Biomarcadores em Imuno-Oncologia

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Disclosure

- Honoraria: Pfizer, Astellas, BMS, Novartis, Roche, Astra-Zeneca
- Scientific Advisory Board: Janssen, Novartis, Roche
- Research Grant: CAPES – CNPq, BMS, Roche, Astra-Zeneca

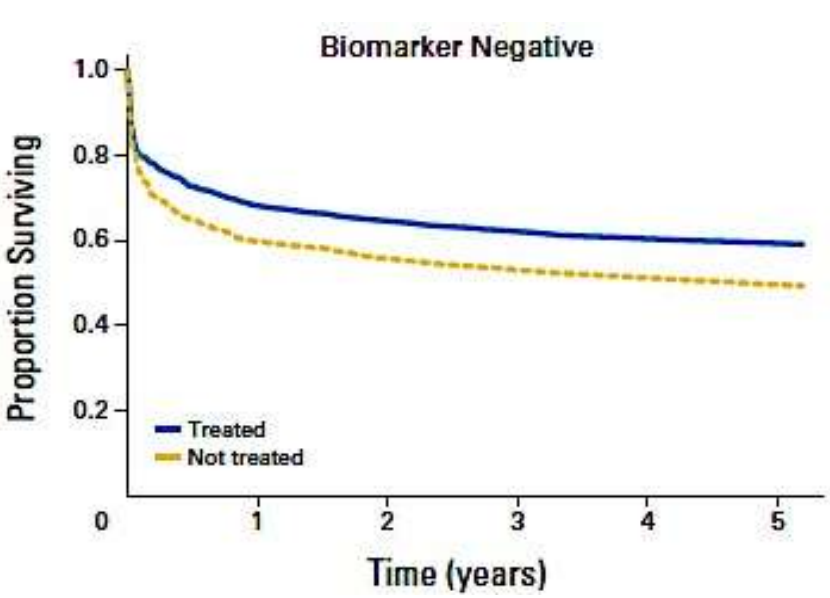
Outline

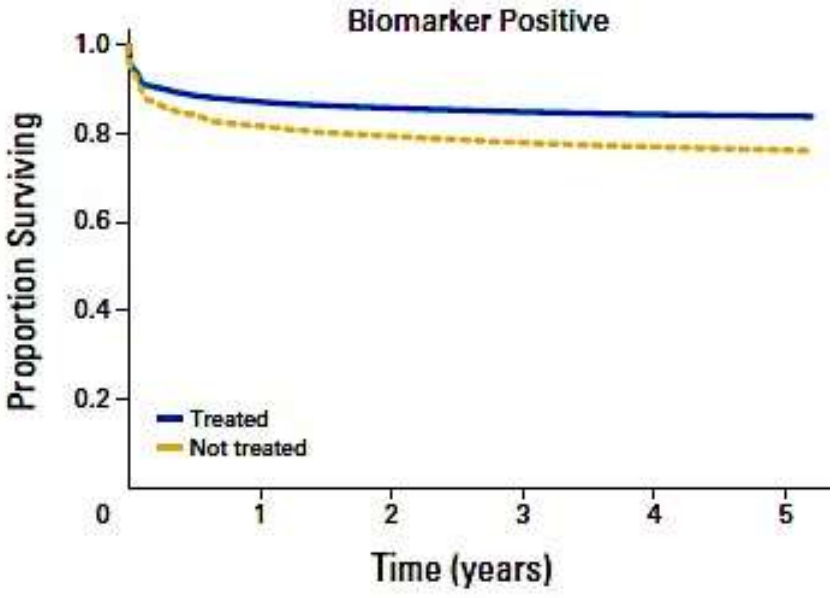
- **In situ markers**
  - Protein expression by IHC (e.g. **PD-L1)**
  - Challenges
- **Genomics:**
  - Overview
  - Integrative genomics
  - Immune signatures
- **Pharmacodynamic changes on therapy and upon resistance**

Biomarkers

- Early diagnosis
- Prognosis
  - Risk of recurrence prediction *(Recurrence scores…)*
- Predictive
  - Selection of treatment (efficacy/toxicity)
- Response/resistance markers

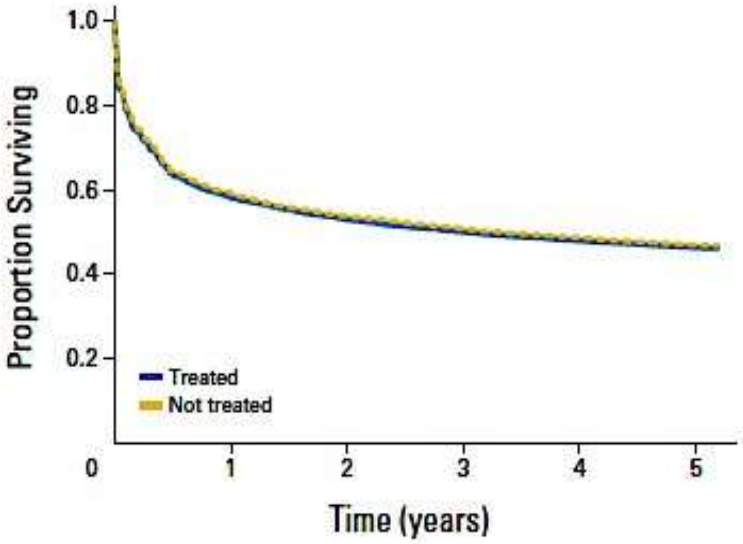
Prognóstico

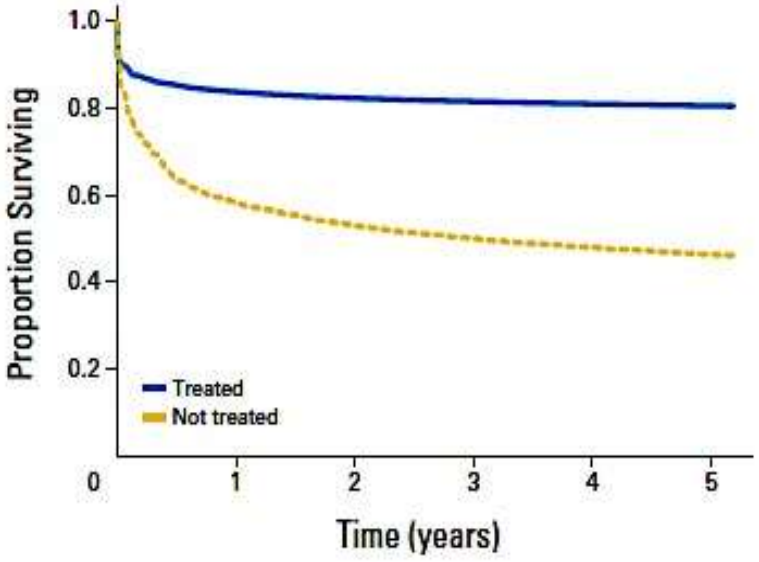




Ballman et al K JCO 2015

Preditivo

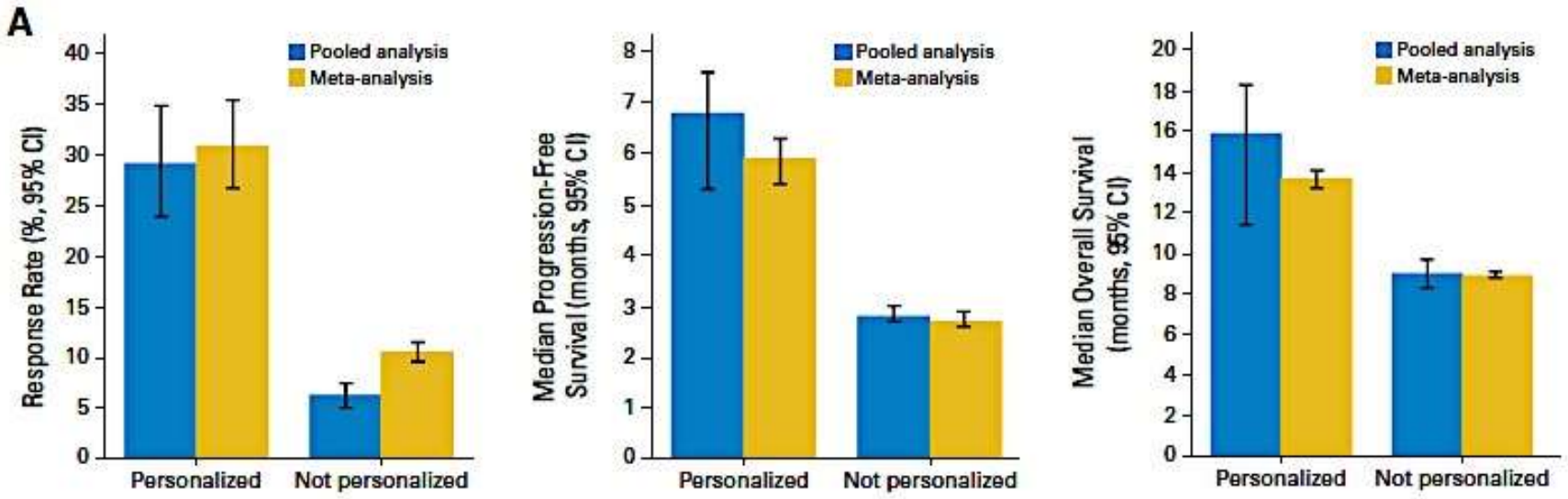




Ballman et al K JCO 2015

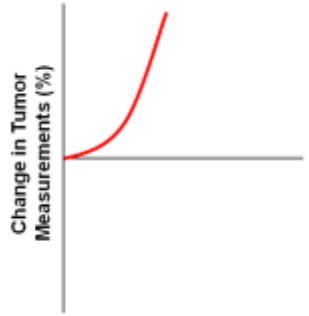
Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials

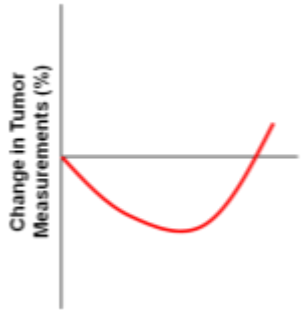
RR PFS OS

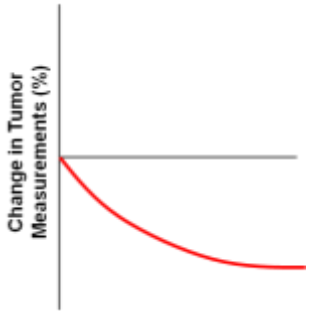


Schwaederle M et al. J Clin Oncol Aug 2015

Patterns of Tumor Progression on Cancer Treatment



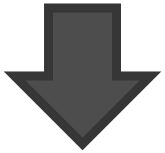




Primary Refractory

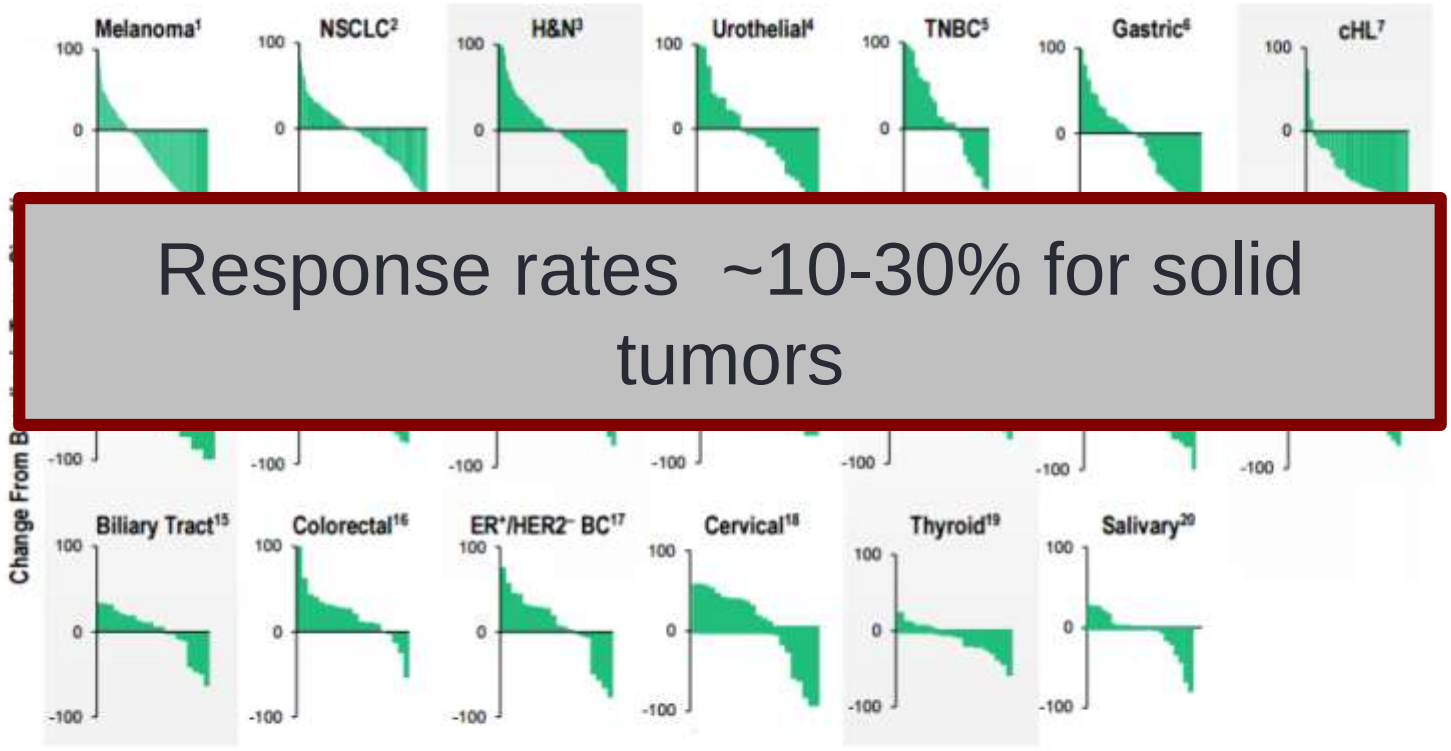
Extreme Responders

To identify **predictive biomarkers** of response



To individualize therapy and optimize benefit from each agent

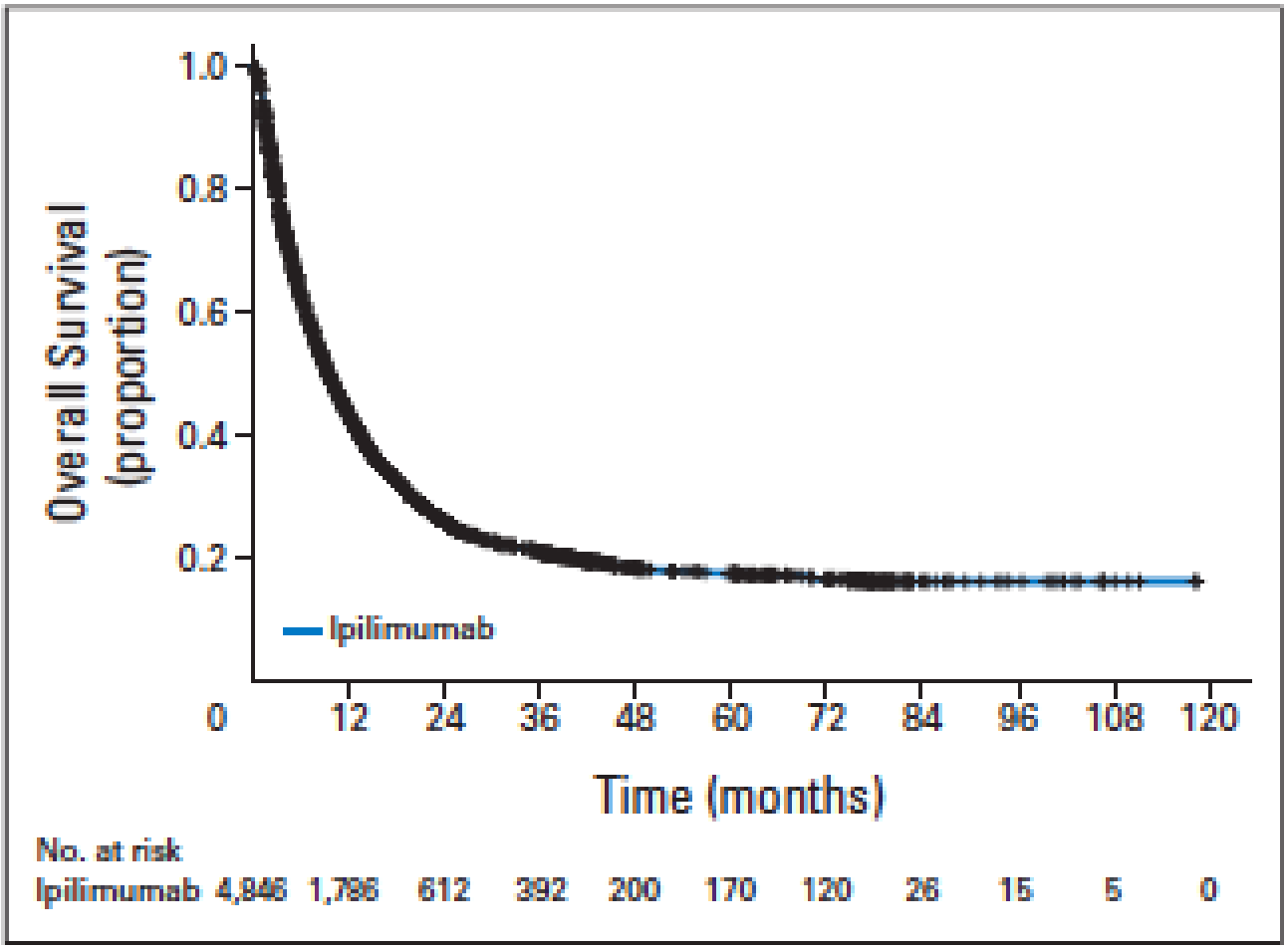
Variable Sensitivity to Immunotherapy



Response rates ~10-30% for solid tumors

1. Daud A et al. 2014 SMR; 2. Garon EB et al. ESMO 2014; 3. Chow LQ et al. ESMO 2014; 4. O'Donnell P et al. 2015 Genitourinary Cancers Symposium; 5. Muro K et al. 2015 Gastrointestinal Cancers Symposium; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. 2014 ASH Annual Meeting; 8. Alley EA et al. 2015 AACR.

