An embarrassment of riches?

Selecting, administering, and monitoring immunotherapy for lung cancer

David E. Gerber, MD

Professor, Internal Medicine and Population & Data Sciences

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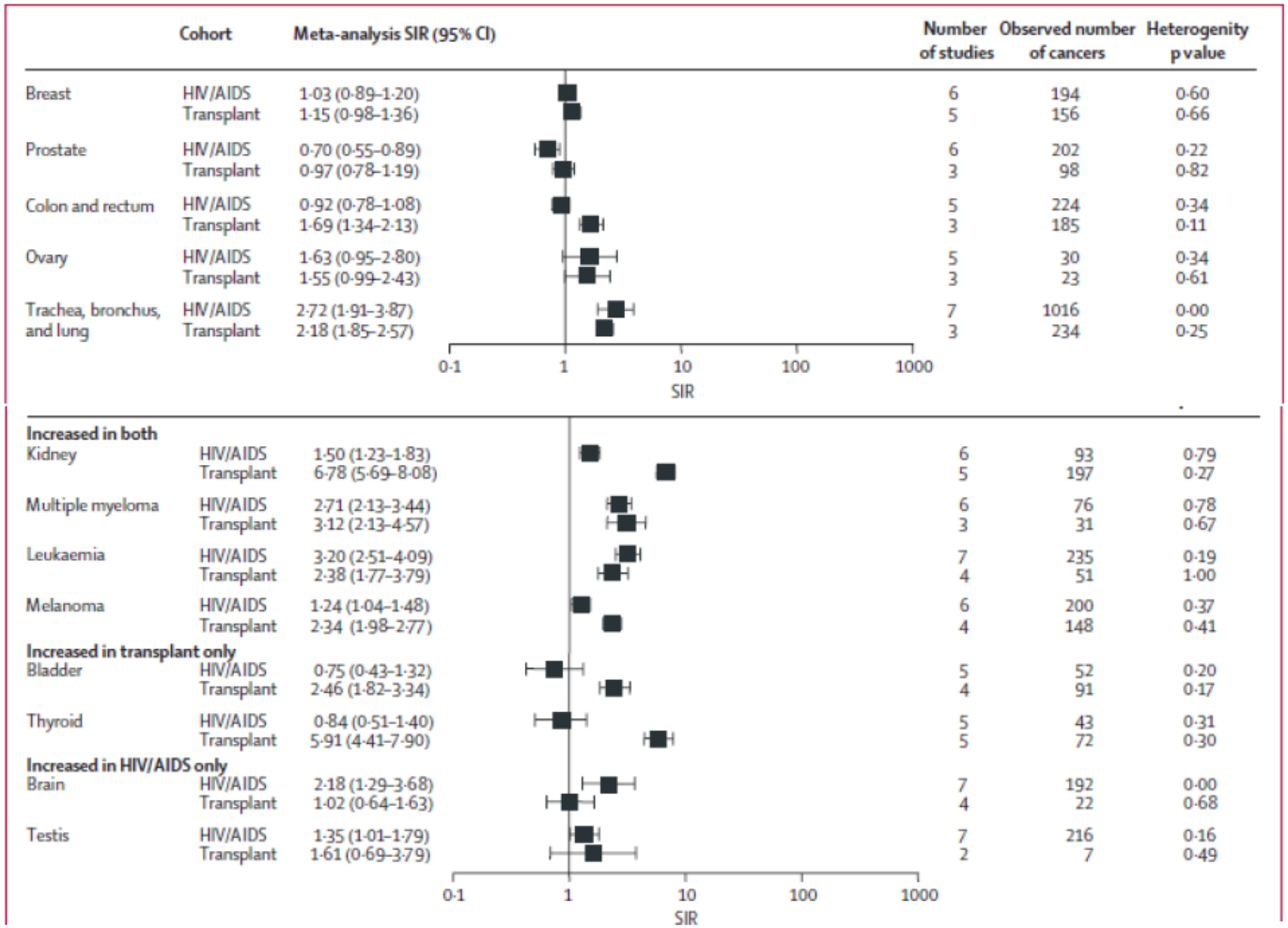
Outline

- Rationale for and history of employing the immune system against cancer
- An overview of immune checkpoint inhibitors
- Selecting patients for immunotherapy
- The role of immunotherapy in the treatment of lung cancer
- Immune-related adverse events

Immune suppression increases cancer risk

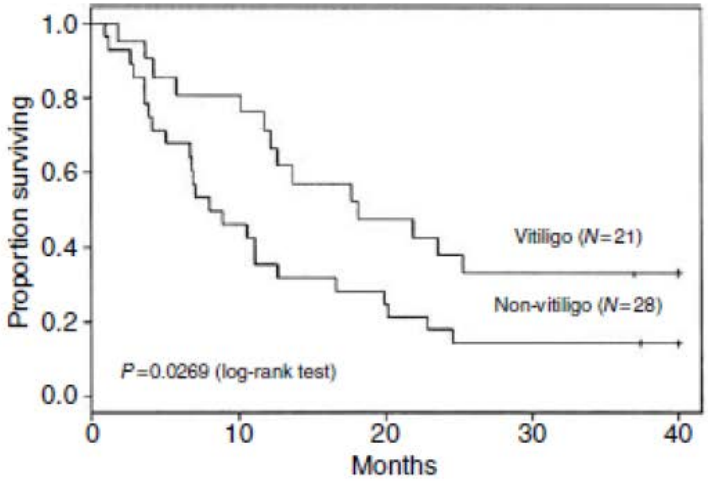


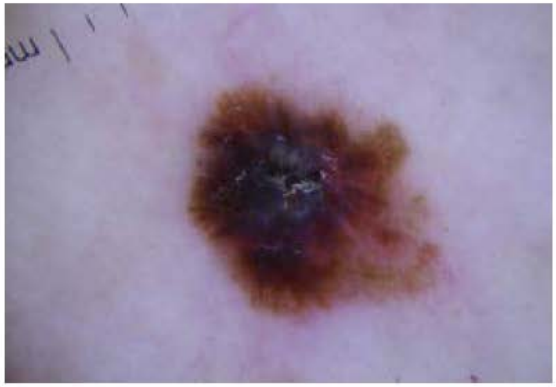
Non-infection-associated cancers

Grulich AE et al. *Lancet* 2007;370:59-67.

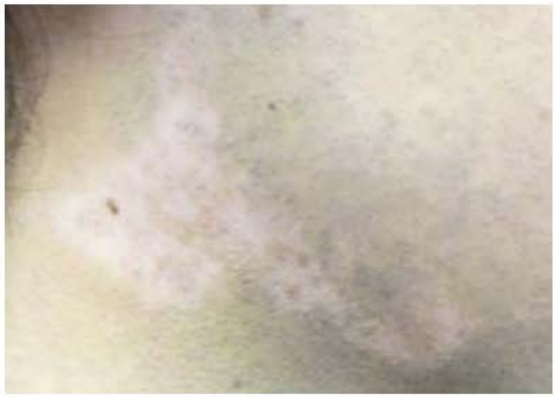
Enhanced immunity improves cancer outcomes

The development of vitiligo improves survival in metastatic melanoma





melanoma

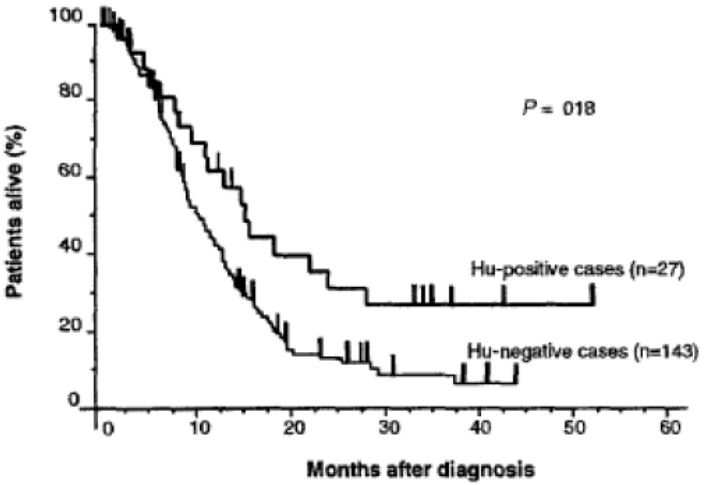


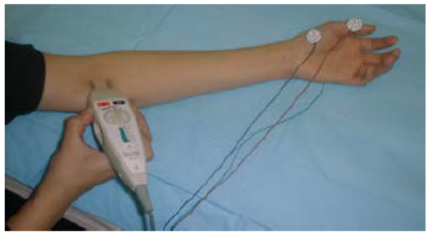
vitiligo

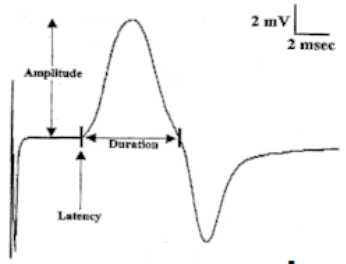
Boasberg PD. *J Invest Derm* 2006;2658-2663.
Hawryluk EB. *Pediatr Clin N Amer* 2014;61:279-291.
Silvergerg NB. *Pediatr Clin N Amer* 2014;61:347-366.

Enhanced immunity improves cancer outcomes

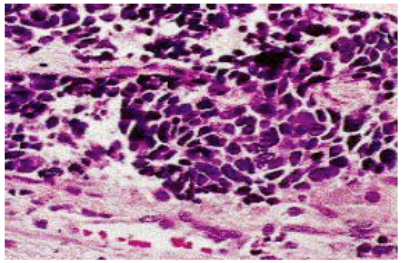
SCLC patients with paraneoplastic peripheral neuropathy live longer than those without it



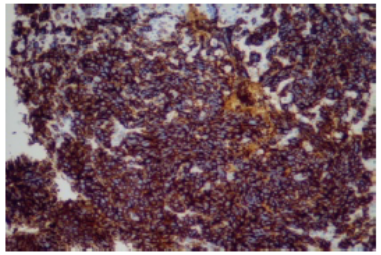




Nerve conduction study to assess sensory changes



H+E

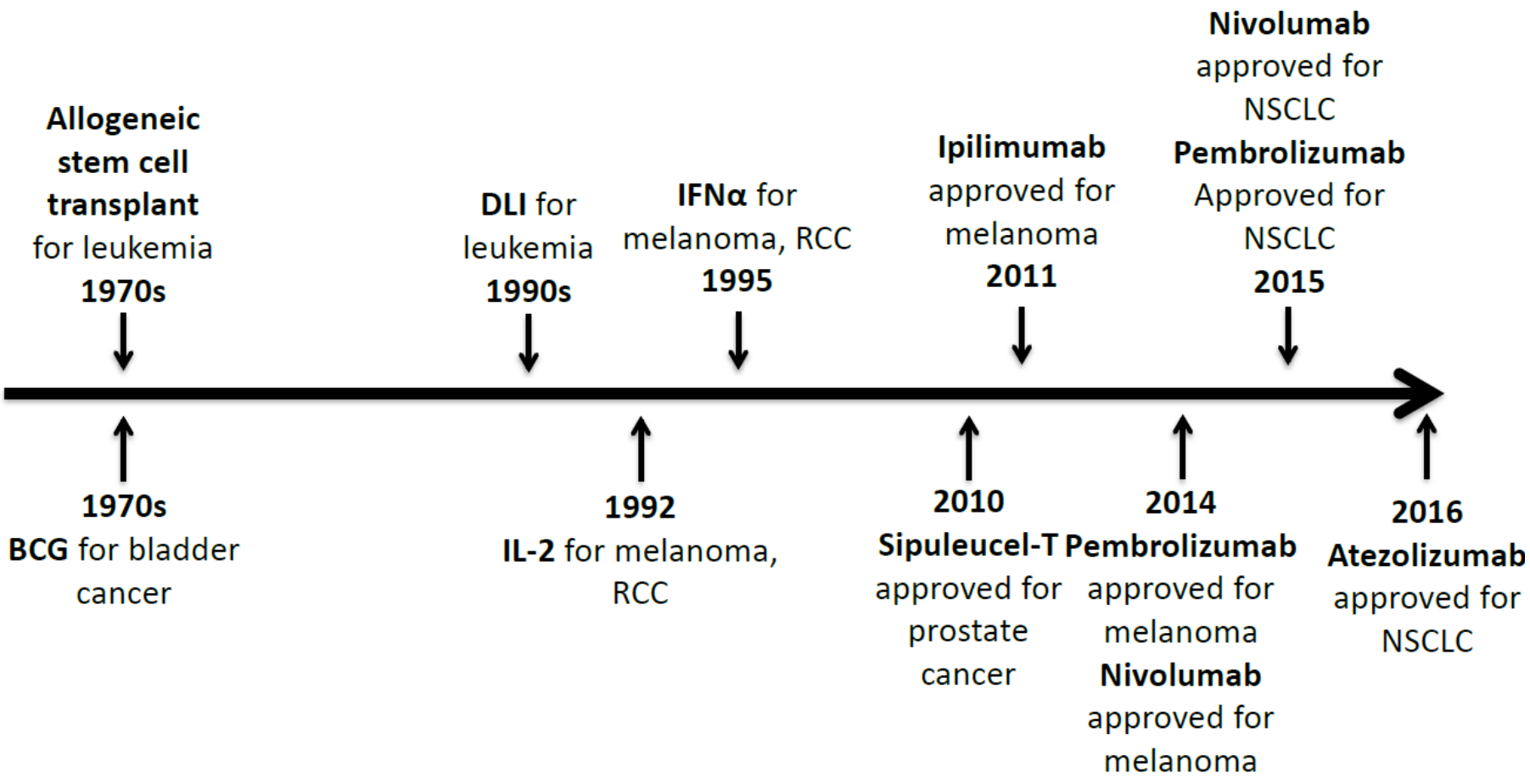


CD56 (NCAM)

