Immunotherapy of Renal and Urothelial Cancer: Evolution of Treatment.

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Disclosures

- Consulting Fees:
  - BMS, Genentech
- Contracted Research:
  - BMS, Corvus, Curis, Genentech

- I will be discussing non-FDA approved indications during my presentation.

Kidney Cancer: Epidemiology

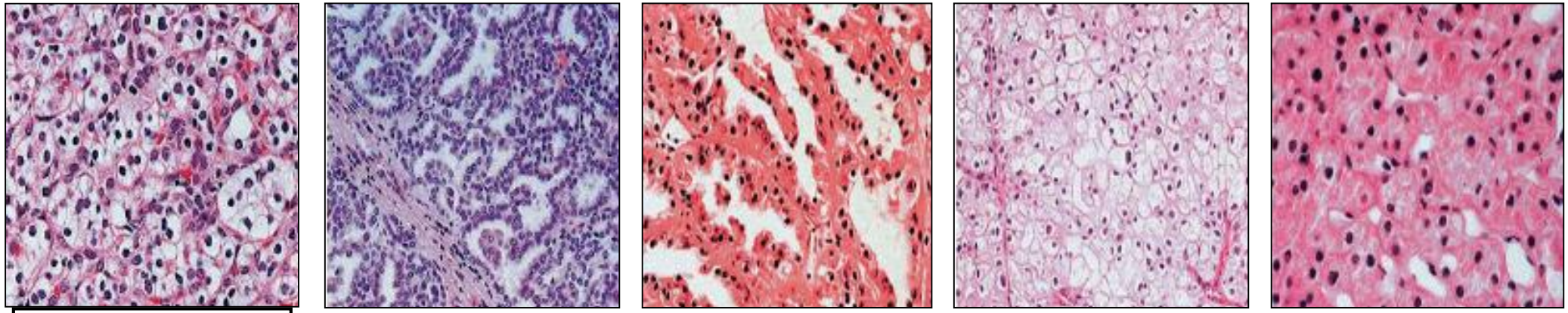
- U.S. New cases/deaths* 80,476/17,600
- % of all cancers/ deaths 2.5% / 2%
- Male predominance 3:2
- Median age ~60
- Smoking and obesity are known risk factors
- Incidental findings increasing
- Stage: local 60-70%
  regional 5-10%
  metastatic 15-20%