Ipilimumab in Melanoma



Schandendorf, J Clin Oncol, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

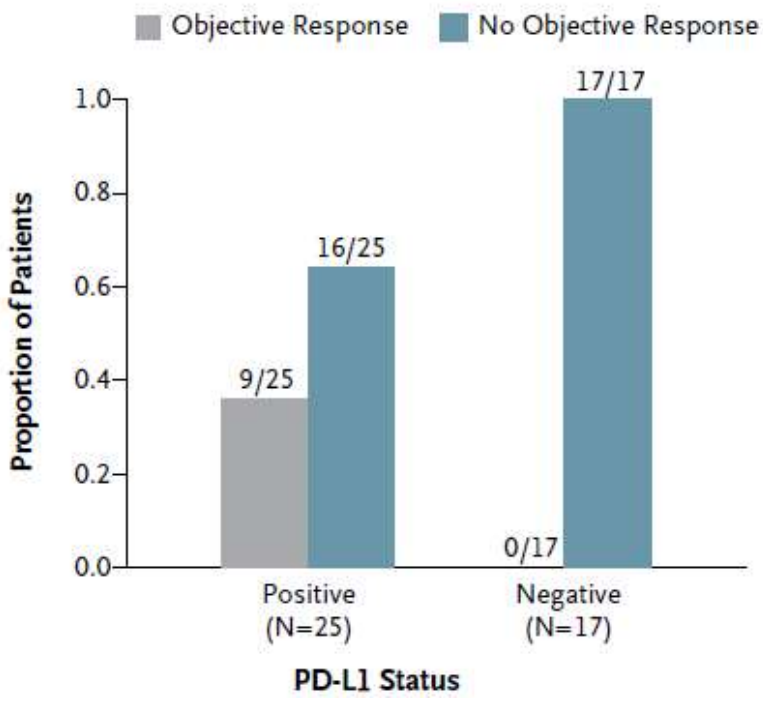
ORIGINAL ARTICLE

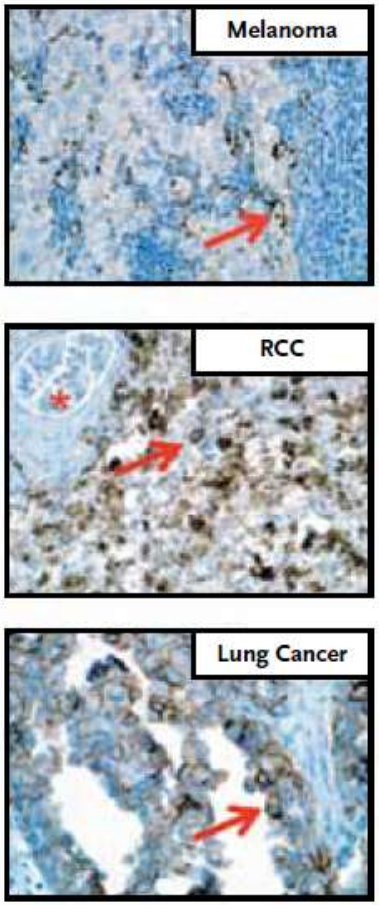
Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

N Engl J Med. June 28, 2012
N Engl J Med. July 11, 2013

PD-L1 Expression by IHC





**Optional biopsies; Non-random subset of the population*

Topalian et al. N Engl J Med 2012;366:2443-54

Positive intra-tumoral PD-L1 expression is associated with better response to PD-1/PD-L1blockade

Response rates	Nivolumab – Solid tumors Topalian NEJM 2012	Nivolumab – Melanoma Weber ASCO 2013	Nivolumab – Melanoma Grosso ASCO 2013	MPDL3280 – Solid tumors Herbst ASCO 2013	MPDL3280 – Melanoma Hamid ASCO 2013	MPDL3280 – NSCLC Soria ECC 2013	Pembrolizumab – Melanoma Daud AACR 2014	Pembrolizumab – NSCLC Gandhi AACR 2014	MPDL3280 – Bladder Powels ASCO 2014	Pembrolizumab – Head+Neck Selwert ASCO 2014	Pembrolizumab – Melanoma Ribas ASCO 2014	Nivolumab – NSCLC Spigel ASCO 2015
N=	42	44	34	94	30	53	113	129	65	55	411	117
unselected	21%	32%	29%	22%	23%	23%	40%	19%	26%	18%	40%	30%
PD-L1 +	36%	67%	44%	39%	27%	46%	49%	37%	43%	46%	49%	21%
PD-L1 -	0%	19%	17%	13%	20%	15%	13%	11%	11%	11%	13%	15%

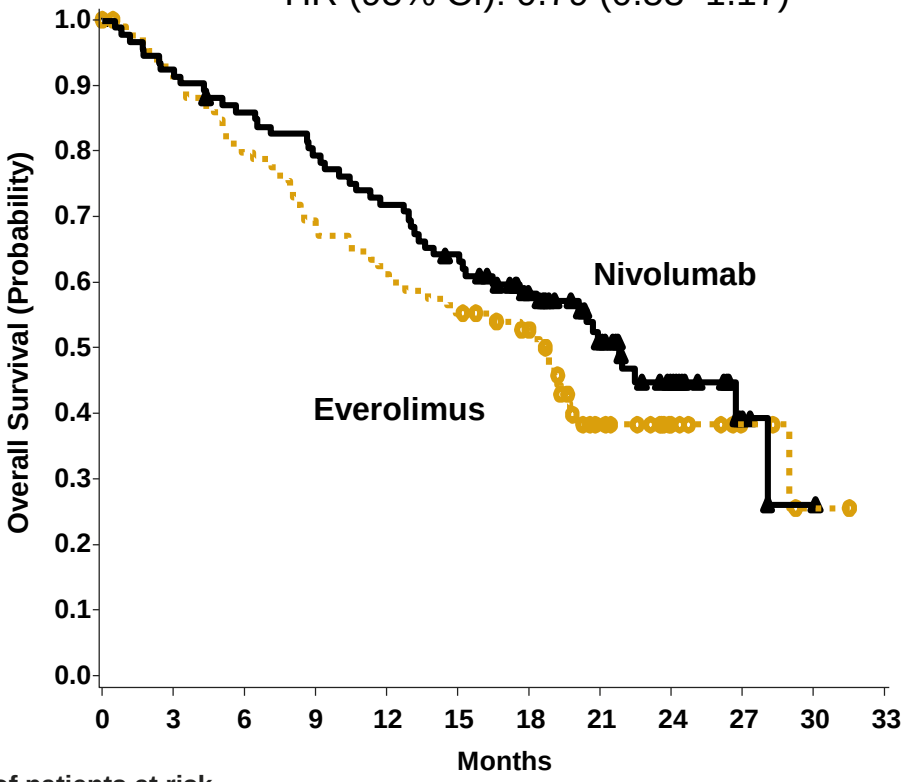
Adapted from slide presented by Margaret Callahan at 2014 ASCO Annual Meeting and updated with 2015 ASCO meeting by TK Choueiri

Overall survival by PD-L1 expression

PD-L1 ≥1% (n = 24%)

Median OS, months (95% CI)	
Nivolumab	21.8 (16.5–28.1)
Everolimus	18.8 (11.9–19.9)

HR (95% CI): 0.79 (0.53–1.17)



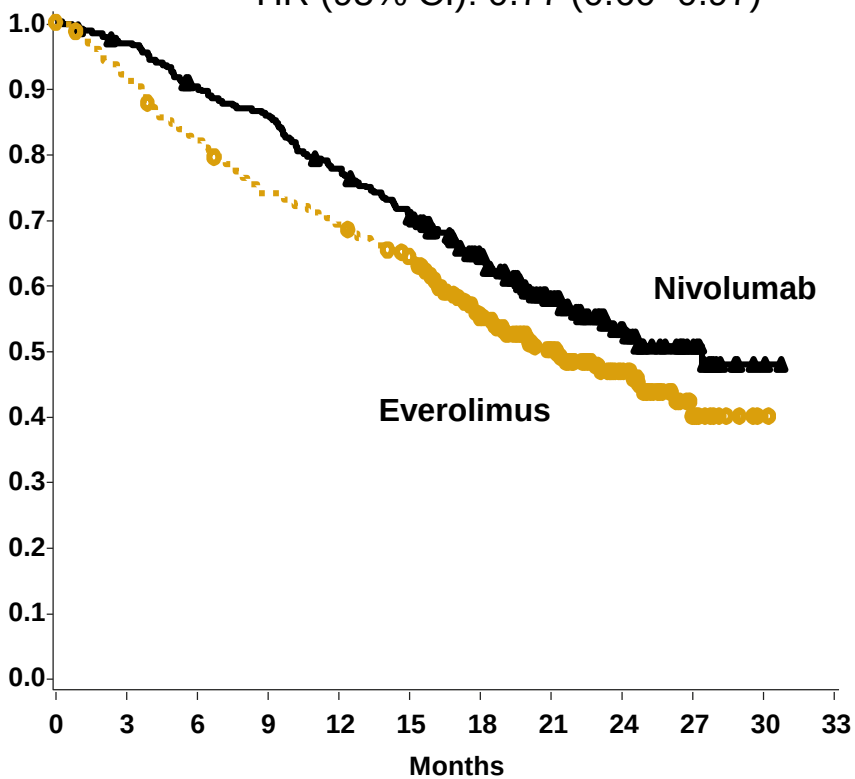
No. of patients at risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	87	77	68	59	52	47	40	19	9	4	1	0

PD-L1 <1% (n = 76%)

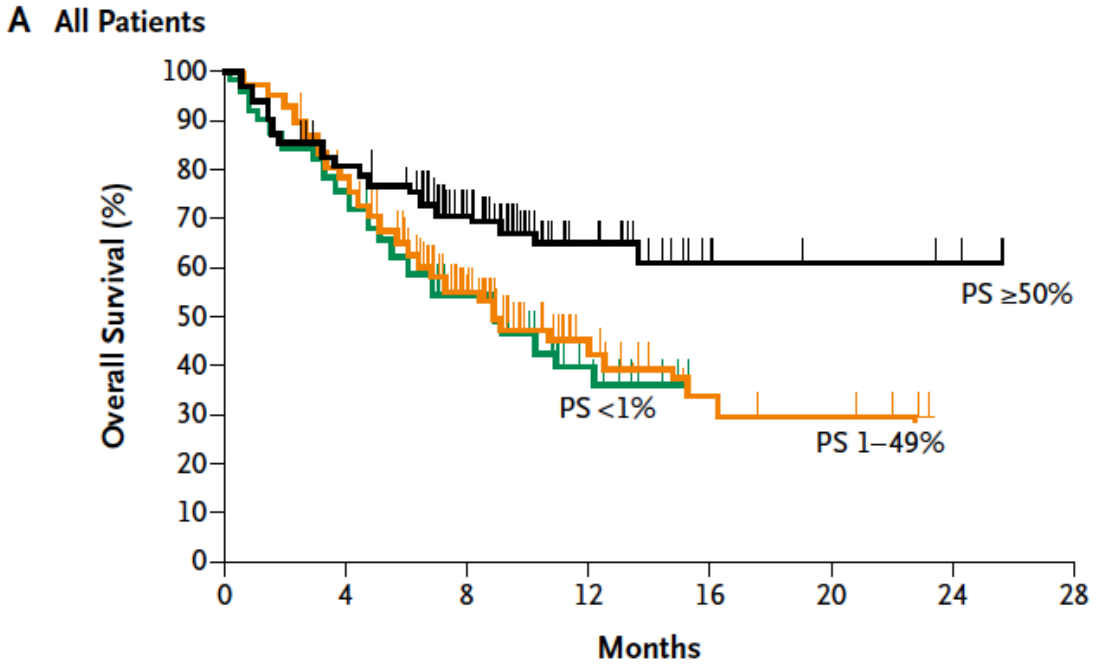
Median OS, months (95% CI)	
Nivolumab	27.4 (21.4–NE)
Everolimus	21.2 (17.7–26.2)

HR (95% CI): 0.77 (0.60–0.97)



Nivolumab	276	265	245	233	210	189	145	94	48	22	2	0
Everolimus	299	267	238	214	200	182	137	92	51	16	1	0

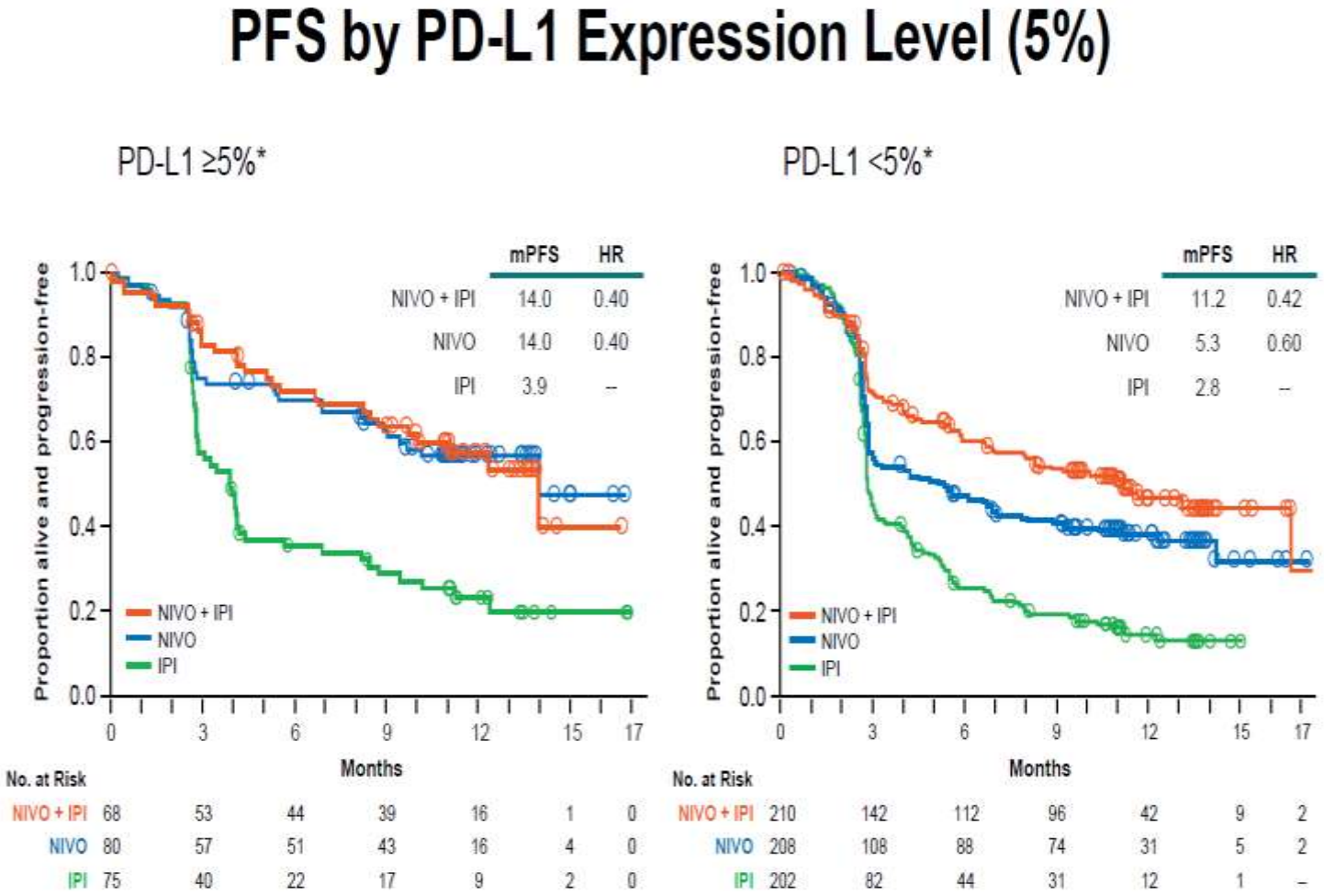
Pembrolizumab in Non Small Cell Lung Cancer



No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

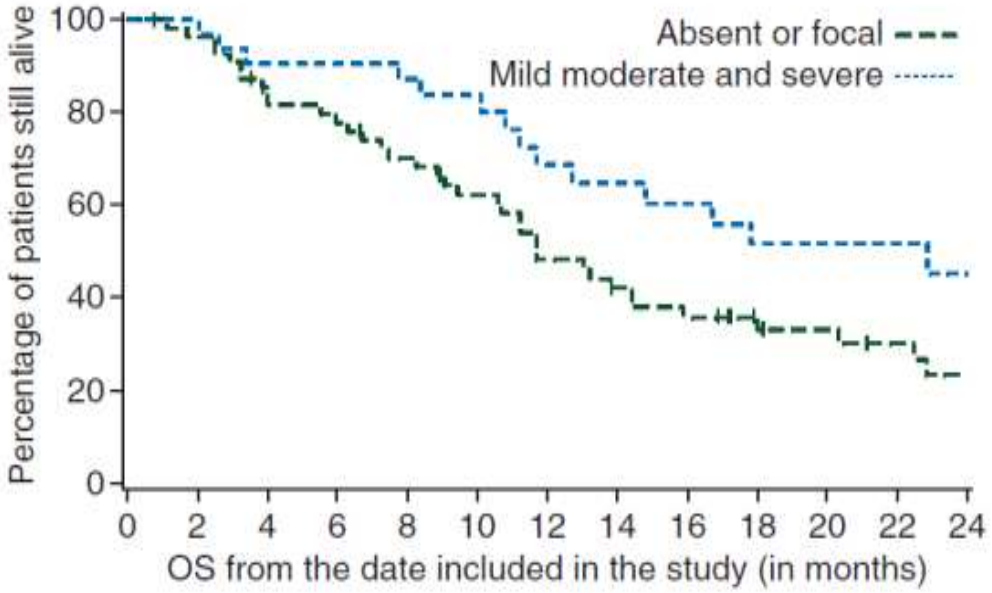
Garon et al. NEJM. 2015

Phase III, Ipilimumab + Nivolumab in Melanoma



Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma

J. Bellmunt[1,2,3,4], S. A. Mullane[1,4,†], L. Werner[1,†], A. P. Fay[1,4], M. Callea[5], J. J. Leow[1], M. E. Taplin[1,2,3,4], T. K. Choueiri[1,2,3,4], F. S. Hodi[3,4,6], G. J. Freeman[3,4] & S. Signoretti[1,3,5]

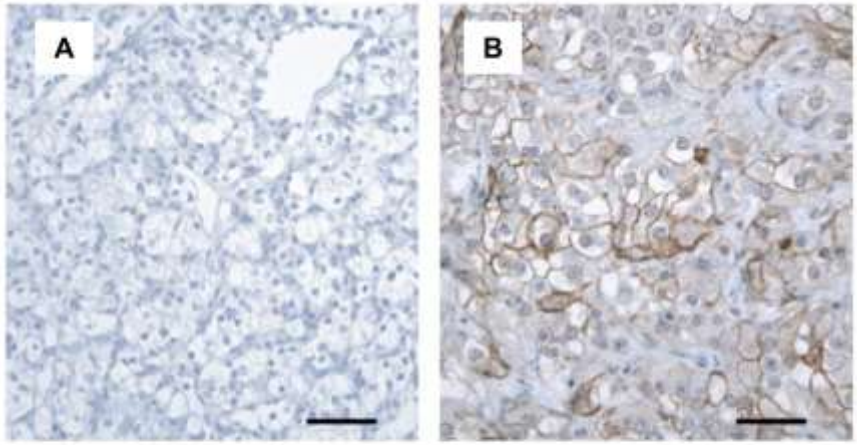


- Positive PD-L1 expression (score of 2–4) in TIMCs was significantly associated with longer OS (12 versus 23 months) in both univariate (P = 0.04) and multivariable analysis (P = 0.0007) (adjusting for ECOG status and visceral disease)
- PD-L1 expression in tumor cell membrane was not associated with survival (P = 0.45)

Annals of Oncology, 2015

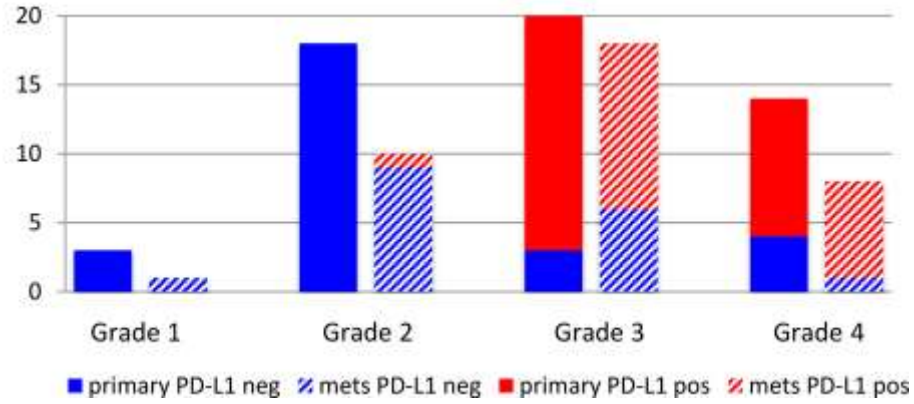
PD-L1 expression was heterogeneous even within individual lesions

a.



