
SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
sitc
Society for Immunotherapy of Cancer

SITC 2017

Science Behind Therapy: Mechanisms of Efficacy & Toxicity

Jeffrey A. Sosman, MD
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

sitc
Society for Immunotherapy of Cancer

Presenter Disclosure Information

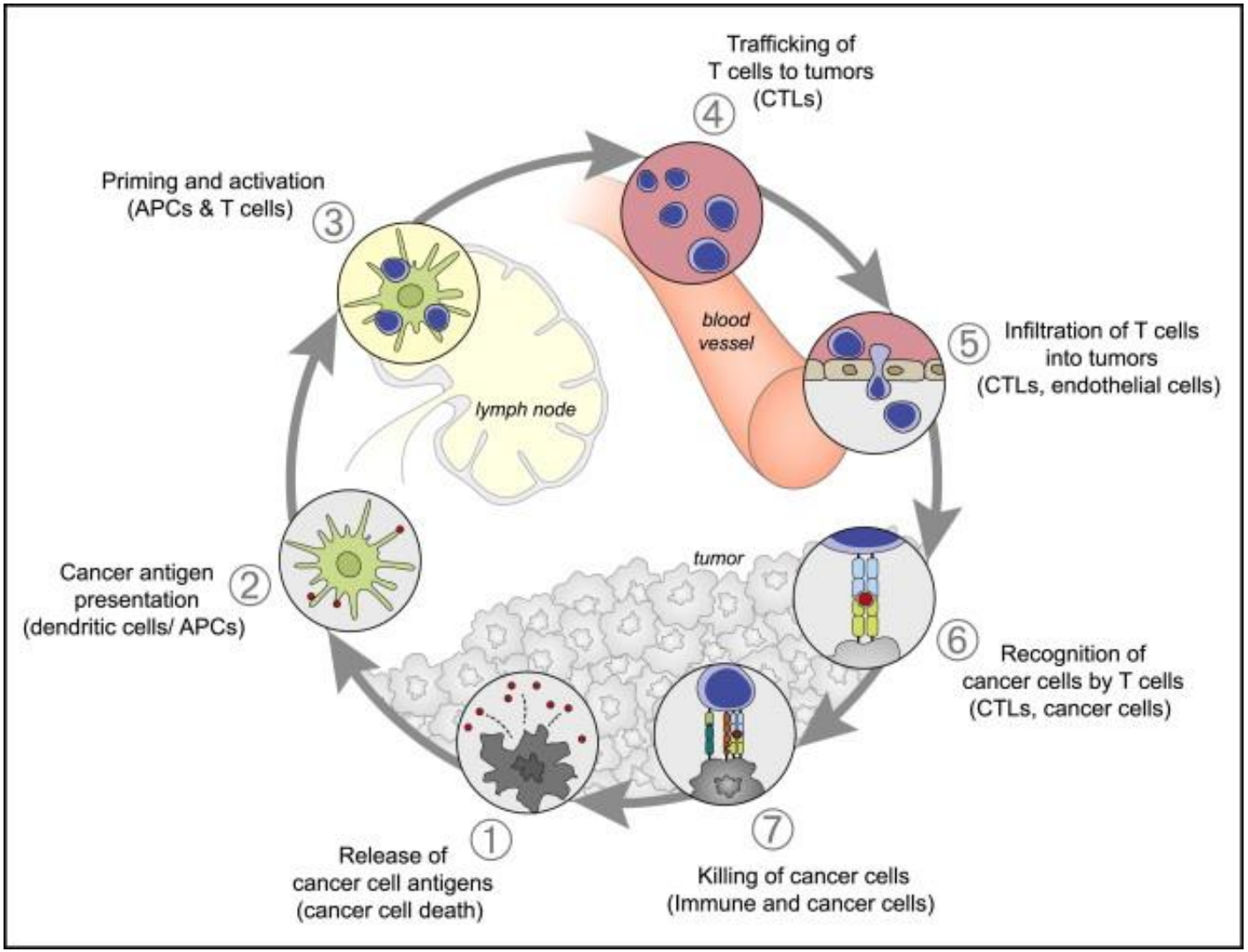
Jeffrey A. Sosman

- Advisory Boards: BMS, Incyte, Array, Novartis
- Research funding: BMS, Amgen

Overview of Talk

- Efficacy
  - Mechanism of Immune checkpoint Inhibition
  - Efficacy of Immune Checkpoint Blockade
  - Biomarkers-
    - PD-L1 expression (by IHC)
    - Mutation burden/neoantigen load
    - Immune signature
- Toxicity
    - Organs Effected
    - Management of Toxicity
    - Cardiac Toxicity: an example

The Cancer–Immunity Cycle

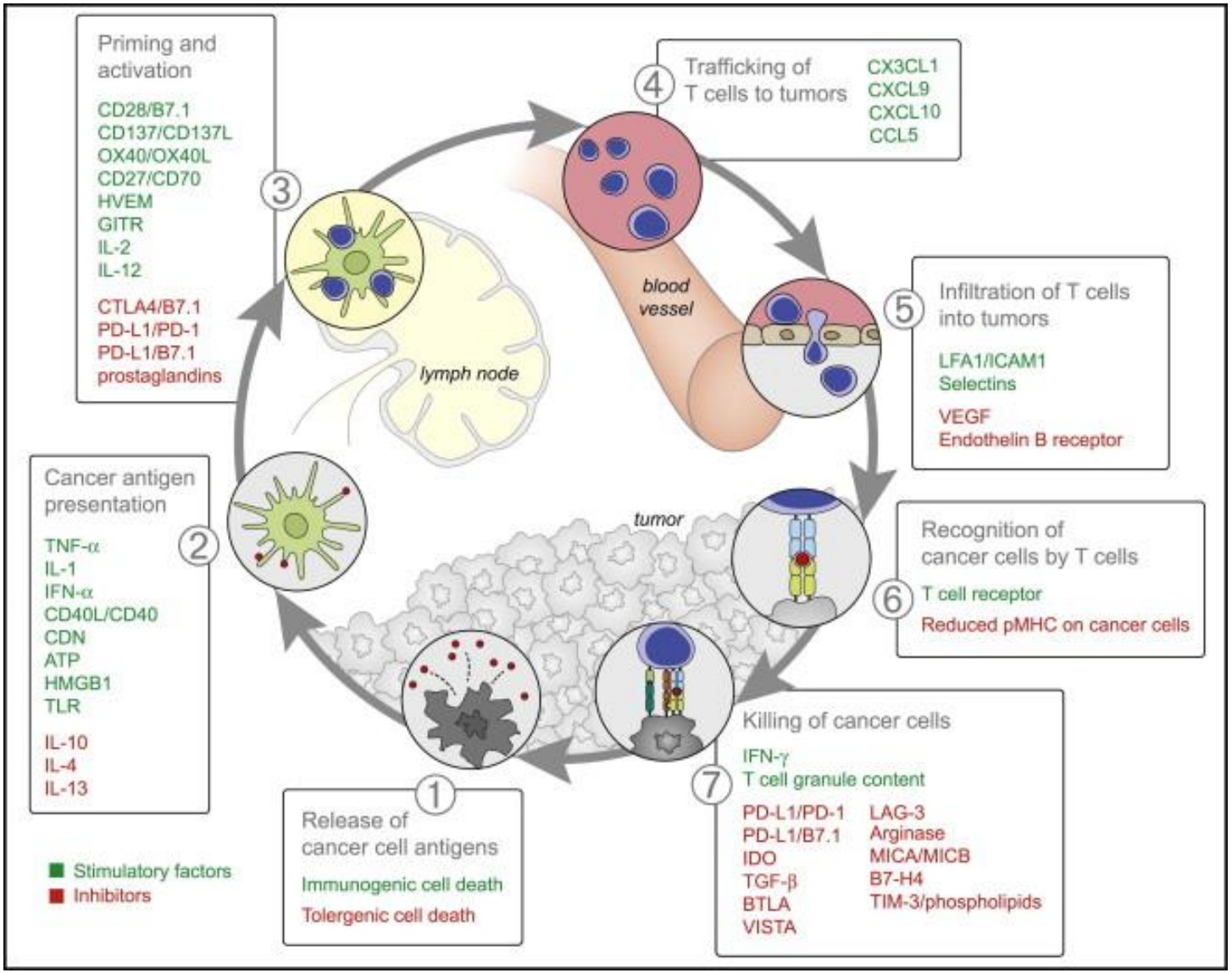


Daniel S. Chen , Ira Mellman

Immunity, Volume 39, Issue 1, 2013, 1 - 10

The Cancer-Immunity Cycle The generation of immunity to cancer is a cyclic process that can be self propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is ...

The Cancer–Immunity Cycle

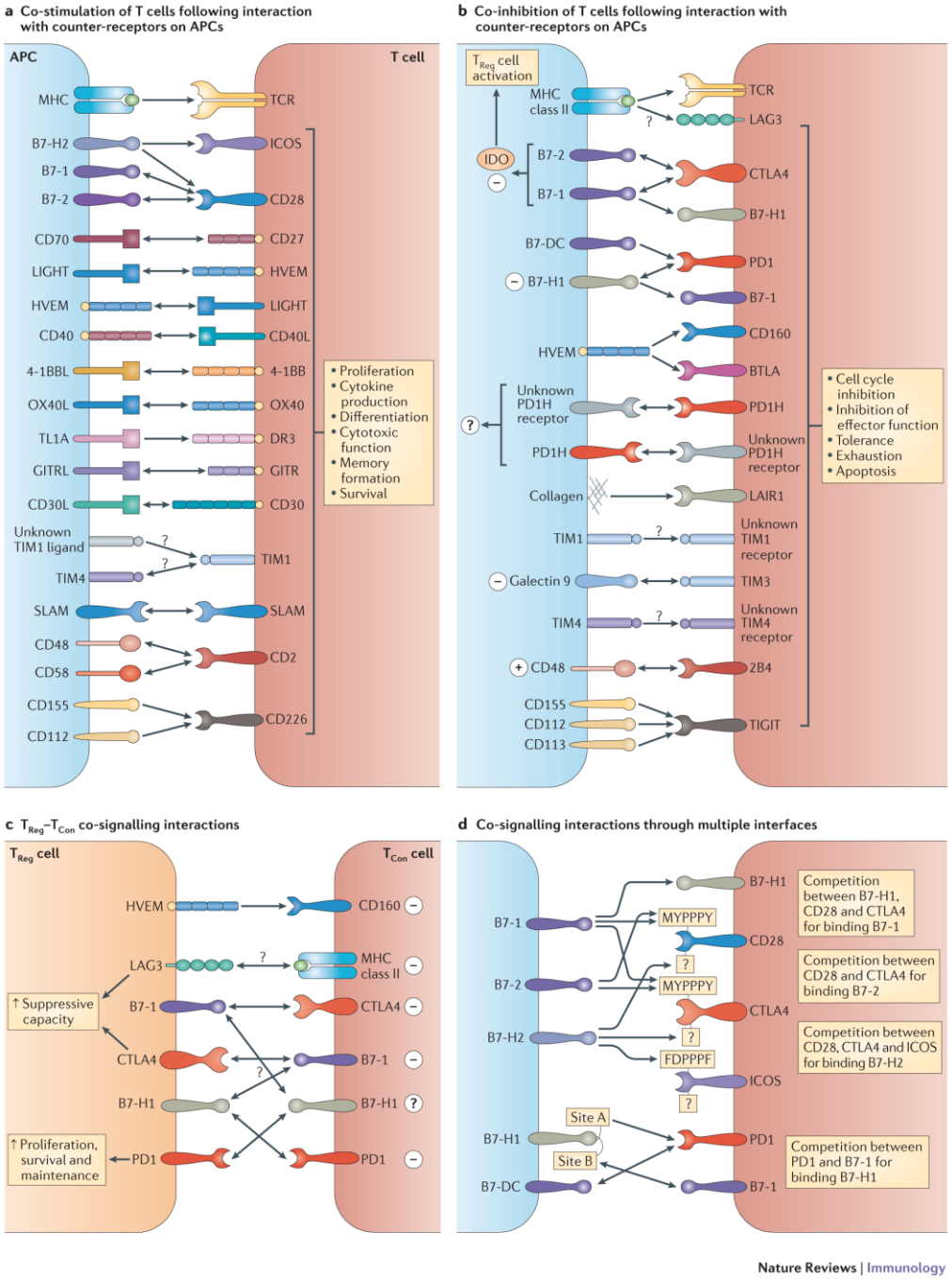


Daniel S. Chen , Ira Mellman

Immunity, Volume 39, Issue 1, 2013, 1 - 10

Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle Each step of the Cancer-Immunity Cycle requires the coordination of numerous factors, both stimulatory and inhibitory in nature. Stimulatory factors shown in green promote immunity, ...

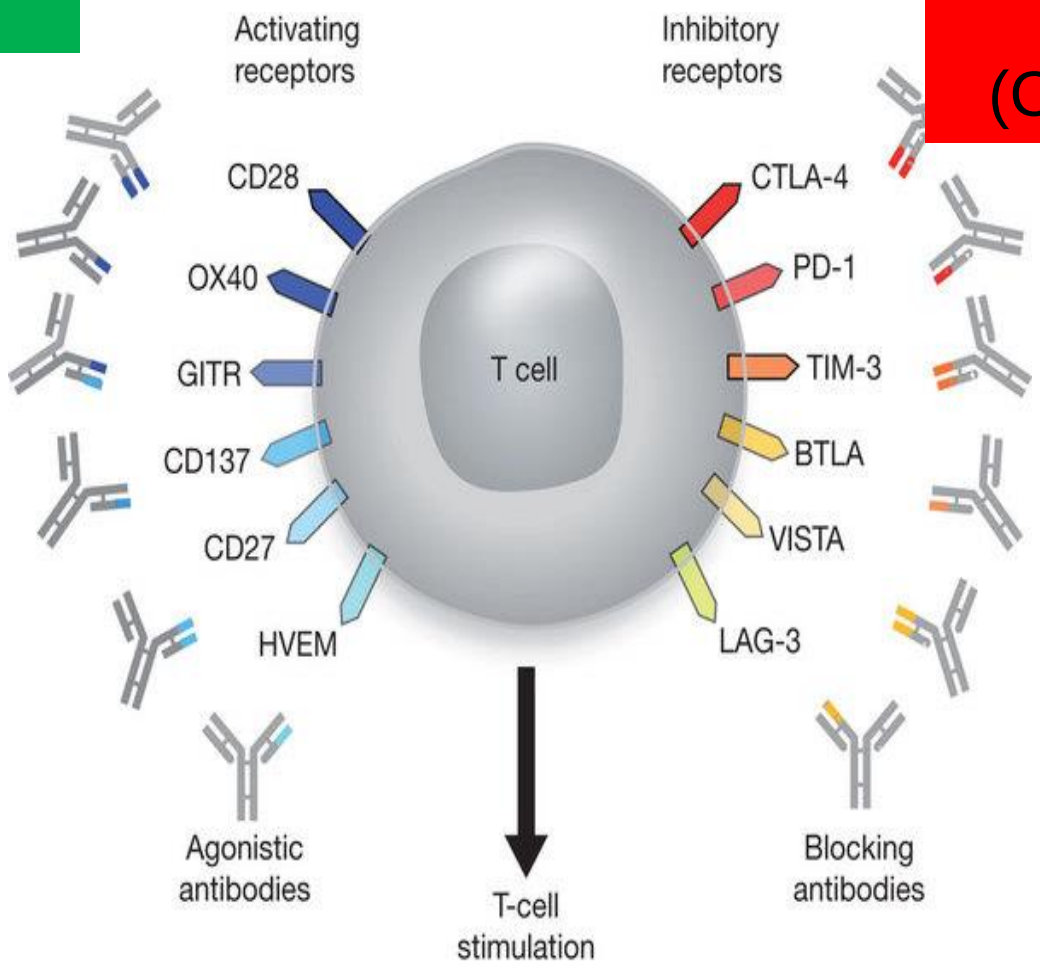
Immunological Synapse



T Cell Regulation

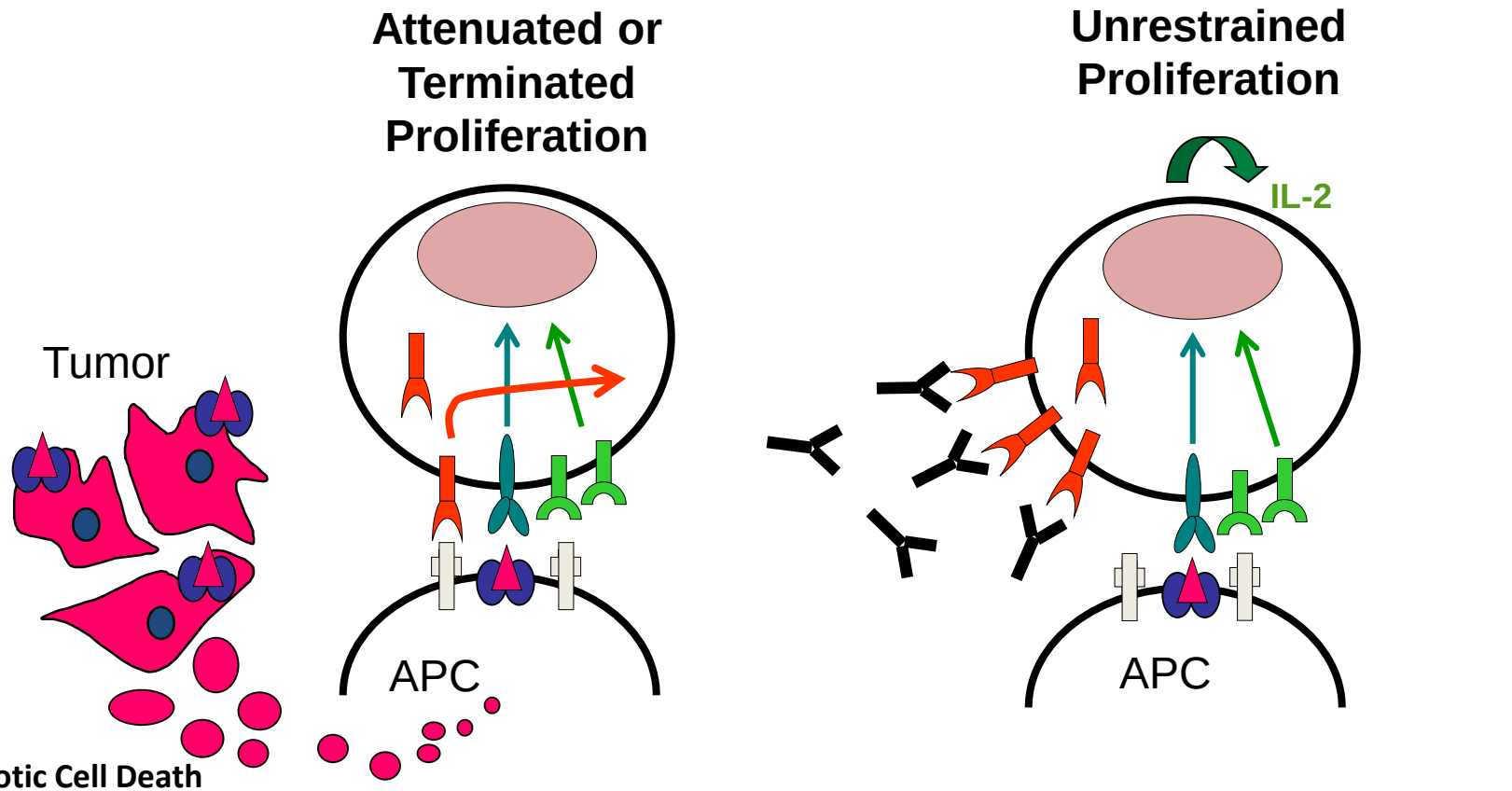
Turning up The Activating

Blocking the Inhibiting (Checkpoints)

