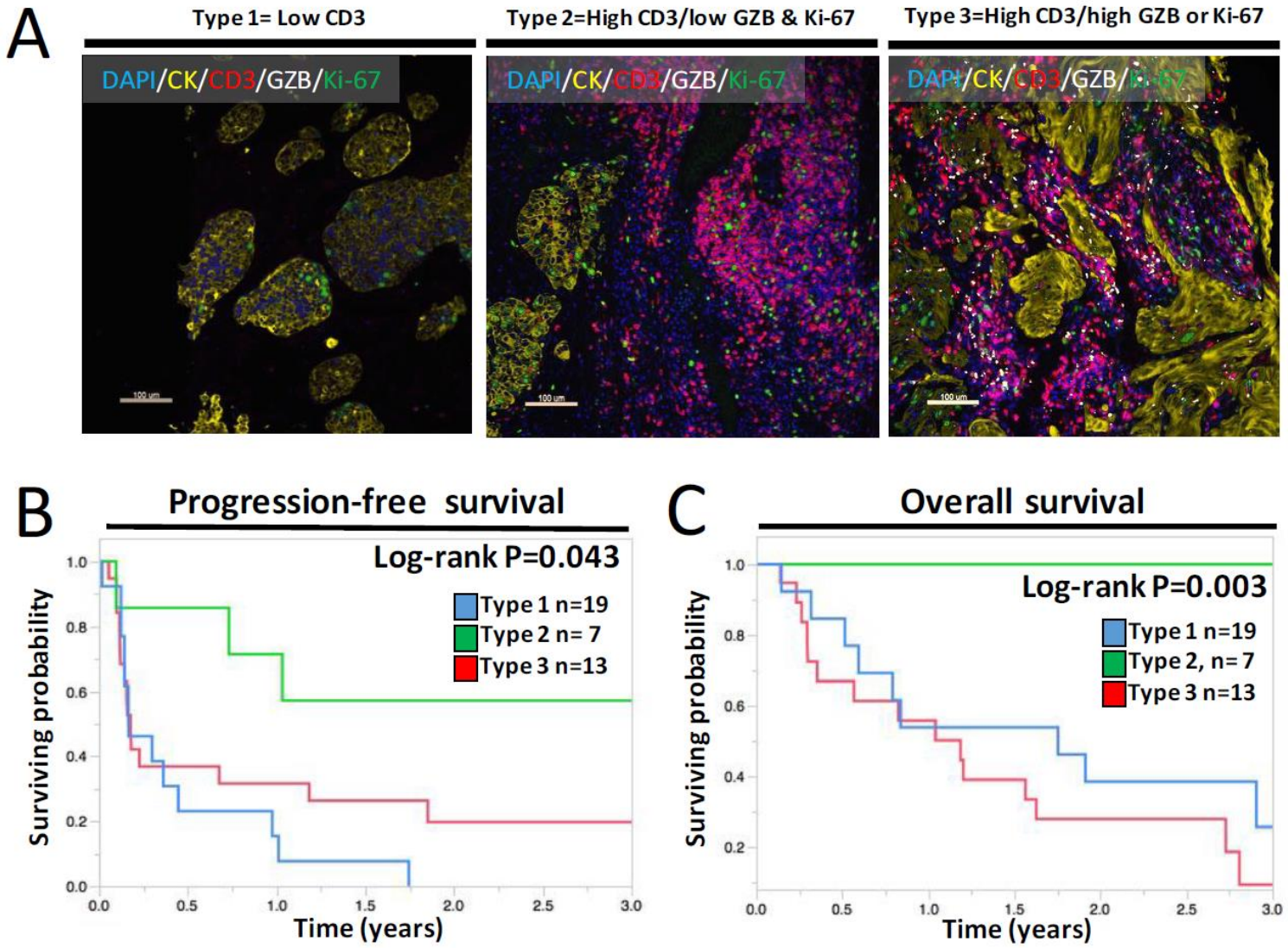
Novel Quantitative Techniques for Evaluation of PD-L1