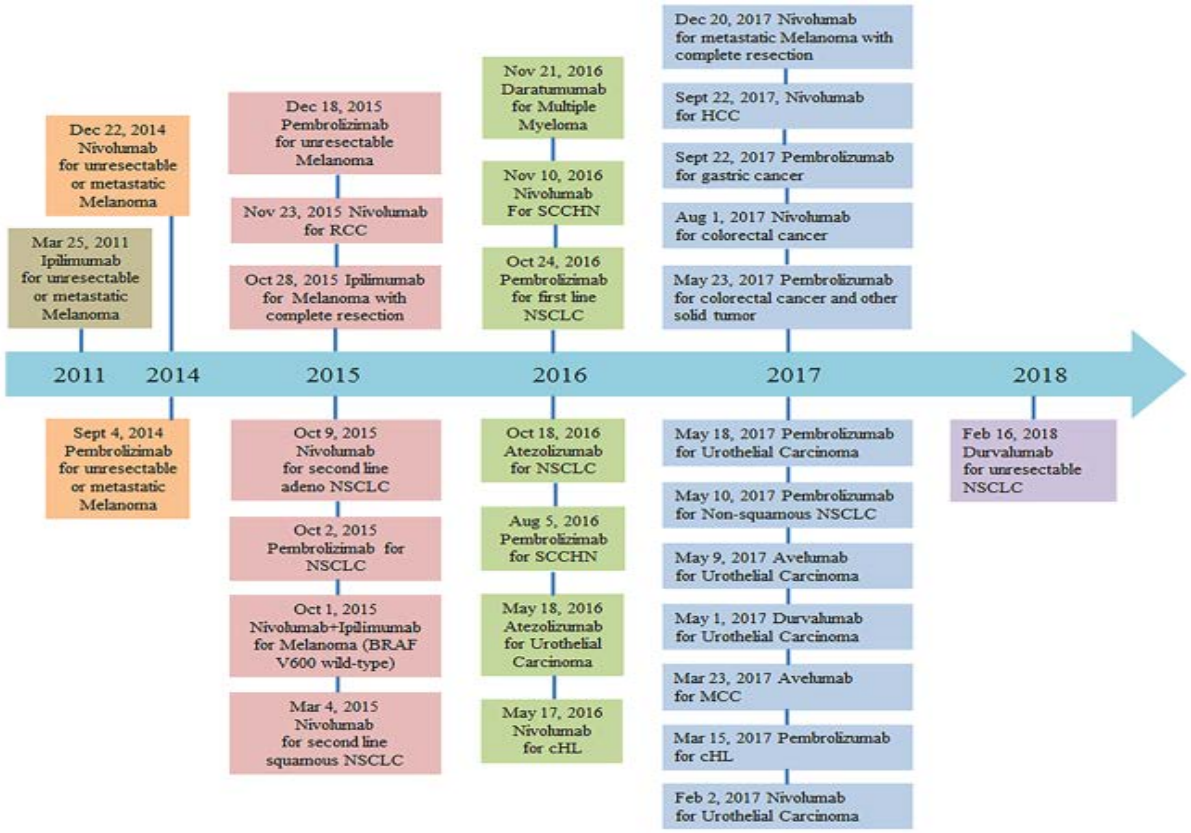
Small cell lung cancer pathologic features

Grauss F et al. *J Clin Oncol* 1997;15:2866-2872..

Immunotherapy has been a component of cancer treatment for decades



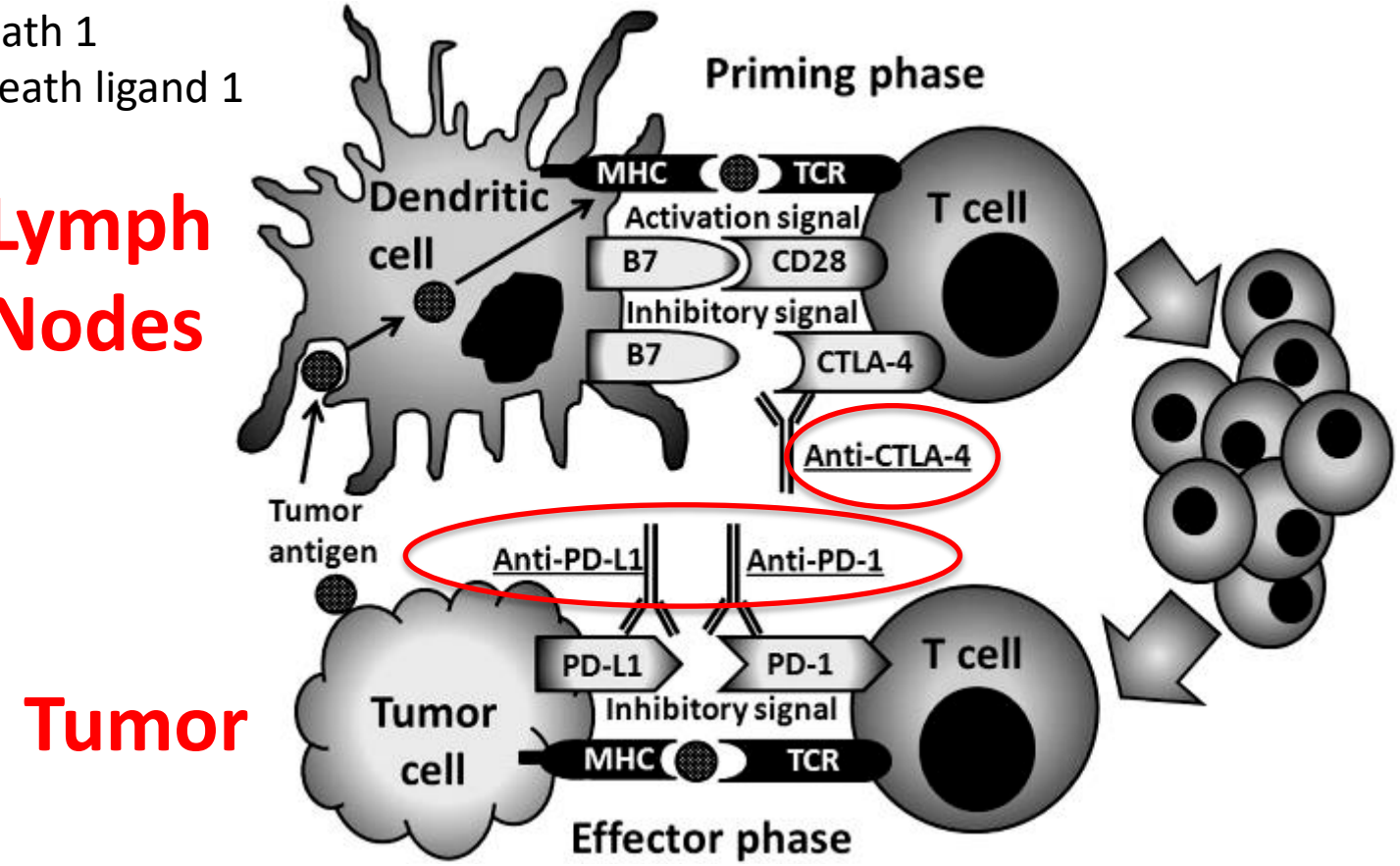
In recent years, the number and uses of immune checkpoint inhibitors has grown rapidly



Zhang J et al. *Front Oncol* 2018;8:351.

Checkpoint inhibitors represent the mainstay of lung cancer immunotherapy

CTLA4: Cytotoxic T lymphocyte antigen 4
PD-1: Programmed death 1
PD-L1: Programmed death ligand 1



Fumito, Chang. *Surg Oncol Clin N Amer* 2013;22:765-783

These drugs have far more similarities than they do differences

Efficacy?
Toxicity?

Half-life?
Infusion reactions?

ADCC?

Target	Company	Drug ID	Generic name	Brand name	Species	Isotype
PD-1	Bristol-Myers Squibb	BMS-936558/MDX-1106	Nivolumab	Opdivo	Fully human	IgG4
PD-1	Merck	MK-3475	Pembrolizumab	Keytruda	Humanized	IgG4
PD-1	CureTech	CT-011	Pidilizumab		Humanized	IgG1
PD-L1	Genentech / Roche	MPDL3280A	Atezolizumab	Tecentriq	Humanized	IgG1
PD-L1	MedImmune / Astra-Zeneca	MEDI4736	Durvalumab	Imfimzi	Fully human	IgG1
PD-L1	Merck KGaA	MSB0010718C	Avelumab	Bavencio	Fully human	IgG1
PD-L1	Bristol-Myers Squibb	BMS-936559/MDX-1105			Fully human	IgG4

. . . similar to other medical treatments

Statins
Simvastatin
Pravastatin
Atorvastatin
Rosuvastatin
Fluvastatin

ACE inhibitors
Quinapril
Benazepril
Perindopril
Captopril
Moexipril
Enalapril
Lisinopril
Fosinopril

For non-small cell lung cancer, most immunotherapy use does not require PD-L1 testing*

Indication	Required?	Result needed
Early-Stage (stages II-III) NSCLC		
Adjuvant atezolizumab	Y	PD-L1 ≥1%
Locally Advanced (stage III) NSCLC		
Consolidation Durvalumab	N	
Advanced (stage IV) NSCLC		
1L Pembrolizumab	Y	TPS ≥1% (was ≥50%)
1L Cemiplimab	Y	PD-L1 ≥1%
1L Carbo-Pem + Pembrolizumab	N	
1L Carbo-Paclitaxel + Bev + Atezolizumab	N	
1L Ipilimumab + Nivolumab	Y	PD-L1 ≥1%
1L Ipilimumab + Nivolumab + Chemo	N	
2L Nivolumab	N	
2L Atezolizumab	N	
2L Pembrolizumab	Y	TPS ≥1%

***Pembrolizumab may also be administered (to any cancer type) if MSI or TMB high**

Different diagnostic antibodies, cut-points, tumor/immune cell evaluation, and platforms complicate PD-L1 assessment

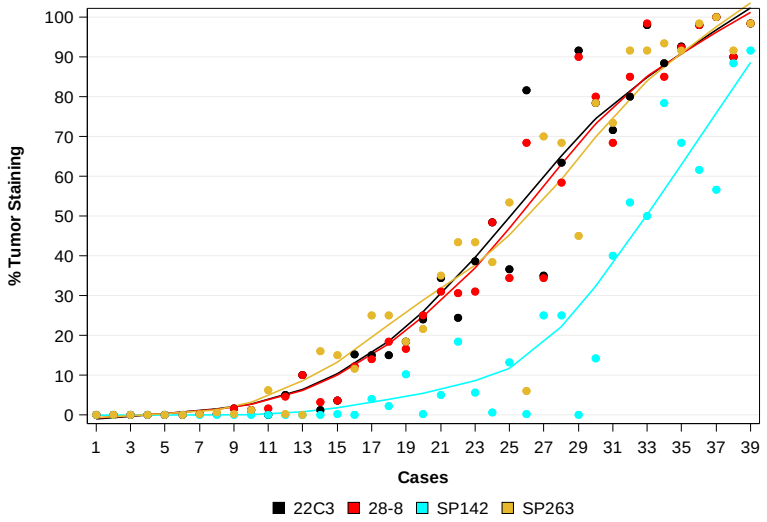
Immune checkpoint inhibitors and matching PD-L1 assay