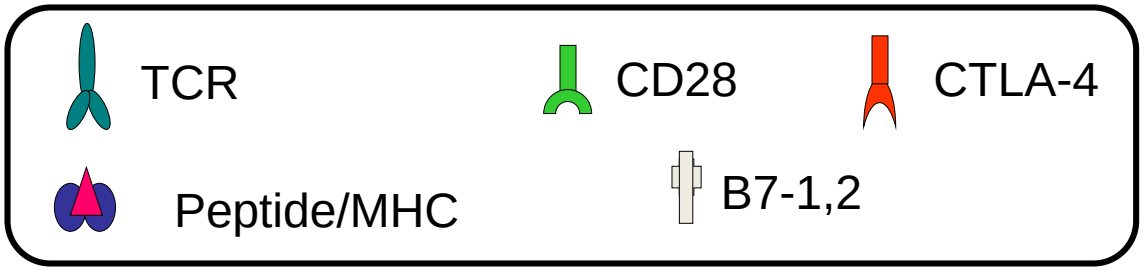


Mellman et al.
Nature 2011

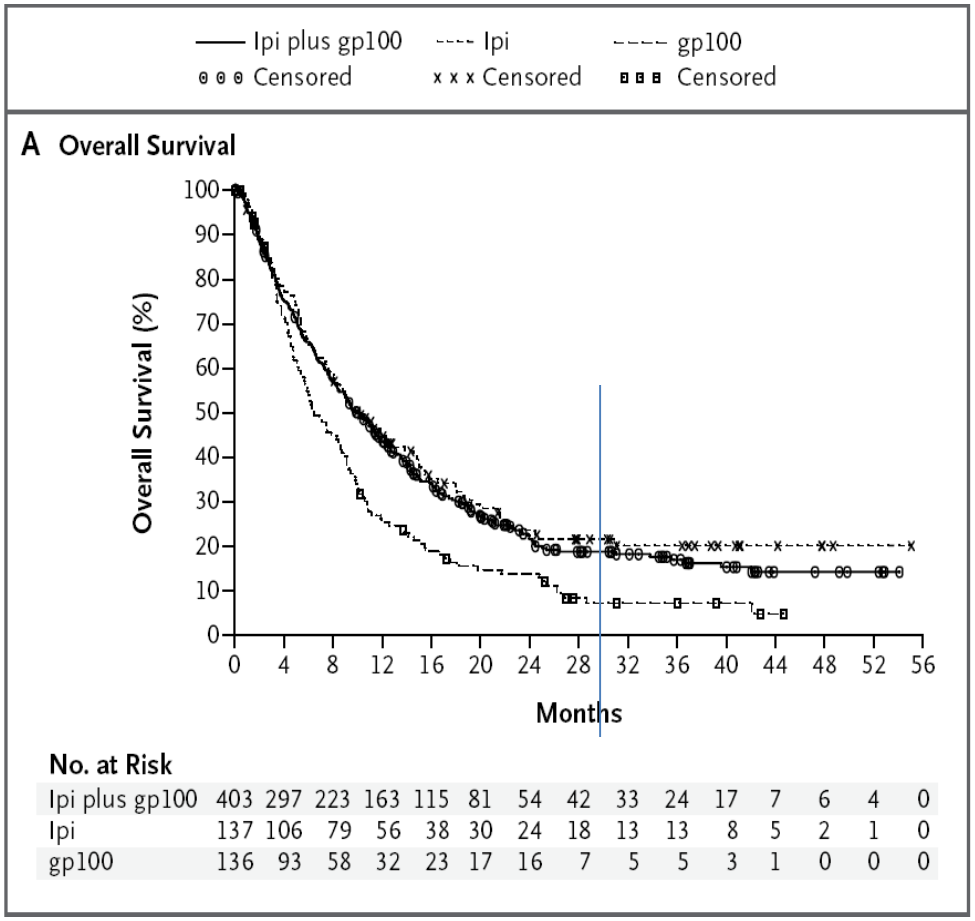
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses



Necrotic Cell Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
Targeted pathway inhibitors



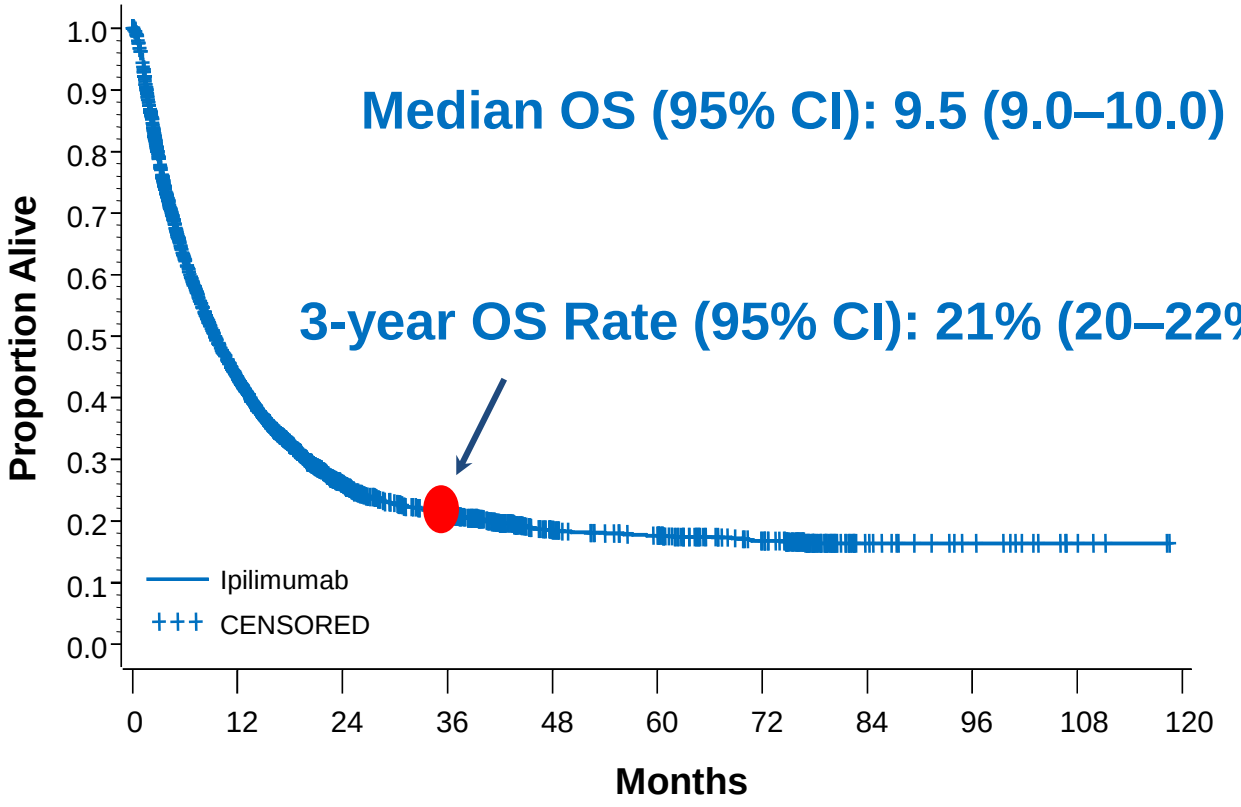
Paradigm Shifting Trial:
Ipilimumab: Phase III in Second Line (3mg/kg dose)



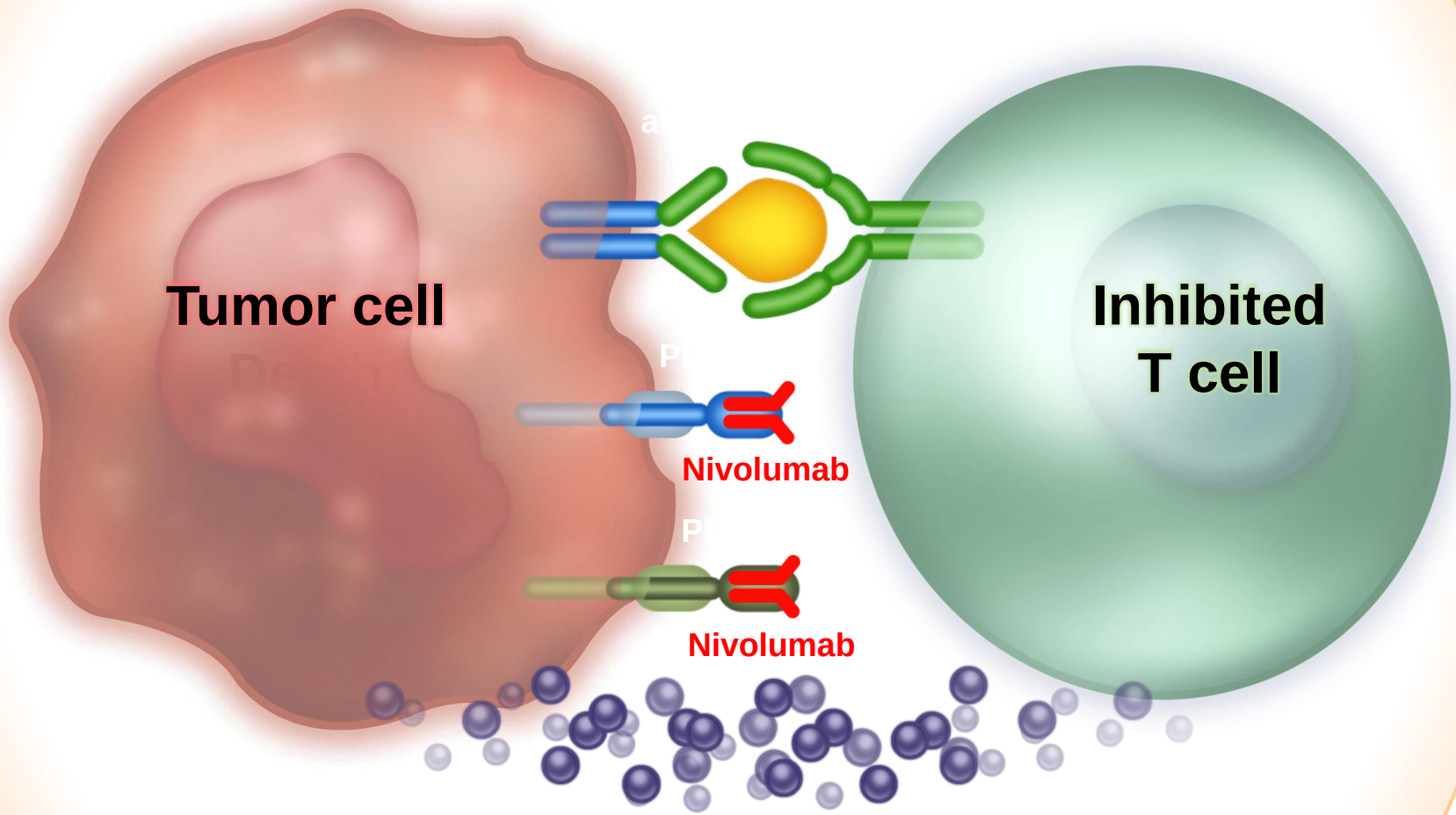
Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-yr	44%	46%	25%
2-yr	22%	24%	14%

N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

Ipilimumab Long Term Pooled Survival Analysis: 4846 Patients

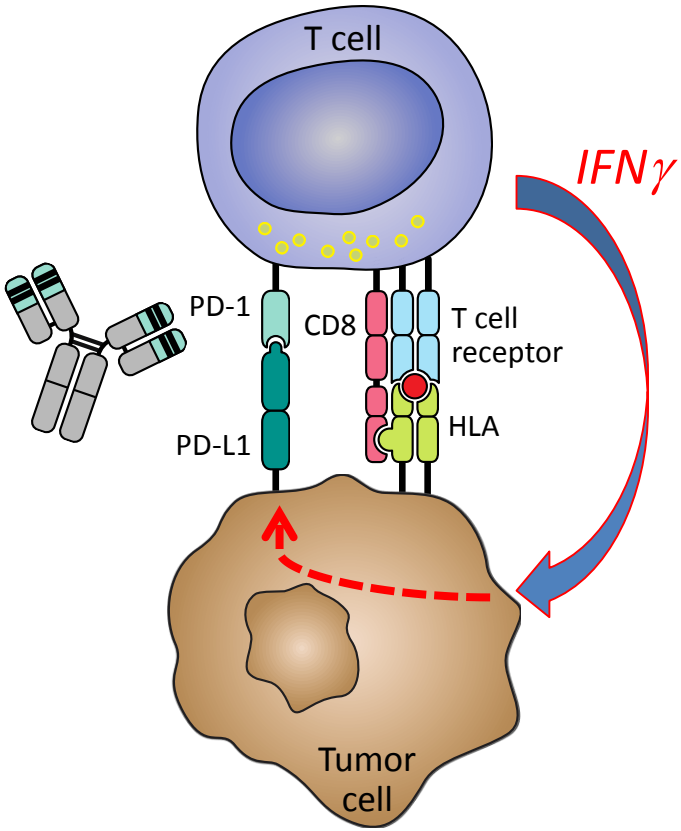


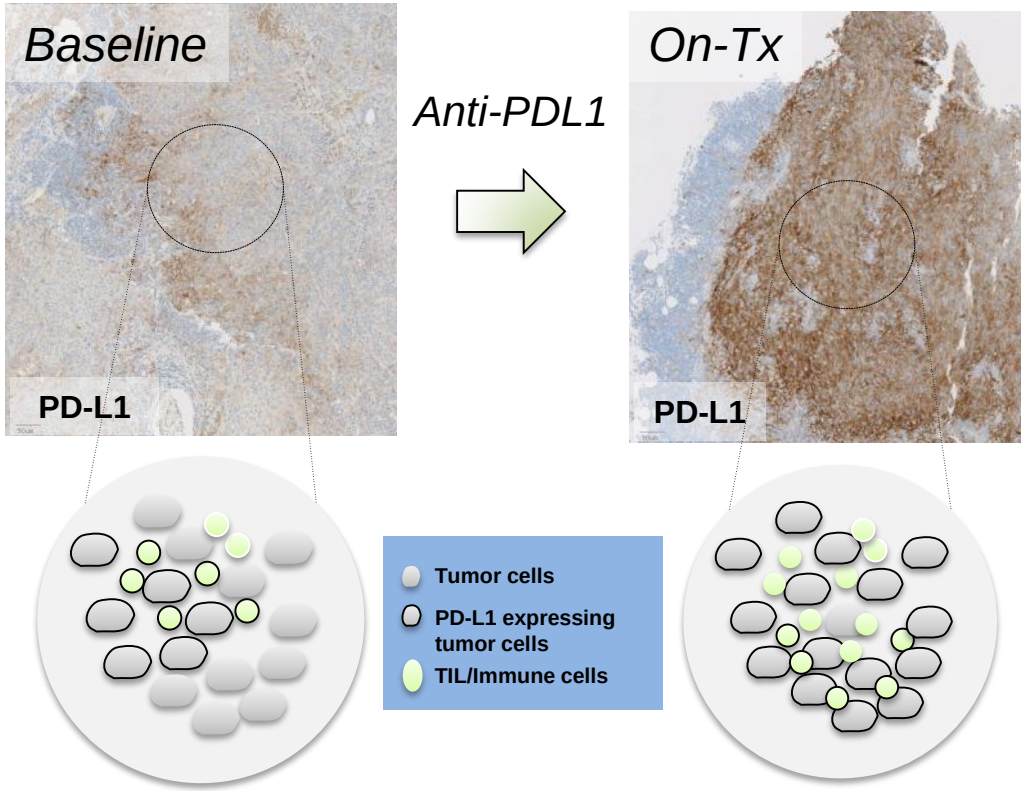
Schadendorf, Hodi Wolchok, ESMO, 2013



Tumor Microenvironment

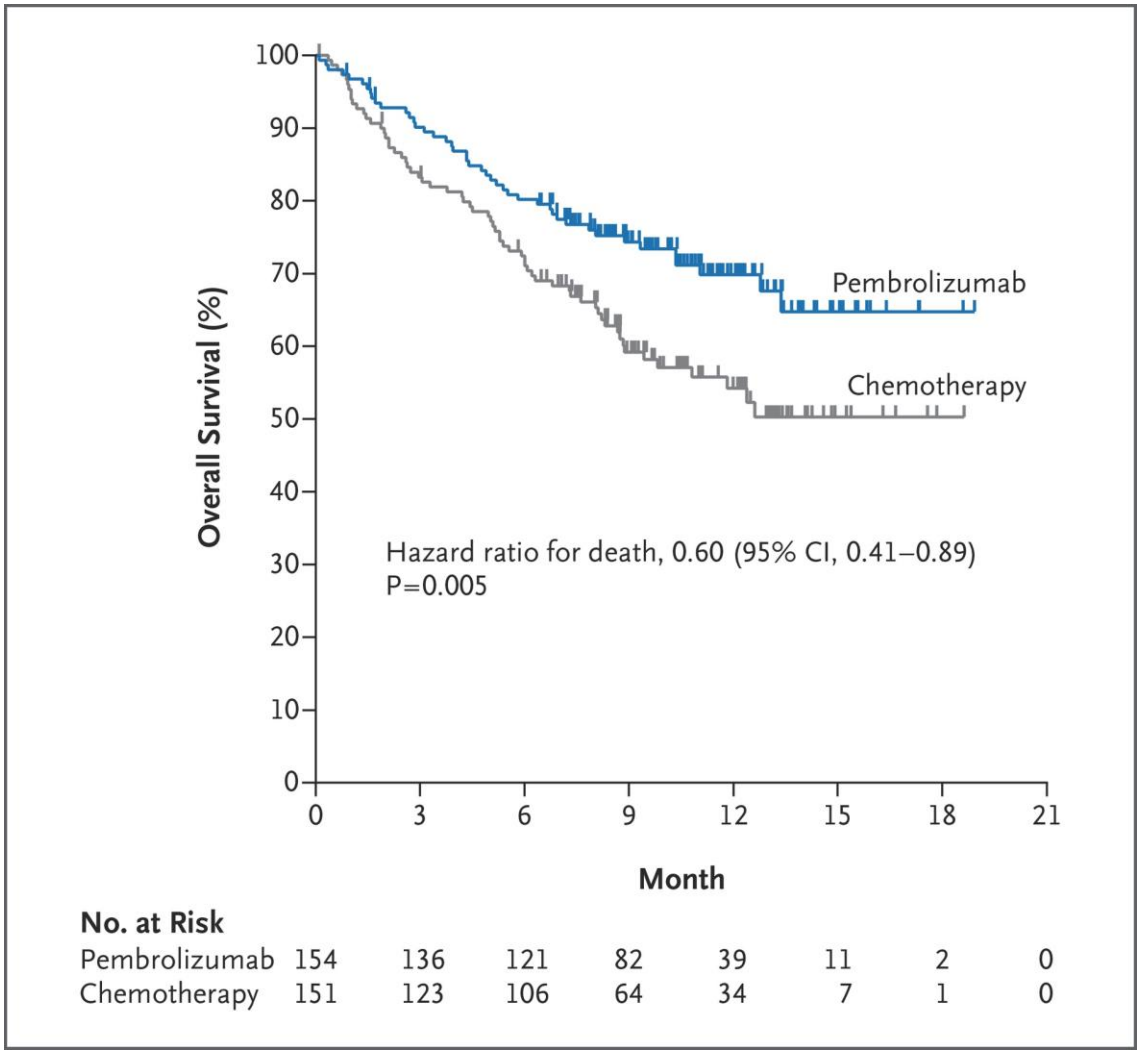
Adaptive Increase in Tumor PD-L1 Expression May Be an Indicator of Local TILs Attacking Tumor





- Demonstration of pharmacodynamic Anti-PD-L1 activity in humans: Adaptive increase in PD-L1 expression in tumor cells

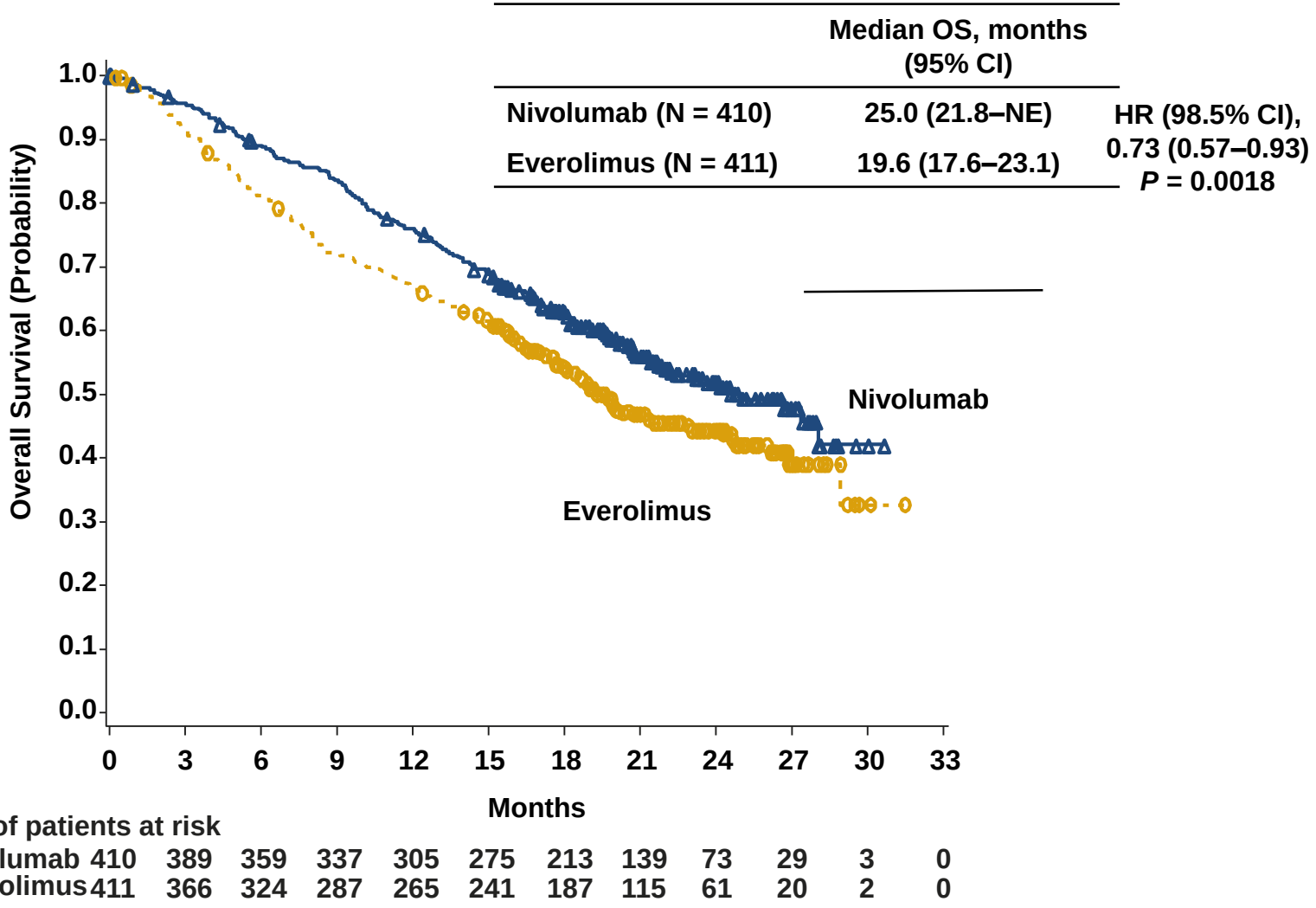
Pembrolizumab versus Chemotherapy for PD-L1–Positive NSCLC Overall Survival in First Line PDL1+(50%) NSCLC Population



Reck M, N Engl J Med 2016;375:1823-33.