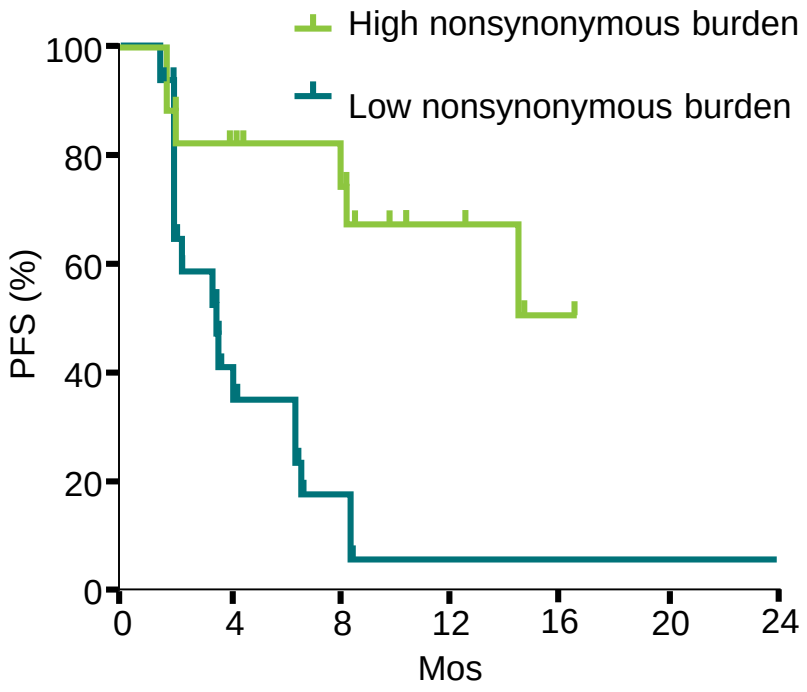
Velcheti, et al. WCLC October 2017, Yokohoma Japan

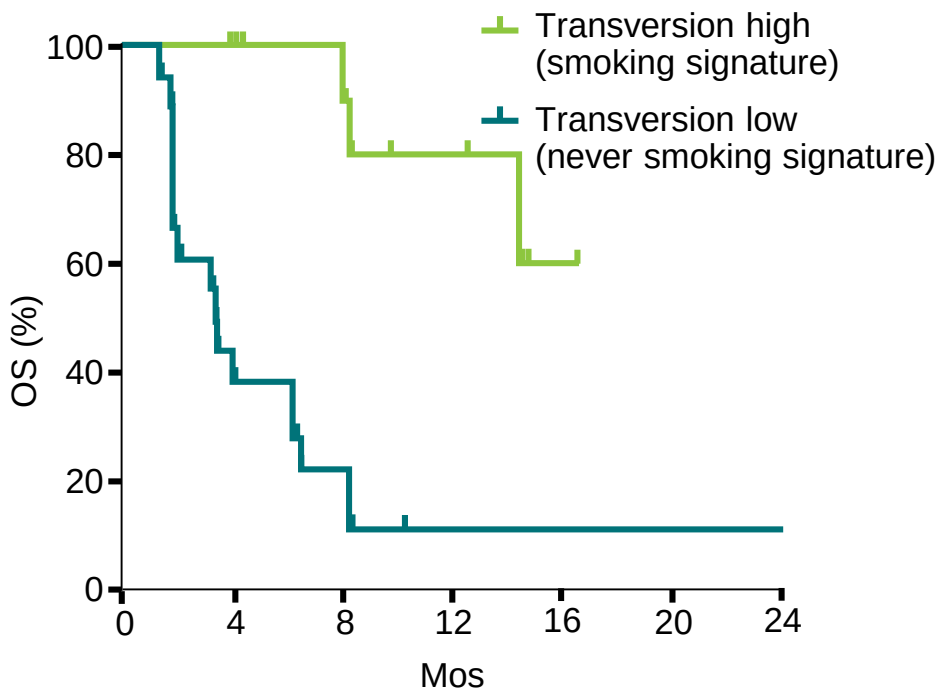
Novel Quantitative Techniques for Evaluation of PD-L1