40% will eventually develop Stage IV disease

*American Cancer Society, 2019

Not all Kidney Cancer is the same

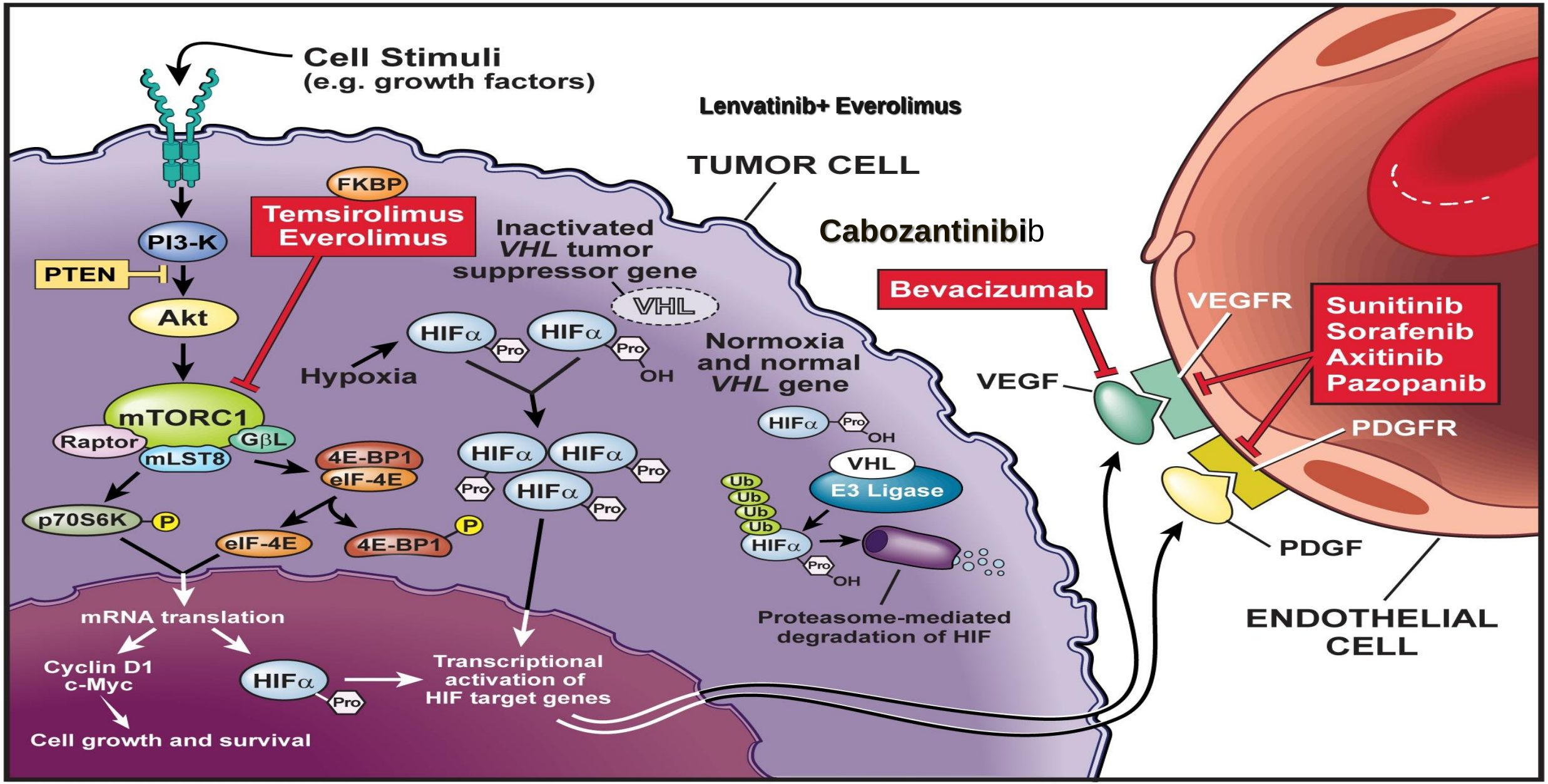
RCC



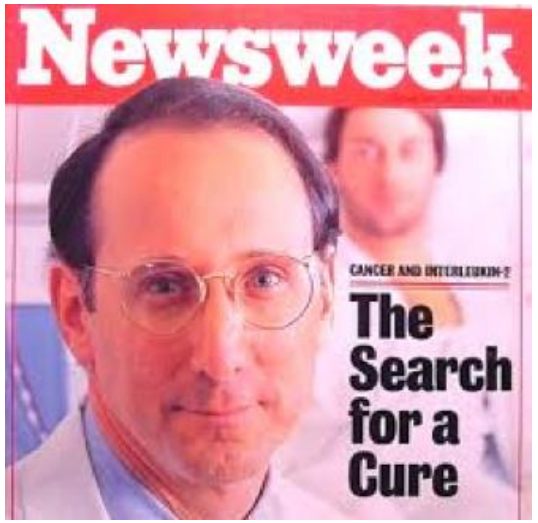
Type	**Clear**	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Incidence (%)	***75%***	*5%*	*10%*	*5%*	*5%*
Associated mutations	***VHL***	*c-Met*	*FH*	*BHD*	*BHD*