Drug	Drug Target	PD-L1 IHC assay	PD-L1 antibody Epitope	Auto stainer	Detection system
Nivolumab	PD1	28-8	Extracellular	Dako Link 48	Envision Flex
Pembrolizumab	PD1	22C3	Extracellular		
Atezolizumab	PD-L1	SP142	Cytoplasmic	Ventana Benchmark	Optiview + Amplification
Durvalumab	PD-L1	SP263	Cytoplasmic		Optiview
Avelumab	PD-L1	73-10	Cytoplasmic	Dako	Envision Flex

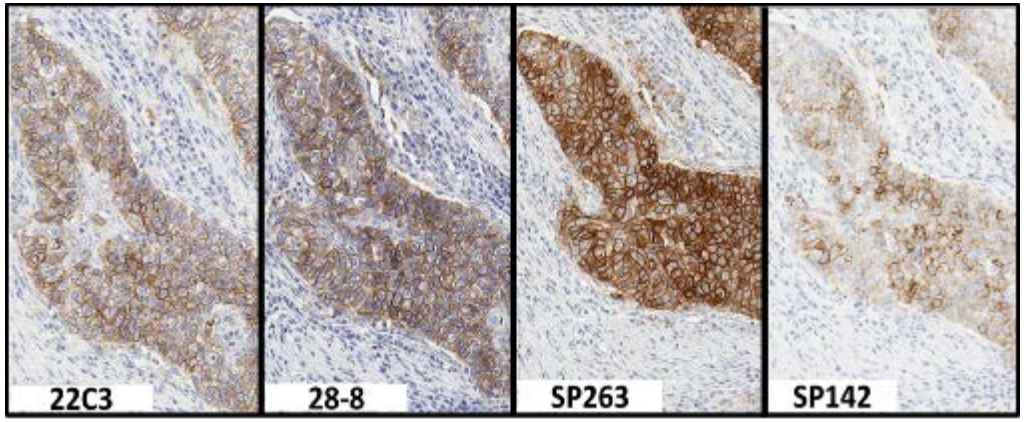
Assesses TC and IC

Courtesy of Fred Hirsch, MD PhD

Fortunately, there is reasonable concordance for PD-L1 staining on tumor cells*



Each dot represents mean score of 3 pathologists



Conclusion: 3 assays showed similar staining characteristics for PD-L1 staining on tumor cells, but SP142 (atezolizumab companion diagnostic) comparatively showed less tumor cells stained

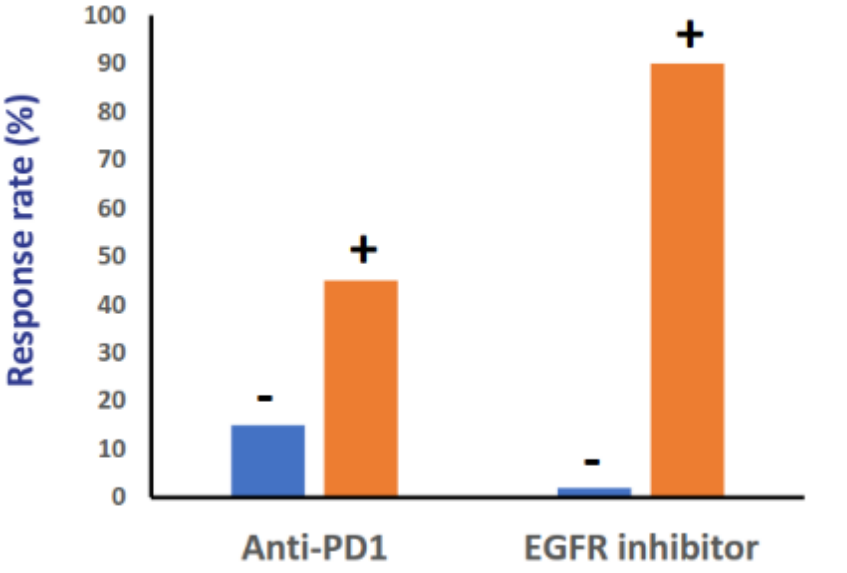
Hirsch FR et al. *J Thorac Oncol* 2017;12:208-222.

Courtesy of Fred Hirsch, MD PhD

***But more variability for immune cell staining**

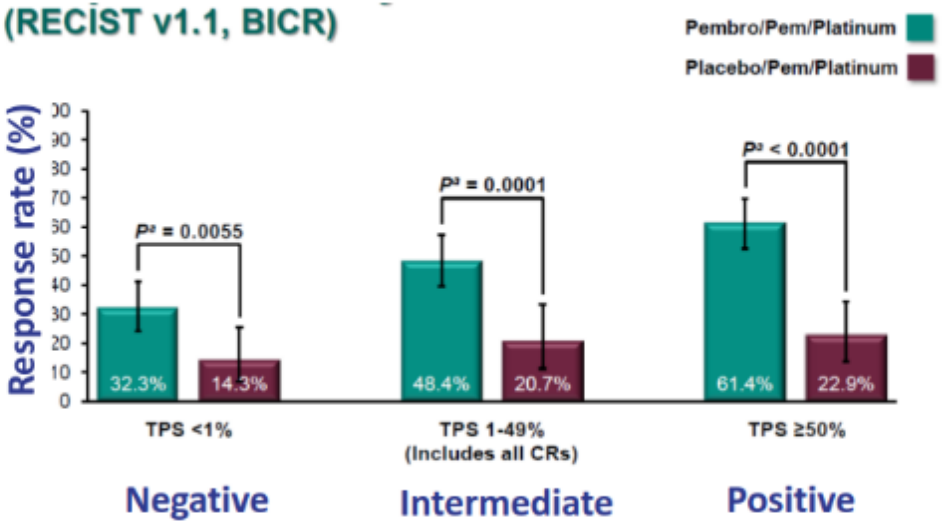
In lung cancer, clinical context limits the predictive capacity of PD-L1

Biomarkers for other therapies may be far more informative



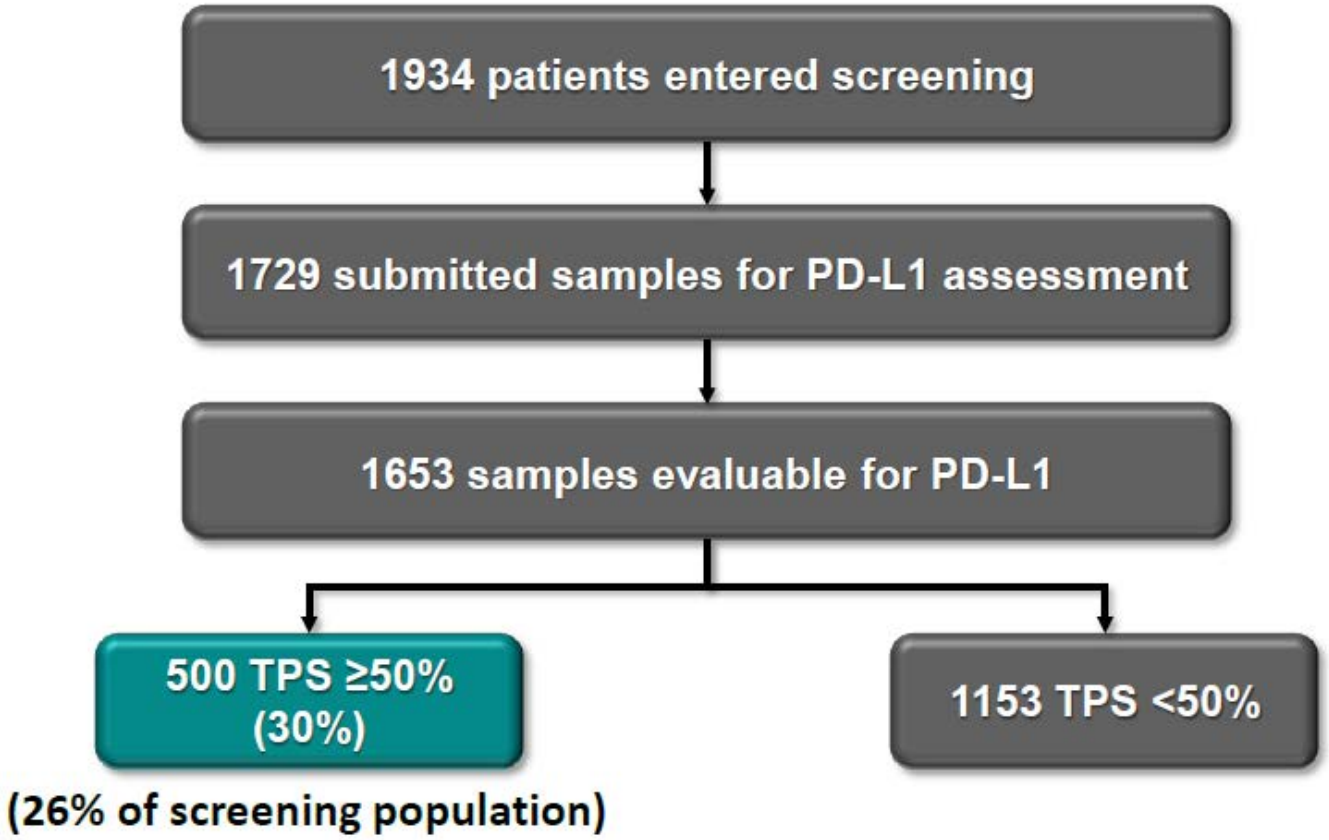
Advanced non-small cell lung cancer

Adding anti-PD1 immunotherapy to chemotherapy improves outcomes regardless of PDL1 expression



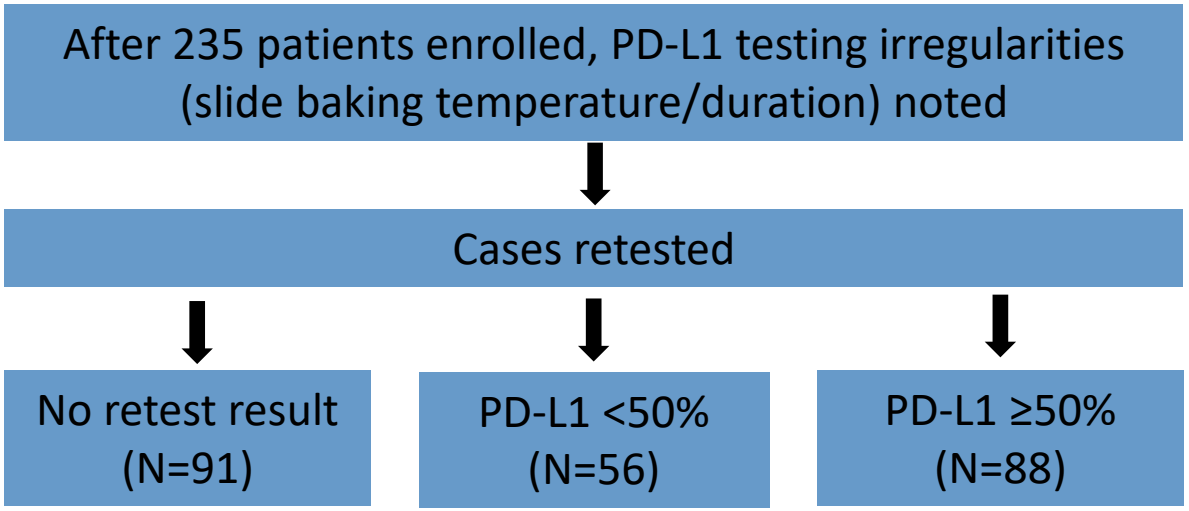
Gandhi L. AACR 2016

Determining PDL1 status up-front may be challenging



KEYNOTE-024. Presented by Martin Reck, MD. ESMO 2016.