Schalper, et al. WCLC October 2016, Vienna Austria

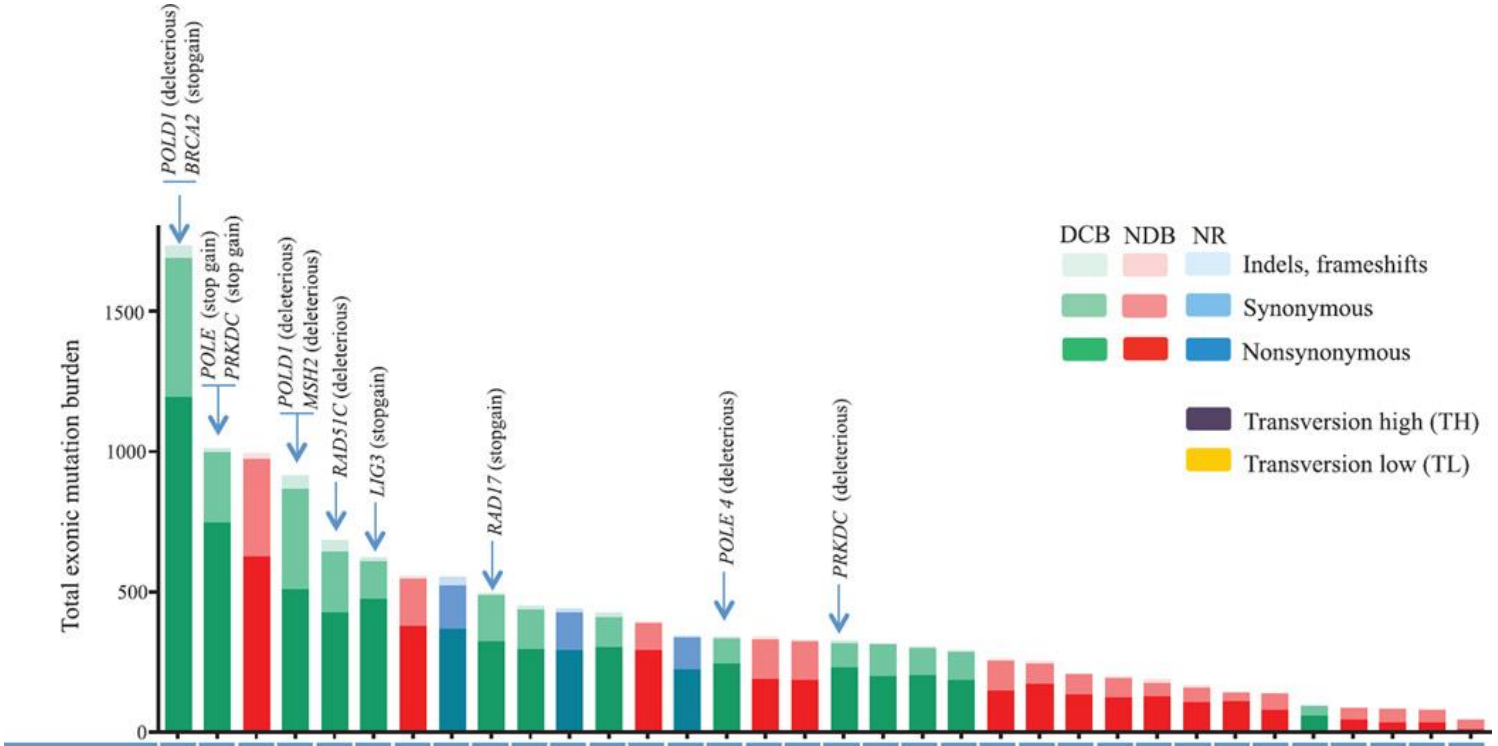
NSCLC Tumor Mutation Burden Associated with Clinical Benefit with Pembrolizumab