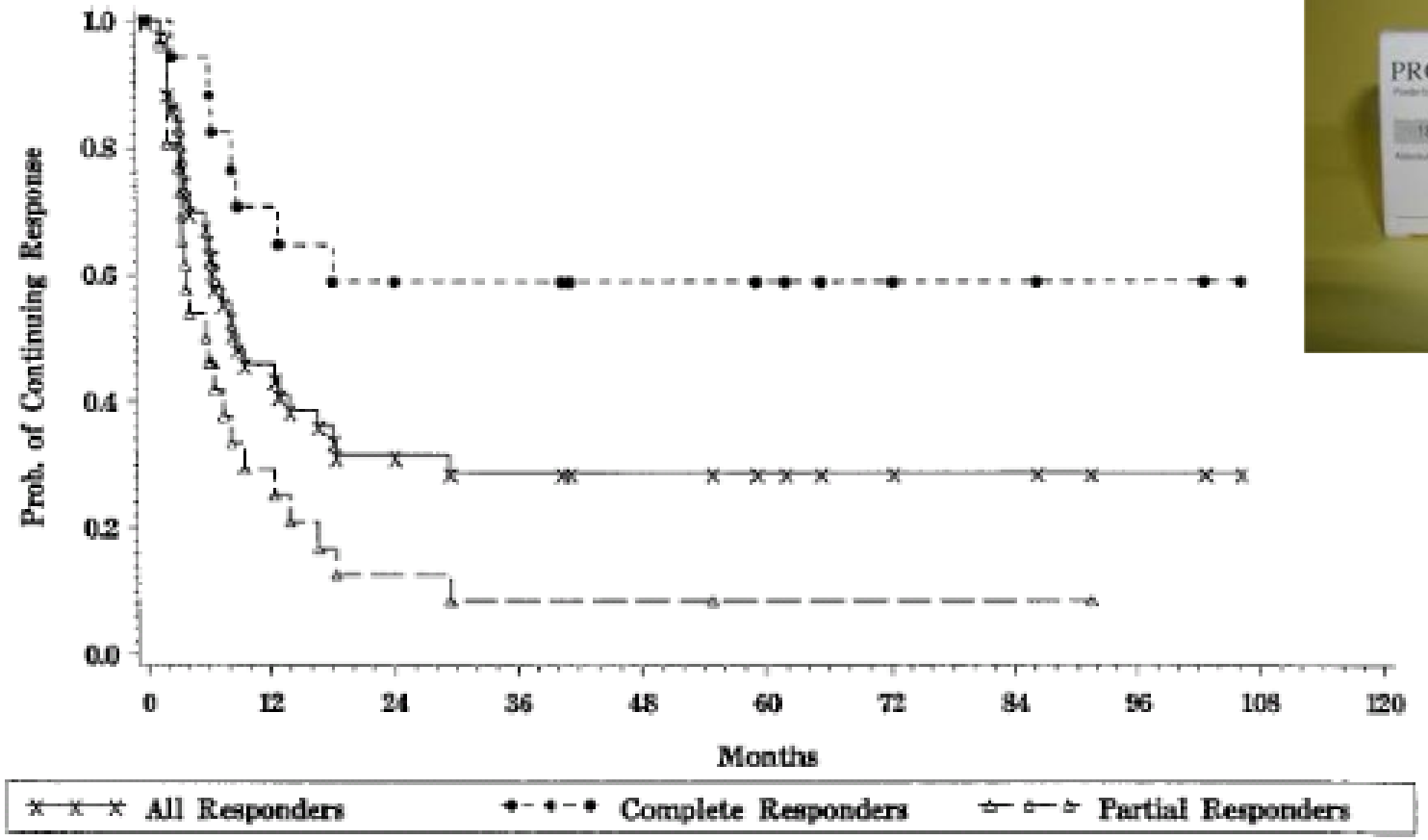
BHD=Birt-Hogg-Dubé, FH=fumarate hydratase, VHL=von Hippel-Lindau.

Modified from Linehan WM et al. *J Urol*. 2003;170:2163-2172.


Cell Stimuli
(e.g. growth factors)
Lenvatinib+ Everolimus
TUMOR CELL
FKBP
Temsirolimus
Everolimus
PI3-K
PTEN
Akt
mTORC1
Raptor
GβL
mLST8
4E-BP1
eIF-4E
p70S6K
P
eIF-4E
4E-BP1
P
mRNA translation
Cyclin D1
c-Myc
Cell growth and survival
HIFα
Pro
Transcriptional
activation of
HIF target genes
Inactivated
VHL tumor
suppressor gene
VHL
Hypoxia
HIFα
Pro
HIFα
Pro
OH
Normoxia
and normal
VHL gene
HIFα
Pro
OH
VHL
E3 Ligase
Ub
Ub
Ub
Ub
HIFα
Pro
OH
Proteasome-mediated
degradation of HIF
Cabozantinibib
Bevacizumab
VEGF
VEGFR
Sunitinib
Sorafenib
Axitinib
Pazopanib
PDGFR
PDGF
ENDOTHELIAL
CELL