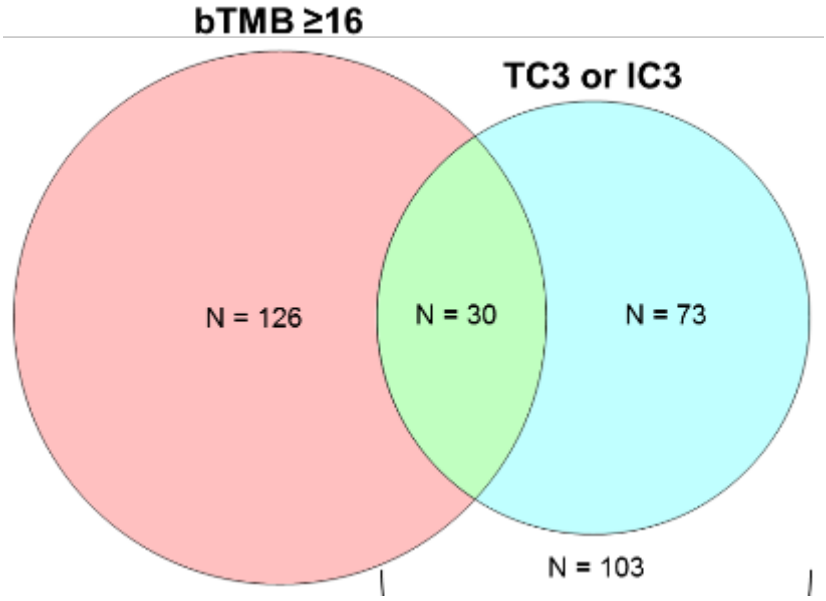
Staying humble: biomarker results reflect technical considerations as well as tumor biology



40% of PD-L1 ≥50% cases were <50% when retested

EMPOWER-Lung trial of Cemiplimab in PD-L1 ≥50% (N=710)

Perhaps surprisingly, there is not a clear association between tumor mutational burden and PD-L1 expression

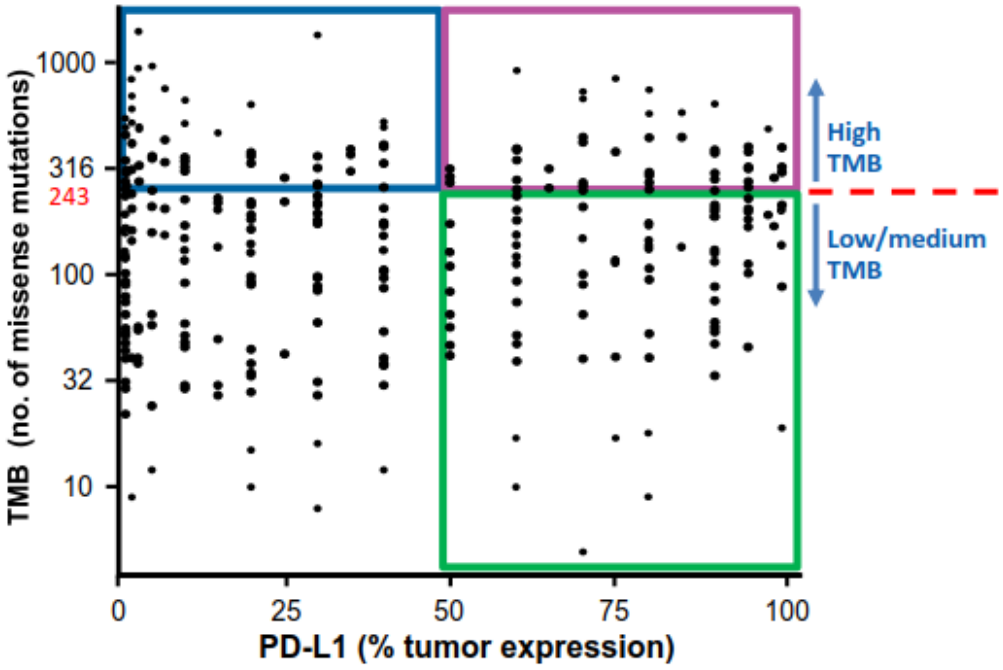


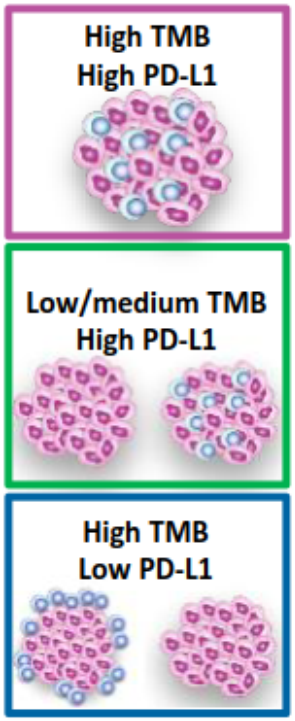
- Non-significant overlap between the bTMB ≥16 and TC3 or IC3 subgroups (Fisher exact test, *P* = 0.62)
  - **19.2%** of tumors with bTMB ≥16 were also TC3 or IC3
  - **29.1%** of tumors with TC3 or IC3 also had bTMB ≥16

[a] PD-L1 expression was evaluated by immunohistochemistry (IHC) using the VENTANA SP142 assay;
TC3 or IC3, ≥50% of TC or ≥10% of IC express PD-L1.
BEP, biomarker-evaluable population; IC, tumor-infiltrating immune cell; TC, tumor cell.

Hellman MD et al. *Cancer Cell* 2018;33:1-9.

Perhaps surprisingly, there is not a clear association between tumor mutational burden and PD-L1 expression





Hypotheses

PD-L1 may be a surrogate marker of high TMB-induced inflammation (T cell infiltration and IFN-γ–associated activation)

TMB may not be the only driver of inflammation, and alternate pathways (e.g., quality neoantigens and strong immunogenicity) may lead to PD-L1 upregulation

Tumors may have T cells excluded, preventing inflammation with lack of PD-L1 upregulation

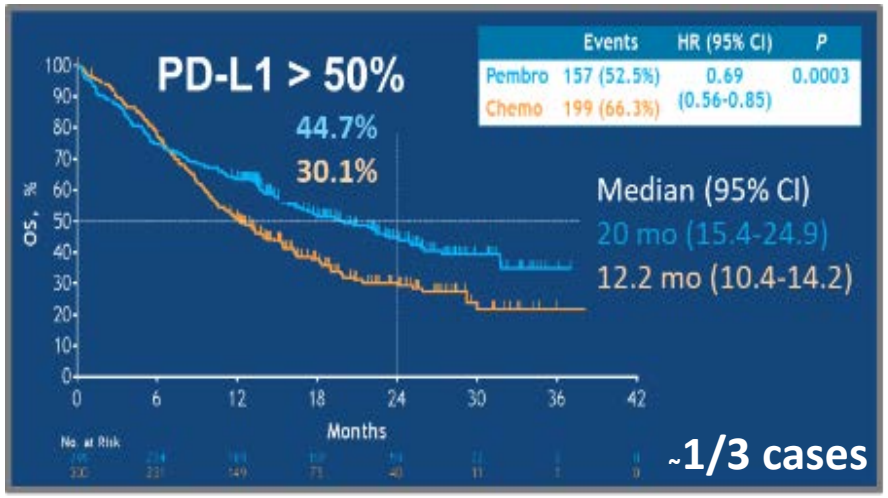
Peters S et al. Oral presentation at AACR 2017. CT082.

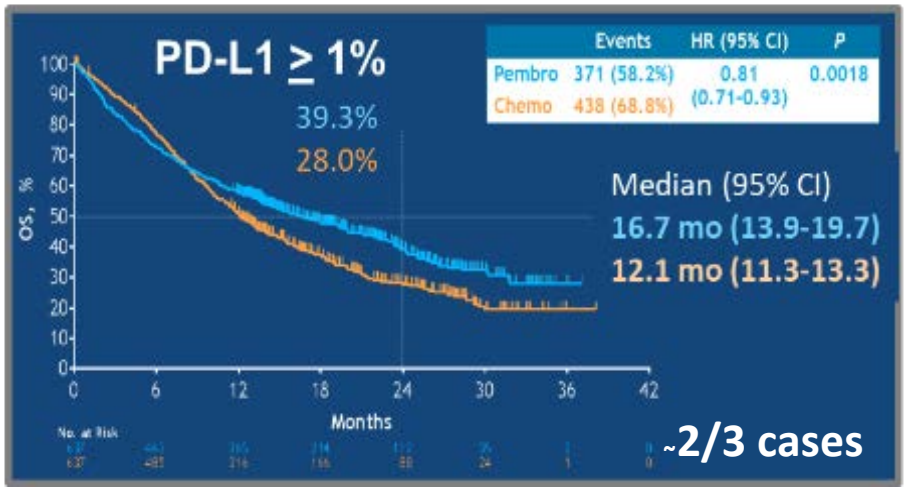
There are too many lung cancer immunotherapy trials to keep track of

Trial title	Drug
Trees (Oak, Poplar) or IMpower	Atezolizumab
EMPOWER	Cemiplimab
Bodies of water (Mystic, Adriatic, Atlantic, Pacific)	Durvalumab
CheckMate	Nivolumab
KEYNOTE	Pembrolizumab

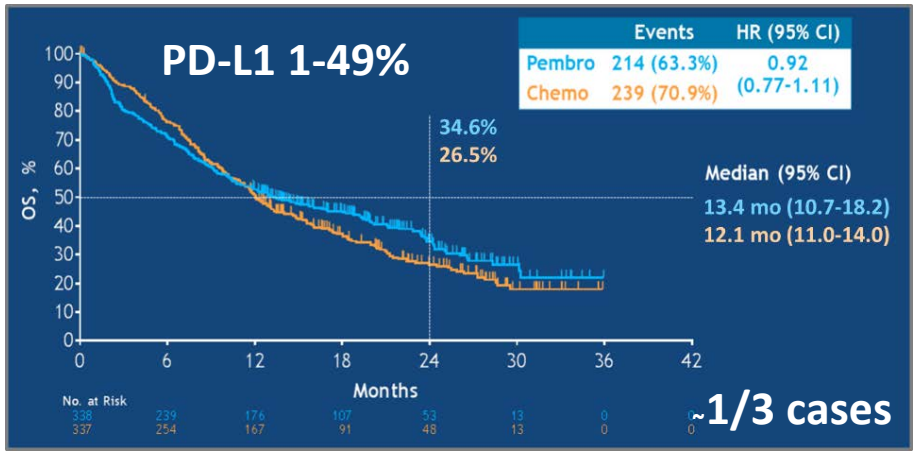
Eliminating chemotherapy: 1L IO monotherapy → still best used in PDL1 high cases?

Initial FDA approval → **Subsequent FDA approval**





Who was added?

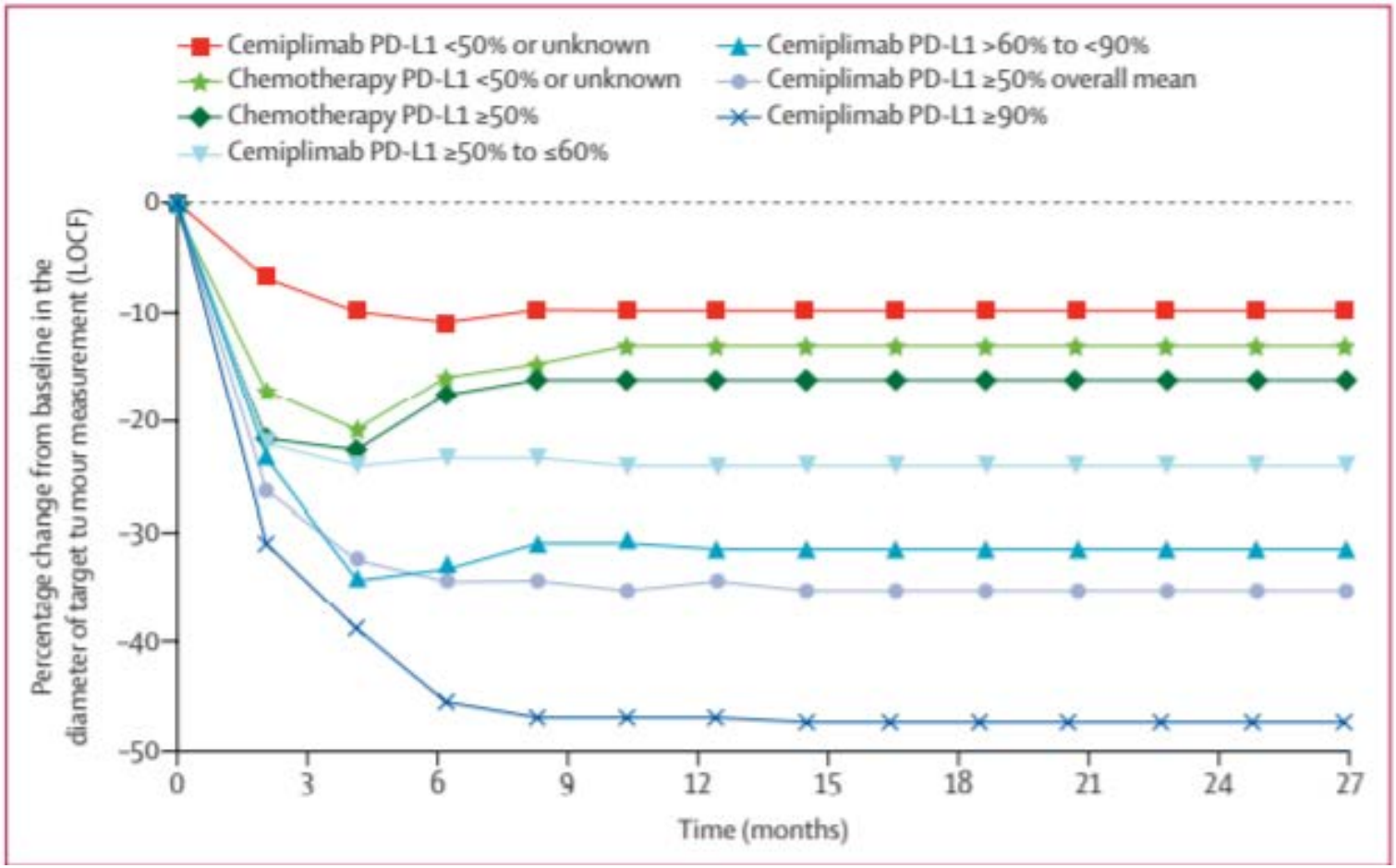


If IO same as chemotherapy, then presumably not as good as chemo + IO

KEYNOTE 042. Lopes G, et al. ASCO 2018. Abstract LBA4.