- PD-L1 was almost exclusively detected **in high nuclear grade areas** (P < 0.001)
- Expression was more heterogeneous in primary tumors than in metastases

b.



Callea et al. Cancer Immunol Res 2015

Extent of discordant PD-L1 expression in primary tumors and metastases

		Metastases		Total
		PD-L1–	PD-L1+	
Primary Tumors	PD-L1–	33	3	36
	PD-L1+	8	9	17
Total		41	12	53

Discordant tumor cells PD-L1 staining:11 of 53 cases **(20.8%)** (95% CI: 10.8% −34.1%).

Callea, Albiges, Fay, Choeuiri,Freeman Signoretti. Cancer Immunol Res. 2015

PD-L1 Antibodies

	Anti-PDL1 mAb Mouse clone 5H1	Genentech mAb	Anti-PDL1 mAb Rabbit clone 28-8	Anti-B7-H1 (MIH1)
RCC	✓ [1,3]	✓ [2]		
Melanoma	✓ [6]	✓ [2]	✓ [5,8]	
NSCLC	✓ [9]	✓ [2]	✓ [5]	✓ [4]
UC			✓ [7]	

[1] *Thompson ,Clin Cancer Res 2007;13:709s-715s*
[2] *Powderly et al, abstract #3001. ASCO 2013*
[3] *Figueroa et al, abstract #3021. ASCO 2013*
[4] *Konishi. Clin Cancer Res, 2004 Aug 1;10(15):5094-100*
[5] *Grosso et al, abstract #3016. ASCO 2013*
[6] *Topalian et al. N Engl J Med 2012;366:2443-54*
[7] *Zhang et al, abstract #4541. ASCO 2013*
[8] *Wolchok et al.N Engl J Med 2013;369:122-33. Suppl. Appendix*
[9] *Boland, Clinical Lung Cancer, 2013*

Positivity Criteria

	Any expression	Cut off: >5%	Semi-quantitatively in 5-10% increments	Tumor cell	Immune Cell	Both
Thompson RCC	-	✓	✓	✓		
MPDL3280A Metastatic Solid Tumors	✓	-	-	-	✓	-
Pos-pazopanib RCC	-	✓	-	-	-	✓
Konishi NSCLC	-	-	✓			
Topalian Metastatic Solid Tumors	-	✓	✓	✓	-	-
Grosso Melanoma, NSCLC	-	✓	-	-	-	✓
Zhang UC	-	✓	-	✓	-	-
Wolchok Melanoma	-	✓	-	✓	-	-

Immune Cell Evaluation

	Marker				Method	
	CD8	Dual staining PD-L1/CD68	CD45	PBMC*	H-score	TIL Absent, focal, moderate, marked
Thompson[1] RCC					✓	✓
MPDL3280A[2] (Genentech)	✓	-	-	✓	-	-
Pos-pazopanib[3]	-	✓	-		✓	-
Konishi[4] NSCLC	-	-	✓		-	-
Grosso[5] NSCLC, Melanoma	-	-	-	✓	-	-

*PBMC: Peripheral Blood mononuclear Cells

[1] *Thompson ,Clin Cancer Res 2007;13:709s-715s*
[2] *Powderly et al, abstract #3001. ASCO 2013*
[3] *Figueroa et al, abstract #3021. ASCO 2013*
[4] *Konishi. Clin Cancer Res,* 2004 Aug 1;10(15):5094-100
[5] *Grosso et al, abstract #3016. ASCO 2013*

Lack of standardization in tissue-based procedures affects data accuracy and biomarker results in solid tumors

Pre-tissue acquisition	Post-tissue acquisition	Tissue analysis
Intra-operative blood loss	Time in fixative	Type of detection system
Renal artery clamping time	Tissue embedding protocol	Use of control tissues
Pre-nephrectomy renal artery embol	Storage temperature	Scoring by pathologist
Type of surgical procedure	Storage duration	Image analysis platform

Standardization of PD-L1 assay is urgently needed!!!!

Signoretti et al, Clin Cancer Res, 2008
Di Napoli and Signoretti, Cancer, 2009

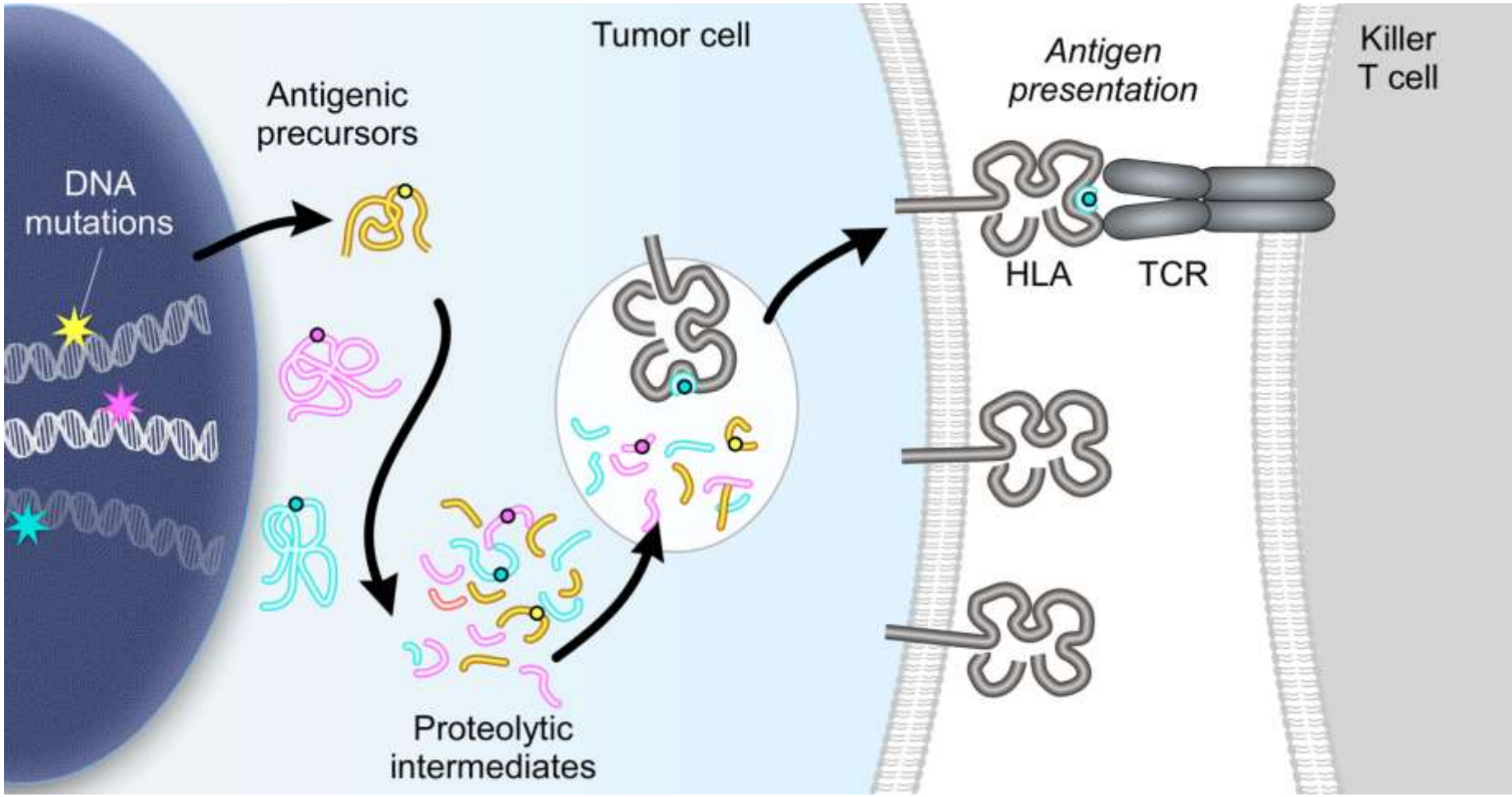
PD-L1 Assay Systems used in the Blueprint Project

	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Primary antibody clone used in the assay system	28-8 (Dako)	22C3(Dako)	SP142(Ventana)	SP263(Ventana)
Interpretative Scoring	Tumor cell membrane	Tumor cell membrane	-Tumor cell membrane - Infiltrating immune cells	Tumor cell membrane
Instrument and Detection Systems Required	EnVision Flex on Autostainer Link 48	EnVision Flex on Autostainer Link 48	OptiView Detection and Amplification on Benchmark ULTRA	OptiView Detection on Benchmark ULTRA
Therapeutic Developer	Bristol-Myers Squibb	Merck	Genentech	AstraZeneca

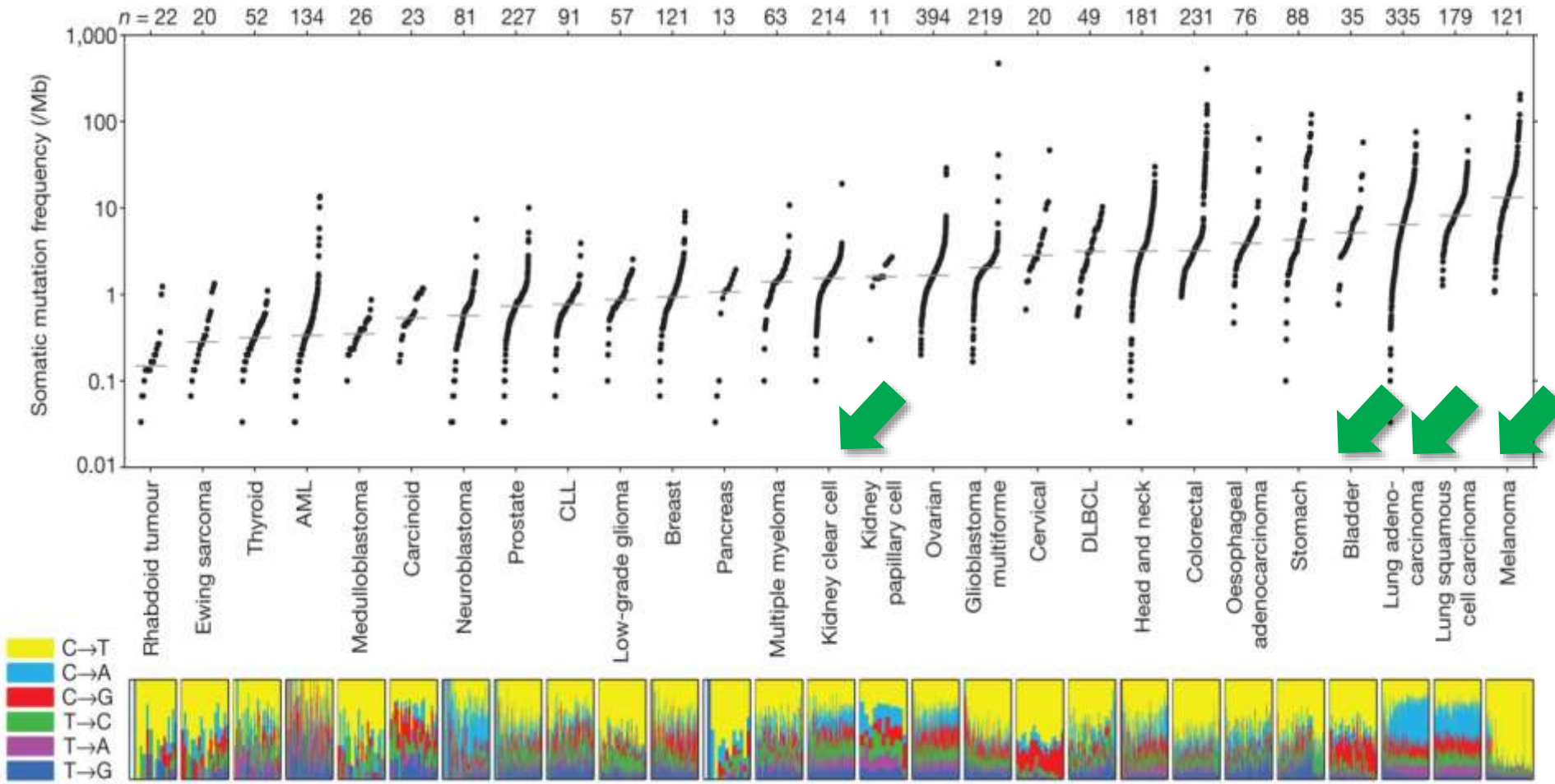
Assay Comparisson: Overall Percentage Agreement

Assay clone used for slide staining	Scoring Algorithm			
	22C3 1% TPS	28-8 1% TPS	SP142 TC1/IC1	SP263 25% TPS
22C3	38/38 (100%)	36/38 (94.7%)	33/38 (86.8%)	34/38 (89.5%)
28-8	36/38 (94.7%)	38/38 (100%)	31/38 (81.6%)	33/38 (86.8%)
SP142	24/38 (63.2%)	24/38 (63.2%)	38/38 (100%)	25/38 (65.8%)
SP263	34/38 (89.5%)	34/38 (89.5%)	33/38 (86.8%)	38/38 (100%)

Somatic mutations have the potential to generate neoantigens



Somatic mutations by tumor type

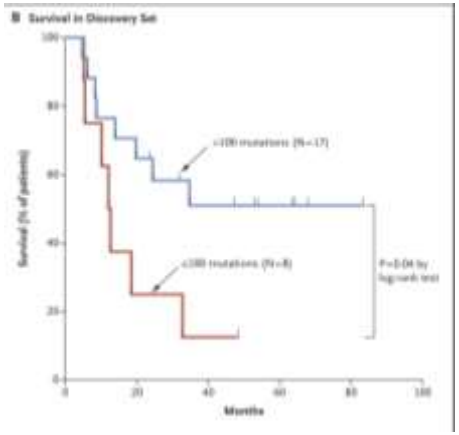


Mutational Burden:
Mutation frequencies vary more than 1000-fold between lowest and highest mutation rates across cancer and also within several tumor types.