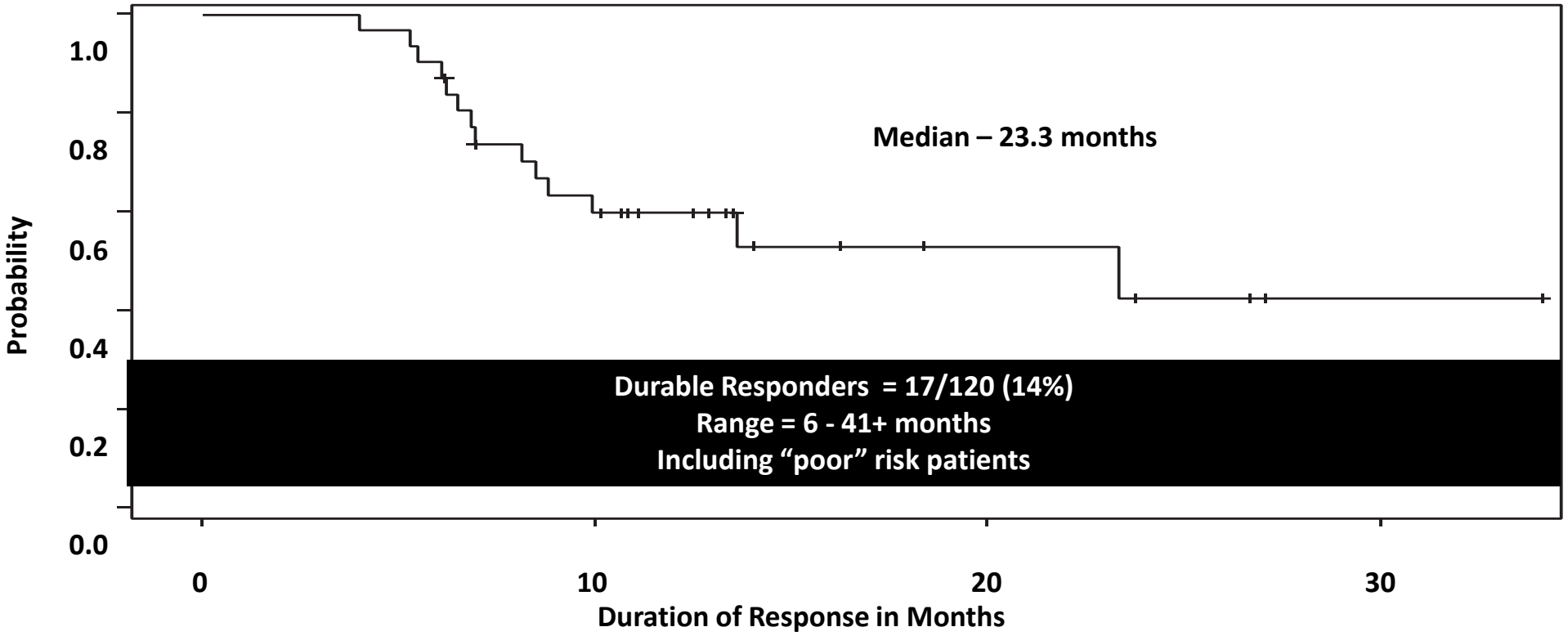
Proof of Principle: Remission is Possible