Within the high PD-L1 stratum, PD-L1 expression level may influence outcomes

EMPOWER Lung: cemiplimab vs chemotherapy in PD-L1 ≥50%



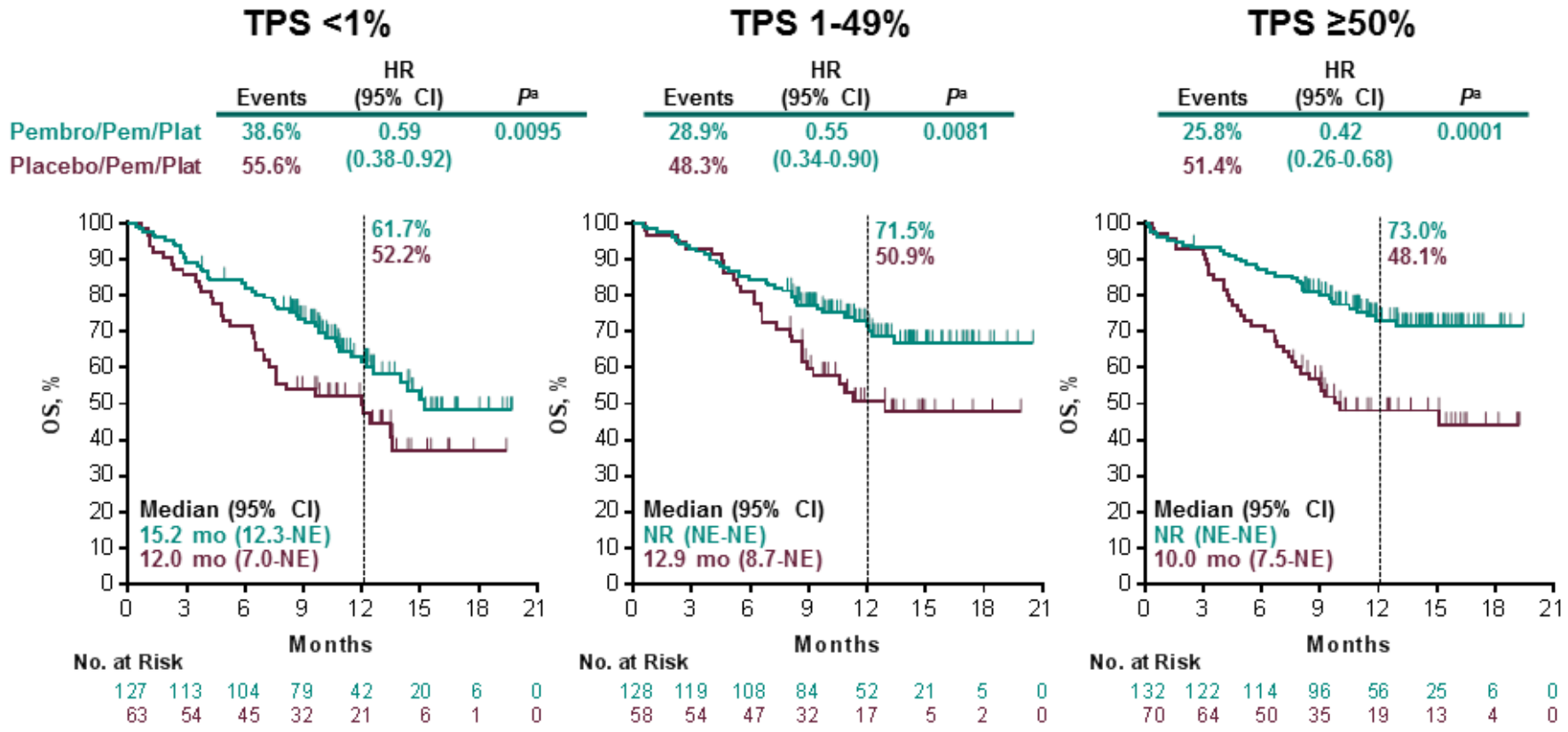
PD-L1 50-60%

PD-L1 60-90%

PD-L1 ≥90%

In PD-L1 <50%, combination with chemotherapy frequently preferred

KEYNOTE-189

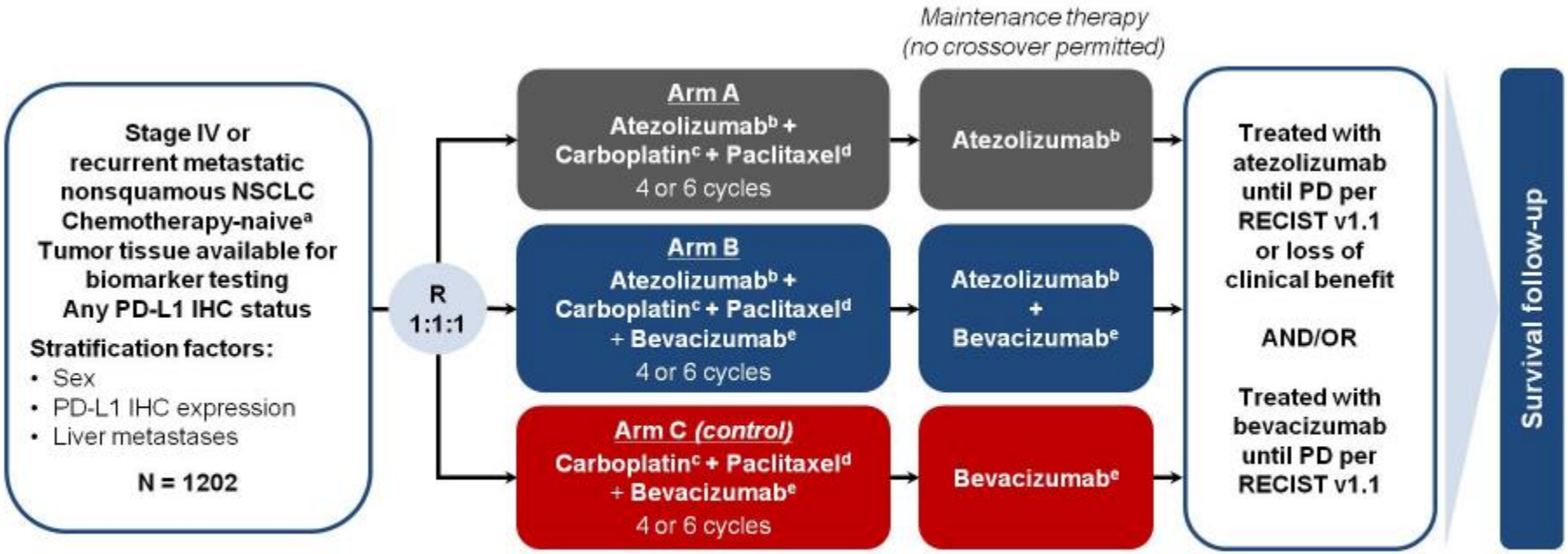


[a]Nominal and one-sided. Data cutoff date: Nov 8, 2017.

KEYNOTE-189.

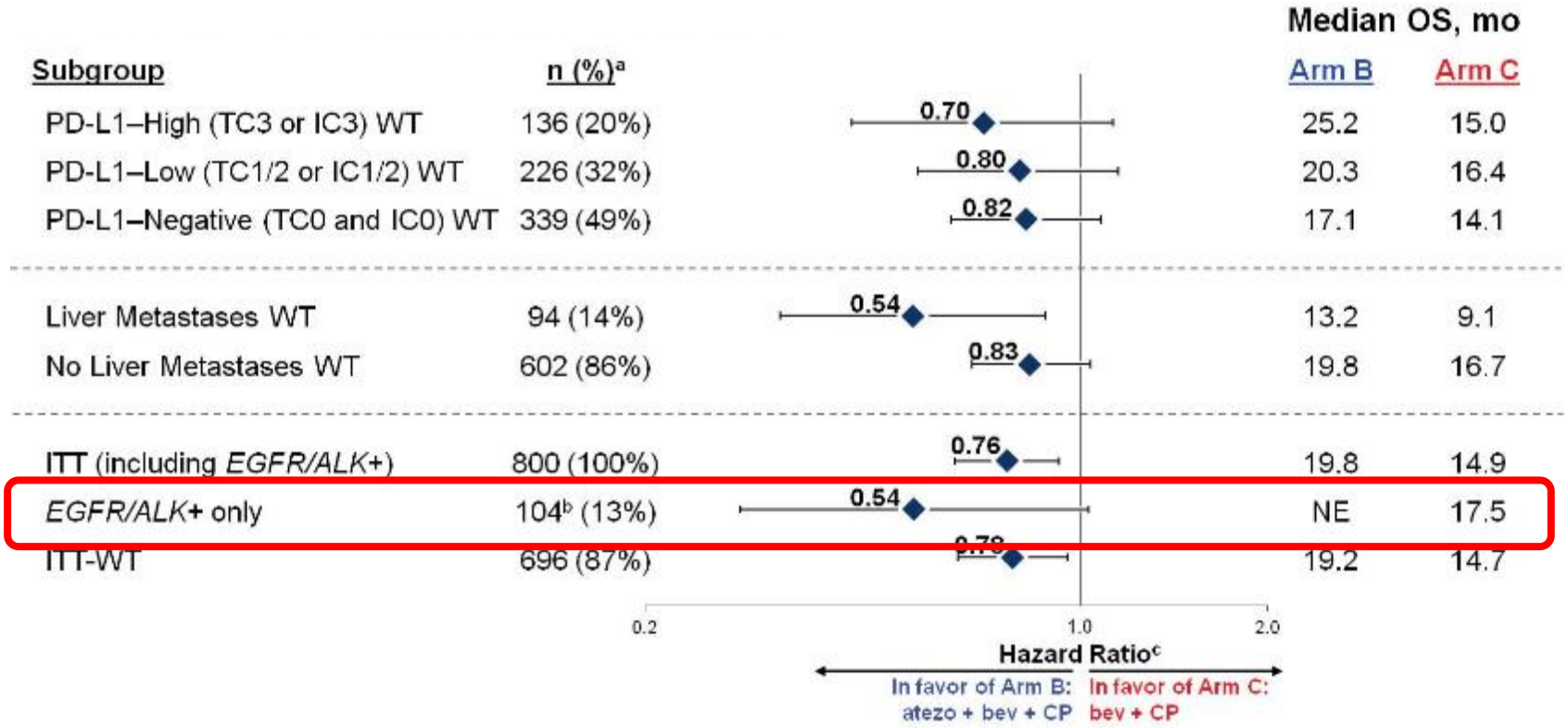
Atezolizumab combinations did not exclude "targeted therapy" populations . . .