The NEW ENGLAND JOURNAL of MEDICINE

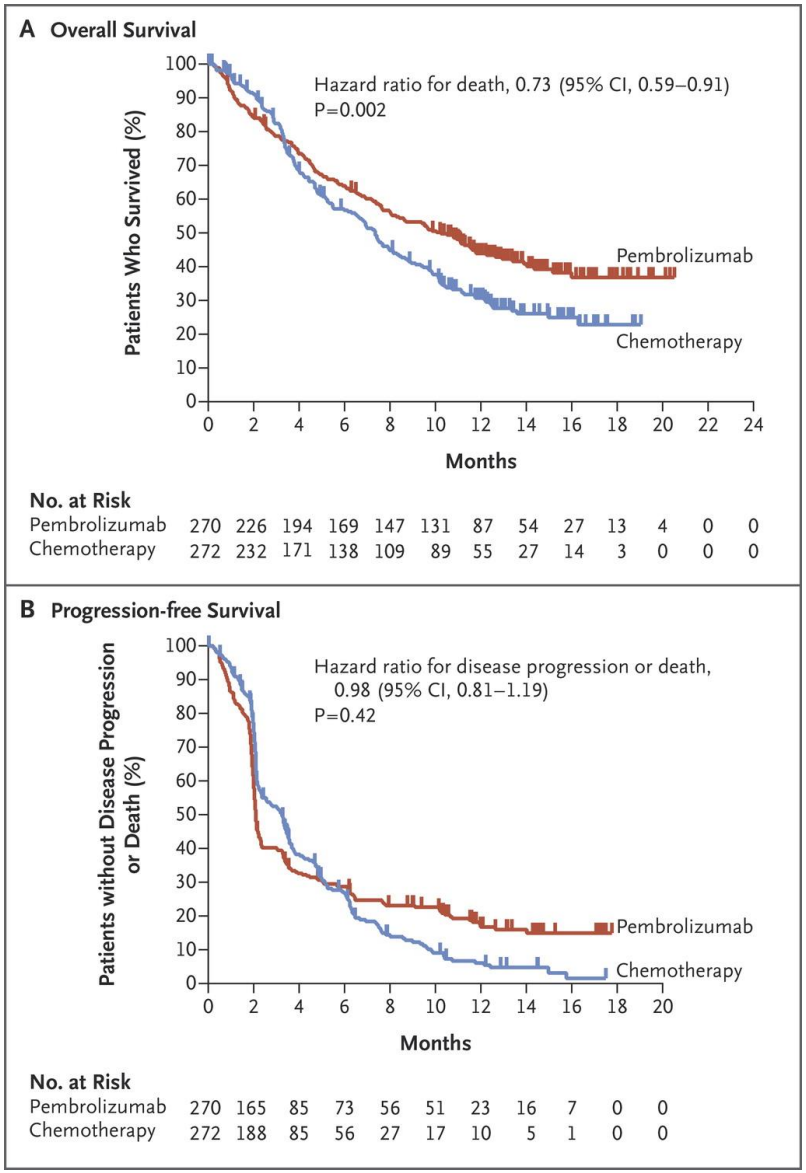
RCC 2nd line Therapy: Everolimus vs Nivolumab: Overall Survival



- Minimum follow-up was 14 months

CI, confidence interval; HR, hazard ratio; NE, not estimable.

Pembrolizumab vs Chemotherapy in 2nd line Urothelial Cancer: OS and PFS

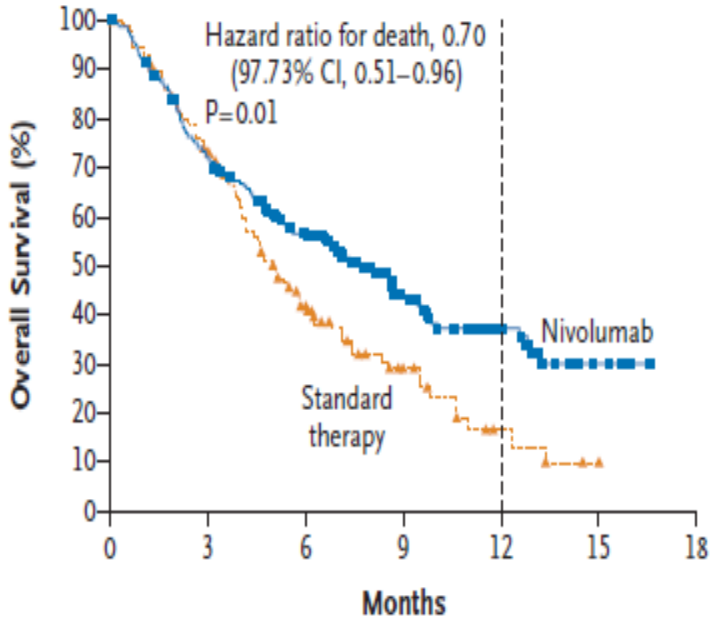


Bellmunt j NEJM 2017

Nivolumab in Recurrent SCC of Head & Neck

A Overall Survival

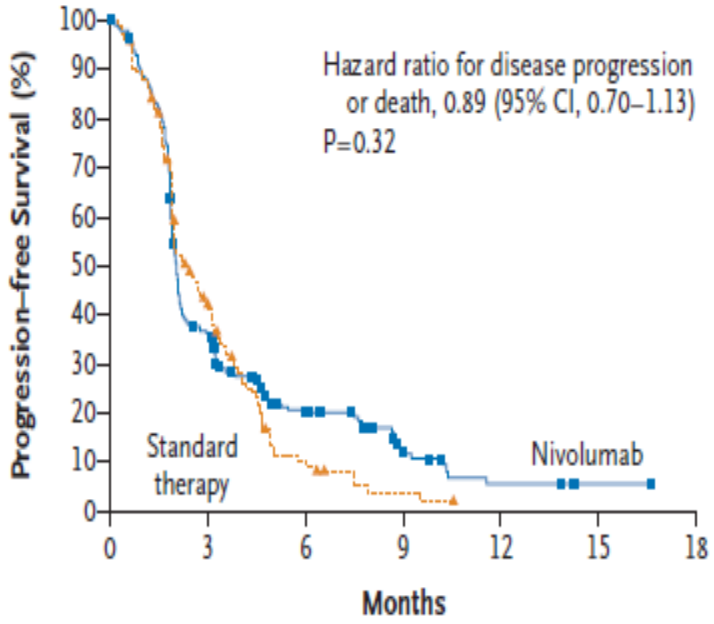
	No. of Patients	No. of Deaths	1-Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

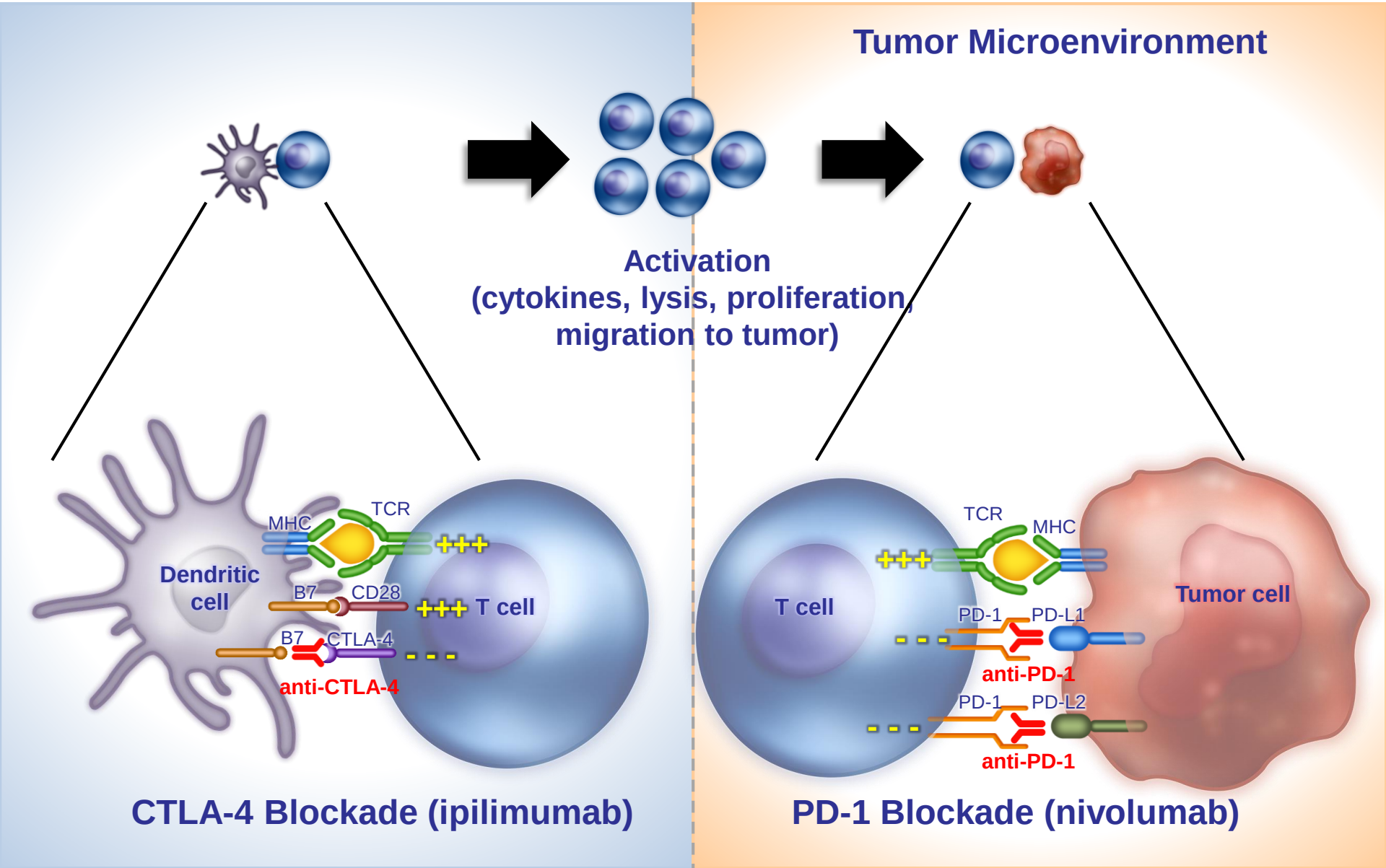
B Progression-free Survival

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Nivolumab	240	190	2.0 (1.9–2.1)
Standard Therapy	121	103	2.3 (1.9–3.1)



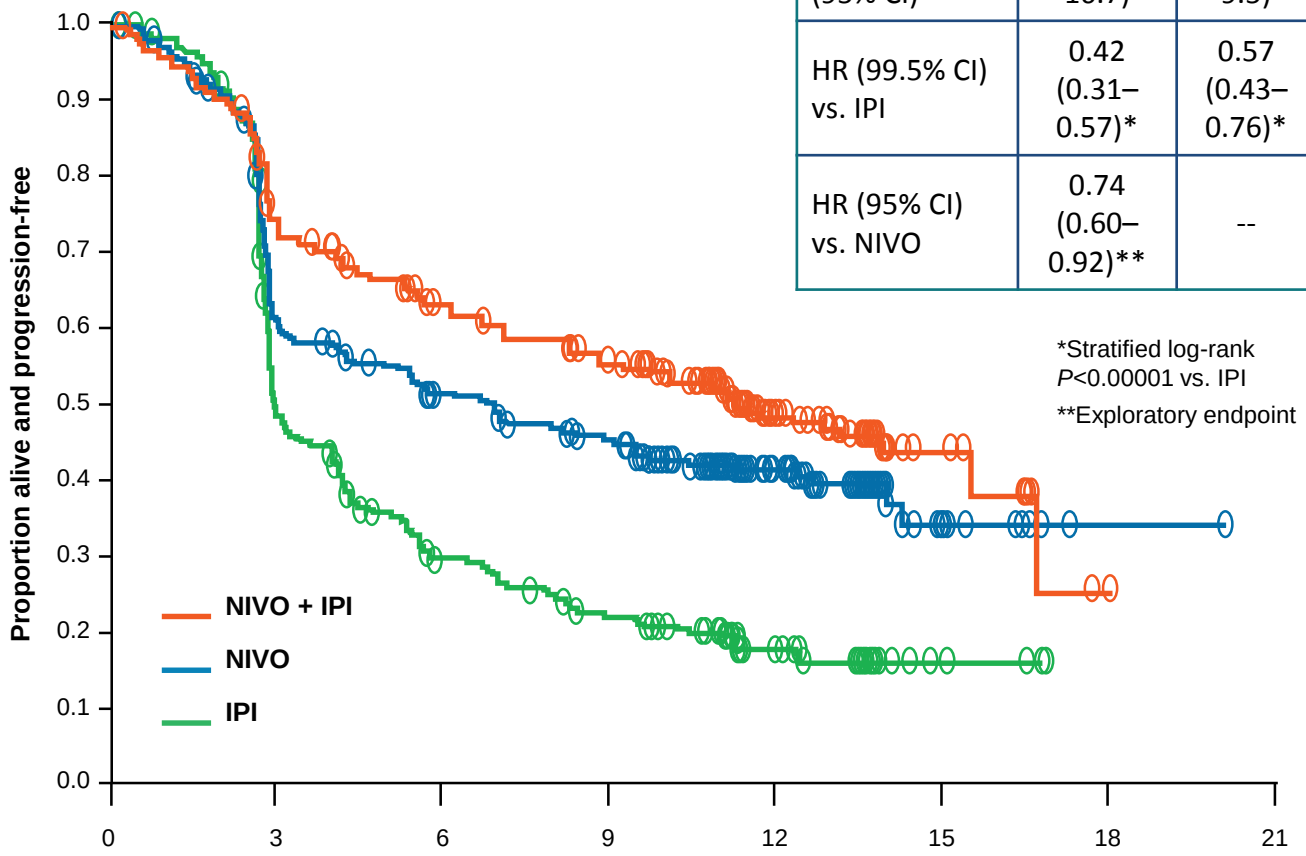
No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Standard therapy	121	43	9	2	0	0	0

Blocking CTLA-4 and PD-1



CA-067 Ipi+Nivo vs Nivo vs Ipi Progression-Free Survival

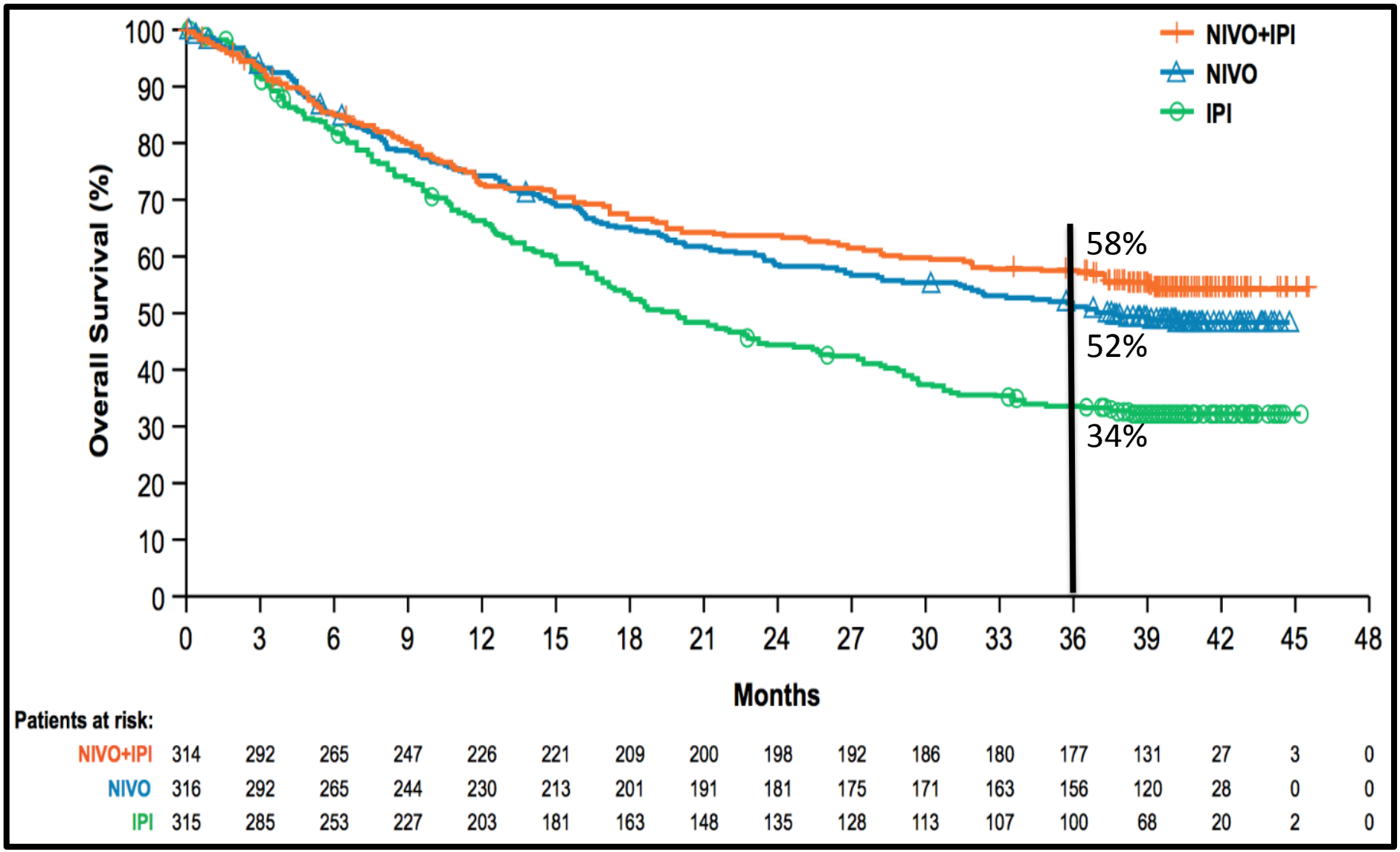
	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--