Lawrence et al. *Nature* 2013

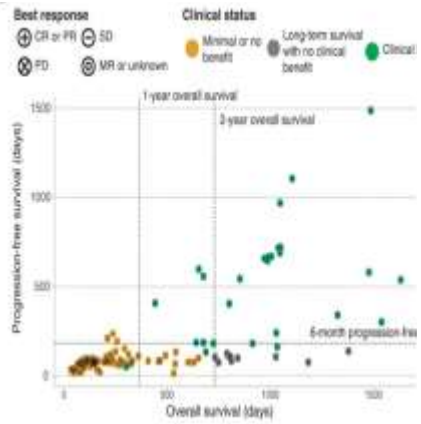
TMB Correlates with ImTx Response in Several Tumor Types

High TMB Melanoma



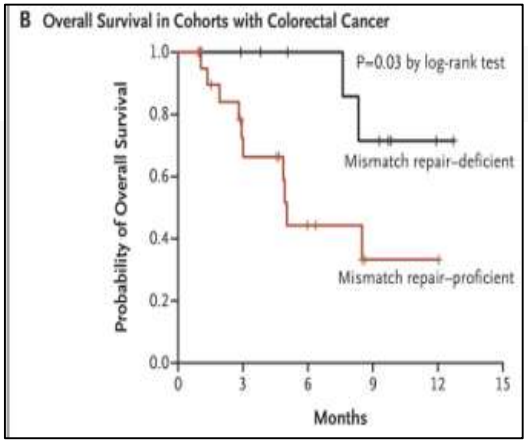
Snyder et al., NEJM, 2014

High TMB Melanoma



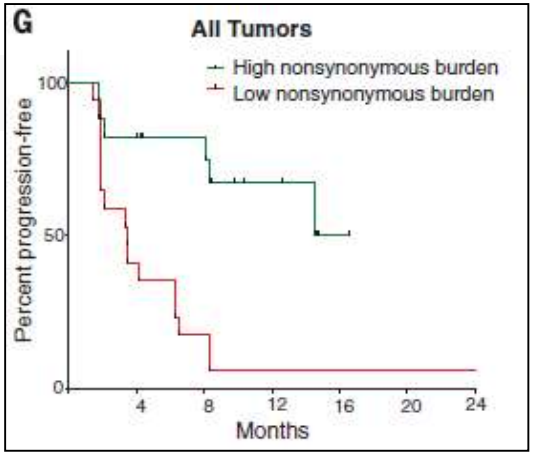
Van Allen *et al*., Science, 2015

MSI-High Colorectal Cancer



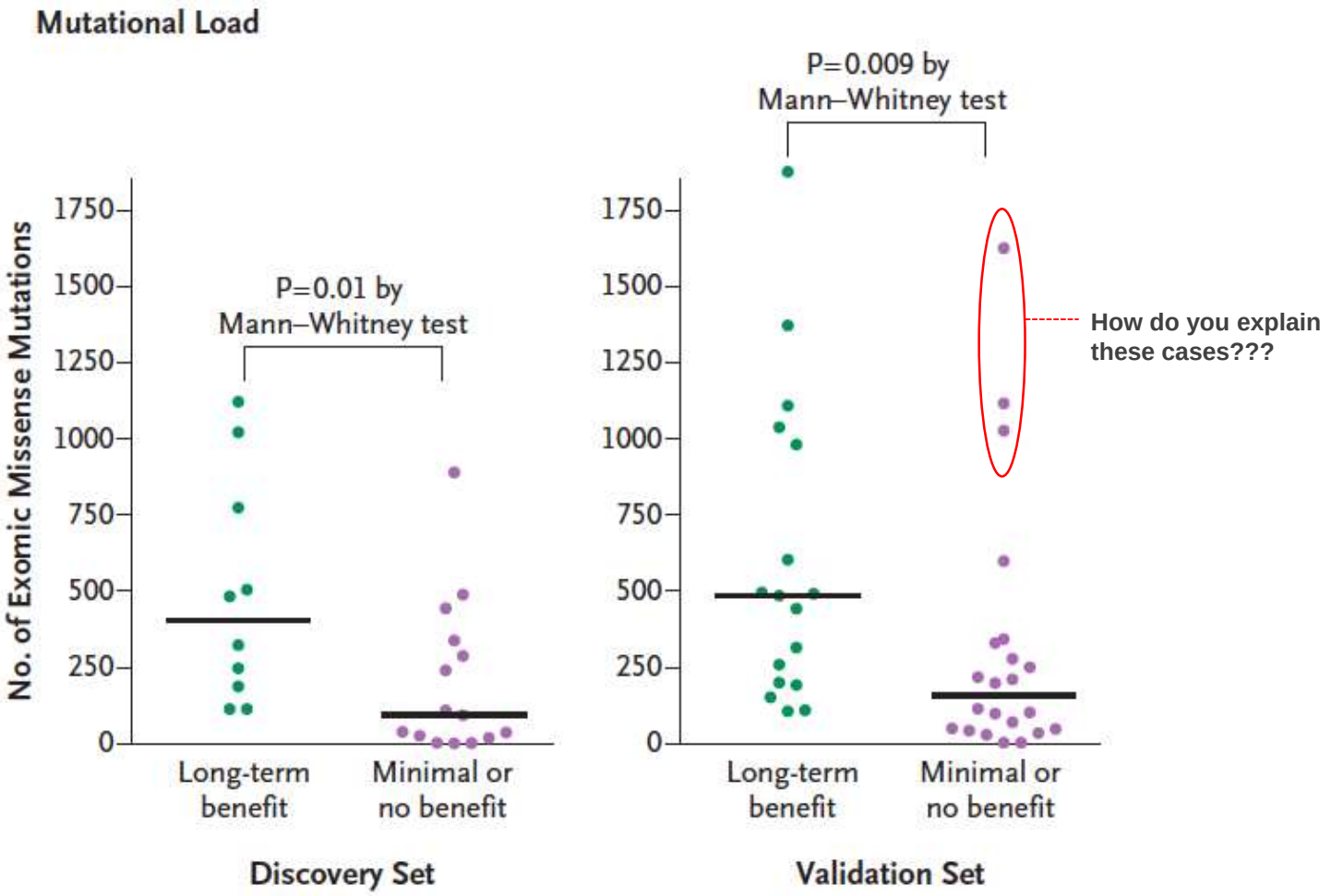
Le et al., NEJM, 2015

High TMB NSCLC



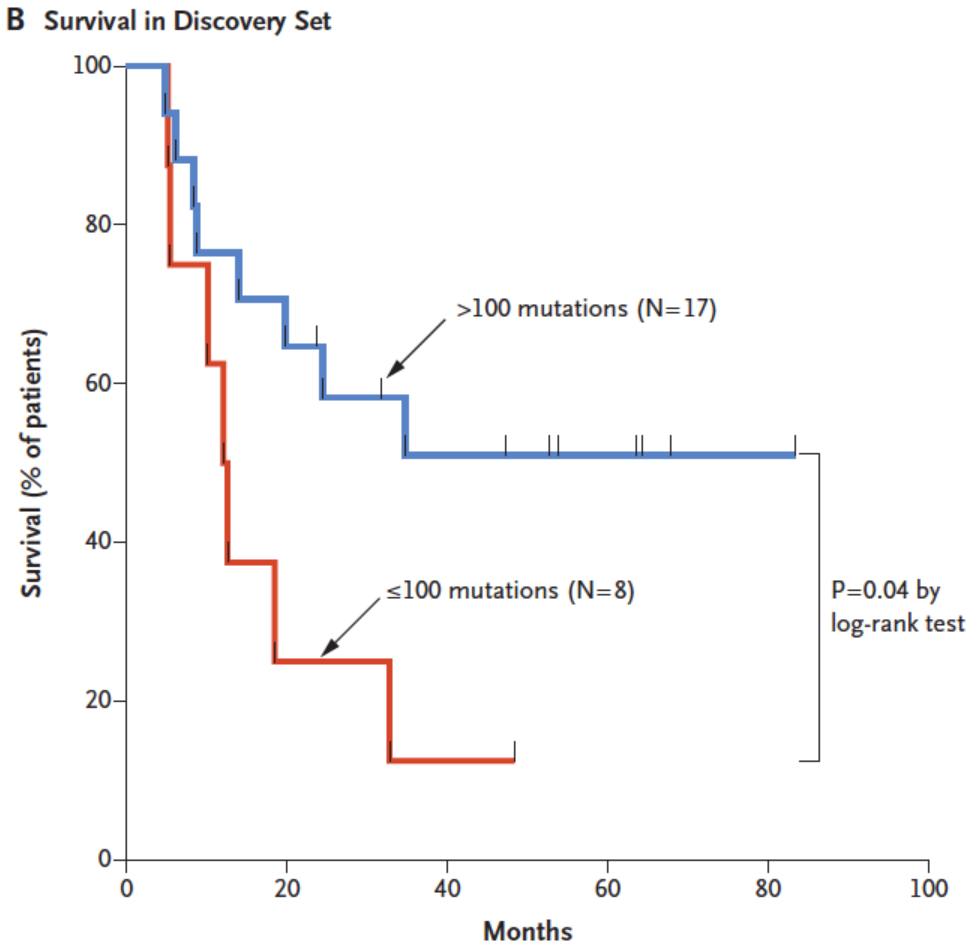
Rizvi *et al*., Science, 2015

Genetic basis for clinical response to CTLA-4 blockade in melanoma



Snyder et al. NEJM, 2014

Overall Survival According to Mutation

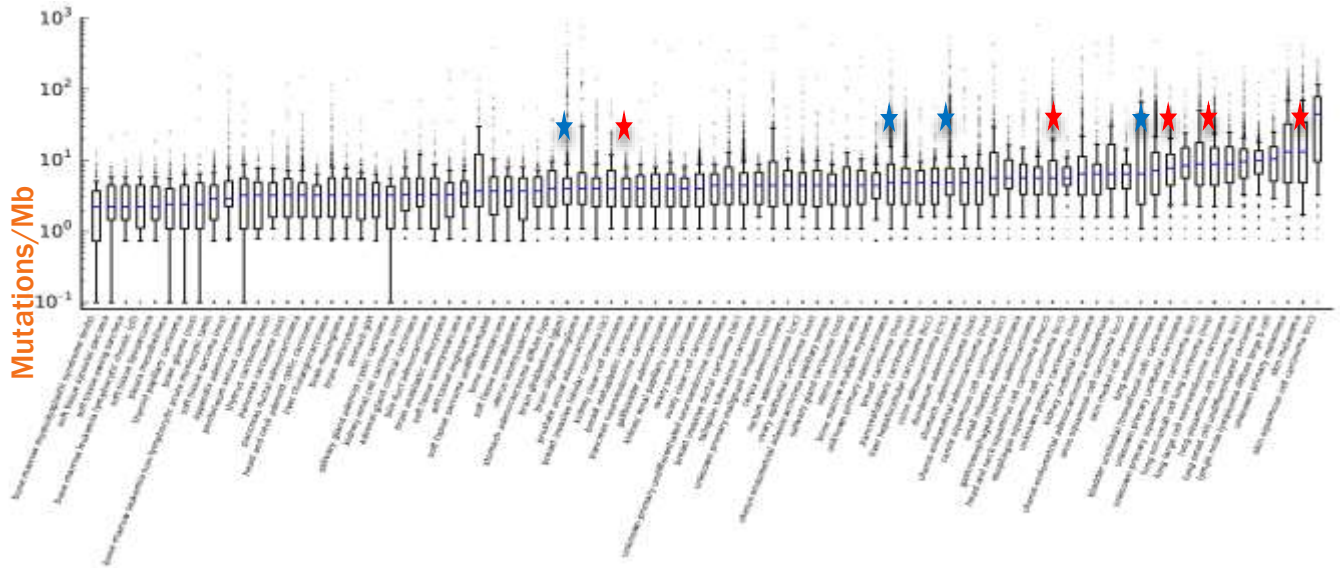


Snyder et al. NEJM, 2014

High TMB may Predict CIT Response Across Most Tumor Types

- Distribution box plots ranks indications according to mutations/Mb
- Red stars indicate approved indications, blue stars indicate likely approvals

Distribution of Mutational Burden Across All Indications at FMI (n = >100,000)



Razelle Kurzrock's group: 63 patients from 19 tumor types (excluding NSCLC and melanoma) demonstrated that HIGH TMB was independently associated with better outcome to CIT (multivariable analysis).

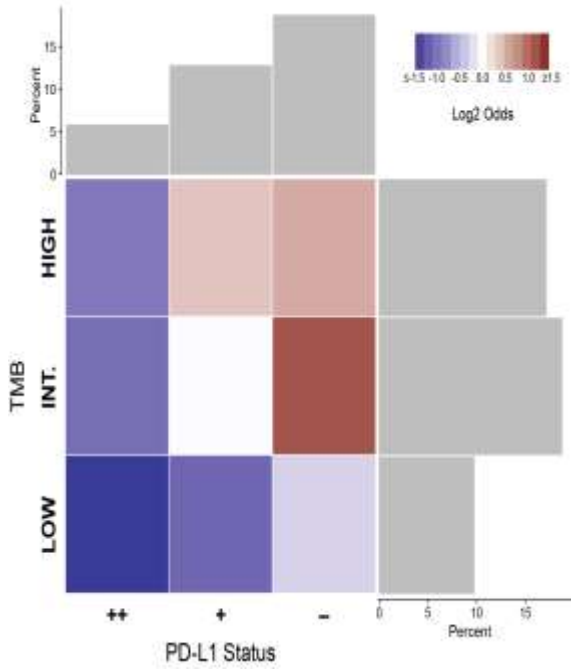
RR for patients with high TMB 58% vs. low to intermediate TMB 20%; (P = 0.0001)

Goodman A et al. Manuscript submitted

Courtesy of Phil Stephens

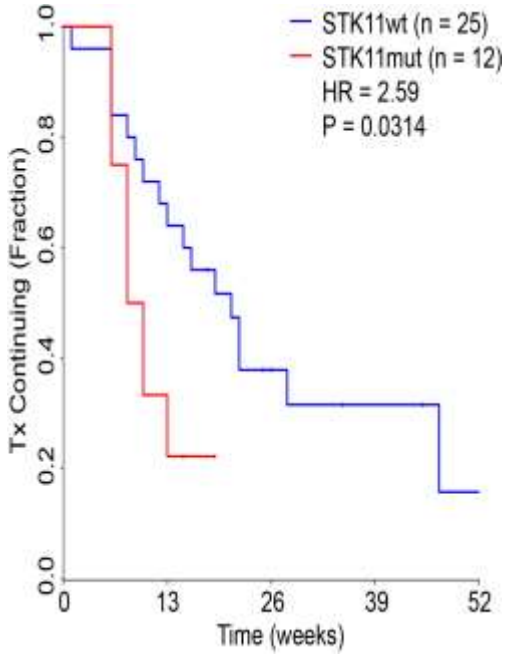
STK11 Alterations may be Immunosuppressive in NSCLC

STK11 alterations enriched in TMB HIGH, PD-L1 LOW tumors



Bonferroni P = $3.23*10^{-12}$

STK11 mutant NSCLCs may do worse on immunotherapies



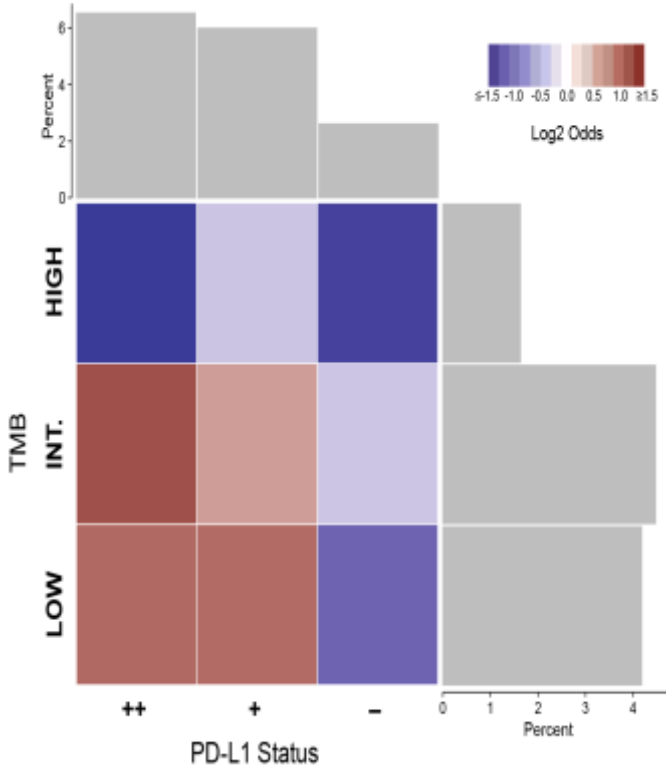
HR = 2.59; P = 0.0314

While provocative, this observation requires validation in additional cohorts

Courtesy of Phil Stephens

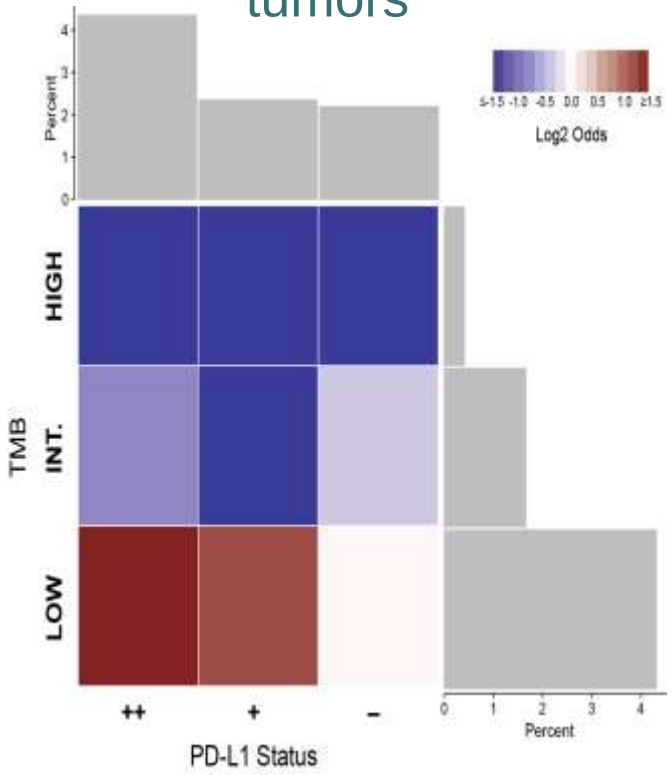
BRAF and *c-MET* Alterations may be Immunogenic in NSCLC

BRAF alterations enriched in TMB LOW, PD-L1 HIGH tumors



$P = 1.43 \times 10^{-4}$

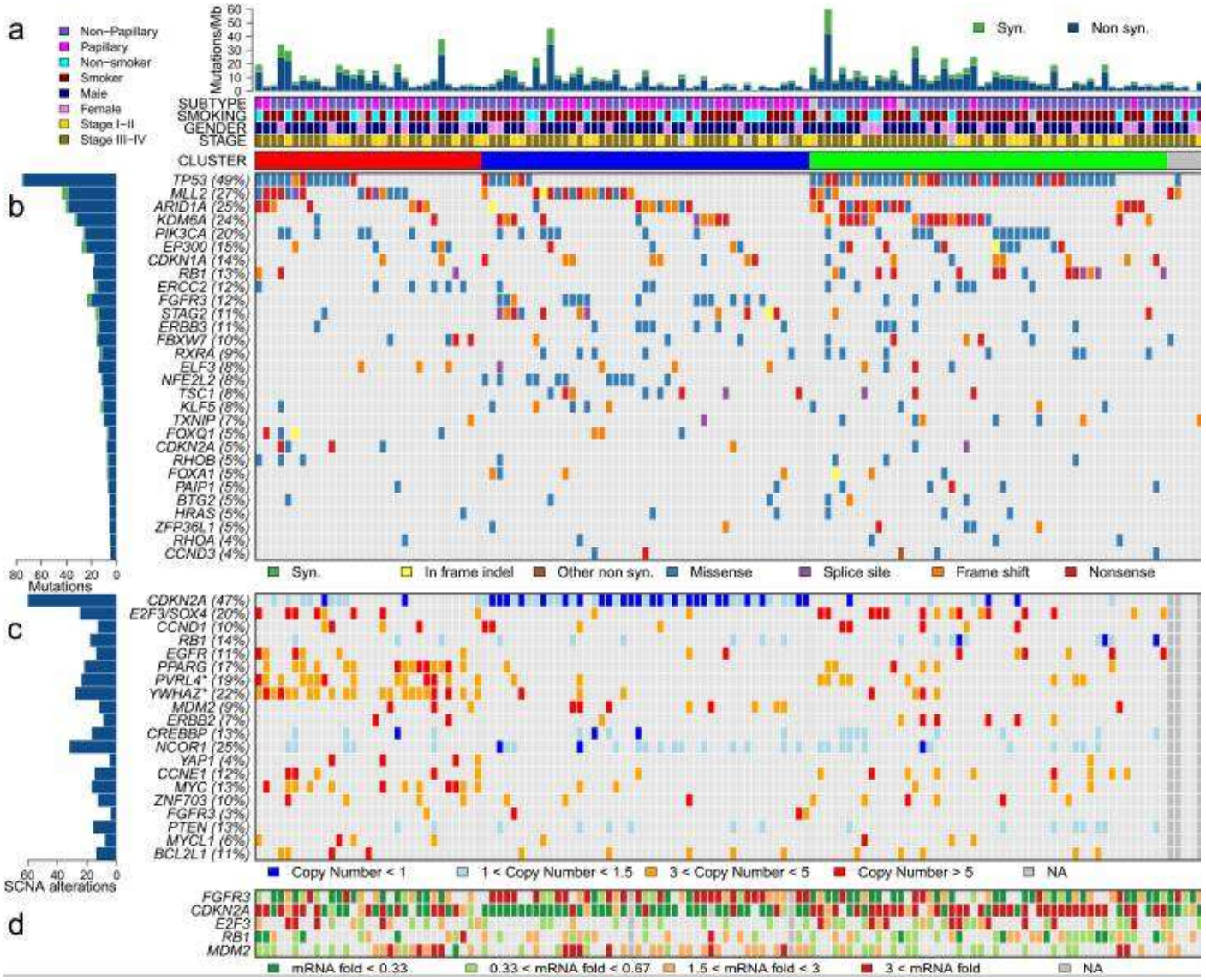
c-MET alterations enriched in TMB LOW, PD-L1 HIGH tumors