IMpower 150



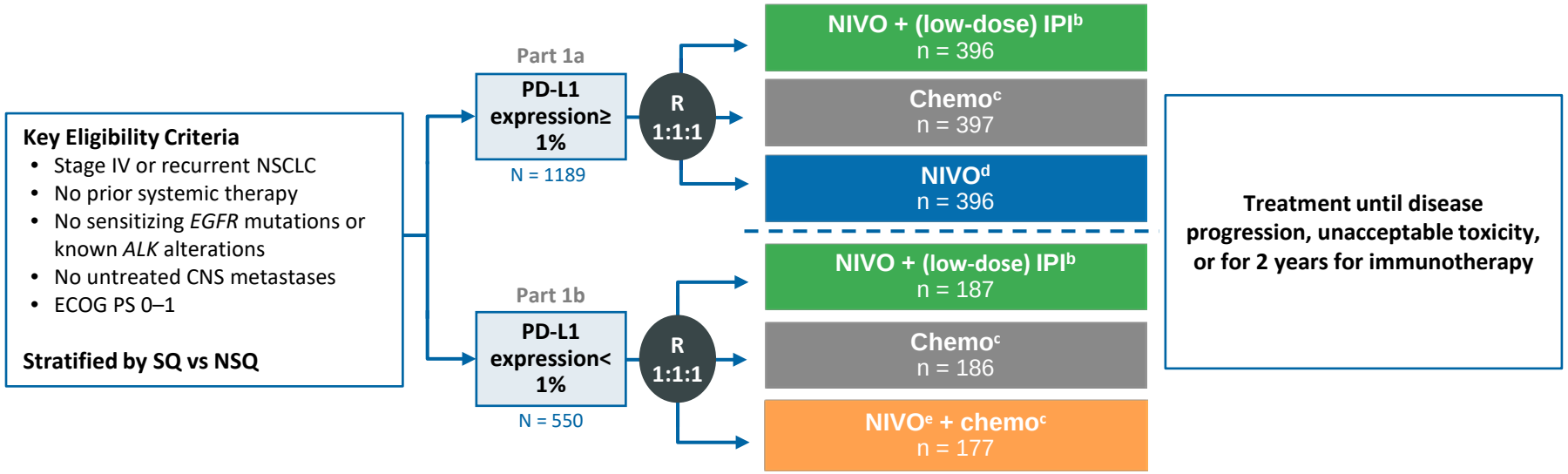
[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

… in which they seemed effective



Combination immunotherapy has also been approved for advanced NSCLC

CheckMate 227 Part 1 Study Design[a]



Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

Secondary endpoints (PD-L1 hierarchy):
- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

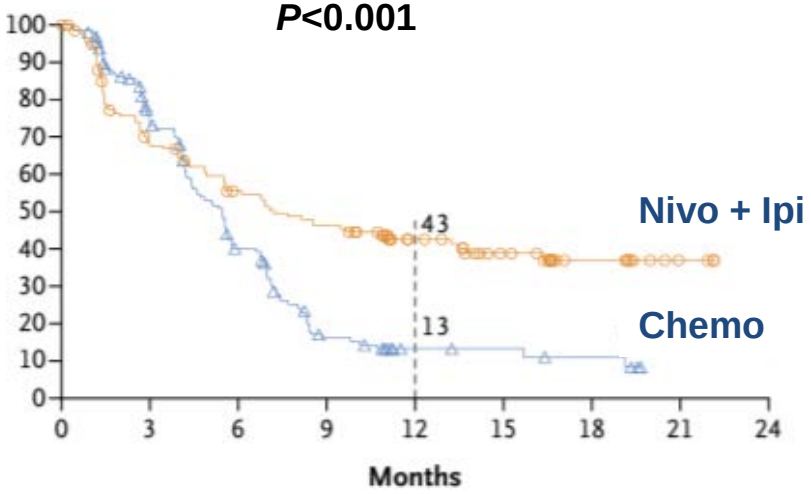
S. Peters, ESMO 2019; Database lock: July 2, 2019; minimum follow-up for primary endpoint: 29.3 months

Courtesy of Hossein Borghaei, MD

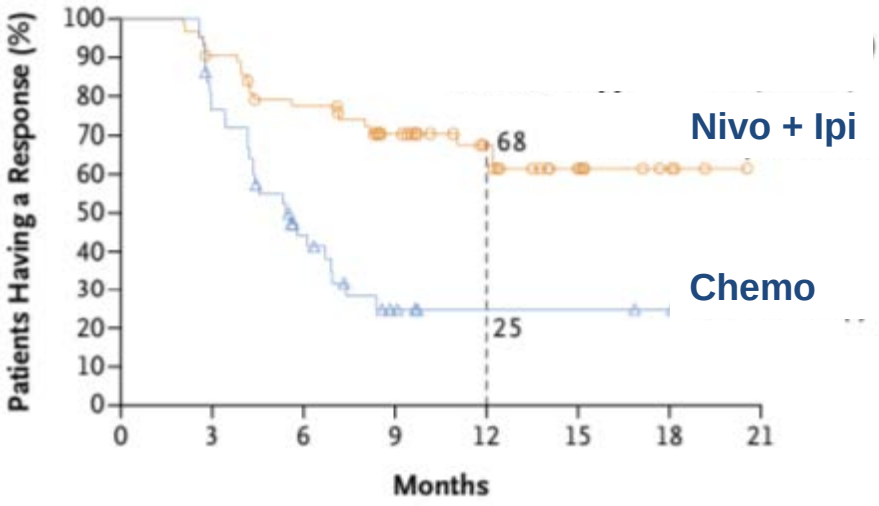
This combination appears particularly beneficial in high tumor mutation burden (TMB) cases . . .

Progression-free survival

HR 0.58 (97.5% CI, 0.41-0.81)
P<0.001

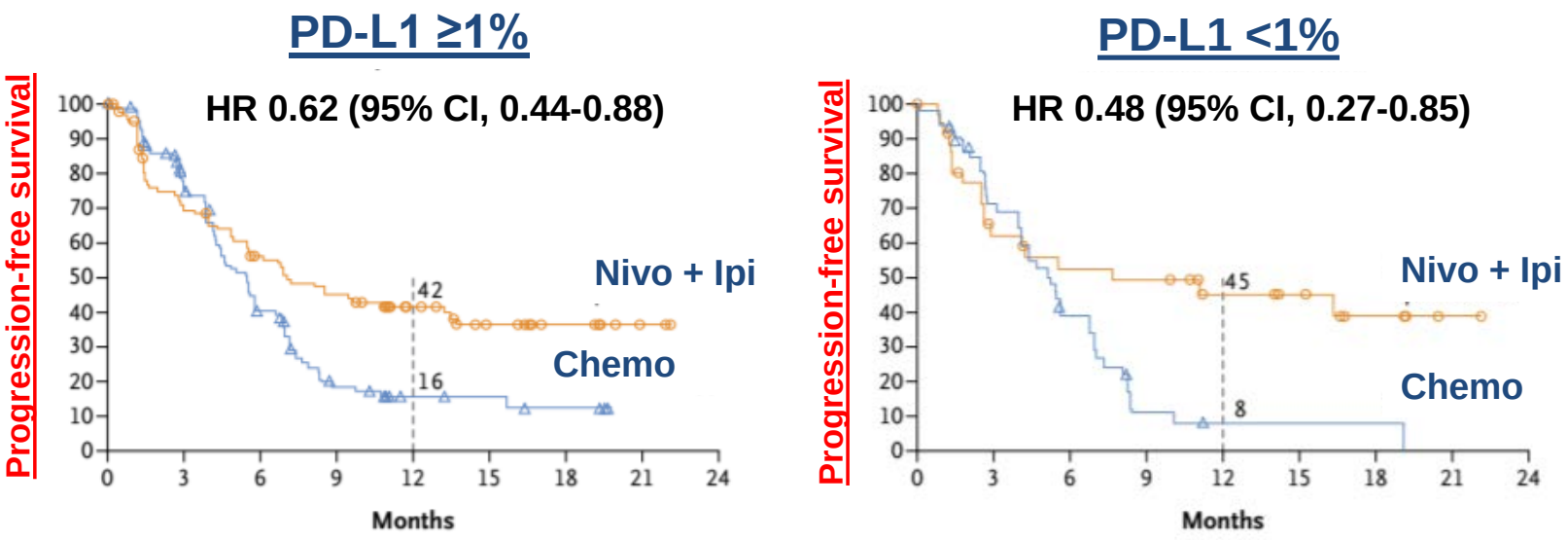


Duration of response



High Tumor Mutation Burden (TMB): ≥10 mutations/Mb

. . . regardless of PD-L1 expression



High Tumor Mutation Burden (TMB): ≥10 mutations/Mb

Selecting among these recently approved combination regimens: clear as mud

PD1 + Chemo **PD1 + CTLA4** **PD1 + CTLA4 + Chemo**

	Keynote 189 (PD-L1 ≥1%)	Keynote 189 (PD-L1 <1%)	CheckMate 227 (PD-L1 ≥1%)	CheckMate 227 (PD-L1 <1%)	CheckMate 9LA (PD-L1 ≥1%)	CheckMate 9LA (PD-L1 <1%)
Follow-up	23.1 months (median)	23.1 months (median)	37.7 months	37.7 months	12.7 months	12.7 months
Median OS (Months)	23.3 vs 11.3	17.2 vs 10.2	17.1 vs. 14.9	17.2 vs. 12.2	15.8 vs 10.9	16.8 vs 9.8
OS (HR)	0.61	0.52	0.70	0.64	0.64	0.62
1y OS (%)	70	63.4	63	60	66	63
2y OS (%)	45.5	38.5	40	40		

Courtesy of Hossein Borghaei, MD

How does a world-class expert in lung cancer (not me) recommend using immunotherapy regimens?

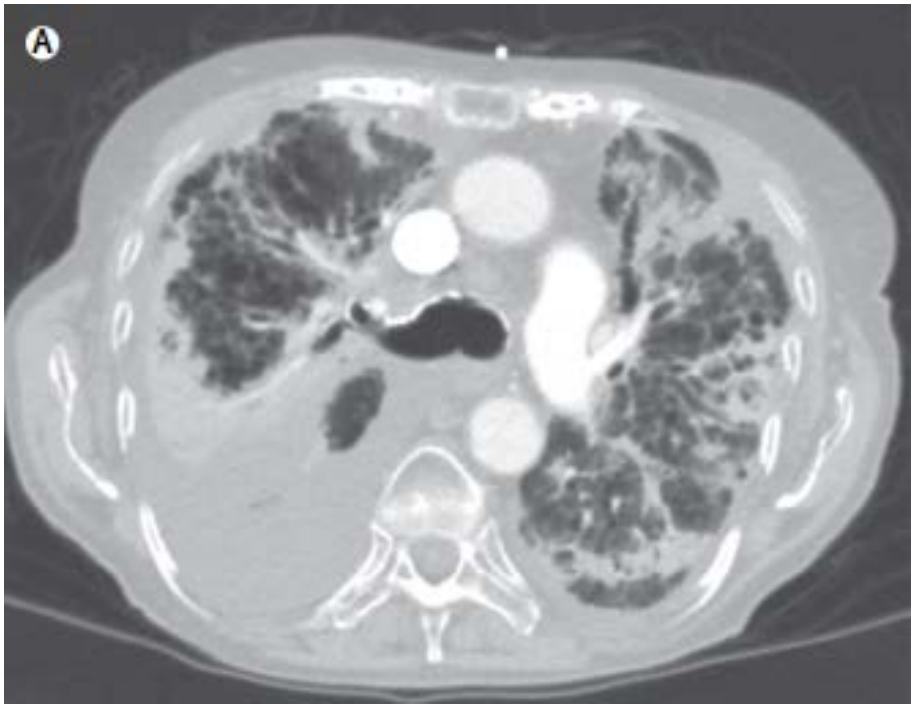
Tx Cohort	Non-Squamous	Squamous
PDL1 ≥ 50%	Pembro > Pem/Carbo/Pembro	Pembro > Taxane/Carbo/Pembro
PDL1 1-50%	Pem/Carbo/Pembro > Pembro	Taxane/Carbo/Pembro > Pembro
PDL1 < 1%	Pem/Carbo/Pembro	Taxane/Carbo/Pembro
PDL1 < 1%, TMB > 10	Pem/Carbo/Pembro vs Ipi/Nivo*	Taxane/Carbo/Pembro vs Ipi/Nivo*
TKI-Refractory**	Pac/Carbo/Bev/Atezo or Pem/Carbo ± Bev	
Tissue QNS	Pem/Carbo/Pembro	Taxane/Carbo/Pembro

*Ipilimumab/Nivolumab ± 2 cycles of histology-appropriate chemotherapy (9LA)