*Stratified log-rank *P*<0.00001 vs. IPI

**Exploratory endpoint

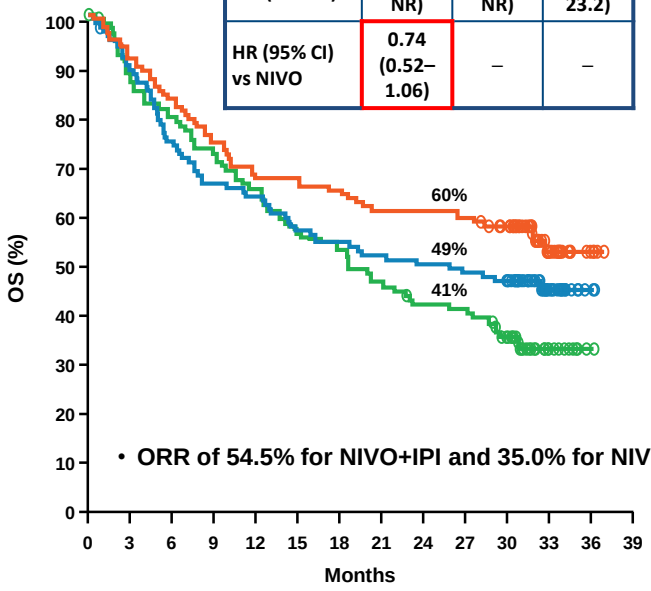
Overall Survival in All Randomized Melanoma Patients : 067 Ipi+ Nivo vs Nivo vs Ipi



Outcomes Observed at a 1% Cutoff

PD-L1 Expression Level <1%

<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (26.5–NR)	23.5 (13.0–NR)	18.6 (13.7–23.2)
HR (95% CI) vs NIVO	0.74 (0.52–1.06)	–	–



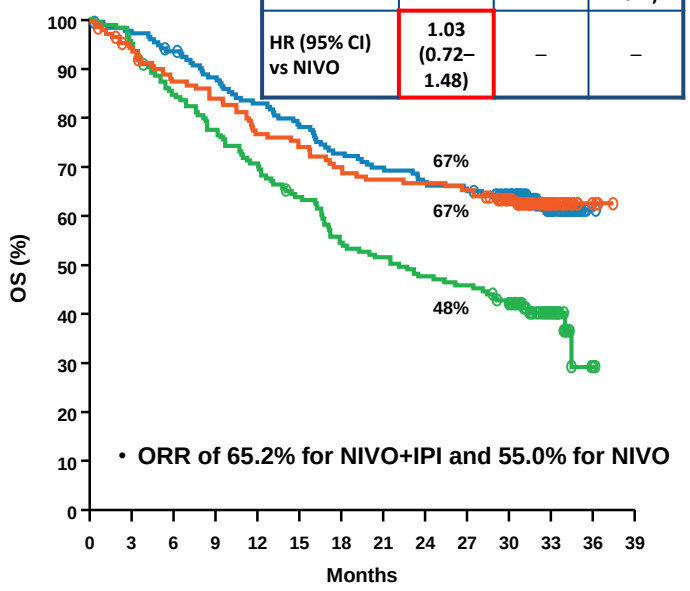
- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

Patients at risk:

NIVO+IPI	123	113	102	91	82	82	79	74	74	72	66	18	4	0
NIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
IPI	113	96	87	79	71	61	57	50	44	43	32	10	1	0

PD-L1 Expression Level ≥1%

≥1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	22.1 (17.1–29.7)
HR (95% CI) vs NIVO	1.03 (0.72–1.48)	–	–



- ORR of 65.2% for NIVO+IPI and 55.0% for NIVO

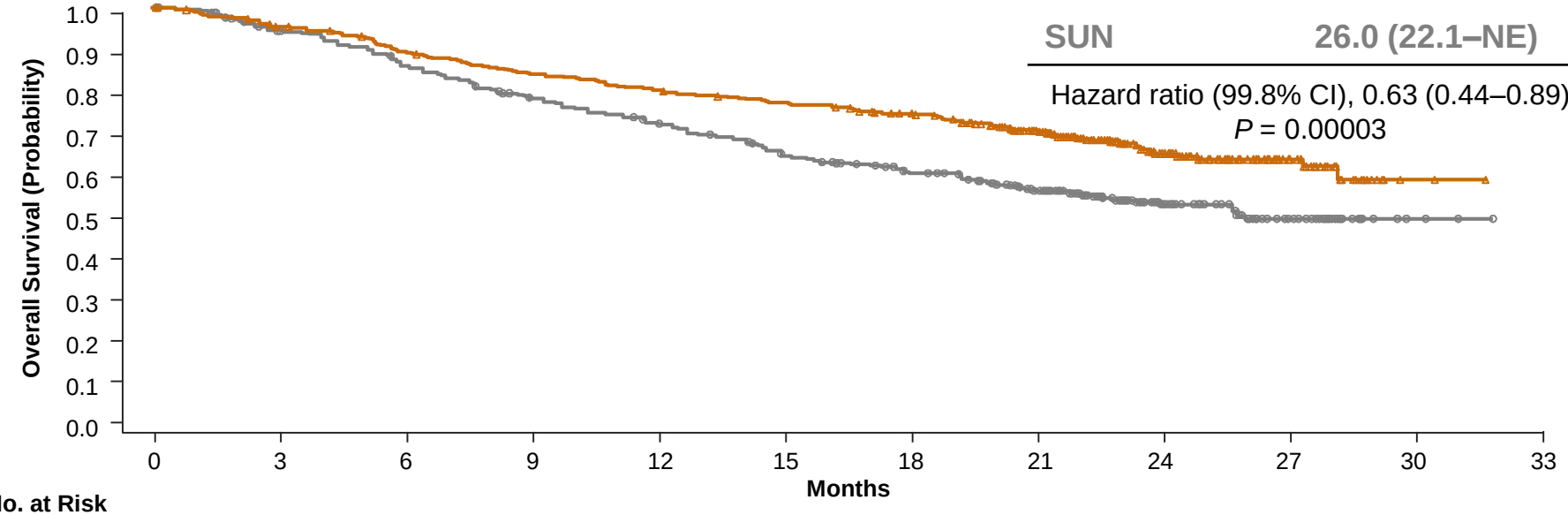
Patients at risk:

NIVO+IPI	155	144	132	127	116	112	105	102	101	99	85	27	3	0
NIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	0
IPI	164	155	138	126	115	102	89	83	77	74	64	21	2	0

Overall Survival in RCC Frontline

Median OS, months (95% CI)	
NIVO + IPI	NR (28.2–NE)
SUN	26.0 (22.1–NE)

Hazard ratio (99.8% CI), 0.63 (0.44–0.89)
P = 0.00003

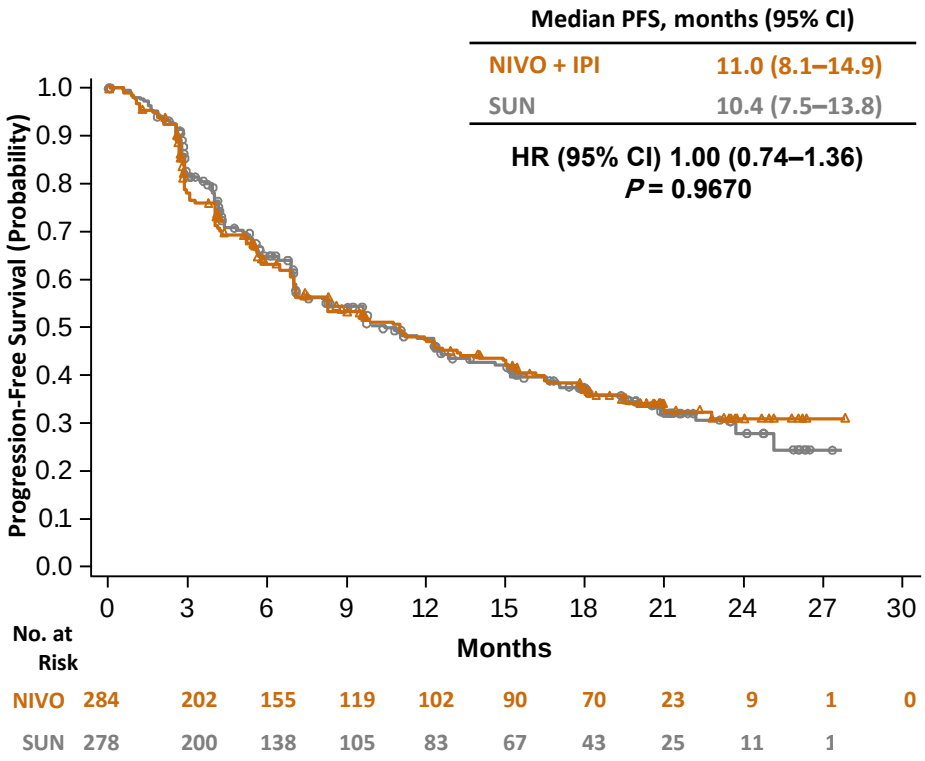


No. at Risk												
NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	3	0

MADRID 2017 ESMO congress

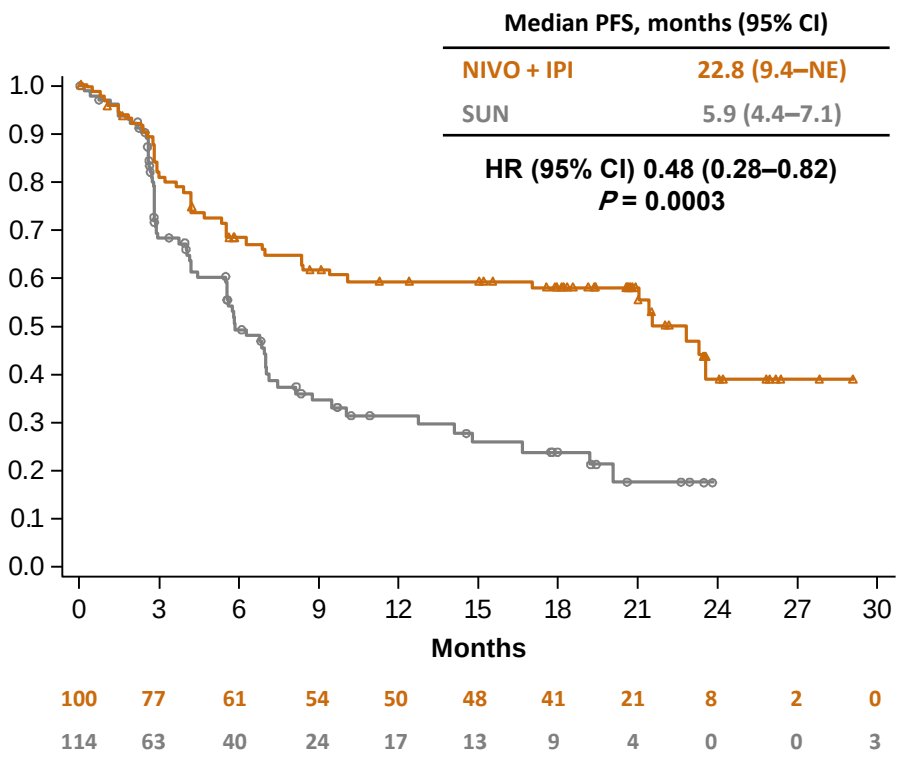
PFS by PD-L1 expression: RCC Frontline

PD-L1 <1% (n = 562)



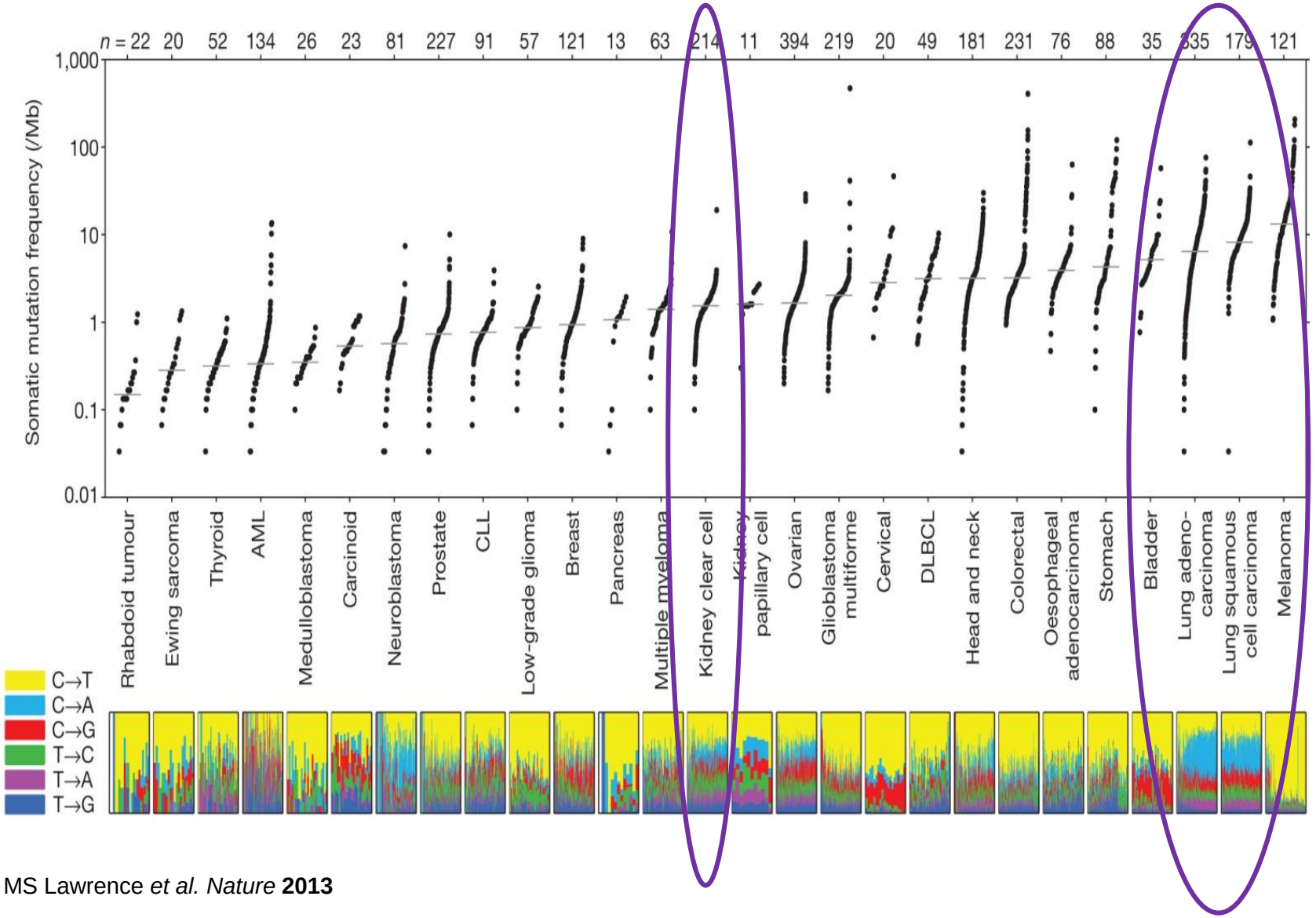
No. at Risk											
NIVO	284	202	155	119	102	90	70	23	9	1	0
SUN	278	200	138	105	83	67	43	25	11	1	

PD-L1 ≥1% (n = 214)



NIVO	100	77	61	54	50	48	41	21	8	2	0
SUN	114	63	40	24	17	13	9	4	0	0	3

Somatic mutations by tumor type



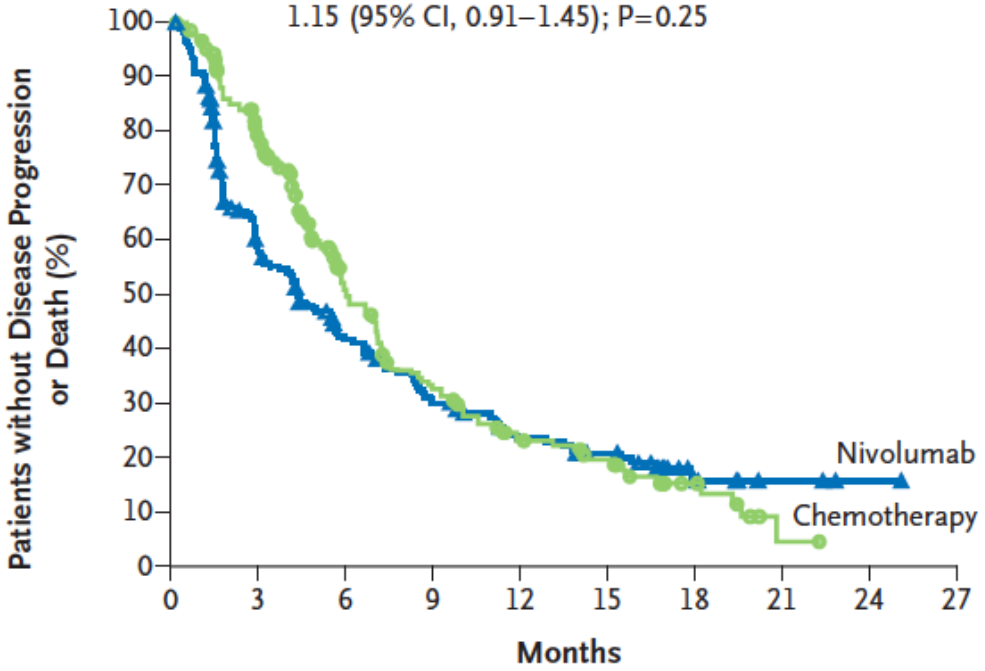
MS Lawrence *et al. Nature* **2013**

CheckMate 026 Nivolumab in First-line NSCLC Unselected Population

A Progression-free Survival

	Median Progression-free Survival (95% CI) *mo*	1-Yr Progression-free Survival Rate %
Nivolumab (N=211)	4.2 (3.0–5.6)	24
Chemotherapy (N=212)	5.9 (5.4–6.9)	23

Hazard ratio for disease progression or death, 1.15 (95% CI, 0.91–1.45); P=0.25

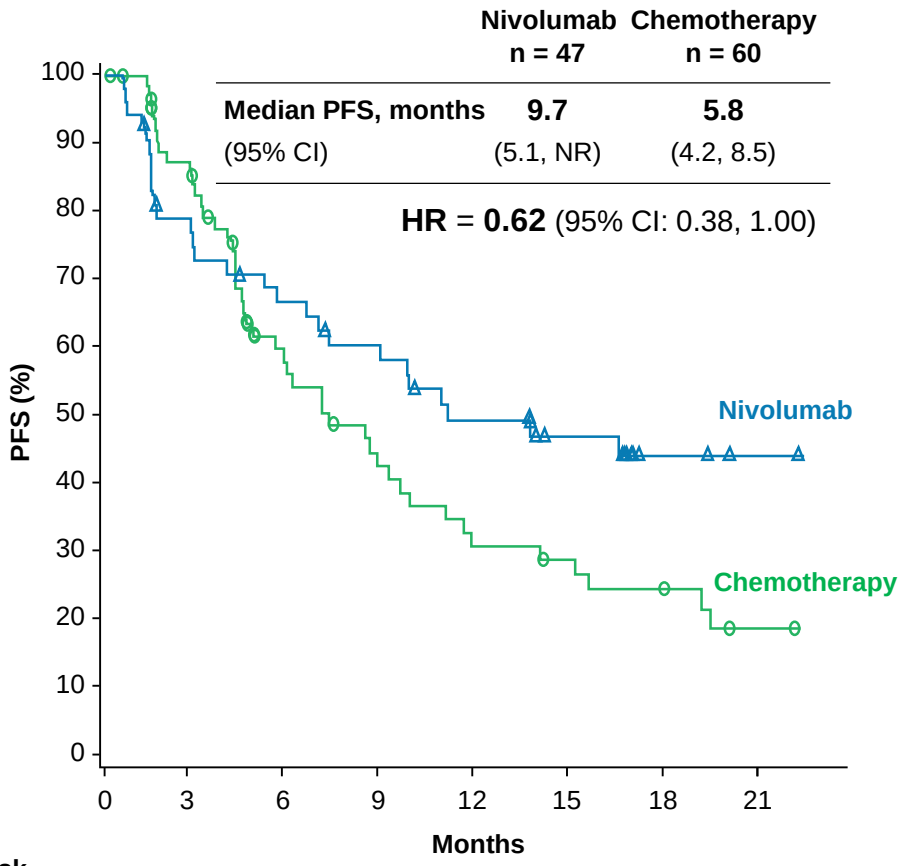


No. at Risk										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

Carbone DP; N Engl J Med 2017;376:2415-26.