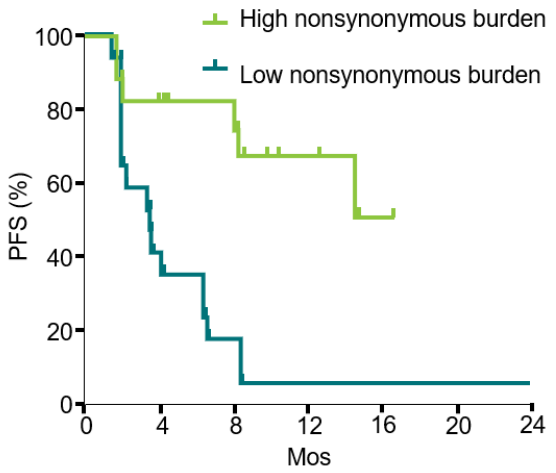


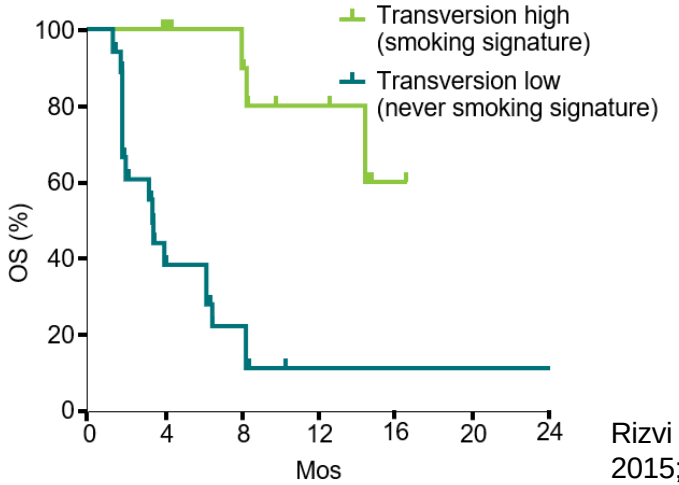
Rizvi NA, et al. Science. 2015;348:124-128.

NSCLC Tumor Mutation Burden Associated with Clinical Benefit with Pembrolizumab



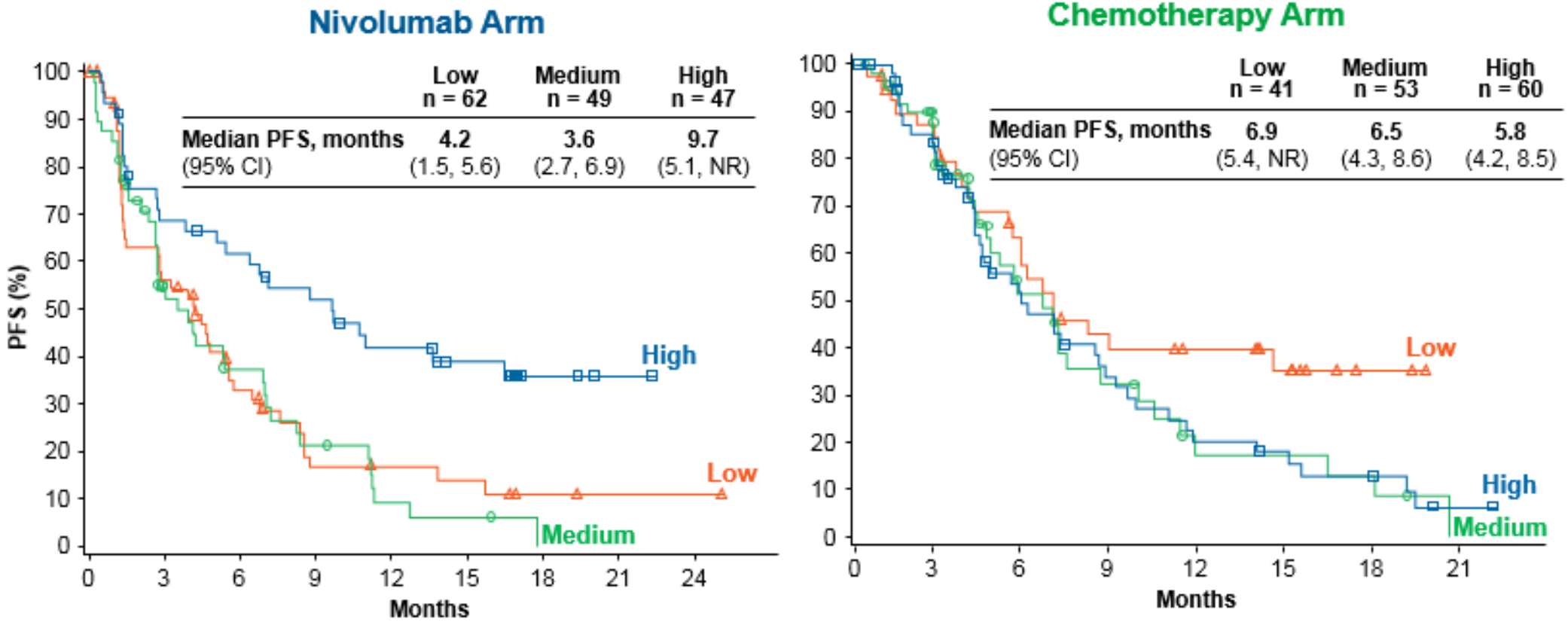
Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL