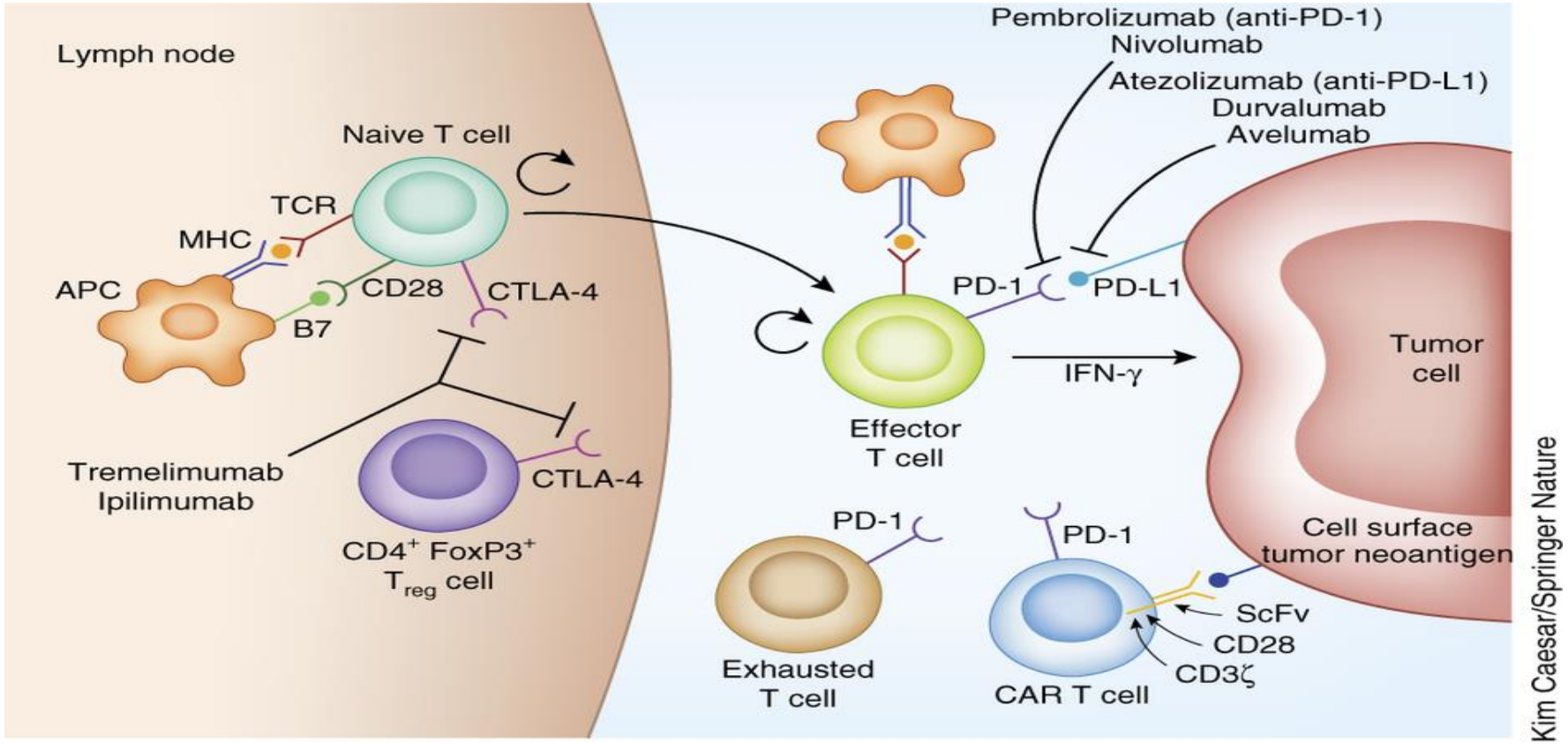
Atkins et al. J Clin Oncol. 1999

High dose Interleukin-2 (IL-2) can induce durable responses



- 15-20% Objective response rate, **5-7% durable CRs**
- Significant toxicity: better selection criteria imperative

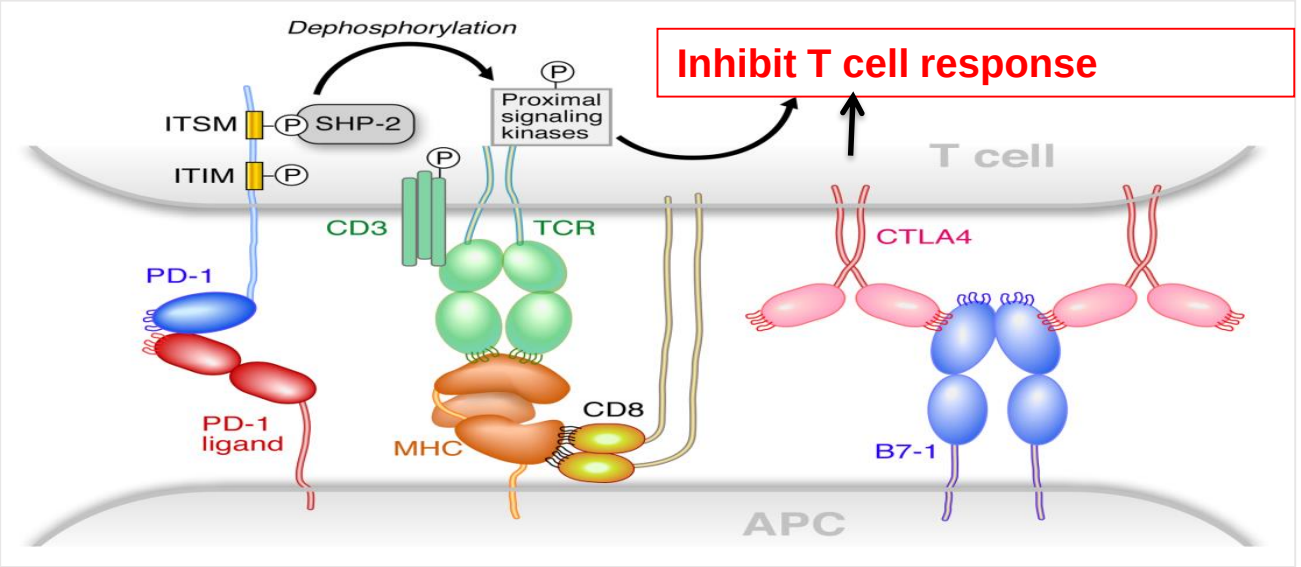
CTLA-4 and PD-1 Checkpoint Blockade



June et.al , Nature Med, 2017

Immune Checkpoint Blockade: Discovery to Translatio

Anti-CTLA-4 mAbs	
B7/CTLA-4 biology	1993
First-into-human trial	2000
Combination with cancer vaccines	2008
Immune response criteria	2009
Pivotal Phase III study	2010
Durability of response	2013



Anti-PD-1/PD-L1 mAbs	
Pathway identification and biology	2000 -
Clinical testing in over 30 tumor types	2012 -
Combination therapies	2013 -