PFS by Tumor Mutation Burden Subgroup
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

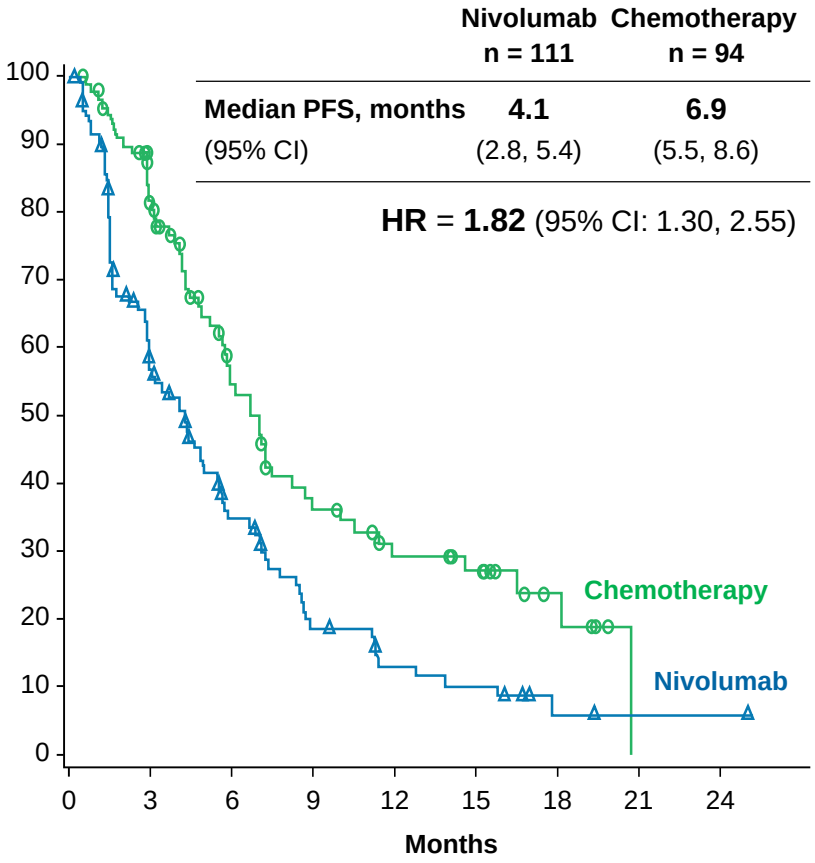
High TMB



No. at Risk

Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

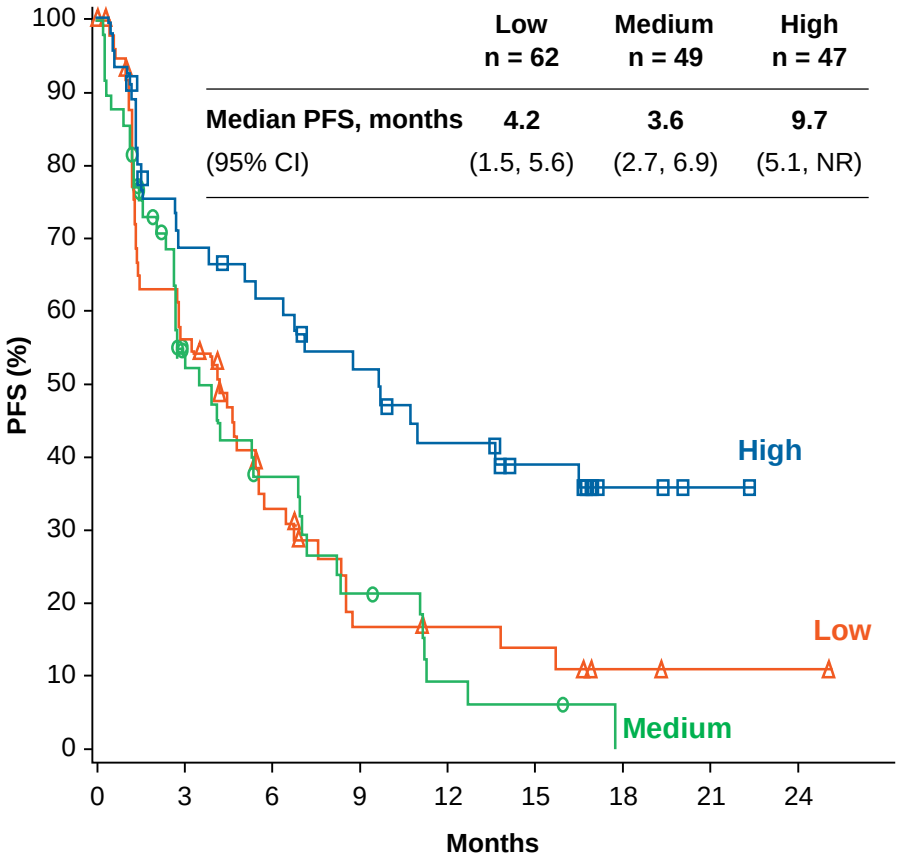
Low/medium TMB



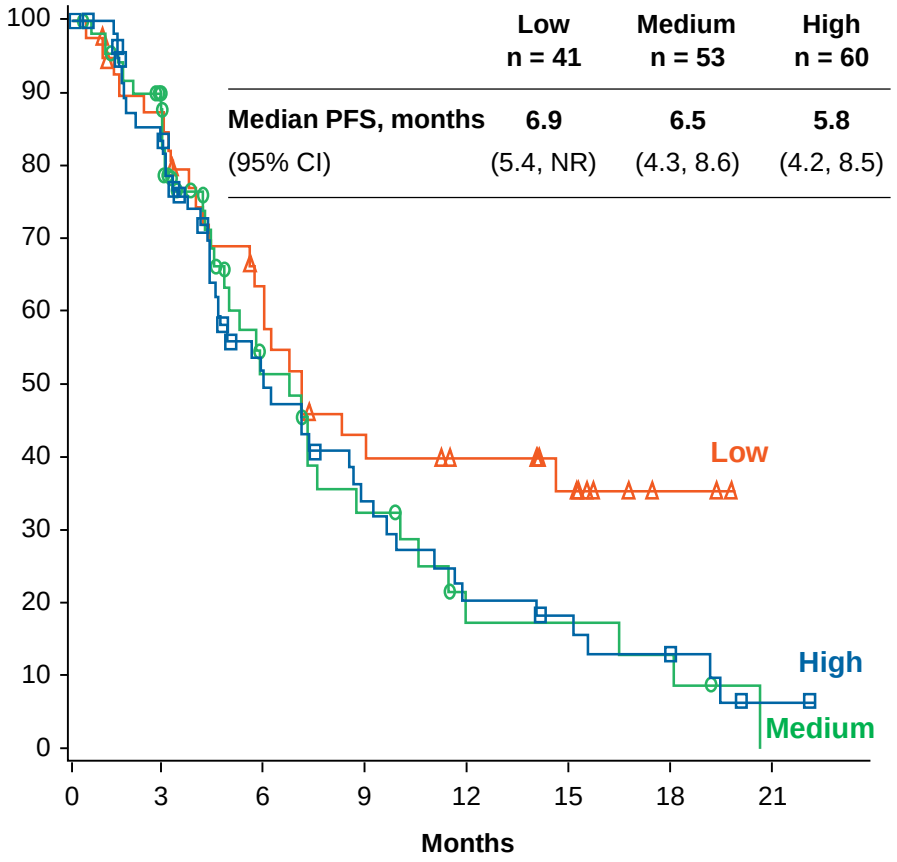
Nivolumab	111	54	30	15	9	7	2	1	1
Chemotherapy	94	65	37	23	15	12	5	0	0

PFS by Tumor Mutation Burden Subgroup
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

Nivolumab Arm

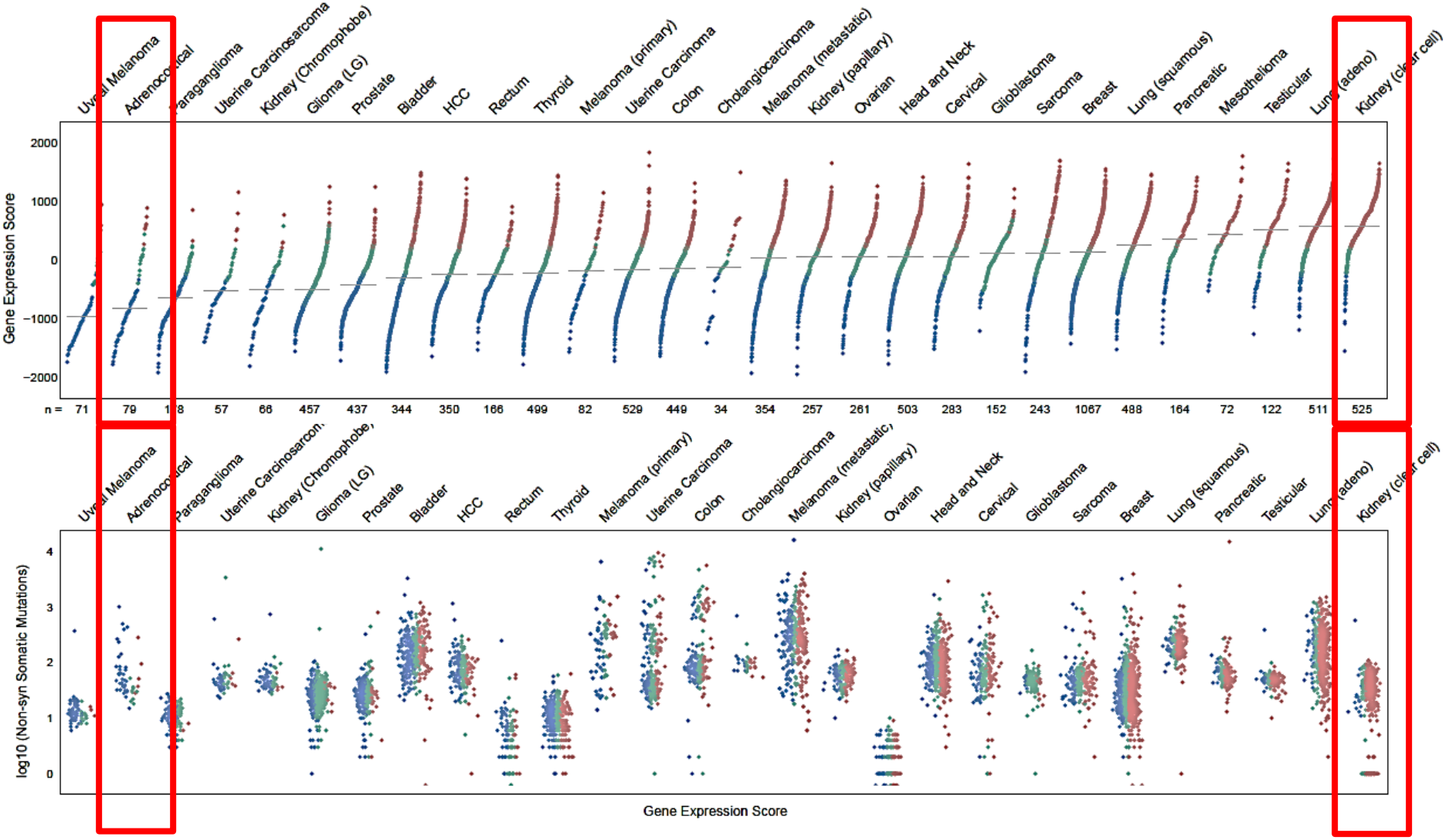


Chemotherapy Arm



- Data for patients with low and medium TMB were pooled in subsequent analyses

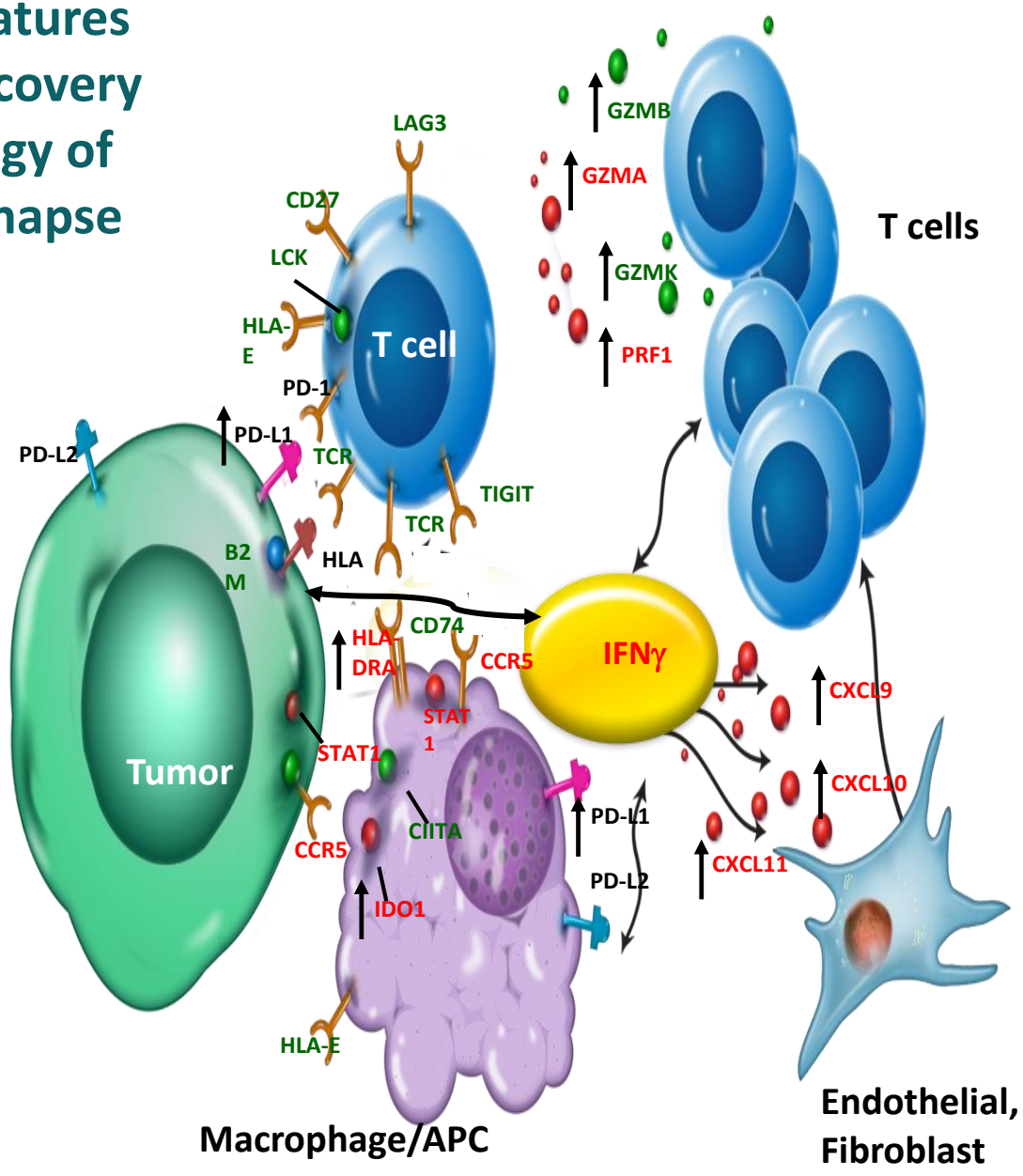
Fraction of tumors with T cell-inflamed tumor microenvironment gene signature does not correlate with mutational load



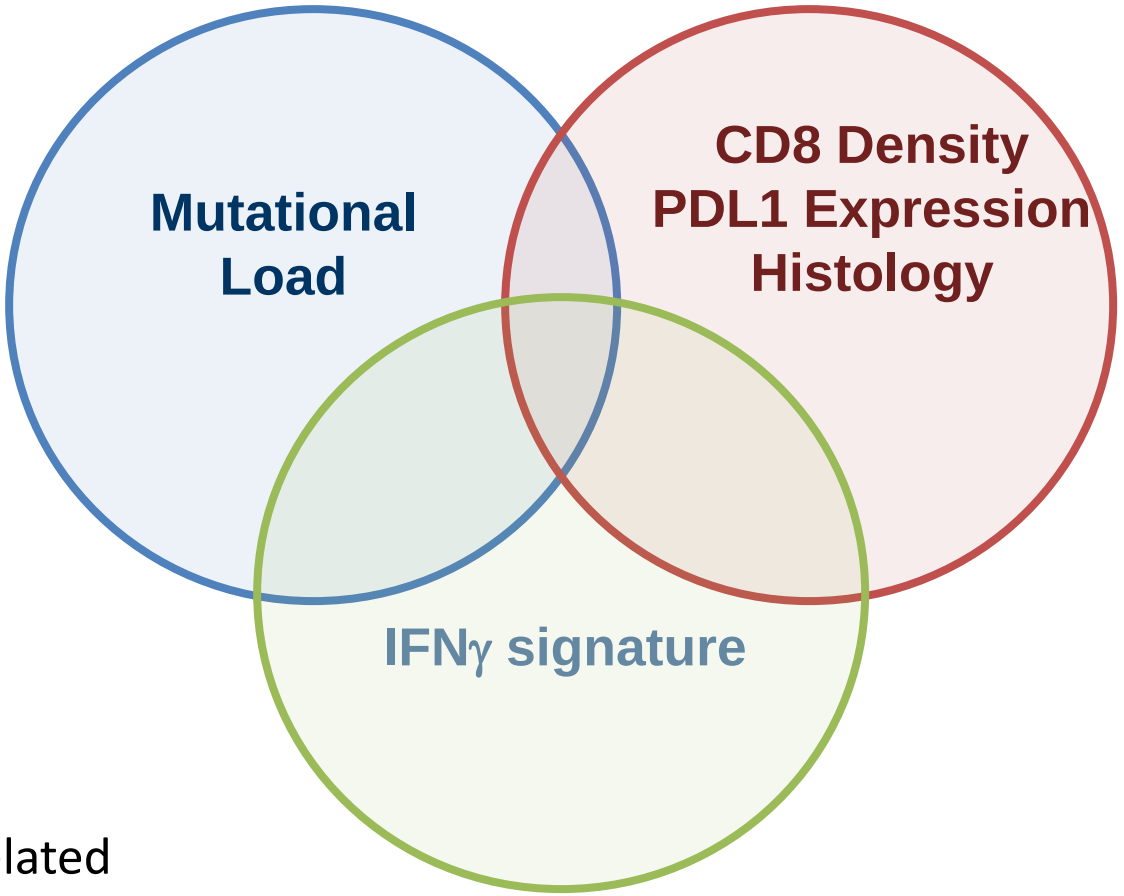
Expanded Gene Signatures Identified During Discovery Analysis Reveal Biology of Complex Immune Synapse

Discovery analysis of entire NanoString melanoma data set led to identification of new genes:

- **IFNγ signaling**
- **MHC class I and II antigen presentation machinery**
- **T-cell activation markers**



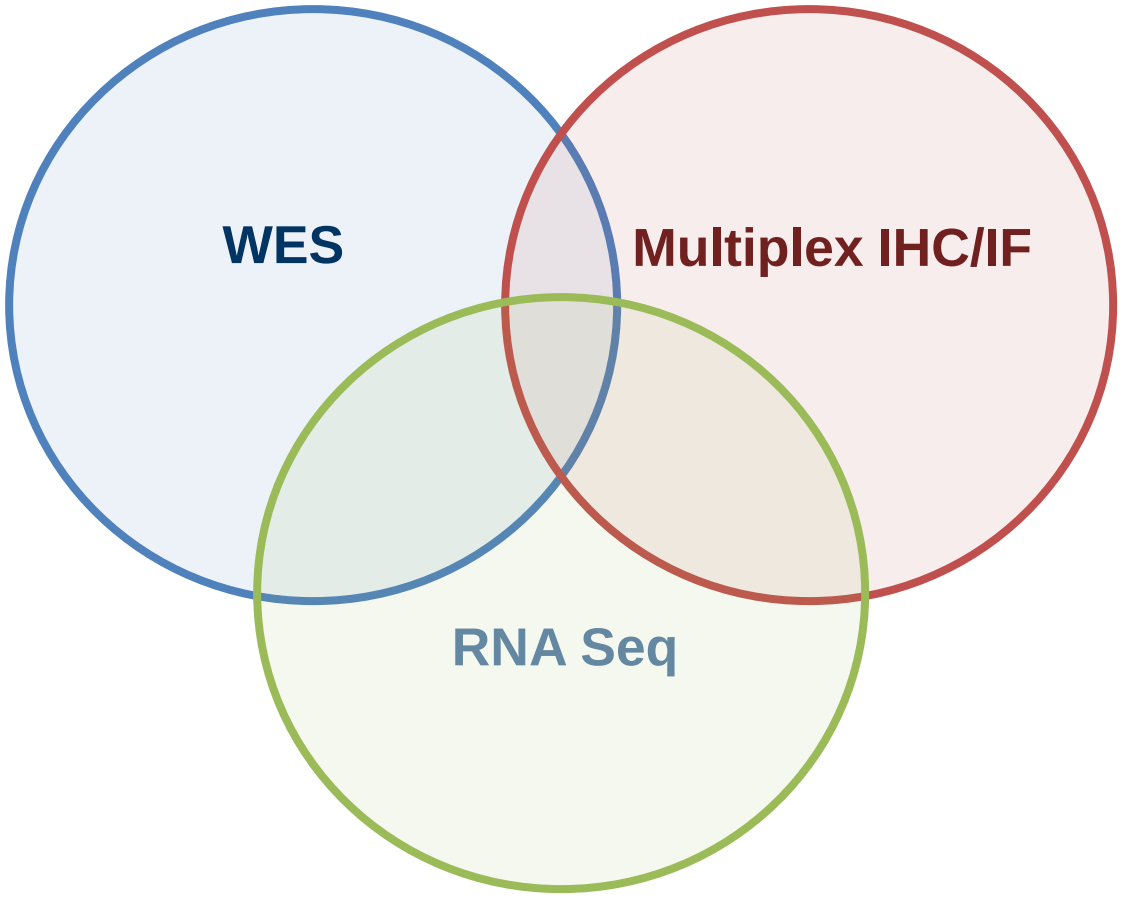
Biomarker Model



- All inter-related
- Some tumors may have a larger sweet spot

M Atkins with permission.