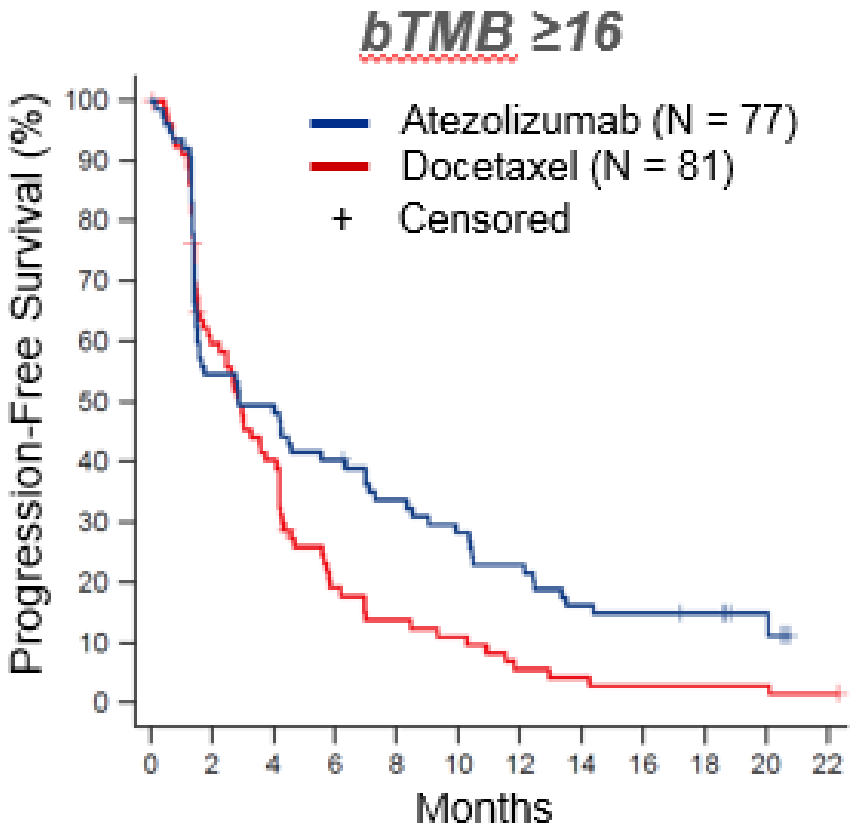
Rizvi NA, et al. Science. 2015;348:124-128.