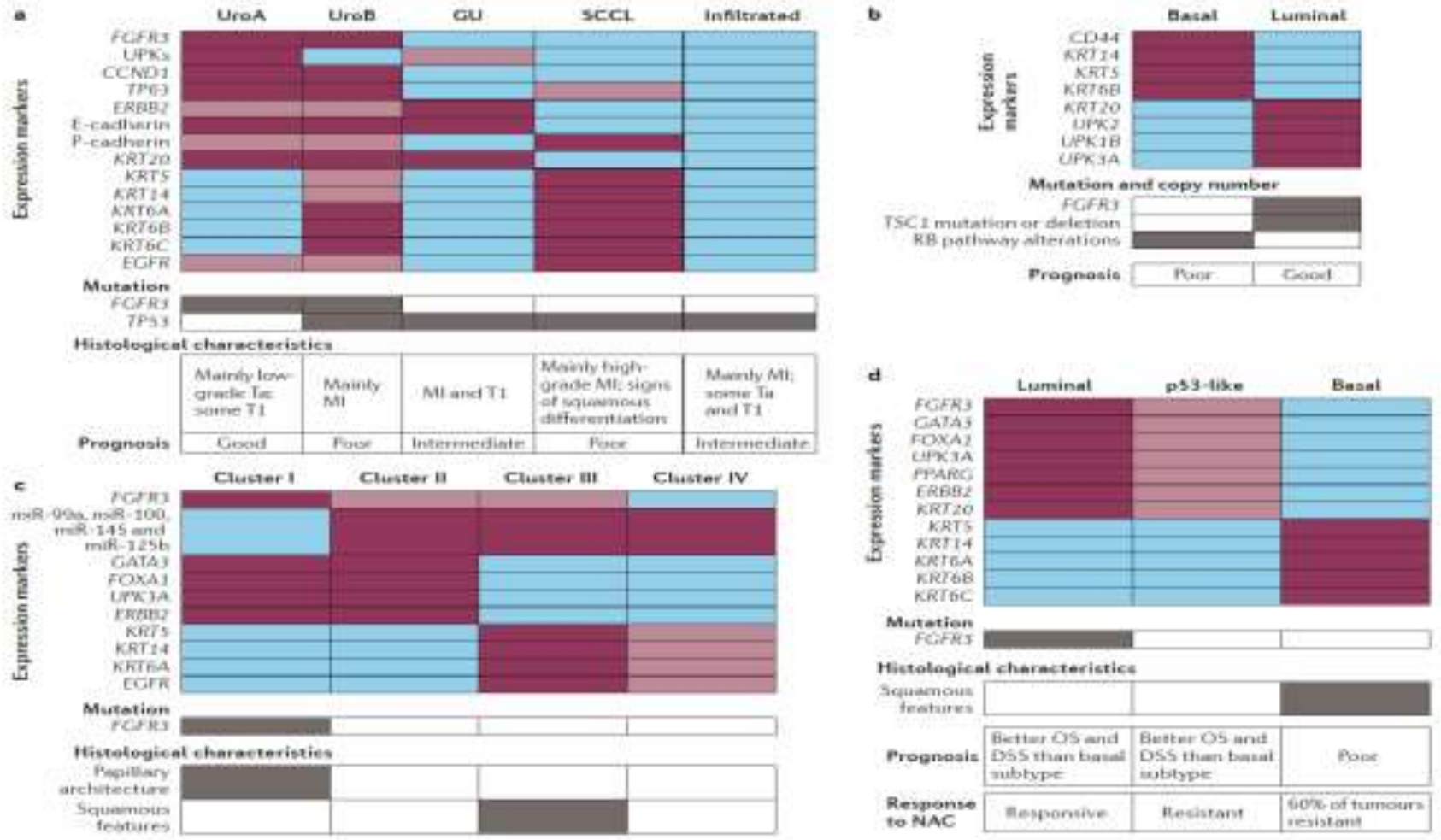


$P = 4.47 \times 10^{-4}$

These observations require validation in additional cohorts

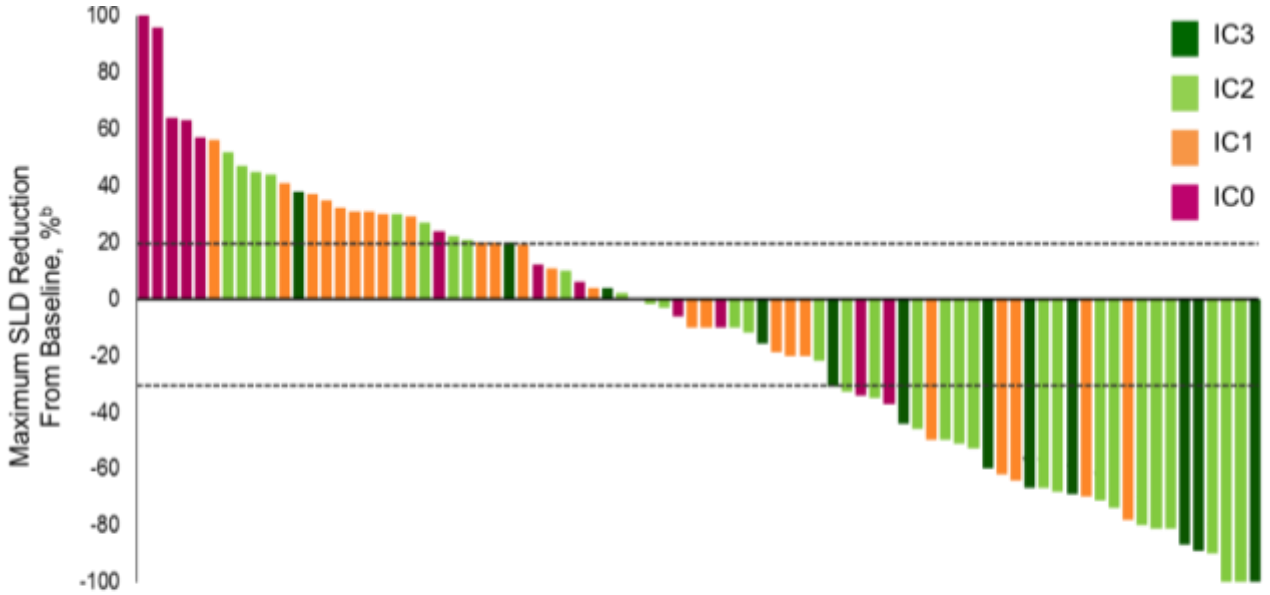
Comprehensive Molecular Characterization of Urothelial Bladder Carcinoma
The Cancer Genome Atlas Research Network




a
UroA
UroB
GU
SCCL
Infiltrated
Expression markers
FGFR3
UPKs
CCND1
TP63
ERBB2
E-cadherin
P-cadherin
KRT20
KRT5
KRT14
KRT6A
KRT6B
KRT6C
EGFR
Mutation
FGFR3
TP53
Histological characteristics
Mainly low-grade Ta; some T1
Mainly MI
MI and T1
Mainly high-grade MI; signs of squamous differentiation
Mainly MI; some Ta and T1
Prognosis
Good
Poor
Intermediate
Poor
Intermediate
b
Basal
Luminal
Expression markers
CD44
KRT14
KRT5
KRT6B
KRT20
UPK2
UPK1B
UPK3A
Mutation and copy number
FGFR3
TSC1 mutation or deletion
RB pathway alterations
Prognosis
Poor
Good
c
Cluster I
Cluster II
Cluster III
Cluster IV
Expression markers
FGFR3
miR-99a, miR-100, miR-145 and miR-125b
GATA3
FOXA1
UPK3A
ERBB2
KRT5
KRT14
KRT6A
EGFR
Mutation
FGFR3
Histological characteristics
Papillary architecture
Squamous features
d
Luminal
p53-like
Basal
Expression markers
FGFR3
GATA3
FOXA1
UPK3A
PPARG
ERBB2
KRT20
KRT5
KRT14
KRT6A
KRT6B
KRT6C
Mutation
FGFR3
Histological characteristics
Squamous features
Prognosis
Better OS and DSS than basal subtype
Better OS and DSS than basal subtype
Poor
Response to NAC
Responsive
Resistant
60% of tumours resistant

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

Jonathan E Rosenberg, Jean Hoffman-Censits, Tom Powles, Michiel S van der Heijden, Arjun V Balar, Andrea Necchi, Nancy Dawson, Peter H O'Donnell, Ani Balmanoukian, Yohann Loriot, Sandy Srinivas, Margitta M Retz, Petros Grivas, Richard W Joseph, Matthew D Galsky, Mark T Fleming, Daniel P Petrylak, Jose Luis Perez-Gracia, Howard A Burris, Daniel Castellano, Christina Canil, Joaquim Bellmunt, Dean Bajorin, Dorothee Nickles, Richard Bourgon, Garrett M Frampton, Na Cui, Sanjeev Mariathasan, Oyewale Abidoye, Gregg D Fine, Robert Dreicer



- Forty-four of 80 patients (55%) with post-baseline tumor assessments experienced a reduction in tumor burden
- Decreased circulating inflammatory marker (CRP) and tumor markers (CEA, CA-19-9) were also observed in patients responding to atezolizumab

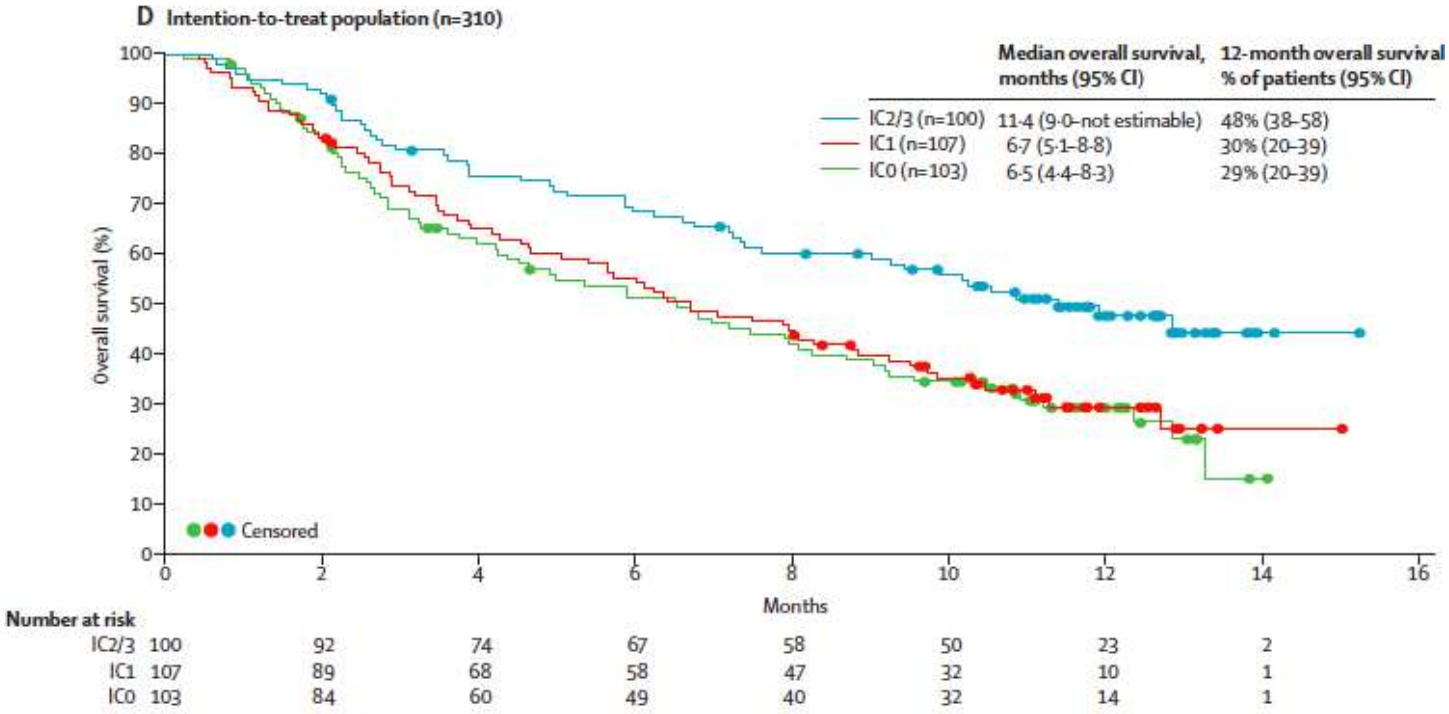
Rosemberg et al. Lancet, 2016

Atezolizumab (MPDL3280A): ORR in UBC by IC Status

PD-L1 IHC n = 87[b]	ORR (95% CI), %[a]		CR, n (%)		PR, n (%)	
IC3 (n = 12)	**67%** (35%-90%)	**50%** (35, 65)	4 (33%)	9 (20%)	4 (33%)	14 (30%)
IC2 (n = 34)	**44%** (27%-62%)		5 (15%)		10 (29%)	
IC1 (n = 26)	19% (7%-39%)	17% (7, 32)	-	-	5 (19%)	7 (17%)
IC0 (n = 15)	13% (2%-40%)		-		2 (13%)	

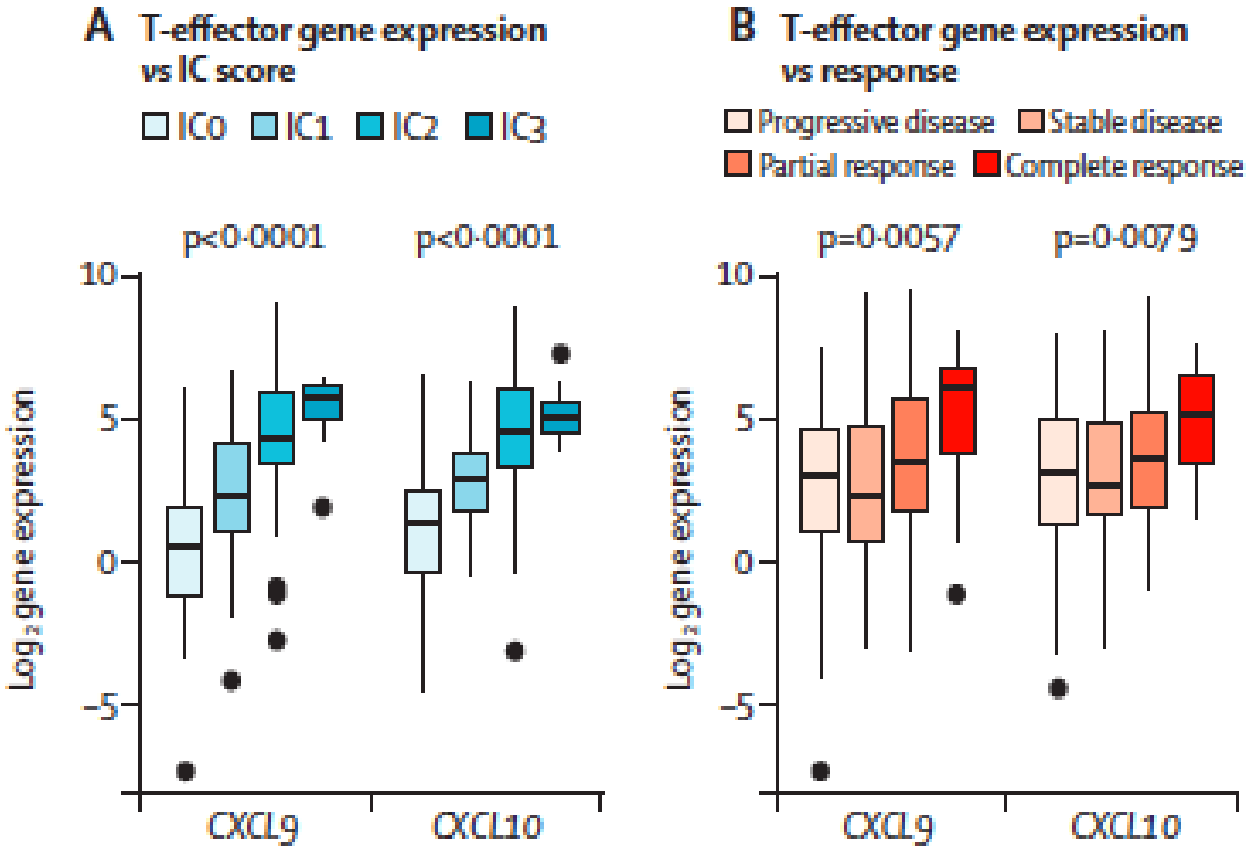
- Responses were observed all PD-L1 subgroups, with higher ORRs associated with higher PD-L1 expression in IC
- Responders also included patients with visceral metastases at baseline: 38% ORR (95% CI, 21%-56%) in 32 IC2/3 patients and 14% (95% CI, 5%-30%) ORR in 36 IC0/1 patients