Biomarker Model



- Needed Technologies

M Atkins with permission.

Tumor Type

ICOS

PD-L1

Intratumoral FOXP3 & IDO

Treg

TCR Clonality

Intratumoral CD8+/FOXP3+

Mutation Burden

Microbiota

NY-ESO-1

IL-17 CD4+ cells

Absolute lymphocyte count

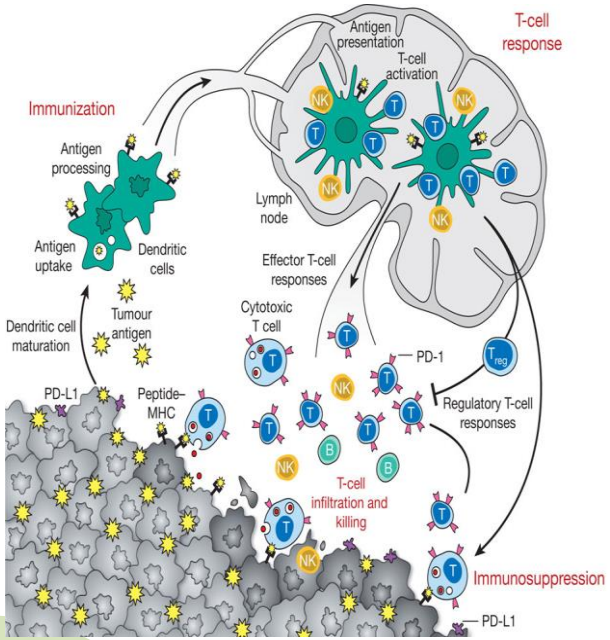
Prior Therapies?

"Inflamed" microenvironment

MDSC

CD45RO

Mellman et al. Nature 2011

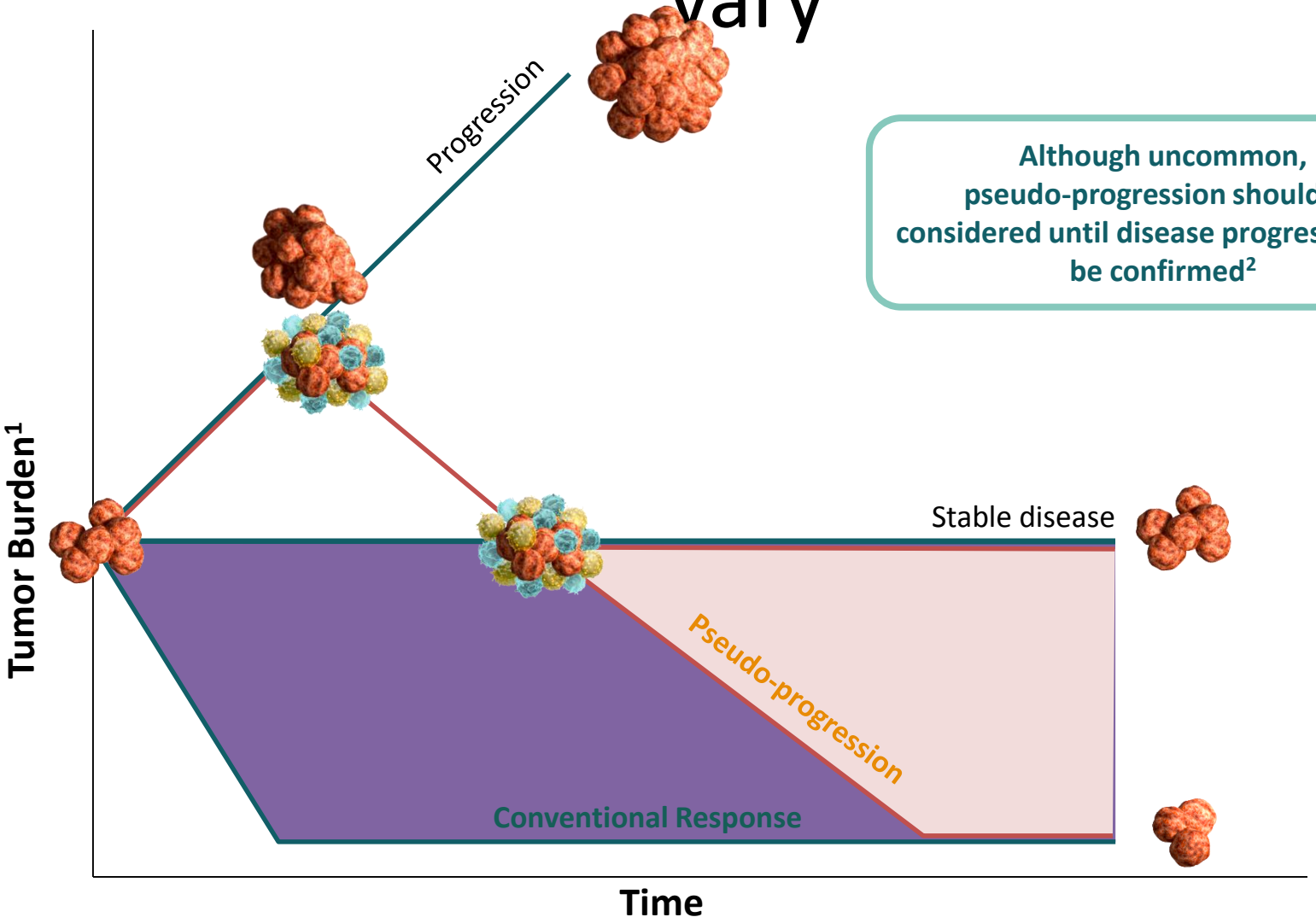


Yuan et al, PNAS 2011;
DiGiacom lo et al Cancer Immunol Immunother 2013;
Queirolog et al,Cancer Invest 2013;
Wolchok et al,Cancer Immun 2010;
Tumeh et al Nature 2105;
Snyder et al NEJM 2014;
Rizvi et al Science 2015;
Van Allen et al Science 2105;
Sivan et al Science 2015;
Vetizou et al Science 2015;
Rosenberg et al Lancet 2016

Ku et al Cancer 2010;
Menard et al Clin Cancer Res 2008;
Weber et al JCO 2009;
Hodi et al PNAS 2008;
Hamid et al JCO 2009;
Ng et al Cancer Immuno Res 2013;
Tarhini et al PLoS One 2014;
Kitano et al Cancer Immunol Res 2013;
Spranger et al Sci Transl Med 2013;
Kitano et al Cancer Immunol Res 2014;
Ji RR et al, Cancer Immunol Immunother 2012;

Presented by: Alexandra Snyder, M.D.

The Antitumor immune response may vary



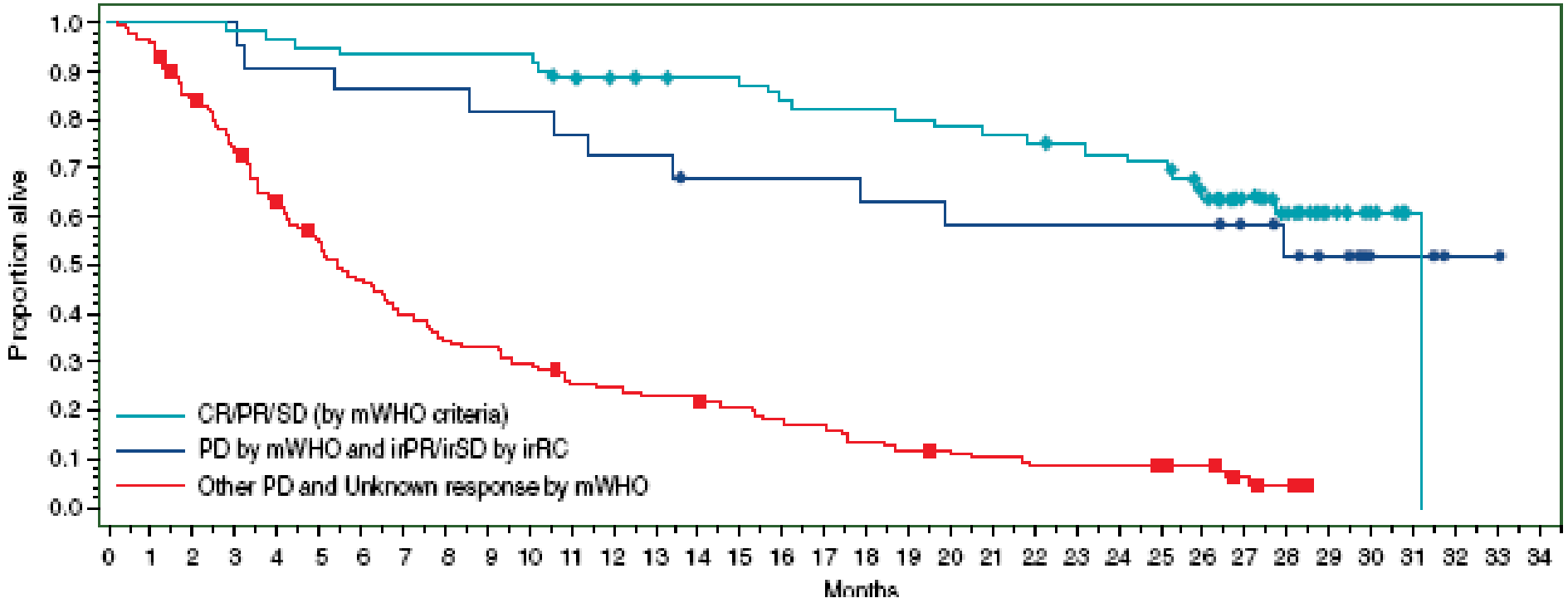
Although uncommon, pseudo-progression should be considered until disease progression can be confirmed[2]

Response levels may vary and figure is for illustrative purposes only.

1. Wolchok JD et al. *Clin Cancer Res*. 2009;15(23):7412-7420. 2. Hales RK et al. *Ann Oncol*. 2010;21(10):1944-1951.

irRC Identifies Survivors in Patients with Progressive Disease by mWHO

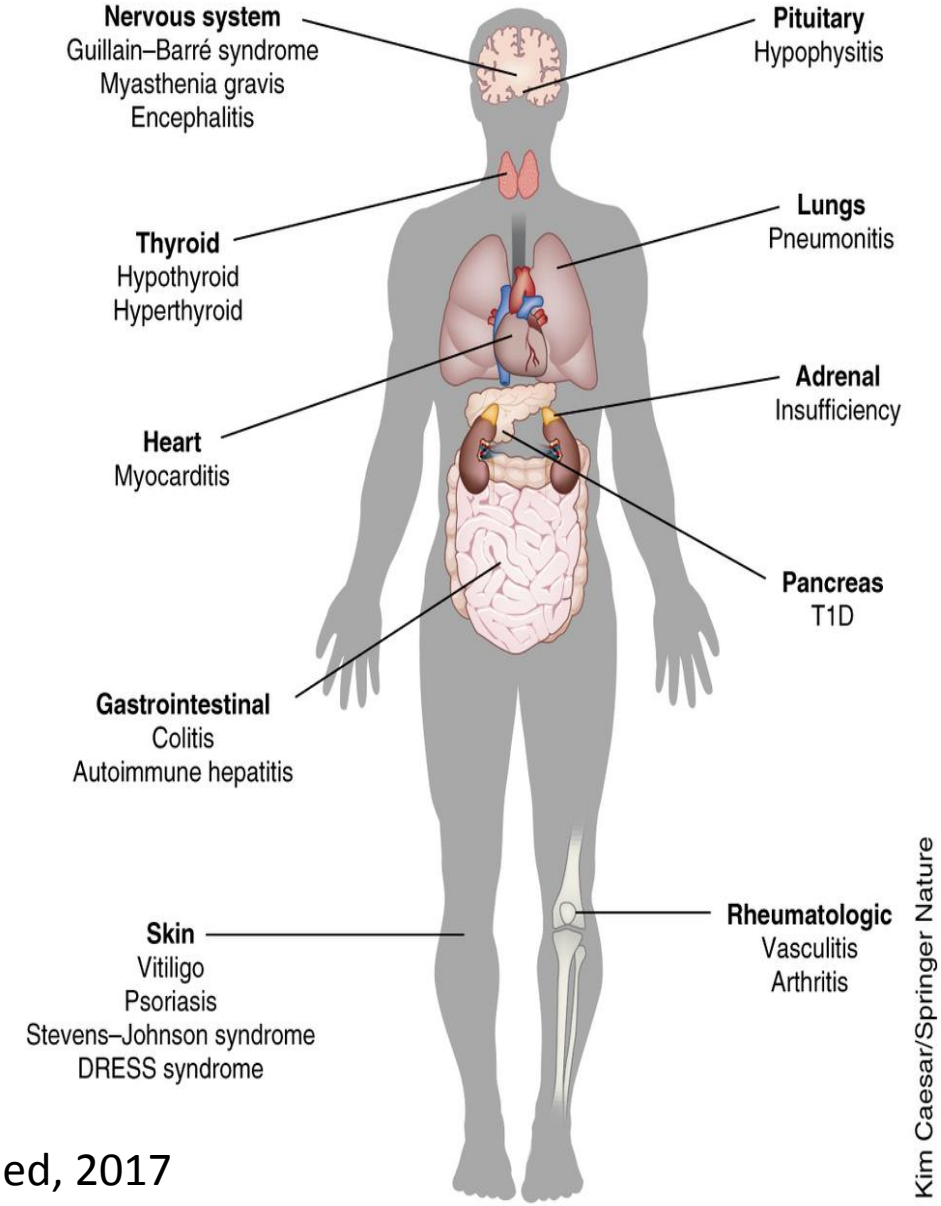
Pooled data from phase II studies CA184-008 and CA184-022: ipilimumab monotherapy 10 mg/kg (N=227)



- Uses WHO criteria
- PD needs to be confirmed.
- New lesions are included in TM not necessarily PD

Wolchok et al, *Clin Cancer Res*, 2009

Sites of Immune Checkpoint Blockade Toxicity (irAE- AE of special interest)



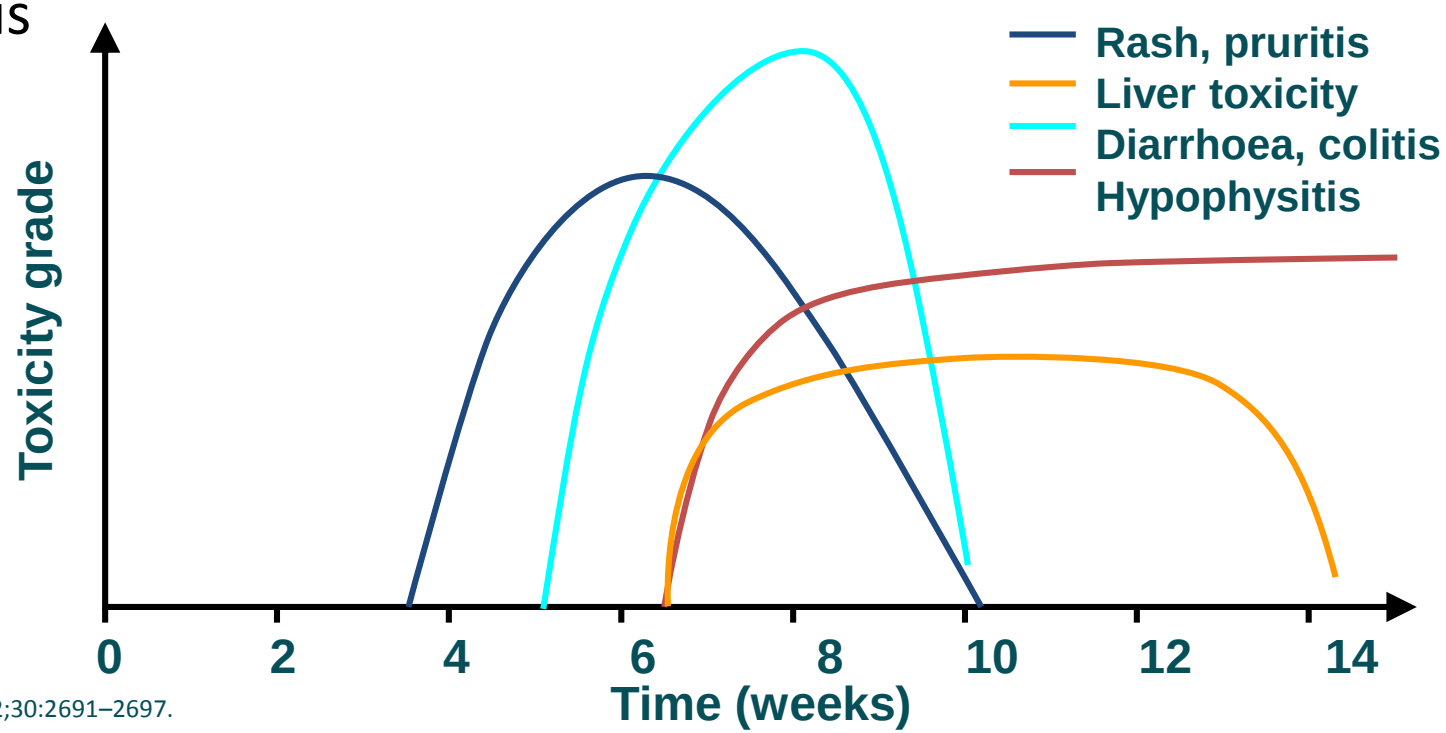
June et.al , Nature Med, 2017

Adverse Events from Immune Checkpoint Inhibitors

- Generally do not induce cytokine like effects
- Autoimmunity can affect any organ system
  - But skin, GI, liver, endocrine organs, and lung most common
  - Multiple organ systems can be affected (concurrently or serially)
- Incidence/severity:
  - **Combination anti-CTLA-4 +anti-PD-1**>
  - *high dose anti-CTLA-4(10mg/kg)*>
  - anti-CTLA-4 (3mg/kg) >
  - Anti-PD-1/PD-L1
- Dose-relationship for anti-CTLA-4; not evident for range of anti-PD-1/PD-L1
- Re-challenge with same agent often (but not always) leads to recurrent toxicity
- High grade AE to one class does not preclude safe administration of the other class

Immune checkpoint inhibitors: immune-related adverse event (irAE) onset

- Most common:
  - Colitis
  - Dermatitis
  - Hepatitis
  - Endocrinopathies
  - Pneumonitis
- Anti–PD-1 antibodies show most irAEs occur by Wk 24 (6 mos),
- "long tail" of rare side effects (neuro, heme, cardiac, musculoskeletal, GI, etc)
- Treatment related deaths are very rare



Weber JS, et al. *J Clin Oncol.* 2012;30:2691–2697.