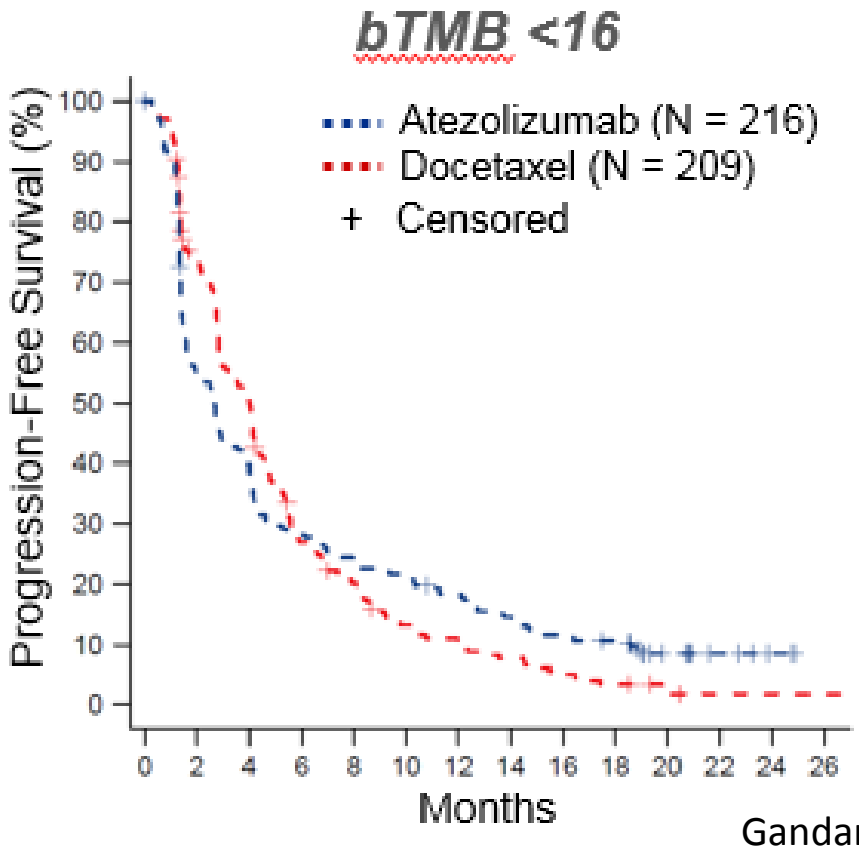
NSCLC Tumor Mutation Burden Associated with Clinical Benefit with Nivolumab in First-line NSCLC