Atezolizumab (MPDL3280A): Overall Survival

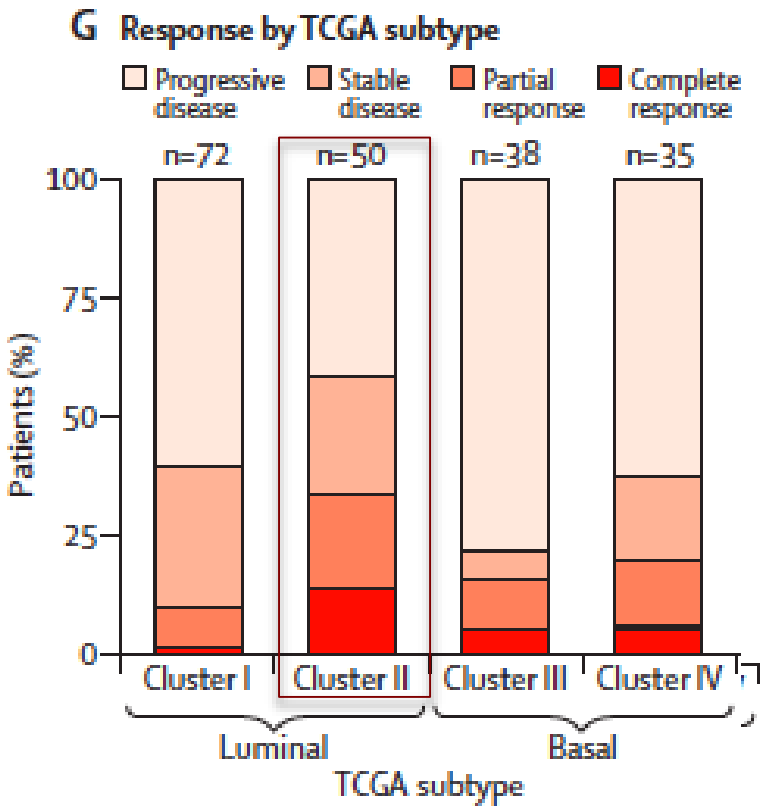


Rosemberg et al. Lancet, 2016

T-effector Gene Expression vs. PD-L1 Status or Response

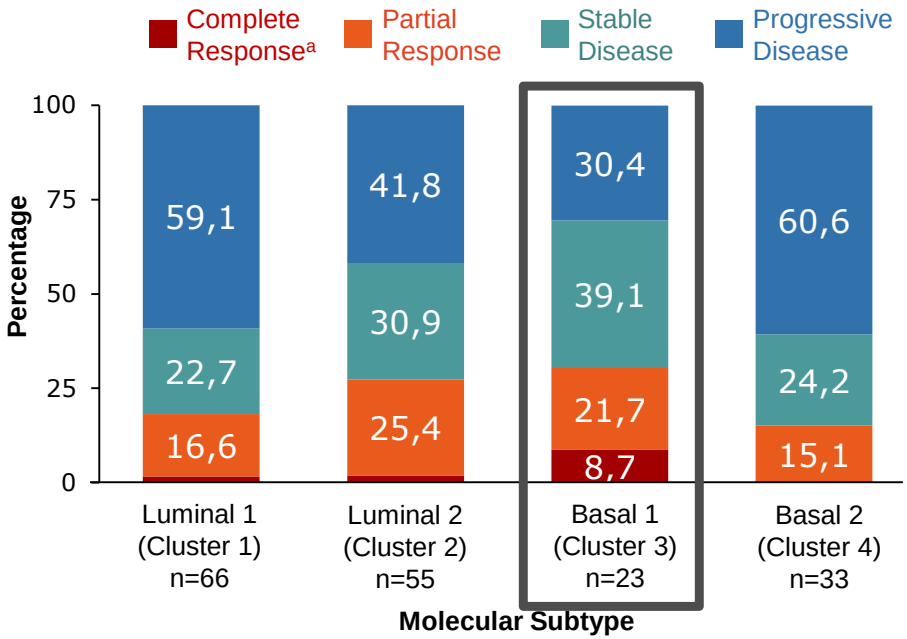


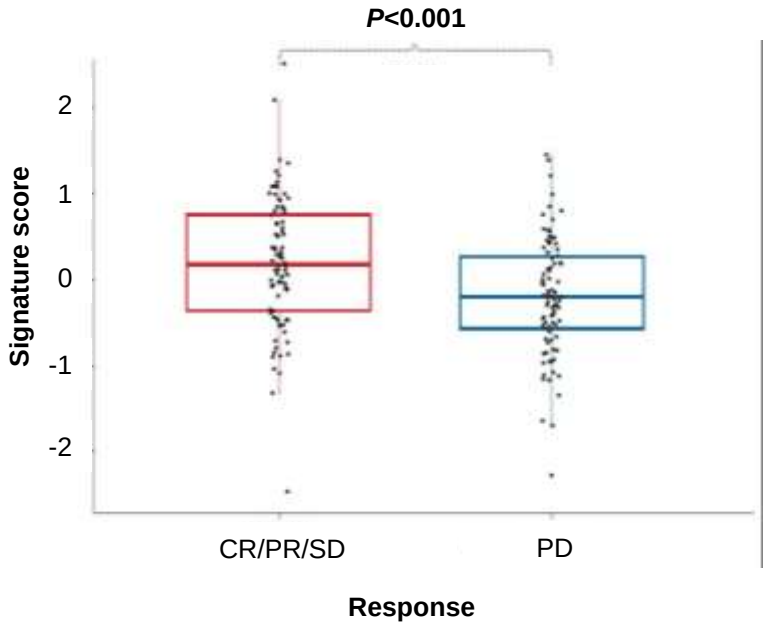
TCGA subtypes and Immunotherapy Outcome



Nivolumab: Association Between UC Molecular Subtype

- Basal 1 and luminal 2 have higher response rates vs the other 2 subtypes

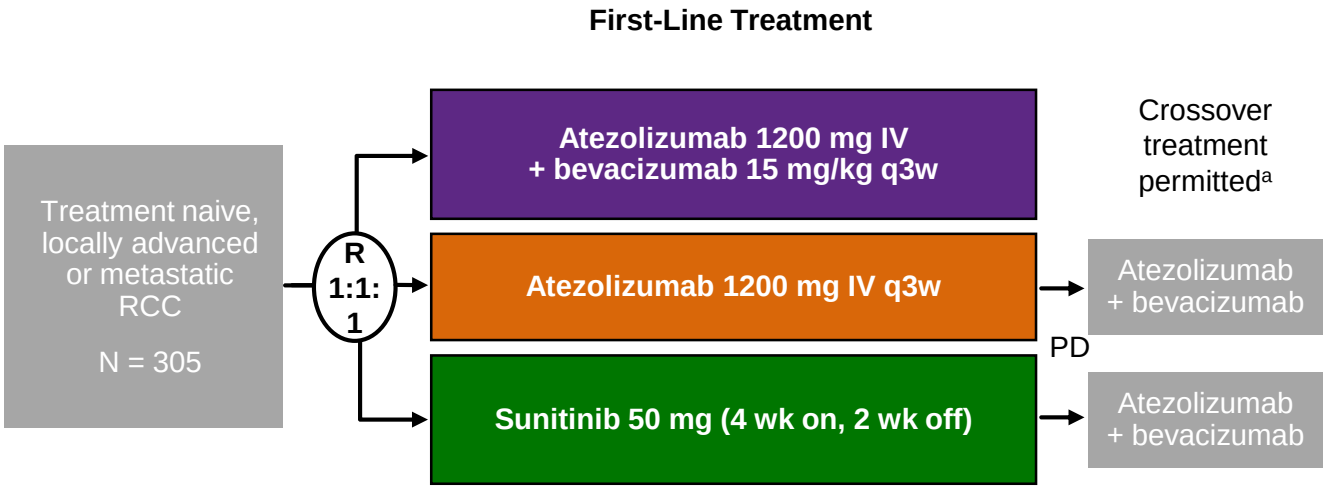




[a]Basal 2 CR, 0%; luminal 1 CR,1.5%; luminal 2 CR, 1.8%

Signature score, 25-gene interferon-γ signature expression

IMmotion150 (Phase II) Trial Design



- IMmotion150 was designed to be hypothesis generating and inform the Phase III study IMmotion151
- Coprimary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with ≥ 1% of IC expressing PD-L1
- Exploratory endpoints included interrogation of the association between outcome and TME gene signatures

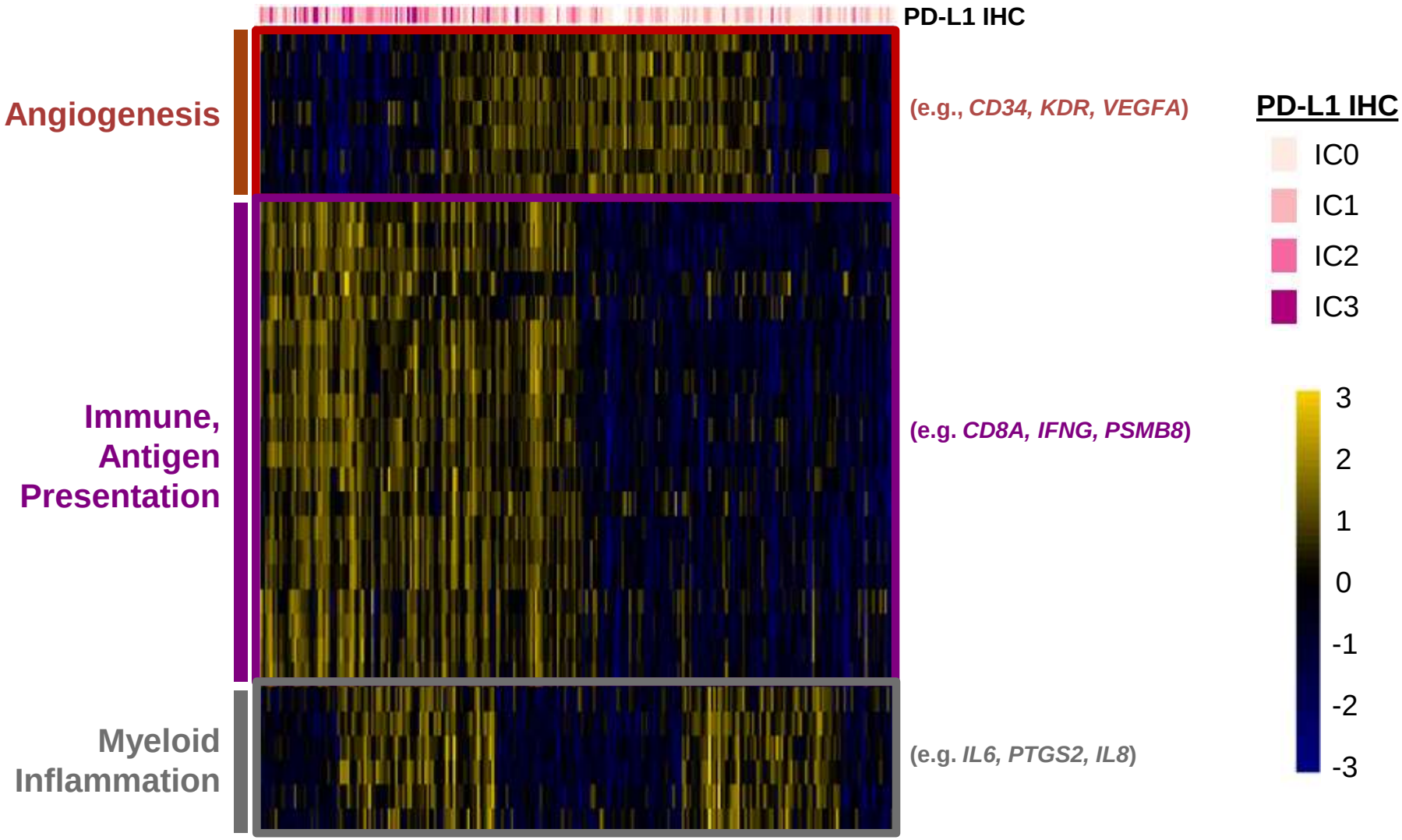
IC, tumor-infiltrating immune cells; IRF, independent review facility; ITT, intention-to-treat; TME, tumor microenvironment.

[a] Crossover from atezolizumab monotherapy not allowed in Europe.

McDermott, *JCO* 2016; McDermott, ASCO GU 2017.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors

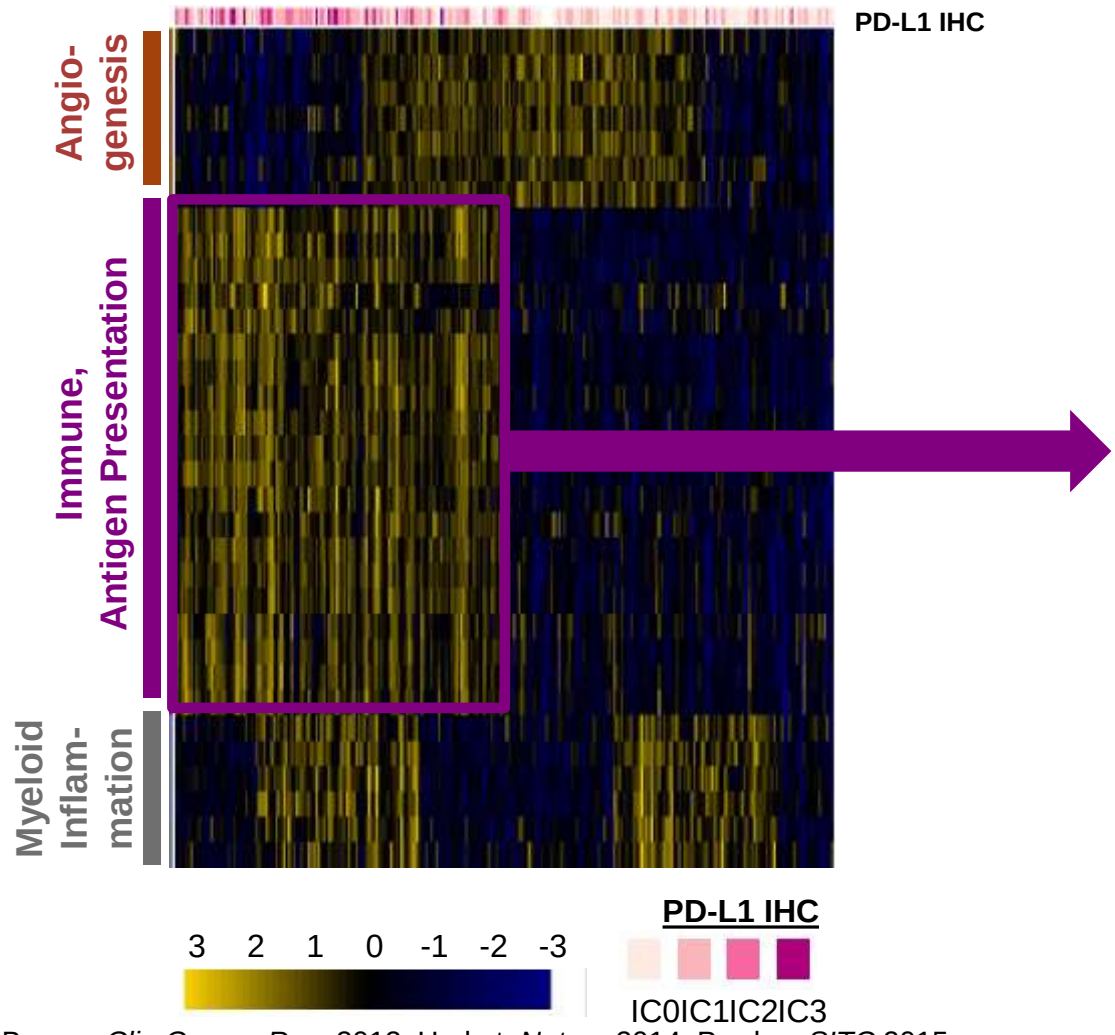


Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

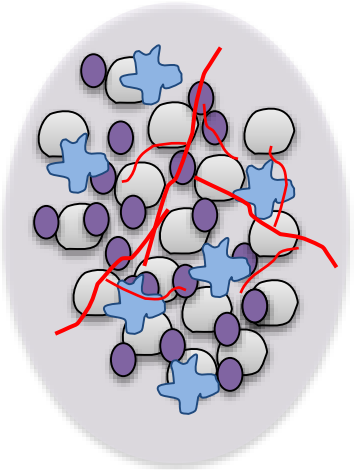
McDermott D, et al. IMmotion150 biomarkers: AACR 2017

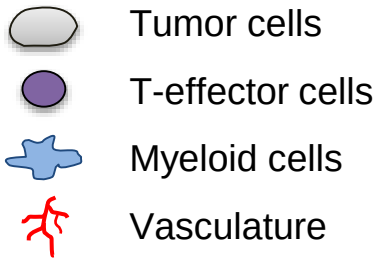
Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors

Immune



T-effector^{High}





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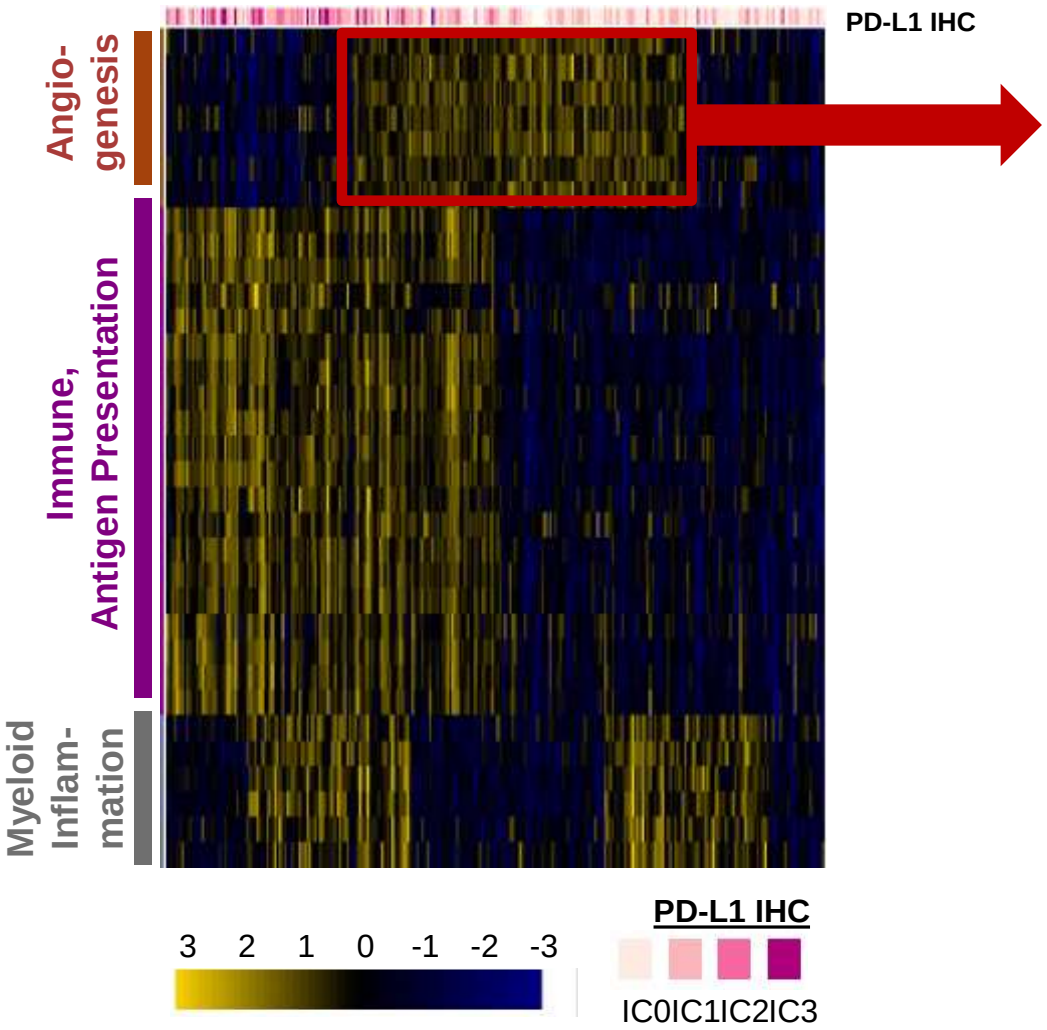
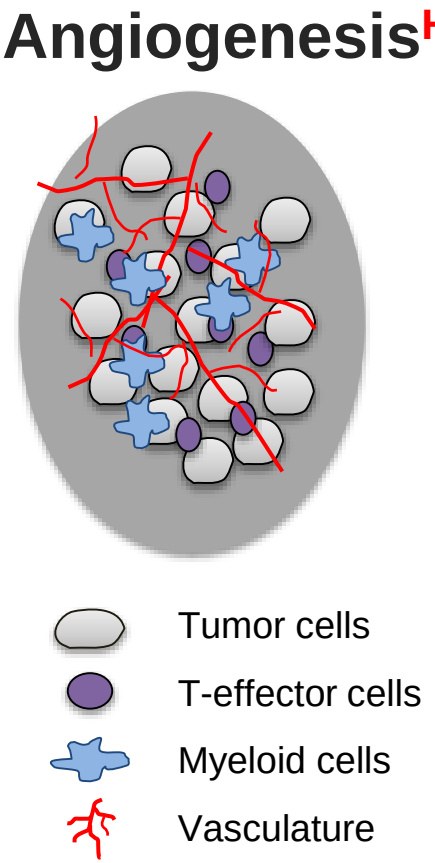
McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors

Angiogenesis



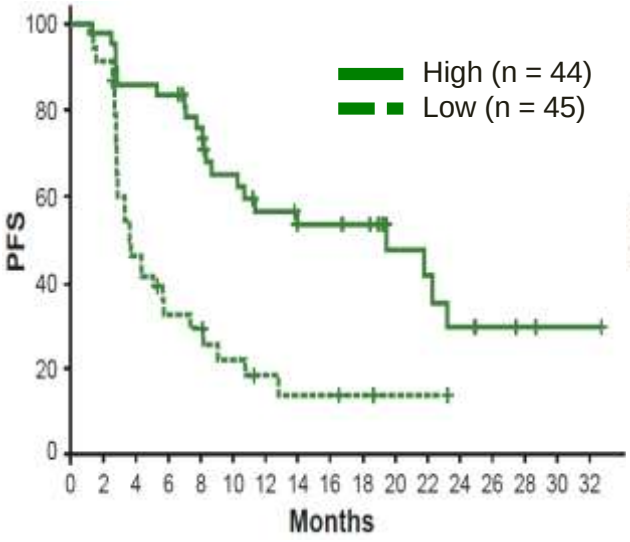
Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.



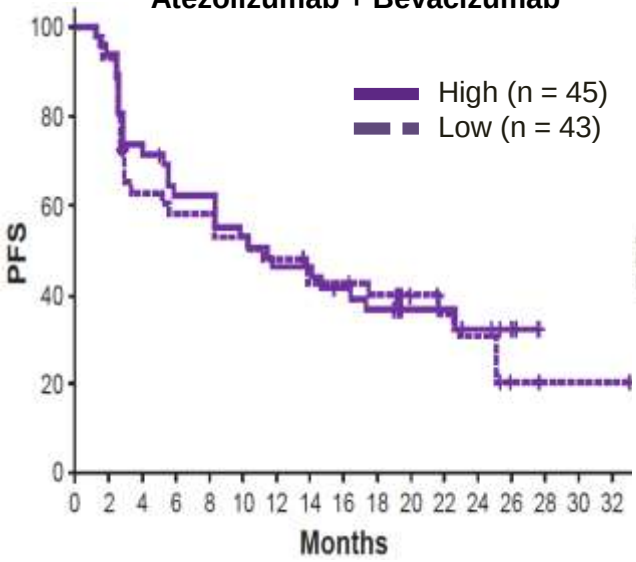
Sunitinib Demonstrated Improved PFS in Angiogenesis^{High} Subset vs Angiogenesis^{Low} Subset

Angiogenesis

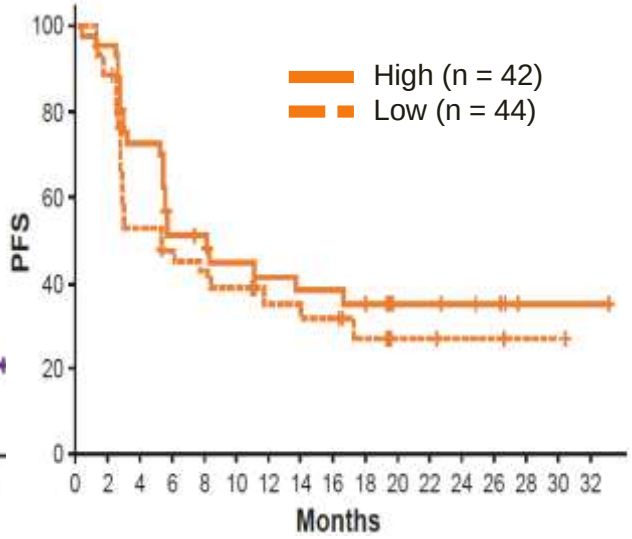
Sunitinib



Atezolizumab + Bevacizumab



Atezolizumab



Sunitinib		
	HR	95% CI
Angiogenesis (High vs Low)	0.31	(0.18, 0.55)

Atezolizumab + Bevacizumab		
	HR	95% CI
Angiogenesis (High vs Low)	0.90	(0.54, 1.51)

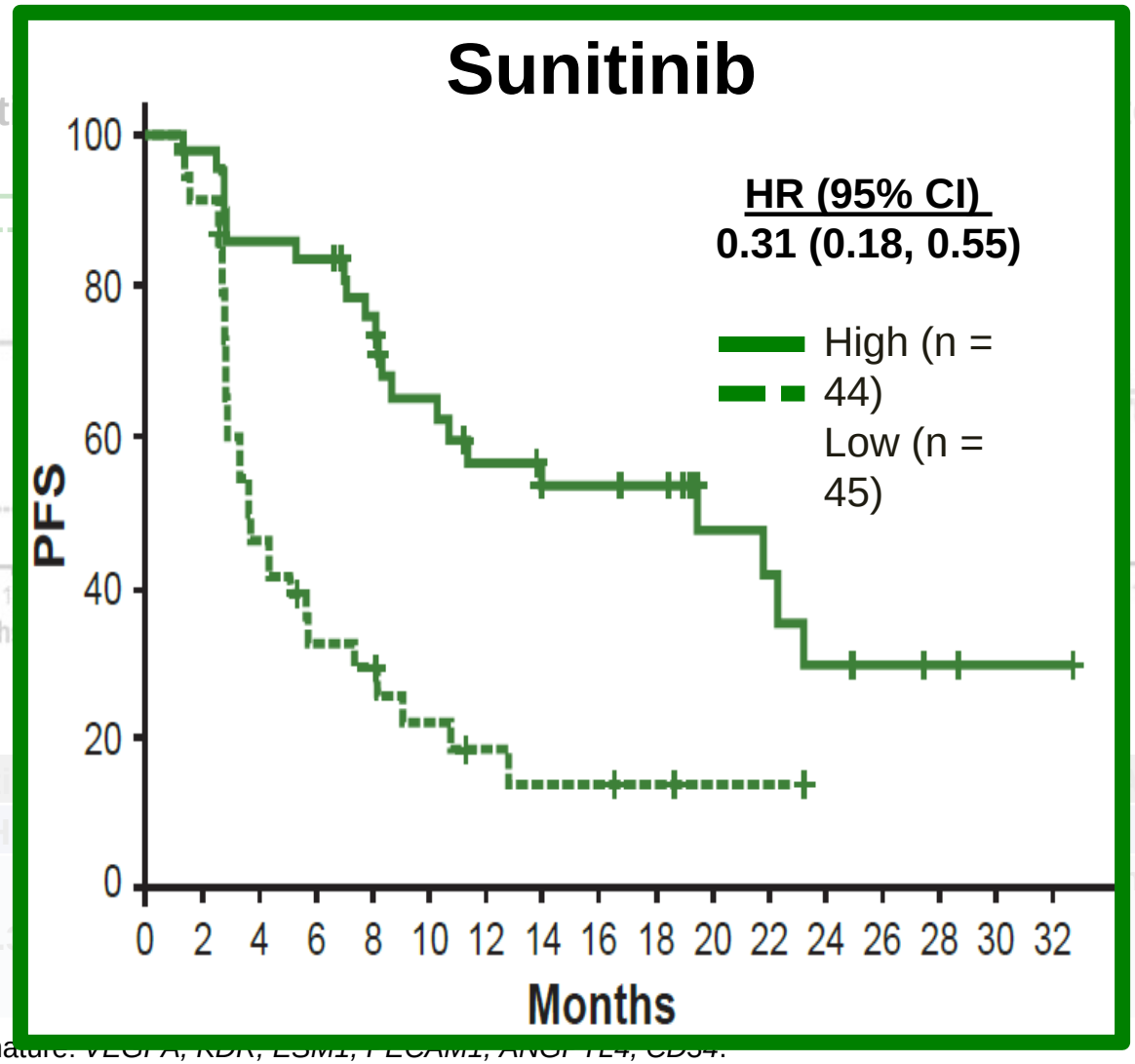
Atezolizumab		
	HR	95% CI
Angiogenesis (High vs Low)	0.74	(0.42, 1.28)

Angiogenesis gene signature: *VEGFA, KDR, ESM1, PECAM1, ANGPTL4, CD34*.
Angiogenesis High: ≥ median expression, Angiogenesis Low: < median expression.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Sunitinib Demonstrated Improved PFS in Angiogenesis^{High} Subset vs Angiogenesis^{Low} Subset

Angiogenesis



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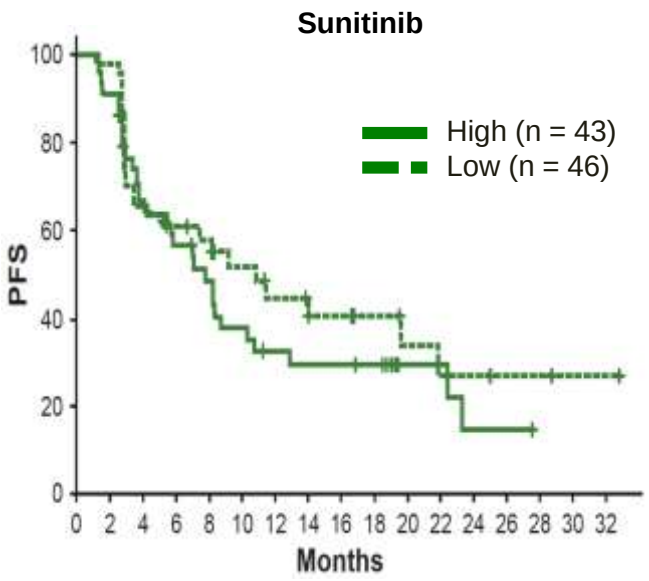
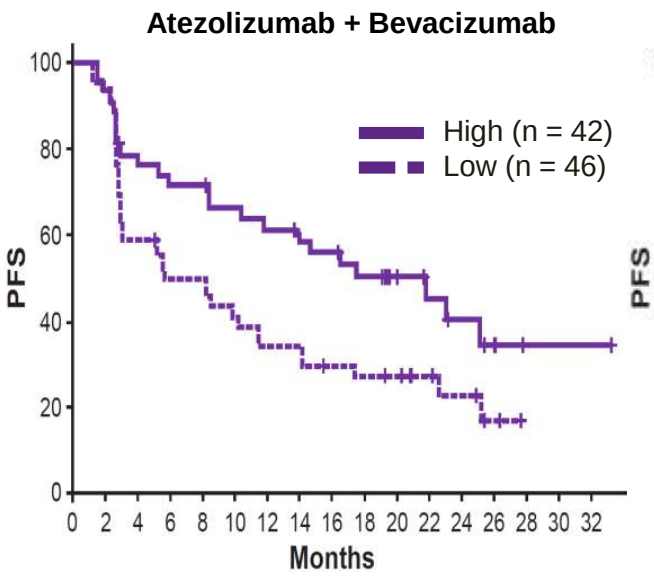
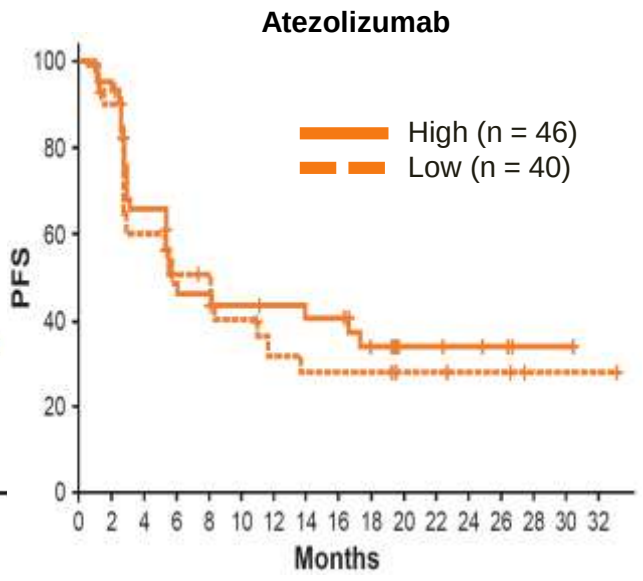
McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Atezolizumab and Bevacizumab Demonstrated Improved PFS in T-Effector^{High} Subset vs T-Effector^{Low} Subset

Immune







Sunitinib		
	HR	95% CI
T-effector (High vs Low)	1.31	(0.77, 2.23)

Atezolizumab + Bevacizumab		
	HR	95% CI
T-effector (High vs Low)	0.50	(0.30, 0.86)

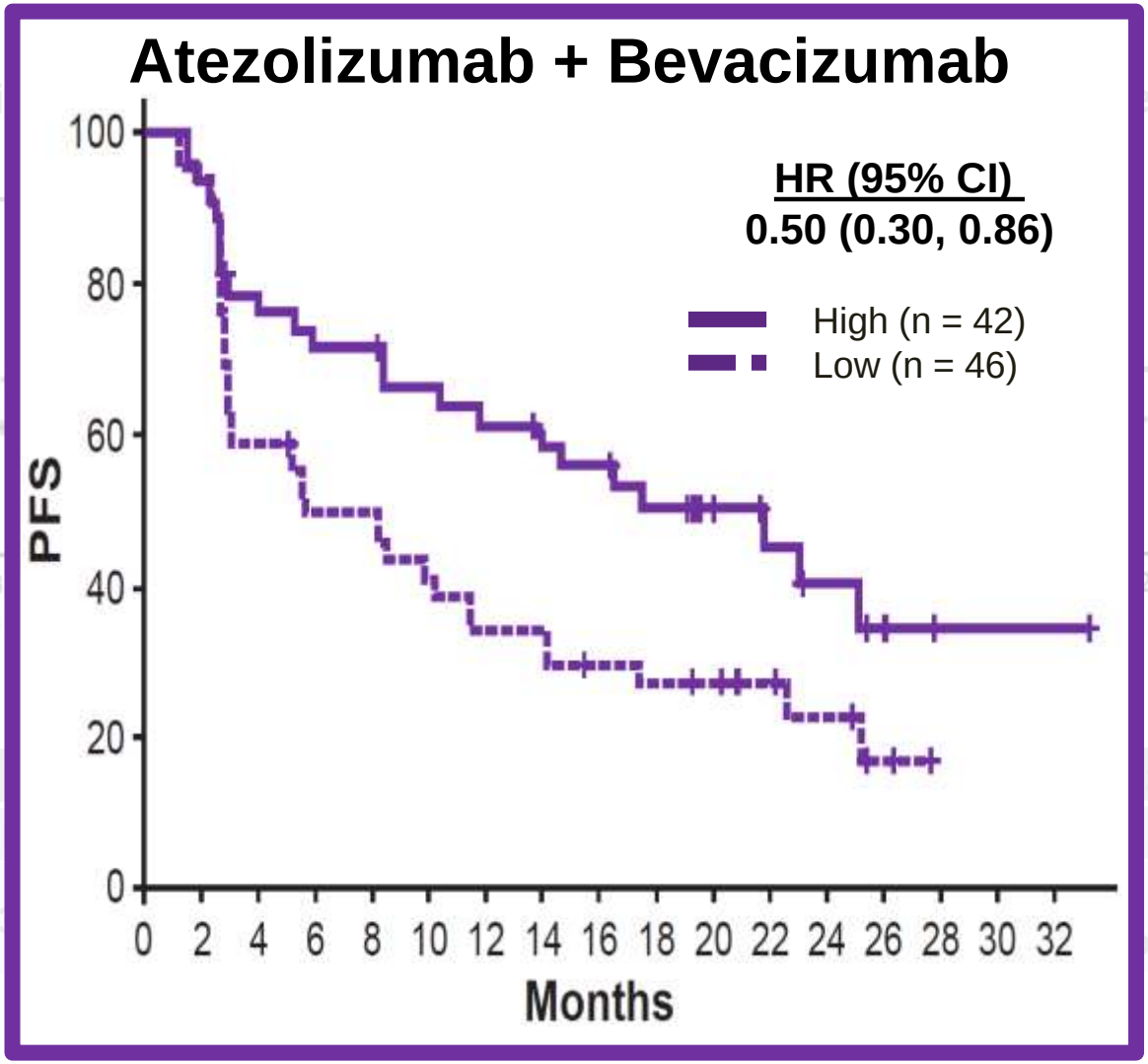
Atezolizumab		
	HR	95% CI
T-effector (High vs Low)	0.83	(0.48, 1.45)