Unusual Immune Checkpoint Adverse Events

- Systemic inflammatory syndrome
- Severe arthritis
- **Myositis**
- **Myocarditis**
- Pneumonitis
- Nephritis
- Bowel perforation
- Meningitis
- **Insulin-dependent Diabetes Mellitus**
- Myasthenia Gravis
- Ascending polyneuropathy (Guillan-Barre)
- Limbic Encephalitis
- Uveitis
- Thrombocytopenia (ITP)
- Dry eye syndrome
- Lichen planus (more common with anti-PD-1
- Alopecia areata

Principles of AE Management

- Onset of adverse effects not predictable for individuals
- Close follow-up of patients, and timely management necessary to minimize morbidity
- Set of basic clinical decisions
  - Autoimmune or other cause?
  - Hold or continue treatment?
  - When to start steroids?
  - Dose? Duration?
  - PO or IV?
  - Inpatient versus outpatient?
  - When to start second-line immune suppressive?

Ipi+ Nivo: Safety Summary

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

CA-067: Randomized phase III Trial of Ipi+ Nivo vs Nivo vs Ipi: Treatment-Related Select AEs Reported in ≥10% of Patients

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin	**59.1**	**5.8**	41.9	1.6	54.0	2.9
Pruritus	**33.2**	**1.9**	18.8	0	35.4	0.3
Rash	**28.4**	**2.9**	21.7	0.3	20.9	1.6
Rash maculo-papular	**11.8**	**1.9**	4.2	0.3	11.9	0.3
Gastrointestinal	**46.3**	**14.7**	19.5	2.2	36.7	11.6
Diarrhea	**44.1**	**9.3**	19.2	2.2	33.1	6.1
Colitis	**11.8**	**7.7**	1.3	0.6	11.6	8.7
Hepatic	**30.0**	**18.8**	6.4	2.6	7.1	1.6
Increase in alanine aminotransferase	**17.6**	**8.3**	3.8	1.3	3.9	1.6
Increase in aspartate aminotransferase	**15.3**	**6.1**	3.8	1.0	3.5	0.6
Endocrine	**30.0**	**4.8**	14.4	0.6	10.9	2.3
Hypothyroidism	**15.0**	**0.3**	8.6	0	4.2	0

- With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85-100% for NIVO + IPI, 50-100% for NIVO, and 83-100% for IPI
- As observed in prior studies, most endocrine events did not resolve

Cardiac toxicities

- Few case reports
  - Heart failure/myocarditis with pembrolizumab
  - Systemic inflammation including myocarditis in patient treated with ipilimumab then nivolumab
  - Fatal myocarditis/hepatitis in ipi/nivo
  - One death with ipilimumab 10mg/kg on adjuvant study

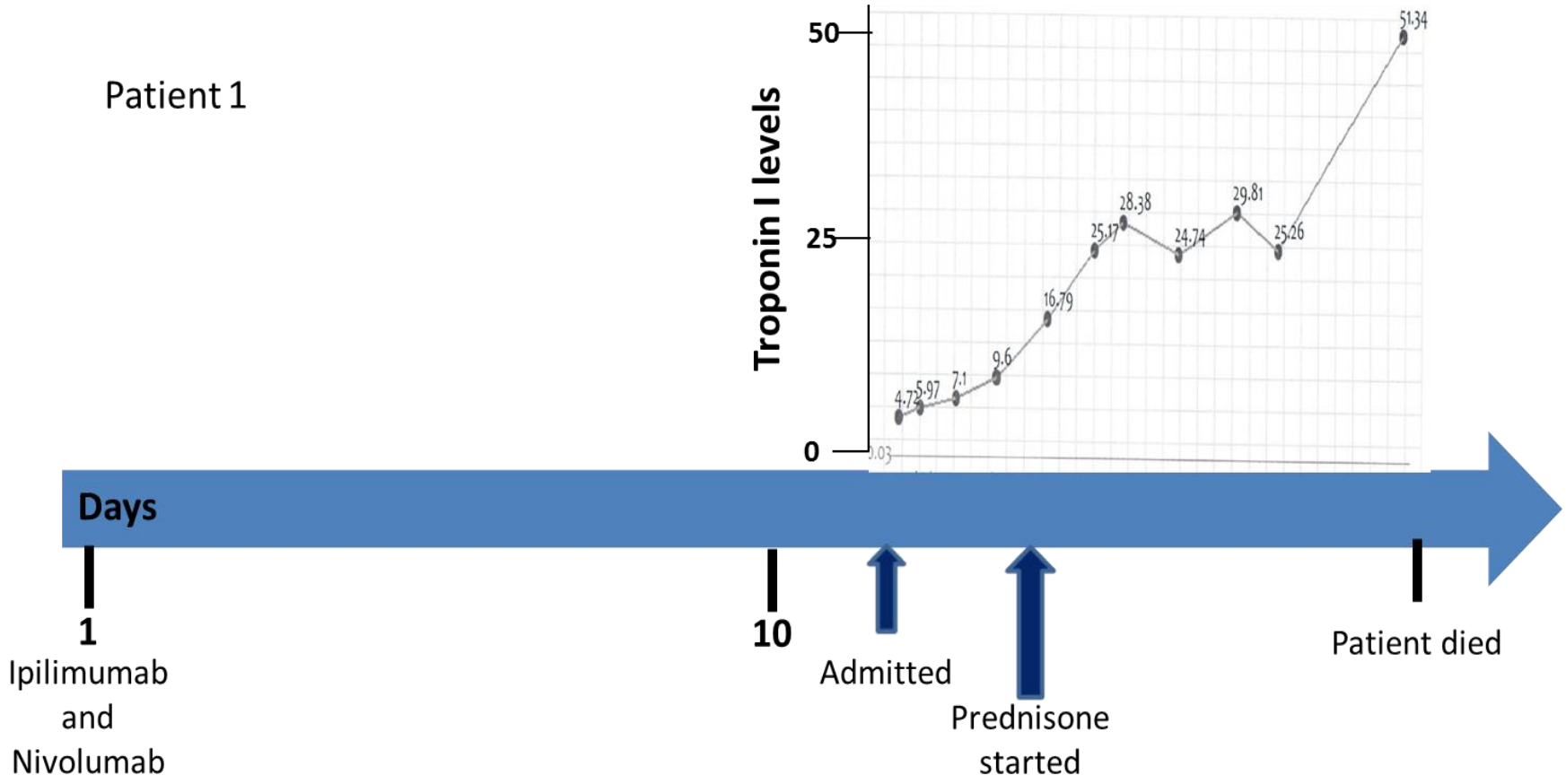
Laubli et al, JITC 2015
Koelzer et al, JITC 2016
Eggermont et al, Lancet Oncology 2014
Henzerling et al, JITC 2016

Case #1

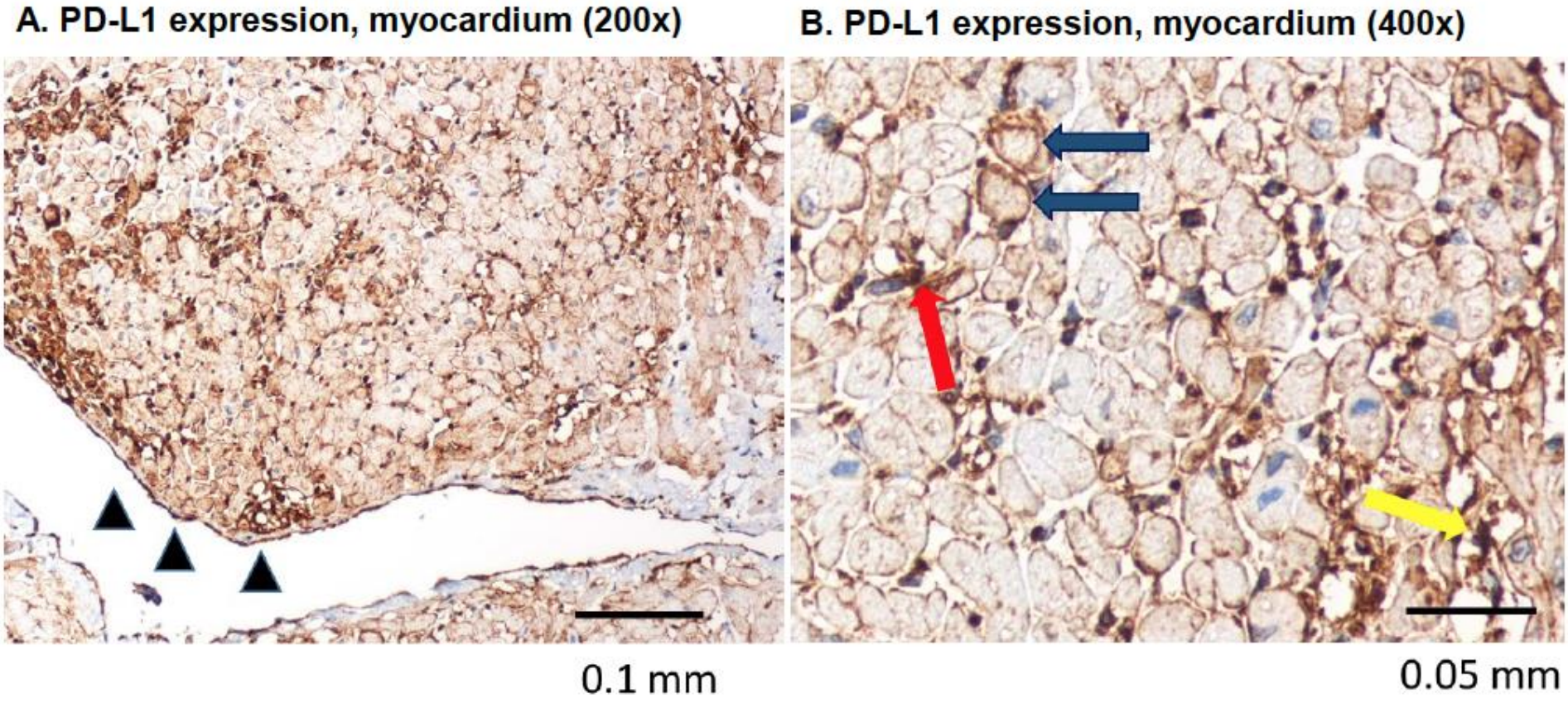
- 65 yo woman, h/o HTN
  - Initial diagnosis 2007
  - Found to have lung/adrenal/skin/lymph node metastases
  - Solitary brain metastasis, asymptomatic
  - Screened and enrolled on MEL14112 → ipilimumab + nivolumab in patients with brain metastases
  - 7 days later presented with headache and some URI symptoms (sinus drainage, malaise, no respiratory symptoms)
  - Head CT negative
  - 5 days after past visit approximately 12 day, developed shortness of breath and some degree of pleuritic chest pain, mild cough x1-2 days
  - Presented to Emergency Department

- Labs:
  CKMBRe: **>600.00*** **MBRat**: **>7.3*** **TRPI**: **7.10*** **CPKTot**: **8178***
  TBil: 0.4 **AlkP**: **198*** **AST**: **932*** **ALT**: **655***
- **BUN**: 22 **Creat**: 0.88

Case #1


Patient 1
Troponin I levels
50
25
0
4.72
5.97
7.1
9.6
16.79
25.17
28.38
24.74
29.81
25.26
51.34
Days
1
Ipilimumab and Nivolumab
10
Admitted
Prednisone started
Patient died

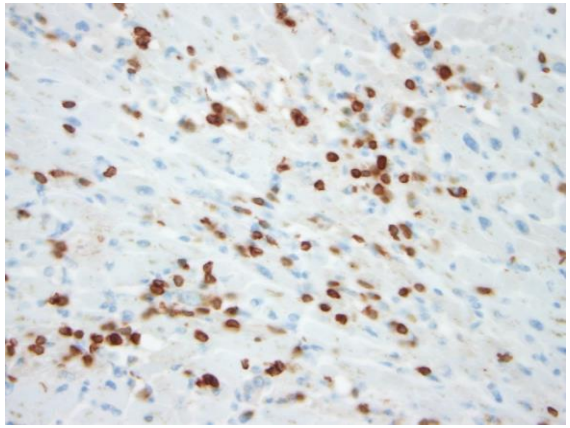
PD-L1 Expression in the Injured Myocardium



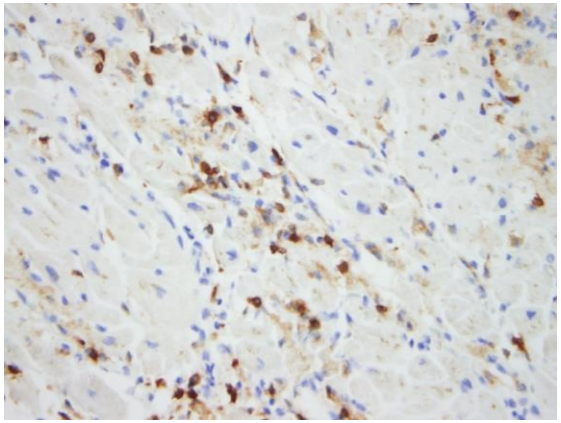
In collaboration with Janis Taube, Bob Anders, Luis Diaz, Johns Hopkins