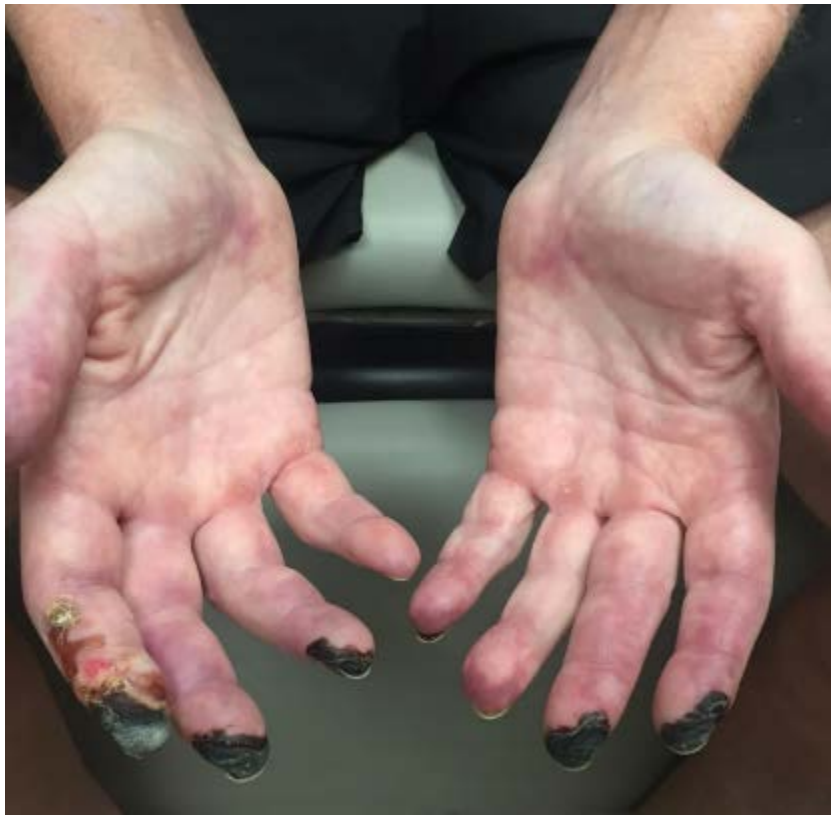
**Bevacizumab-containing regimens may also have role if effusions or edema from brain mets

Corey J. Langer, MD, FACP
Director, Thoracic Oncology
Abramson Comprehensive Cancer Center
University of Pennsylvania
Philadelphia, PA

Regardless of IO regimen, immune-related adverse events are largely unpredictable and potentially severe



Pneumonitis after 3 doses



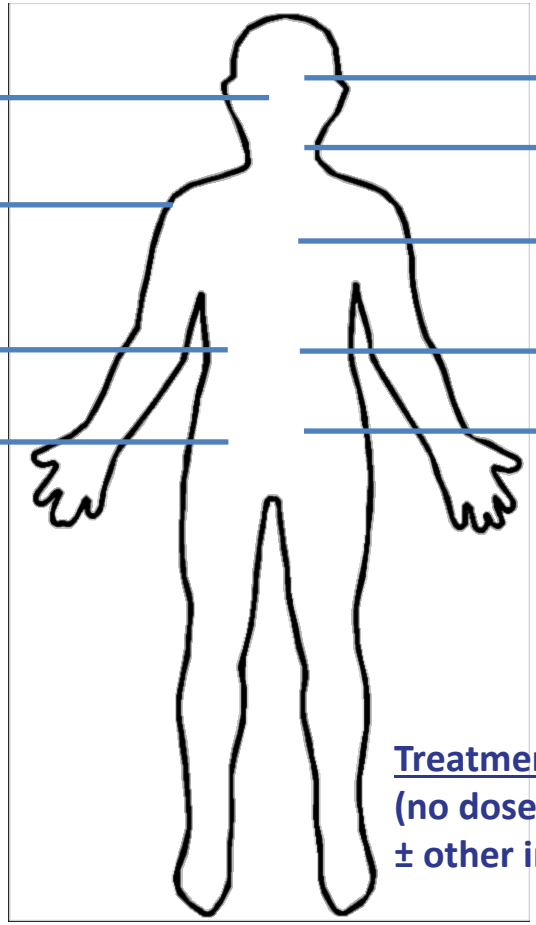
Antiphospholipid syndrome after 4 doses

Rashdan S et al. *Lancet Respir Med* 2018;6:472-478.

Gupta A et al. *Melanoma Res* 2017;27:171-173.

Immune-related adverse events may affect almost any organ system

Immune-related adverse events (irAE) may affect almost any organ system



Pre-existing active autoimmune diseases requiring immune suppression generally considered contraindication to checkpoint inhibitor immunotherapy

Treatment: withhold/discontinue therapy (no dose modifications), administer steroids ± other immunosuppression

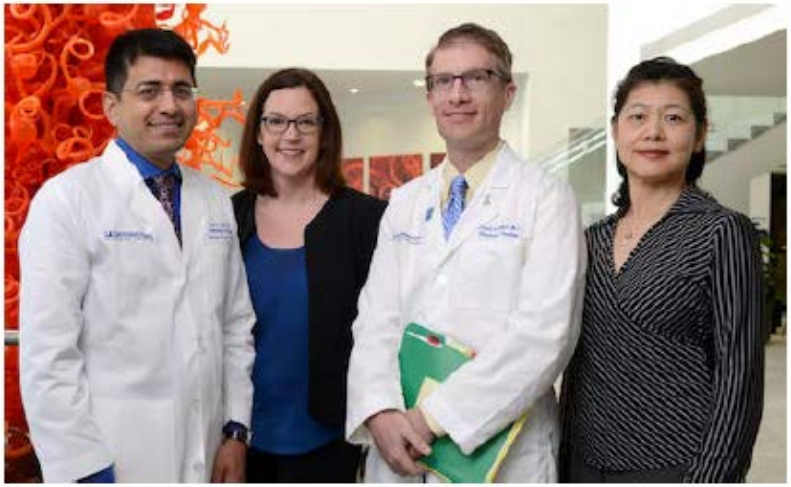
https://www.appitierre.com/blog/the-adapt-learning-framework-and-the-elephant-in-the-room/

Autoimmune disease occurs in a substantial minority of patients with cancer, and may be challenging to diagnose

RESEARCH LETTER

Prevalence of Autoimmune Disease Among Patients With Lung Cancer: Implications for Immunotherapy Treatment Options

Saad A. Khan, MD
Sandi L. Pruitt, PhD
Lei Xuan, PhD
David E. Gerber, MD



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CANCER

Cancer treatment untested in many patients with immune problems

msn lifestyle

The Reason Millions Of Cancer Patients Are Excluded From Immunotherapy

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Almost 25 Percent Of Cancer Patients Are Ineligible For Immunotherapy, Researchers Say

Khan SA et al. *JAMA Oncol* 2016;2:1507-1508.

Autoimmune disease occurs in a substantial minority of patients with cancer, and may be challenging to diagnose

Table 1. Characteristics of Lung Cancer Patients With Autoimmune Disease

Patient Characteristics	All Patients, No.	With Autoimmune Disease, No. (%)	*P* Value[a]
Total	210 509	28 453 (13.5)	
Age			
<75	94 804	11 664 (12.3)	<.001
≥75 to <85	92 045	13 529 (14.7)	<.001
≥85	23 660	3260 (13.8)	<.001
Sex			
Female	97 494	16 374 (16.8)	<.001
Male	113 015	12 079 (10.7)	<.001
Stage (AJCC)			
I	36 152	6331 (17.5)	<.001
II	6758	1028 (15.2)	<.001
III	51 542	6692 (13)	<.001
IV	77 833	9302 (12)	<.001
Other	38 224	5100 (13.3)	<.001

Table 2. Prevalence of the 10 Most Common Individual Autoimmune Diseases Among 210 509 Patients With Lung Cancer

Autoimmune Disease	Prevalence, %
Rheumatoid arthritis	5.9
Psoriasis	2.8
Polymyalgia rheumatic	1.8
Addison disease	1.0
Systemic lupus erythematosus	0.9
Ulcerative colitis	0.8
Giant cell arteritis	0.8
Sicca syndrome	0.6
Regional enteritis	0.5
Ménière disease, unspecified	0.5
Total (any autoimmune disease)	13.5

Estimated prevalence:

- **13.5%** (claims "rule-out" method: ≥2 outpt claims ≥30 days apart or ≥1 inpt claim)
- **24.6%** (more liberal method: ≥1 claim of any type)

If autoimmune disease is difficult to diagnose, what about diagnosing immune-related adverse events?

Khan SA et al. *JAMA Oncol* 2016;2:1507-1508.

Remember that most chemotherapy toxicities are readily diagnosed and characterized

	Ref. Range	1/24/2019 1022
CK, TOTAL	Latest Ref Range: 39 - 308 U/L	24
LD	Latest Ref Range: 135 - 225 U/L	499
SODIUM	Latest Ref Range: 135 - 145 mmol/L	139 *
POTASSIUM	Latest Ref Range: 3.6 - 5.0 mmol/L	4.1 *
CHLORIDE	Latest Ref Range: 98 - 109 mmol/L	104 *
CO2	Latest Ref Range: 22 - 31 mmol/L	19 *
ANION GAP	Latest Ref Range: 6 - 16 mmol/L	16 *
GLUCOSE	Latest Ref Range: 70 - 139 mg/dL	243 *
BUN	Latest Ref Range: 6 - 23 mg/dL	29 *
CREATININE	Latest Ref Range: 0.67 - 1.17 mg/dL	1.08 *
eGFR African American	Latest Ref Range: >60 mL/min/1.73 m2	>60 *
eGFR Non-African American	Latest Ref Range: >60 mL/min/1.73 m2	>60 *
BUN/CREAT RATIO	Latest Ref Range: 10.0 - 20.0 mg/mg creat	26.9 *
CALCIUM	Latest Ref Range: 8.4 - 10.2 mg/dL	9.5 *
Protein Total	Latest Ref Range: 6.6 - 8.7 g/dL	6.3 *
ALBUMIN	Latest Ref Range: 3.5 - 5.2 g/dL	3.1 *
ALK PHOS	Latest Ref Range: 40 - 129 U/L	462 *
BILIRUBIN, TOTAL	Latest Ref Range: 0.2 - 1.3 mg/dL	0.5 *
GLOBULIN	Latest Ref Range: 1.5 - 3.3 g/dL	3.2 *
A/G RATIO	Unknown	1.0 *
MAGNESIUM	Latest Ref Range: 1.6 - 2.6 mg/dl	1.7
PHOSPHORUS	Latest Ref Range: 2.4 - 4.5 mg/dL	3.4
URIC ACID	Latest Ref Range: 3.4 - 7.0 mg/dL	7.9
ALT	Latest Ref Range: 10 - 50 U/L	54 *
AMYLASE	Latest Ref Range: 28 - 100 U/L	92
AST	Latest Ref Range: 10 - 50 U/L	46 *
LIPASE	Latest Ref Range: 7 - 59 U/L	15
PROTIME	Latest Ref Range: 9.5 - 12.8 Sec	11.9
INR	Latest Ref Range: 0.9 - 1.3	1.2 *
PTT	Latest Ref Range: 23.0 - 32.5 Seconds	33.7
WBC	Latest Ref Range: 4.00 - 11.00 x10(9)/L	9.35
RBC	Latest Ref Range: 4.00 - 5.80 x10(12)/L	3.25
HEMOGLOBIN	Latest Ref Range: 12.4 - 17.3 g/dL	9.1
HEMATOCRIT	Latest Ref Range: 37.0 - 50.0 %	28.0
MCV	Latest Ref Range: 80.0 - 98.0 fL	86.2
MCH	Latest Ref Range: 27.0 - 33.0 pg	28.0
MCHC	Latest Ref Range: 33.0 - 35.0 g/dL	32.5
RDW	[illegible]	[illegible]
PLATELETS	Latest Ref Range: 150 - 450 x10(9)/L	55
MPV	[illegible]	[illegible]
NRBC	Latest Ref Range: <=0.0 %	0.9
NRBC ABS	Latest Ref Range: <=0.00 x10(9)/L	0.08

SMS
UTSW01-06
C9D1- Delayed

gr 1
gr 2
gr 1
gr 1
gr 2
gr 2 CS
Held 1x

D1W NCS
2/1/19

Thrombocytopenia:

- Quantified by lab value
- No other likely cause

Chemotherapy toxicities are also relatively easy to predict

1 **CHEMO** Inf. Rxn. Acute N/V Tissue inj.	2 Acute N/V	3 Delayed N/V	4 Delayed N/V	5 Delayed N/V	6 Delayed N/V	7 Delayed N/V
8	9	10 Count nadir	11 Count nadir	12 Count nadir	13 Count nadir	14 Count nadir
15 Count nadir	16	17	18	19	20	21
22 **CHEMO**	23 Alopecia this cycle	24	25	26	27	28
29	30	31				

Clear differences between trial reports and institutional experiences suggest otherwise for immune-related AE

CheckMate 057: 4% pneumonitis

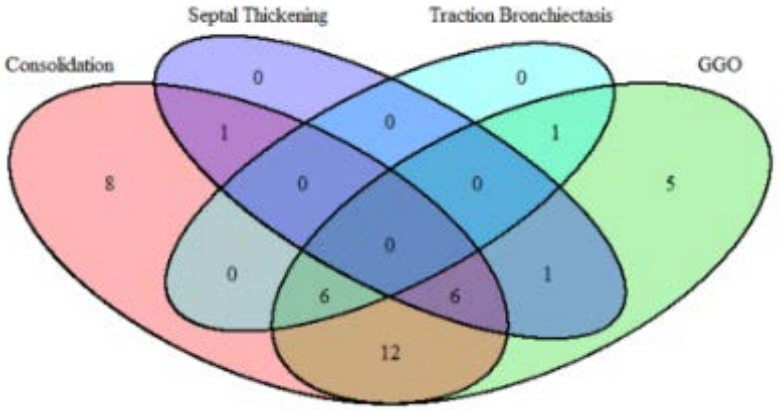
Select adverse event category	Nivolumab n = 287	
	Any Grade	Grade 3-4
Pulmonary		
Pneumonitis	8 (3)	3 (1)
Interstitial lung disease	2 (1)	1 (<1)

Borghaei H et al. *N Engl J Med* 2015;373:1627-39.