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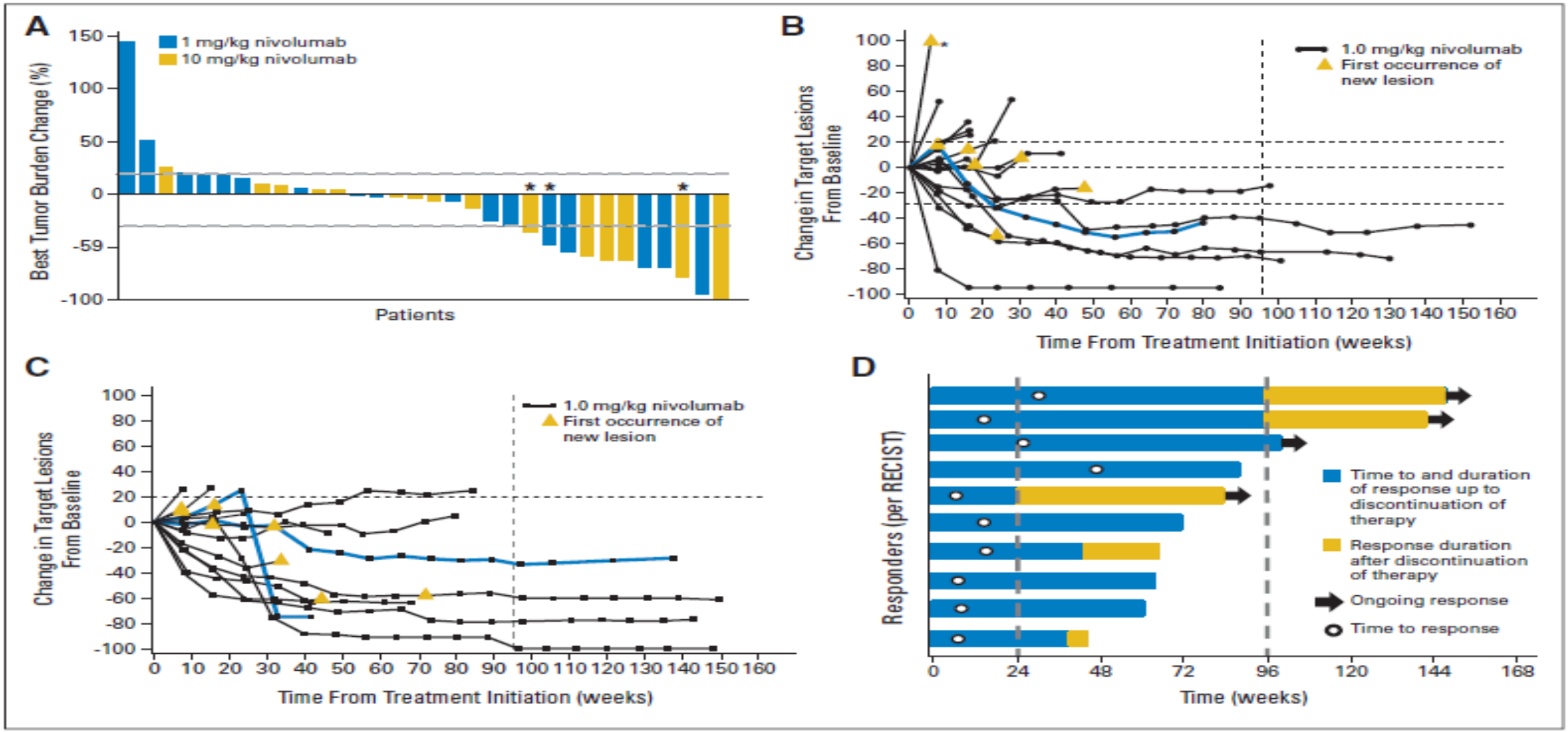
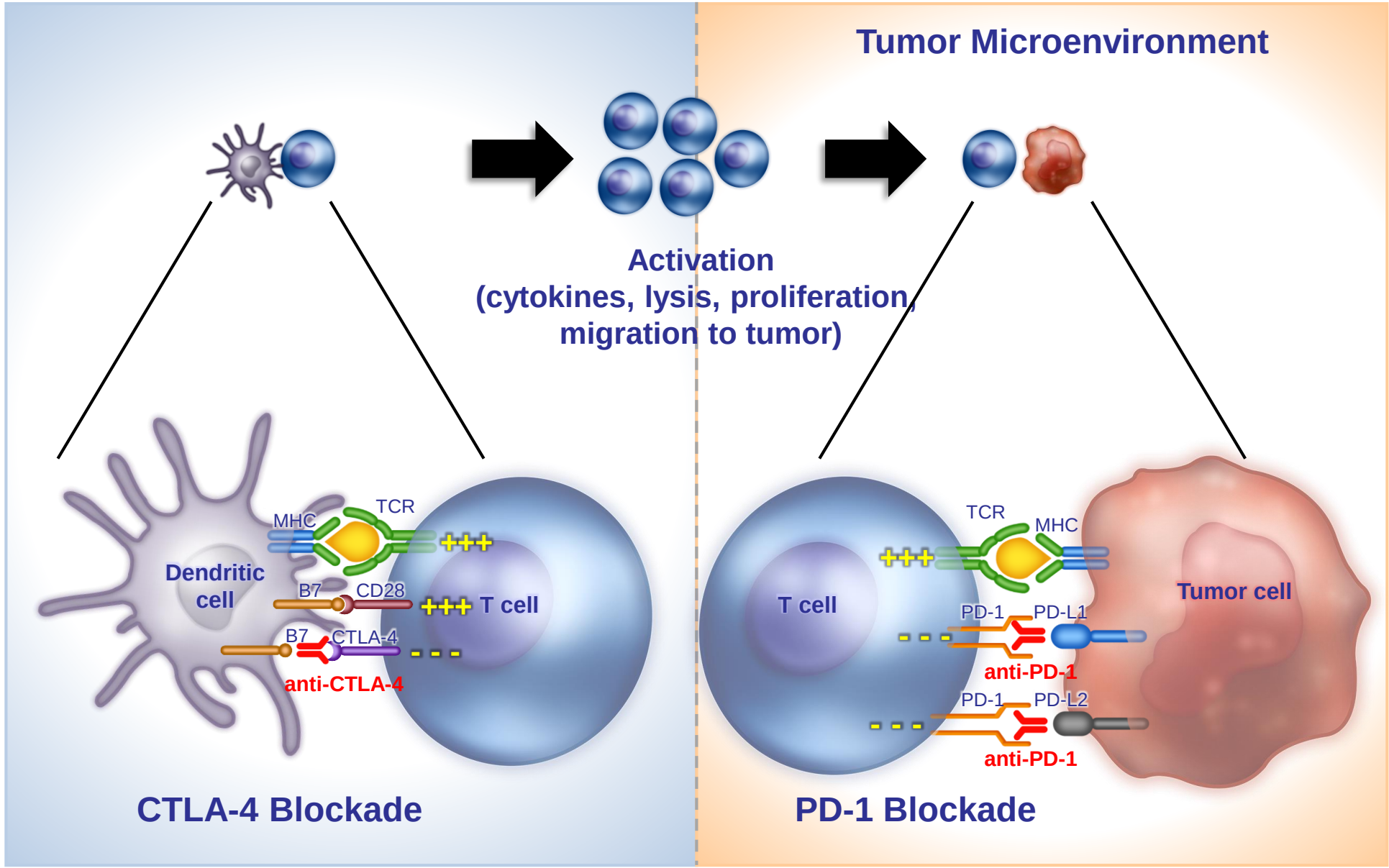