T-effector gene signature: *CD8A, EOMES, PRF1, IFNG, CD274*.
T-effector High: ≥ median expression, T-effector Low: < median expression.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Atezolizumab and Bevacizumab Demonstrated Improved PFS in T-Effector^{High} Subset vs T-Effector^{Low} Subset

Immune



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T-effector High: ≥ median expression, T-effector Low: < median expression.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

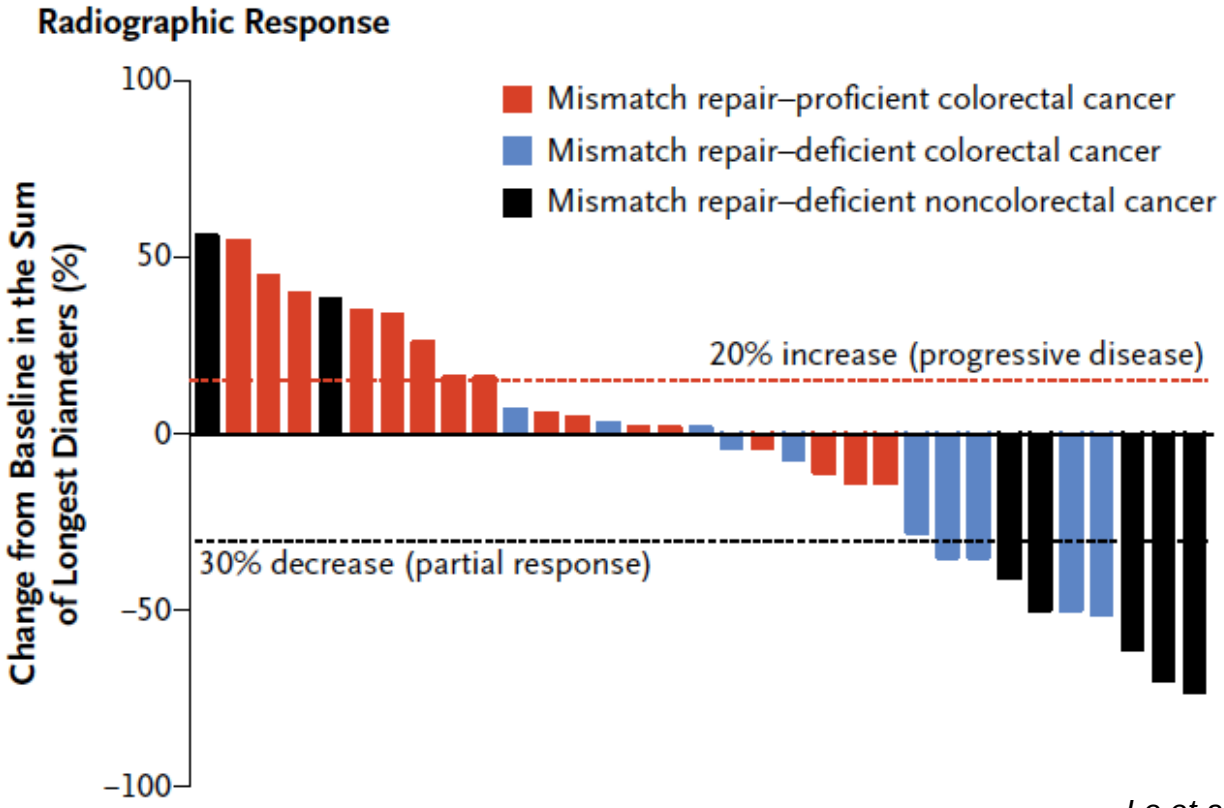
Mismatch Repair–Deficient Colorectal Cancer (N=11)	Mismatch Repair–Proficient Colorectal Cancer (N=21)	Mismatch Repair–Deficient Noncolorectal Cancer (N=9)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability

Le et al. NEJM, 2015

Table 2. Objective Responses According to RECIST Criteria.

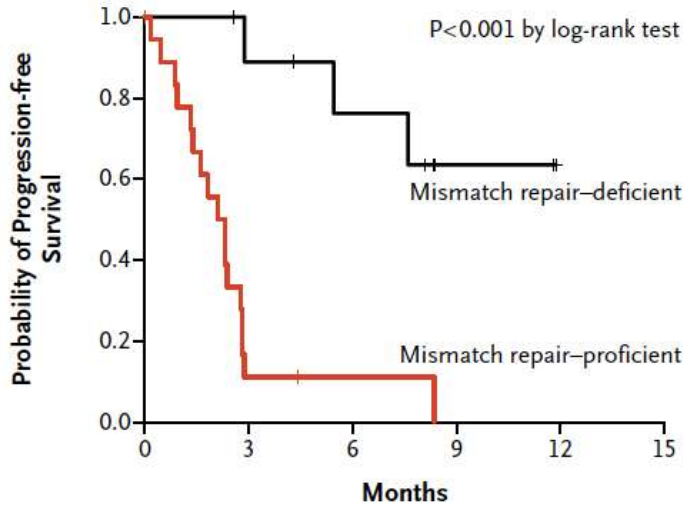
Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)



Le et al. NEJM, 2015

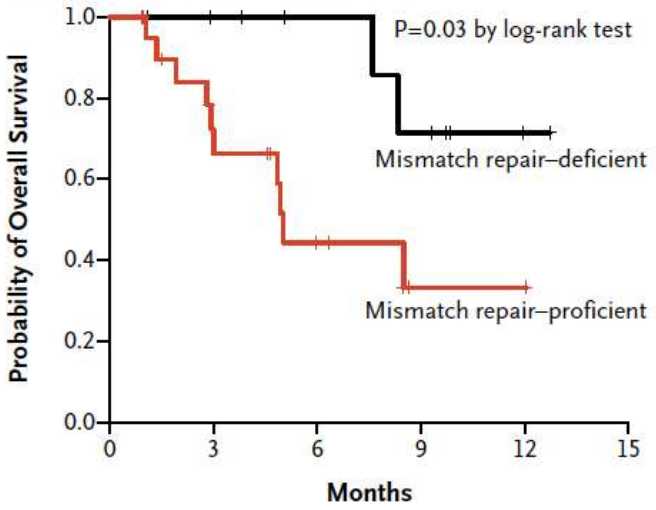
Clinical Benefit of Pembrolizumab according to MMR-deficiency status

Progression-free Survival in Cohorts with Colorectal Cancer



No. at Risk						
Mismatch repair–deficient	11	8	6	2	0	0
Mismatch repair–proficient	21	2	1	0	0	0

Overall Survival in Cohorts with Colorectal Cancer



No. at Risk						
Mismatch repair–deficient	11	9	7	5	1	0
Mismatch repair–proficient	21	12	5	1	1	0

1782 vs. 73 mutations per patient (p=0.007)

578 vs. 21 neoantigen-associated mutations

Le et al. NEJM, 2015

Clinical resistance to IO in melanoma (N=4)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 1, 2016 VOL. 375 NO. 9

Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

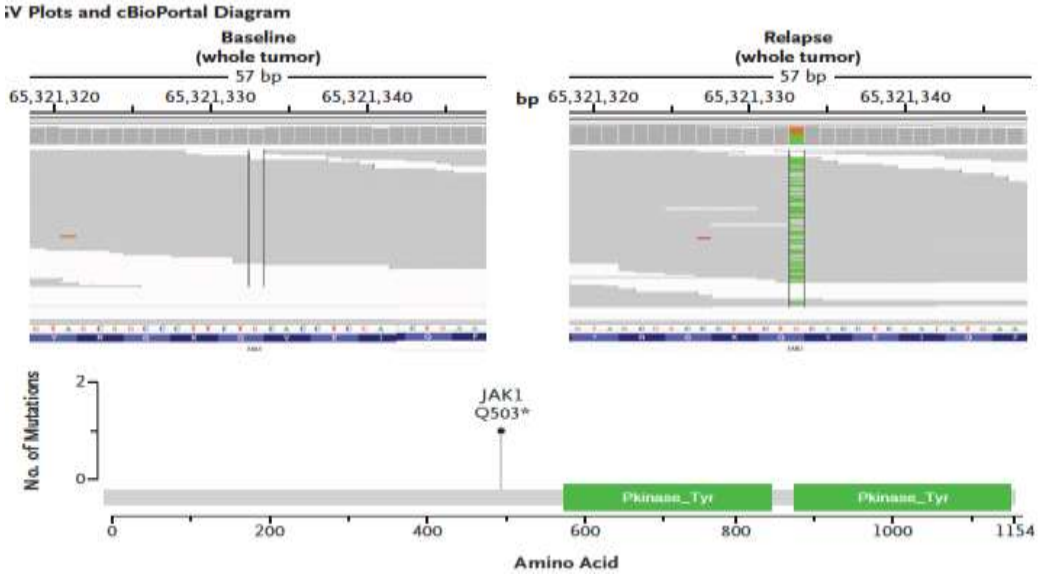
Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., Riccardo Mezzadra, M.Sc., Bartosz Chmielowski, M.D., Ph.D., Kathleen Ruchalski, M.D., I. Peter Shintaku, Ph.D., Phillip J. Sanchez, Ph.D., Cristina Puig-Saus, Ph.D., Grace Cherry, R.N., N.P., Elizabeth Seja, B.A., Xiangju Kong, M.Sc., Jia Pang, B.S., Beata Berent-Maoz, Ph.D., Begoña Comin-Anduix, Ph.D., Thomas G. Graeber, Ph.D., Paul C. Tumeh, M.D., Ton N.M. Schumacher, Ph.D., Roger S. Lo, M.D., Ph.D., and Antoni Ribas, M.D., Ph.D.

-*JAK1/2* LOF mutations:

=>Lack of response to IFN

-*B2M* truncating mutation:

=> Loss of MHC class I



Zaretsky JM, NEJM 2016

Hyper-Progression to Immunotherapy
(PD-1/PD-L1 inhibitors)

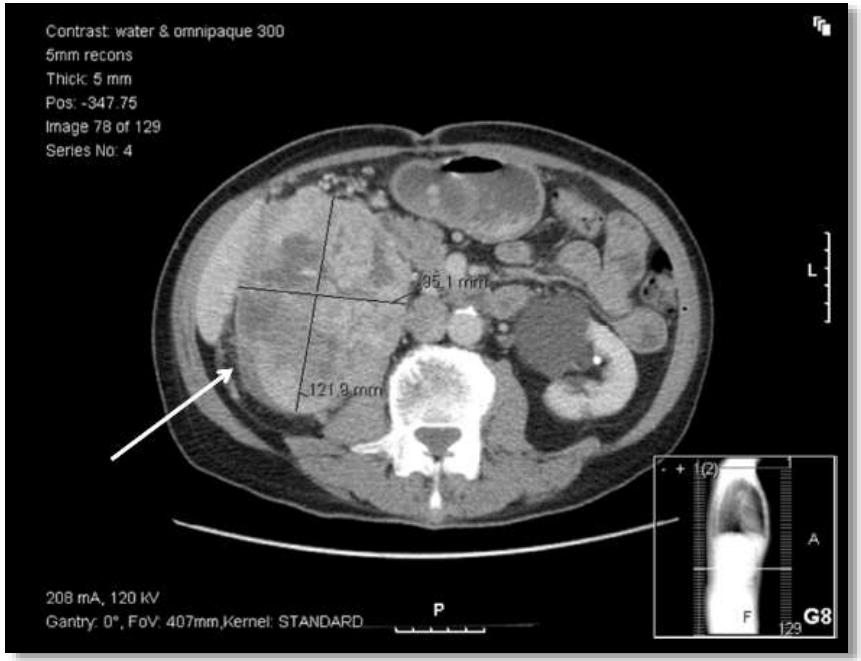
- **hyper-progression:**
  - Time-to-treatment failure (TTF) <2 months
  - >50% increase in tumor burden compared to pre-immunotherapy imaging
  - >2-fold increase in progression pace

MDM2 family amplification or **EGFR aberrations:** poor clinical outcome and significantly increased rate of tumor growth.

Kato et al. Clin Cancer Res. March 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10



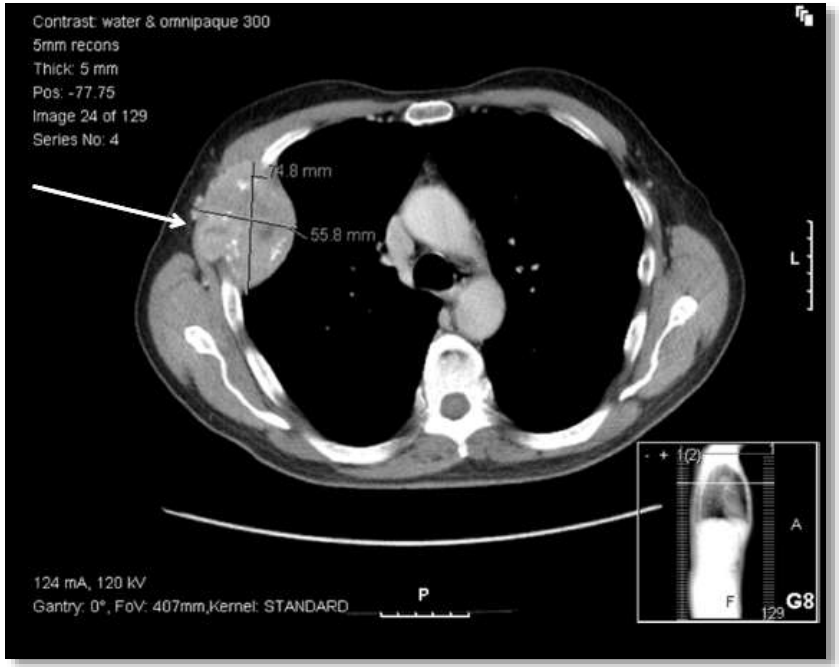
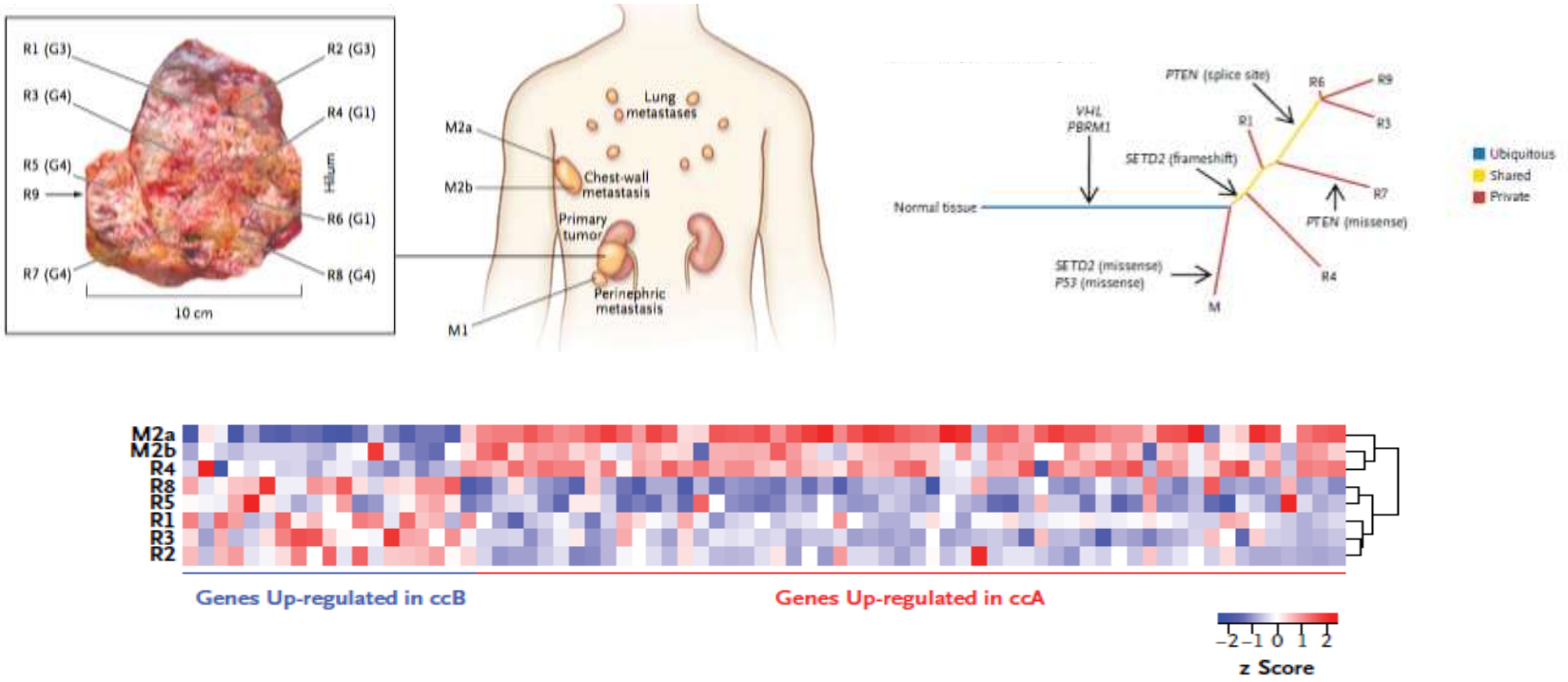


Image-guided (single) biopsies of large tumors might not be representative of an entire primary or metastatic site

Gerlinger M, et al. NEJM 366:883, 2012

Tumor-based Biomarkers Confounded by Intratumor Heterogeneity



- 63-69% of all mutations not detectable across regions in same tumor

Gerlinger et al. NEJM, 2012

Take Home Messages

- Immune-checkpoint blockers are redefining the field of oncology:
- “Precision Immuno-Oncology” is an open field:
  - PD1/PD-L1 expression
  - Tumor infiltrating lymphocytes
  - Tumor Mutation Burden (TMB) / neoantigen load
  - Tetrapeptide neoepitopes
  - Loss of function JAK1/2 alterations (interferon unresponsiveness)
  - Loss of function B2M alterations (MCH/I presentation)
  - Hyper-progressors
  - Biomarkers for treatment selection is crucial
  - Sequential biopsies in responders with secondary resistance

PUCRS

ESCOLA DE MEDICINA

Biomarcadores em Imuno-Oncologia

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