Johns Hopkins: 19% pneumonitis

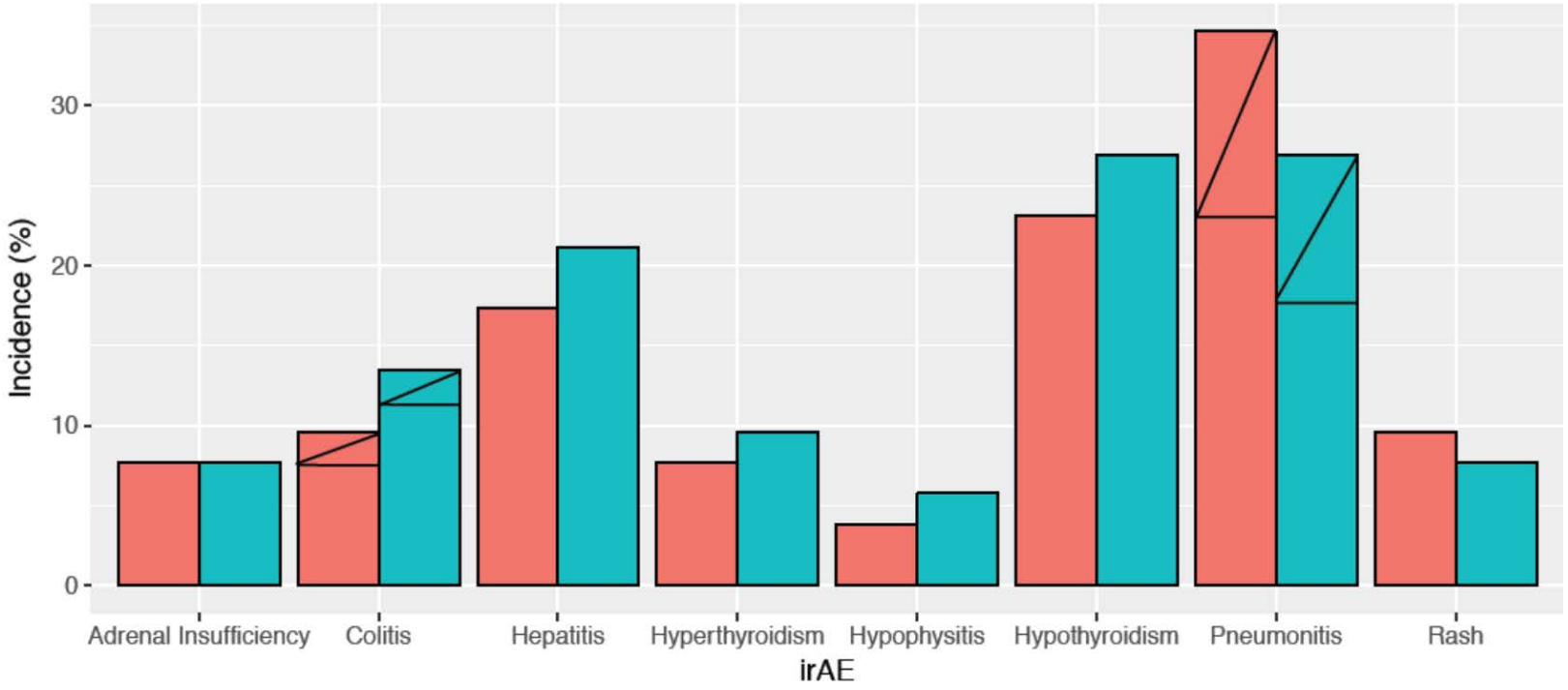
Table 1. Baseline Characteristics

Characteristic	CIP (n = 39)	No CIP (n = 166)	All Patients (N = 205)



Suresh K et al. *J Thorac Oncol* 2018;13:1930-9.

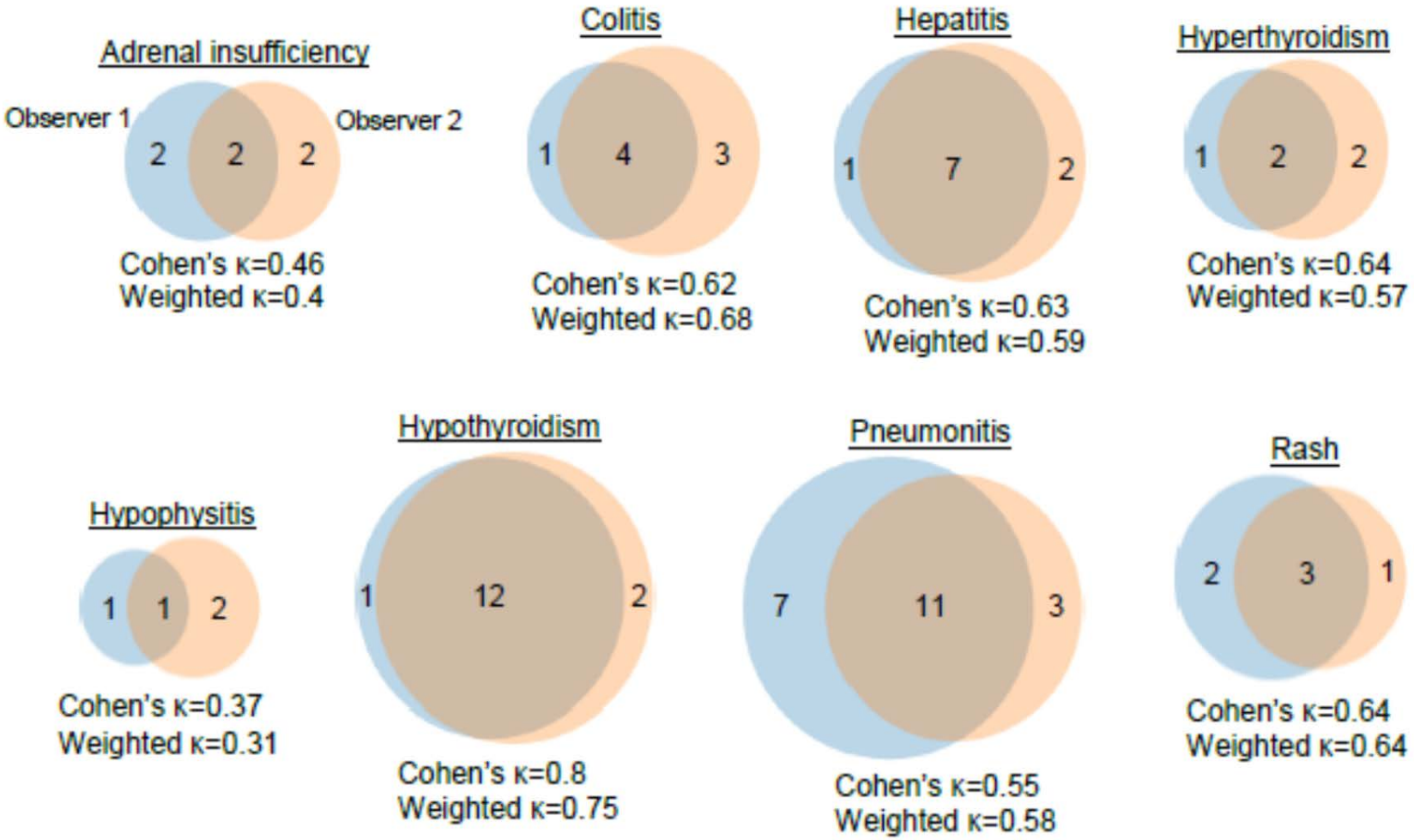
Rates of immune-related AE varied between reviewers and generally exceeded those reported in clinical trials



Neither reviewer consistently identified more/fewer toxicities than the other reviewer

Hsieh D et al. *JAMA Network Open* 2019.

Inter-observer agreement was poor (κ<0.7) for all immune-related AE except hypothyroidism

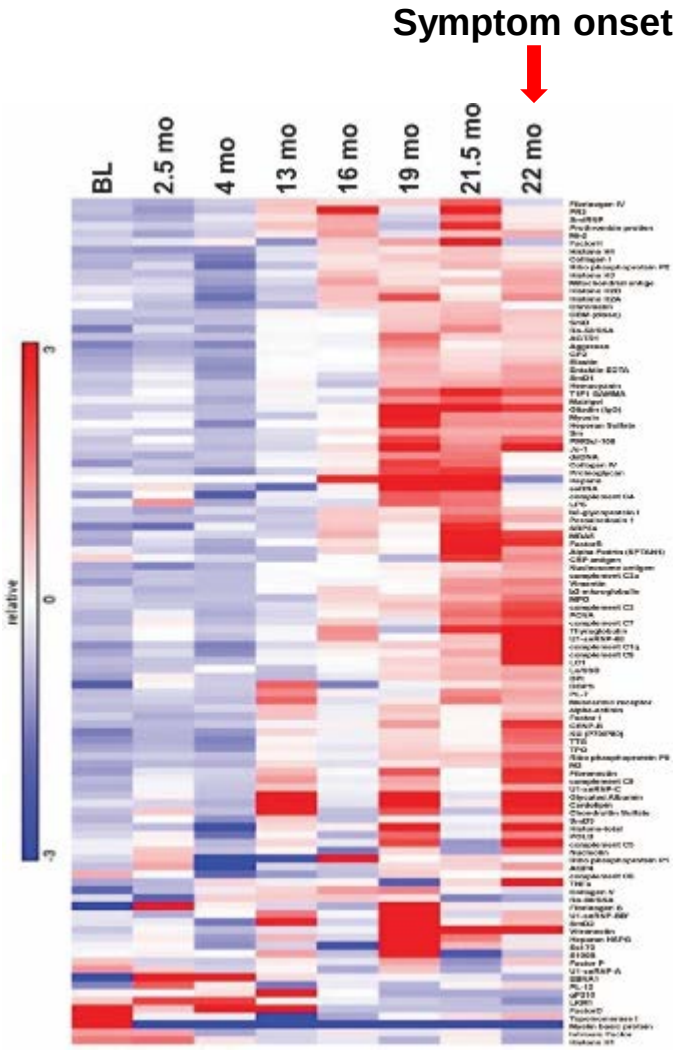


Agreement on immune-related AE grading similarly limited (weighted κ 0.31-0.75)

Hsieh D et al. *JAMA Network Open 2019* press.

The unpredictable timing of immune-related adverse events also keeps us on our toes

New-onset Raynaud's phenomenon 22 months after anti-PD1 + anti-CTLA4 started



125 autoantibodies over time

Khan S et al. *Oncologist* 2020.

Conclusions

- There is a strong rationale to harness the immune system for cancer treatment
- Despite decades of efforts, only recently have we seen meaningful progress, in the form of immune checkpoint inhibitors (ICI)
- Differences between various anti-PD1 / PDL1 inhibitors appear to be negligible
- Tumor PD-L1 expression is a useful but clearly imperfect biomarker
- Most lung cancer ICI indications do not require PD-L1 results
- Selecting among the various ICI-containing regimens in advanced NSCLC is difficult and lacks high-level evidence to support the decision
- Factors that may influence selection of regimens: (a) PD-L1 availability, (b) PD-L1 results, (c) functional status, (d) EGFR/ALK status, (e) tumor burden, (f) effusions/brain mets, (g) tolerance for autoimmune toxicities
- Immune-related adverse events (irAE) remain largely unpredictable, potentially severe, and difficult to diagnose

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