McDermott et al, JCO 2015

Blocking CTLA-4 and PD-1



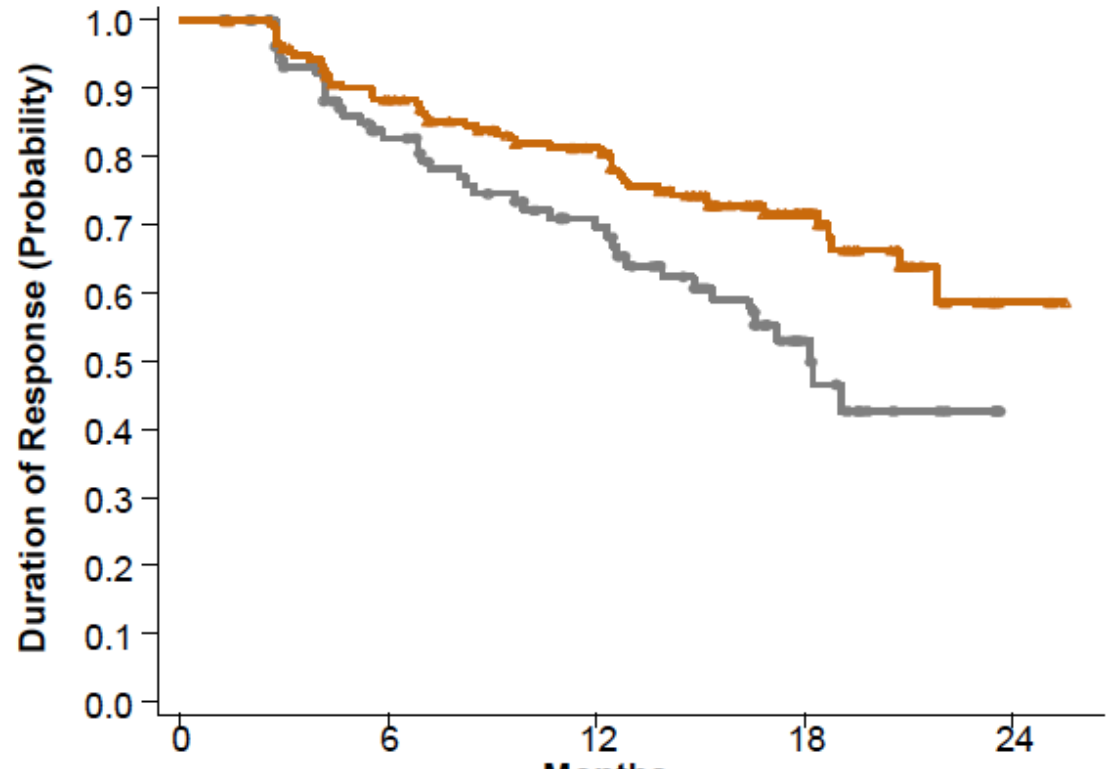
Rationale for Ipilimumab plus Nivolumab in Advanced RCC