Peters S, et al. AACR 2017

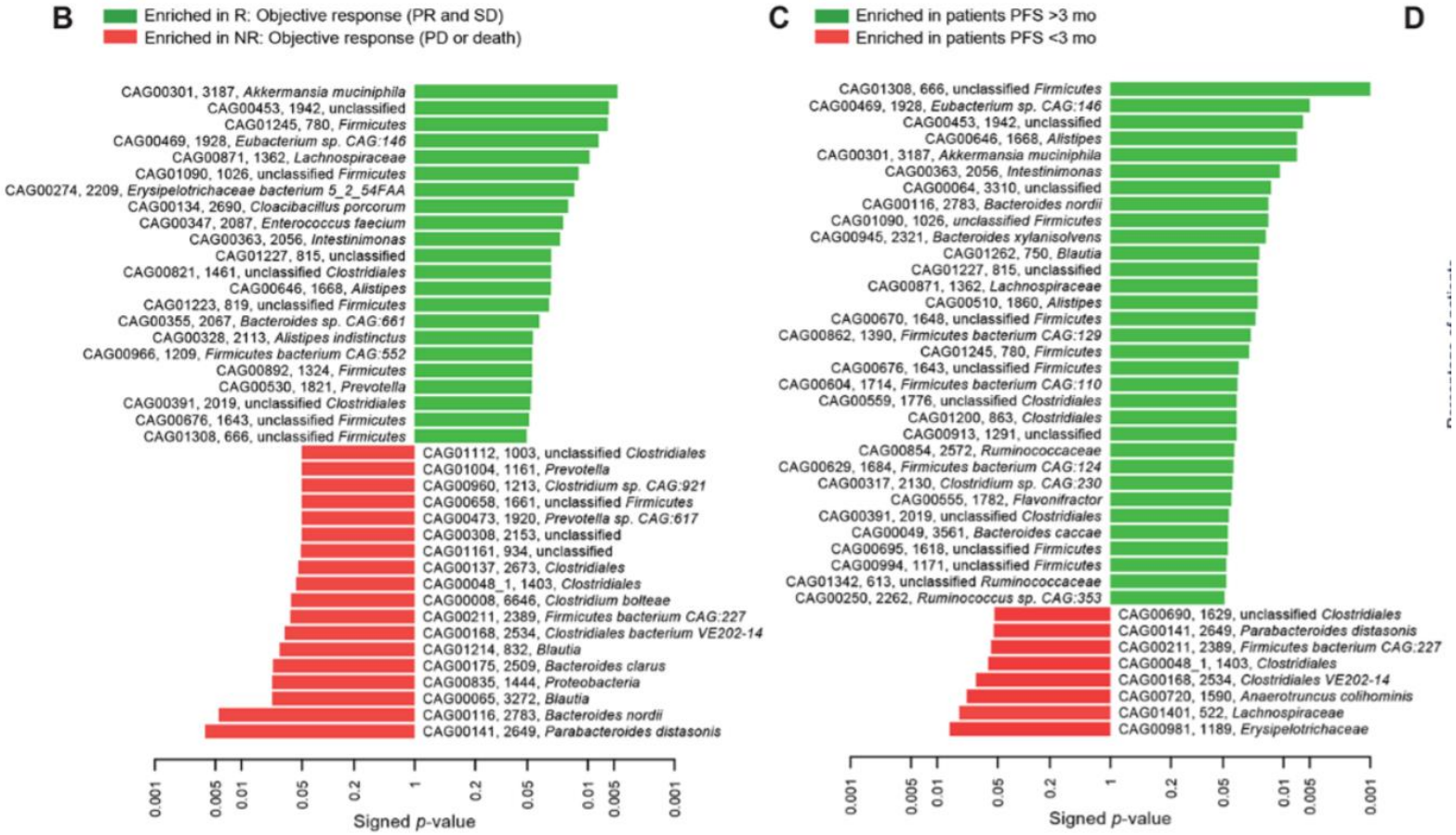
NSCLC ctDNA based Tumor Mutation Burden Associated with Clinical Benefit with Atezolizumab (OAK trial)





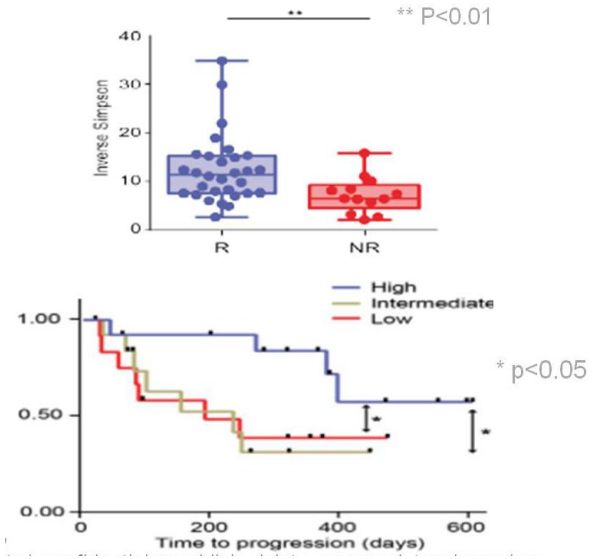
Gandara D, et al. ESMO 2017

Microbiome and Immunotherapy



B Routy, et al. Science. Nov. 2017

Patients with metastatic melanoma, PD-1
~45 patients



Responders to PD-1 had higher gut microbiota diversity than non-responders.

Wargo, et al. *ASCO* 2017

Conclusion

- PDL-1 testing and MSI are the only approved diagnostic tests for selecting patients for PD-1 axis inhibitors.

- Interrogating the tumor microenvironment using phenotype/immunology and genomic metrics could provide future strategies for selecting patients for single agent and combination I-O therapy.

Thank you for participating in the webinar. Presentation slides and archived recording will be available at accc-iclio.org