T Cell Infiltrates in the Heart

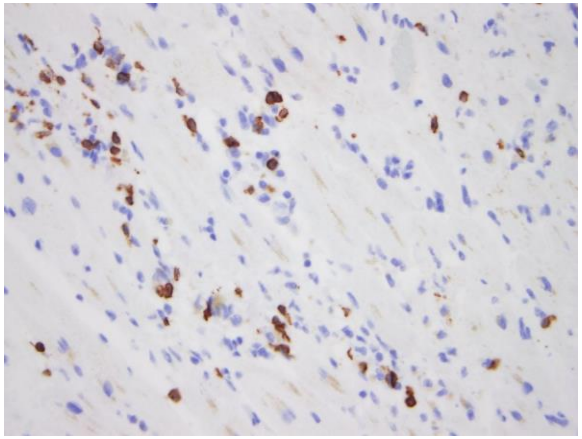
CD3



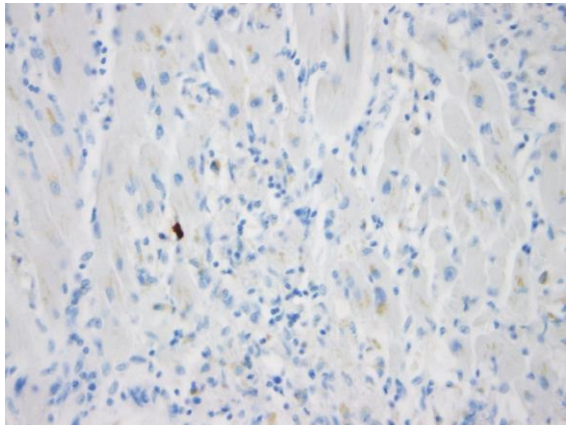
CD4



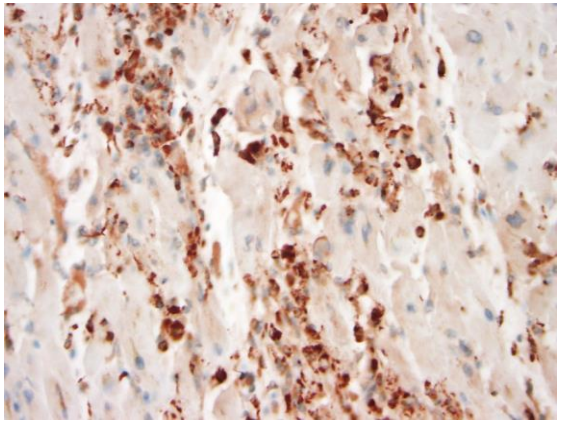
CD8



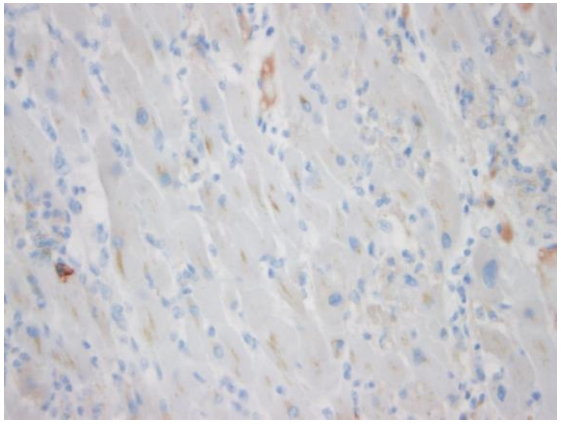
CD20



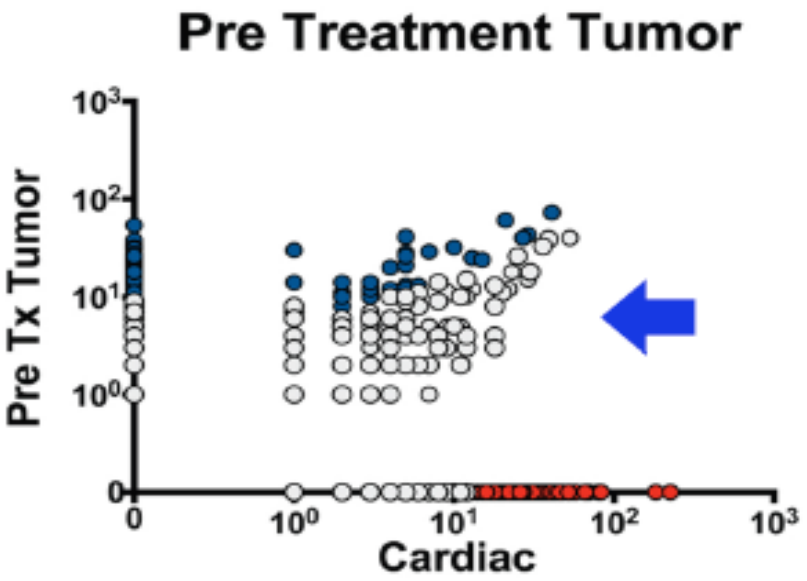
CD68

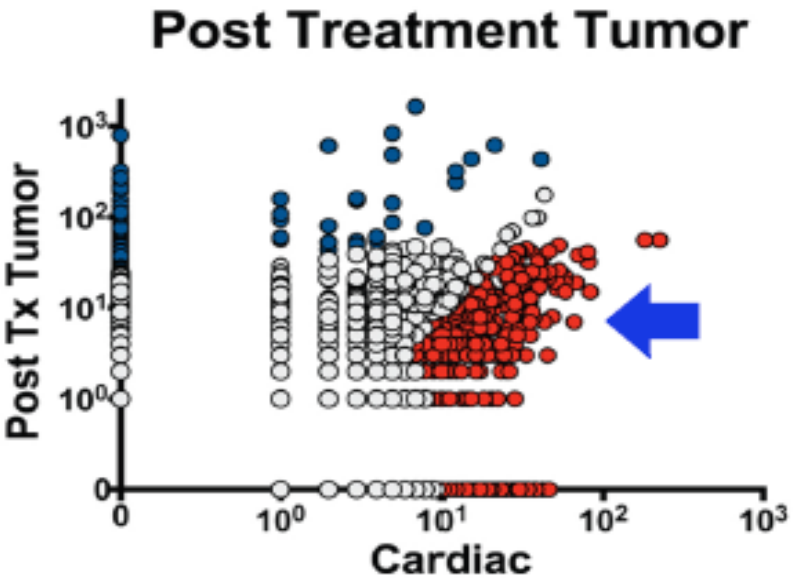


CD138

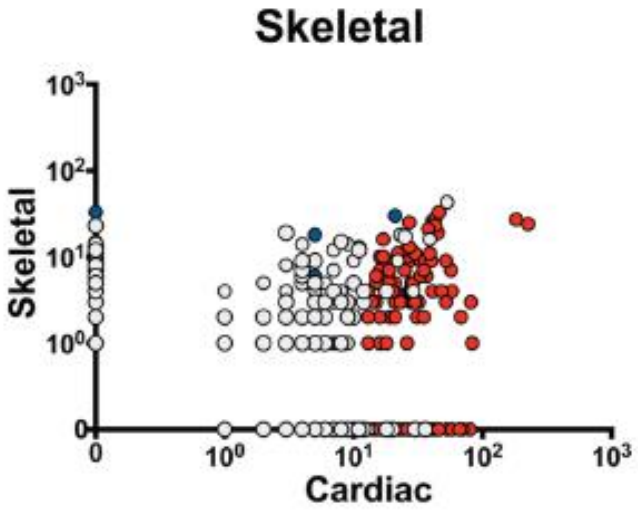


Next Generation TCR sequencing,

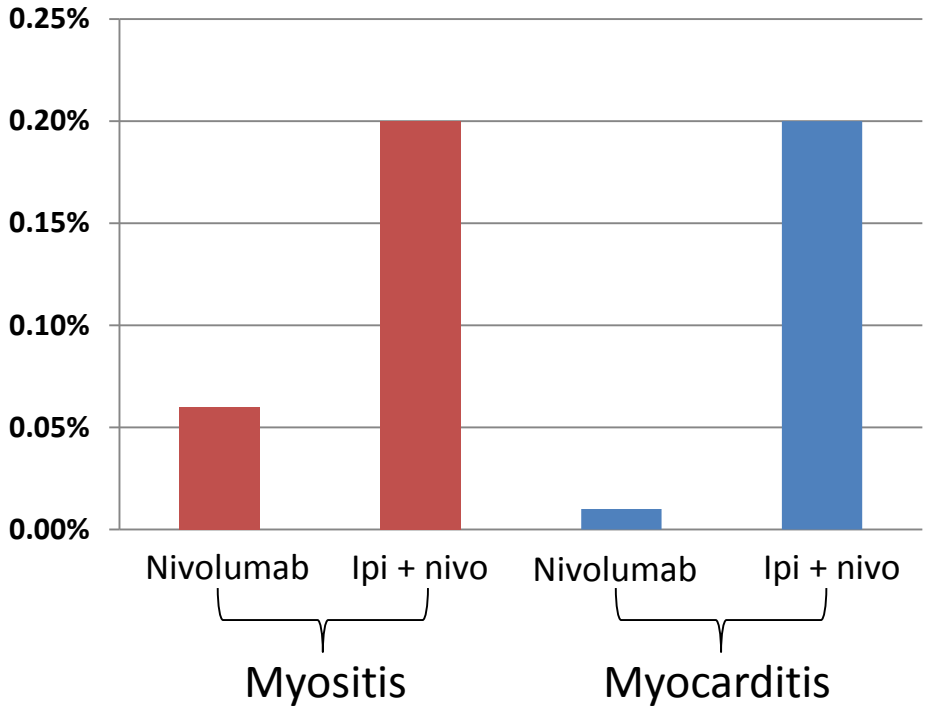




- Numerous T cell clones are present in all affected tissues in patient 1 . Blue denotes T cell clones more prevalent in Tumor tissue and Red denotes more frequent clones in Cardiac tissue as calculated by Fisher's exact test..
- Blue arrow denotes that few prevalent T cell clones were shared between pre-treatment tumor and heart, but numerous shared clones expanded in the post-treatment tumor.



Incidence of myocarditis and myositis



Myositis

- 34 cases, 31 listed as severe, 3 non-severe
- 5 patients on statins
- 3 cases fatal

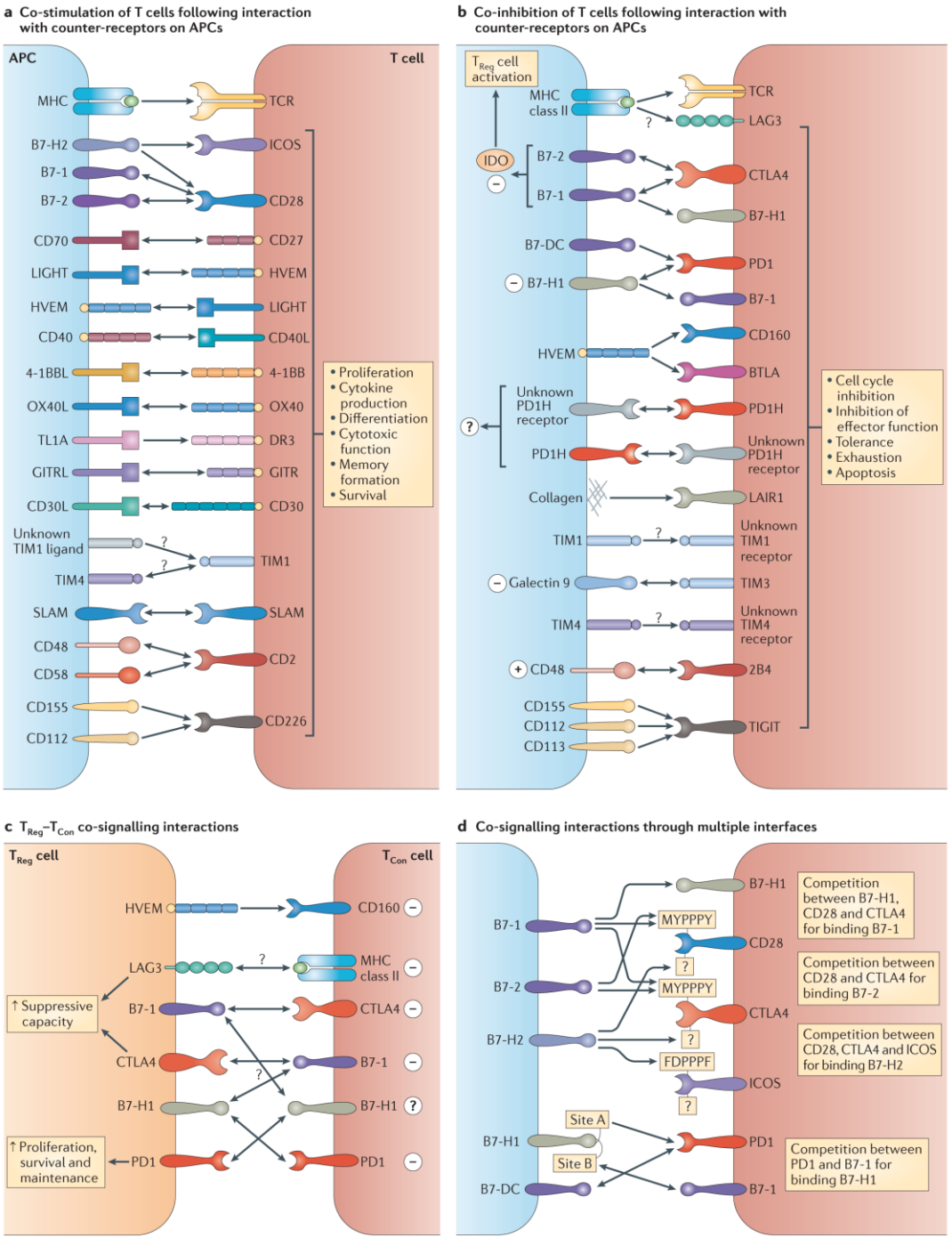
Myocarditis

- 18 cases
- 6 fatal (5 of 8 with ipi + nivo)
- Time to onset 13-64 days
- 12 M, 5F
- 5 with prior cardiac disease

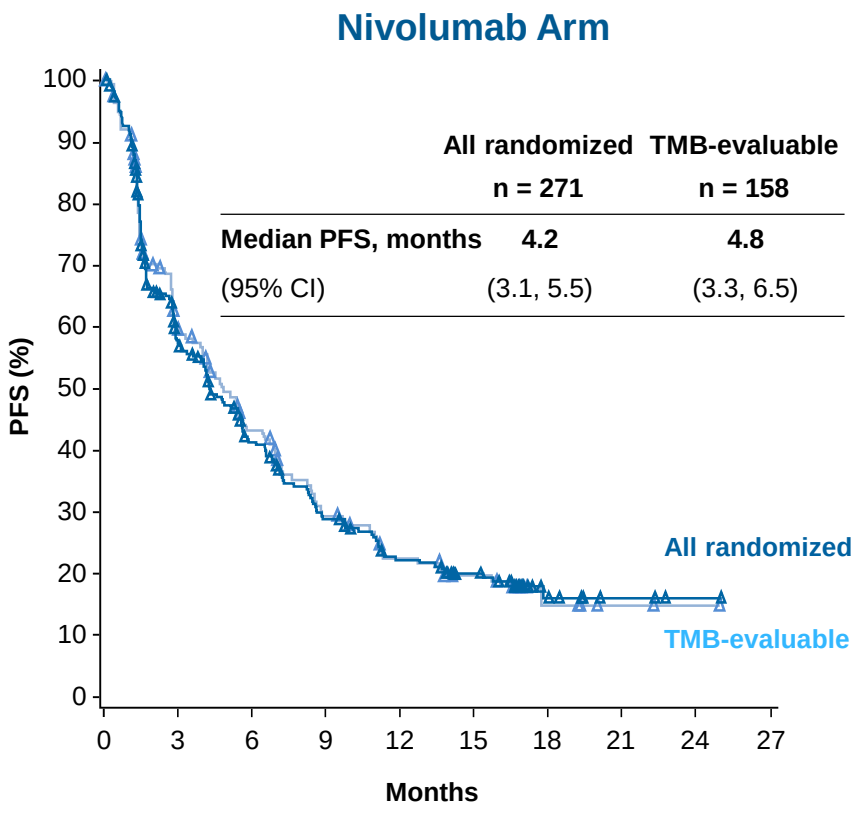
Nivolumab alone = 17,620 patients

Nivolumab+ Ipilimumab = 2974 patients

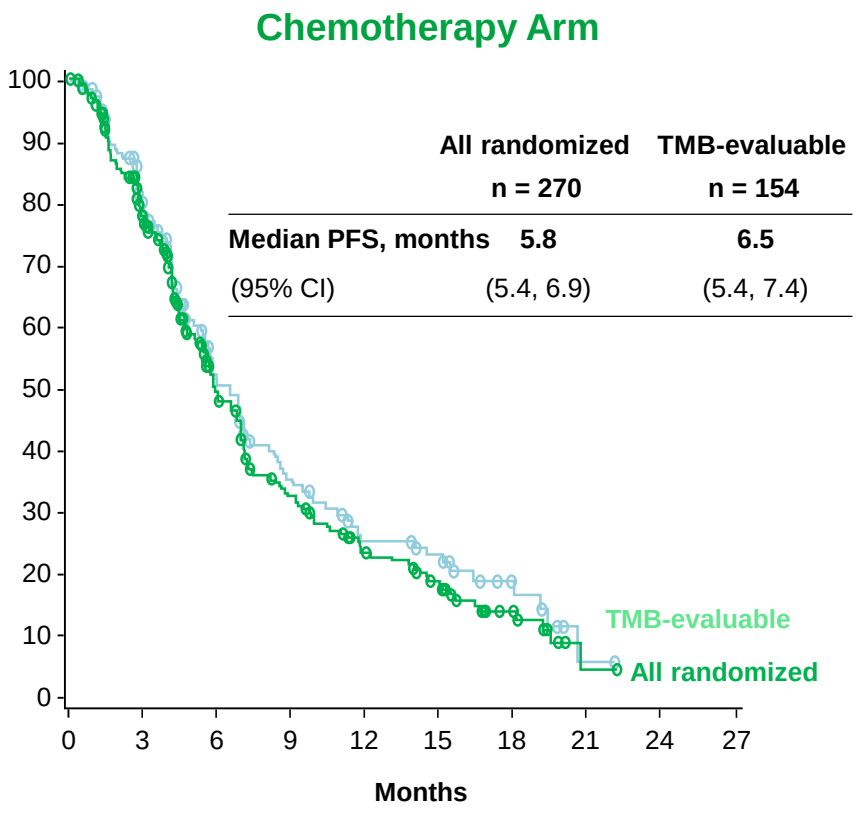
Immunological Synapse



PFS (All Randomized Patients and TMB-Evaluable Patients) CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	All randomized	TMB-evaluable
	n = 271	n = 158
Median PFS, months	4.2	4.8
(95% CI)	(3.1, 5.5)	(3.3, 6.5)

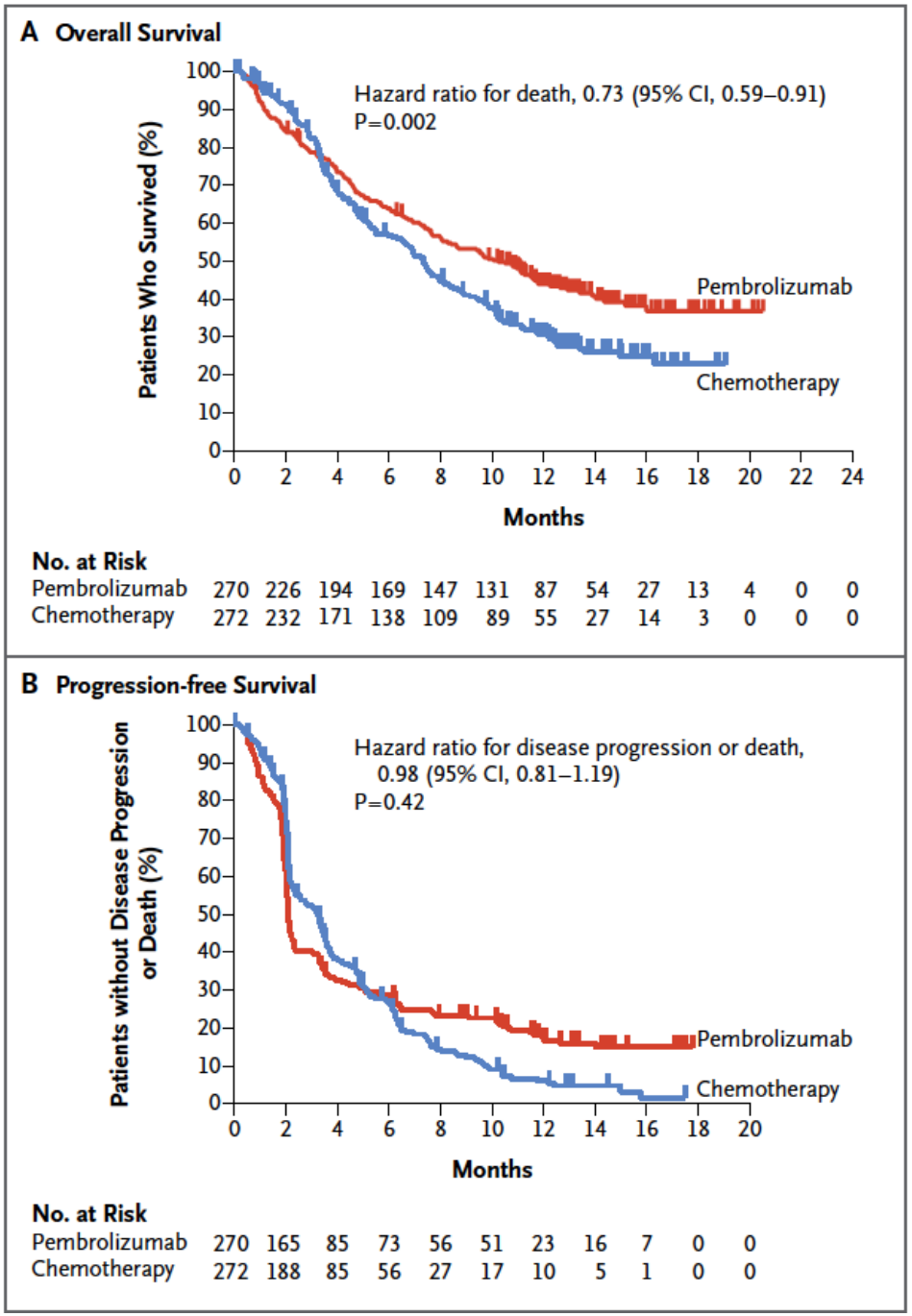


	All randomized	TMB-evaluable
	n = 270	n = 154
Median PFS, months	5.8	6.5
(95% CI)	(5.4, 6.9)	(5.4, 7.4)

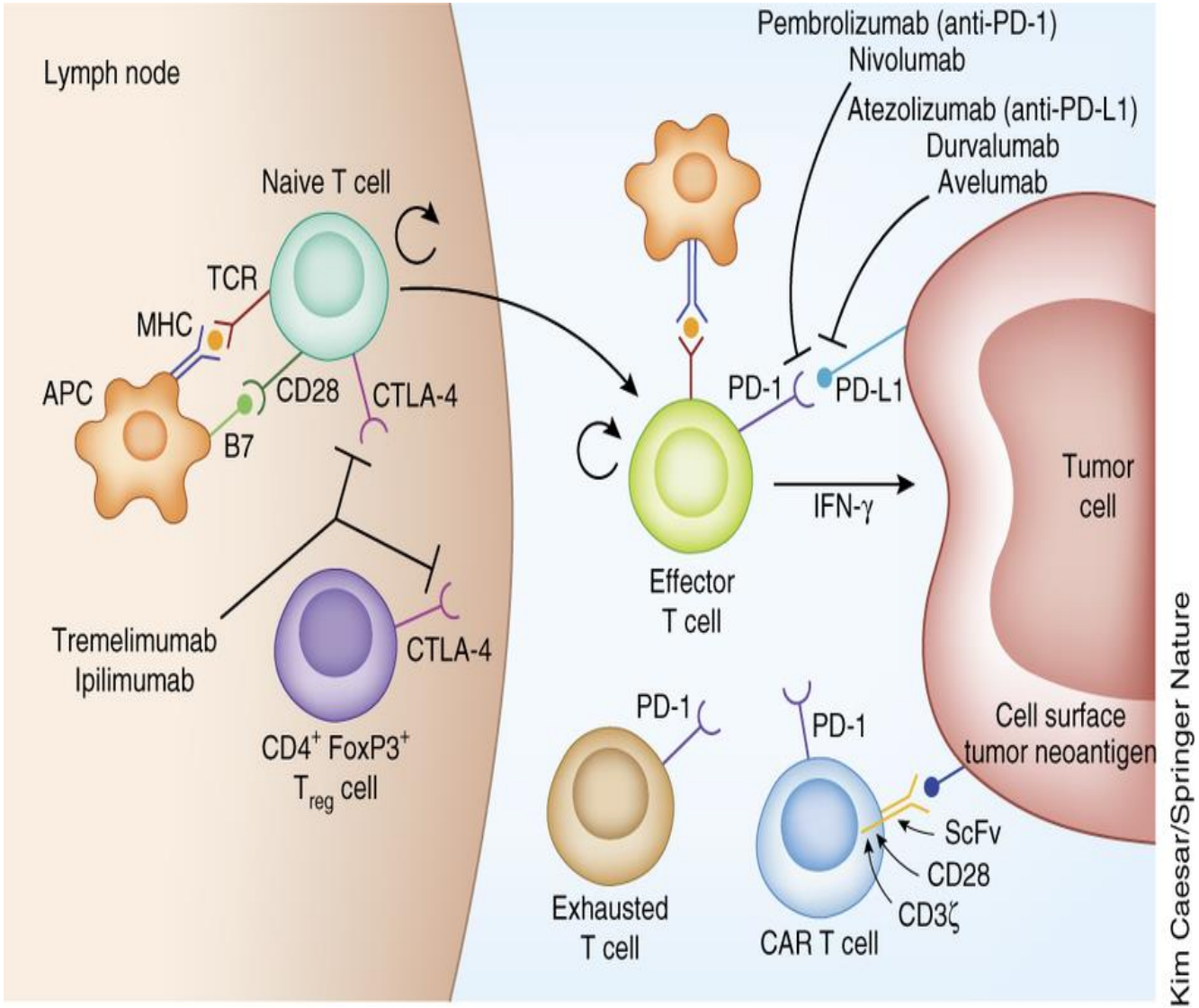
- OS in each treatment arm was also similar in patients with evaluable TMB data and all randomized patients

Urothelial Cancer:

Overall Survival and Progression-free Survival in the Intention-to-Treat Population.



CTLA-4 and PD-1 Checkpoint Blockade



June et.al , Nature Med, 2017