- Nivolumab is a PD-1 inhibitor approved for previously treated advanced (a) RCC
- Nivolumab + ipilimumab (CTLA-4 antibody) combination therapy (NIVO + IPI) has shown manageable safety and high antitumor activity in previously treated and treatment-naïve patients with aRCC in the phase Ib CheckMate 016 study[1]
  - ORR: 40%
  - Ongoing responses: 42%
  - Median PFS: 7.7 months
  - 2-year OS rate: 67%
- We report the first results from the phase III CheckMate 214 study of NIVO + IPI versus sunitinib (SUN) for treatment-naïve aRCC

ORR and DOR: IMDC intermediate/poor risk

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42 (37–47)**	**27 (22–31)**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	**9[b]**	**1[b]**
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12

	Median duration of response, months (95% CI)	Patients with ongoing response, %
NIVO + IPI	NR (21.8–NE)	72
SUN	18.2 (14.8–NE)	63



No. at Risk					
NIVO + IPI	177	146	120	55	3
SUN	112	75	52	17	0

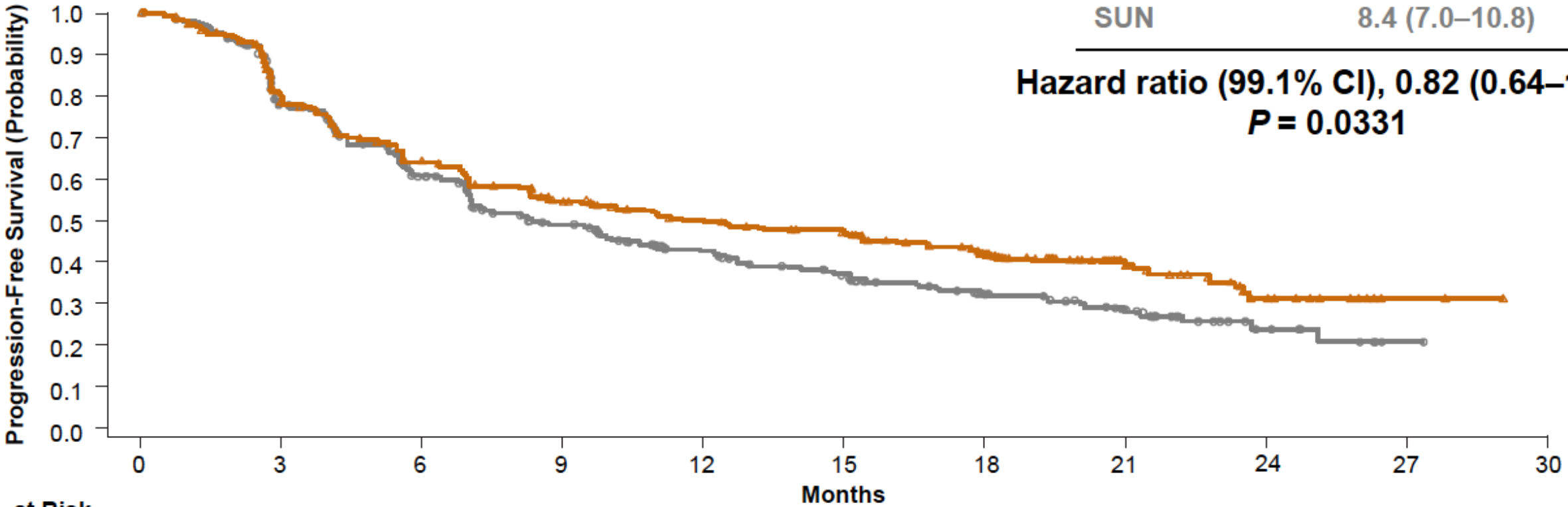
MADRID 2017 ESMO congress

[a]IRRC-assessed ORR and BOR by RECIST v1.1; [b]*P* < 0.0001

PFS per IRRC: IMDC intermediate/poor risk

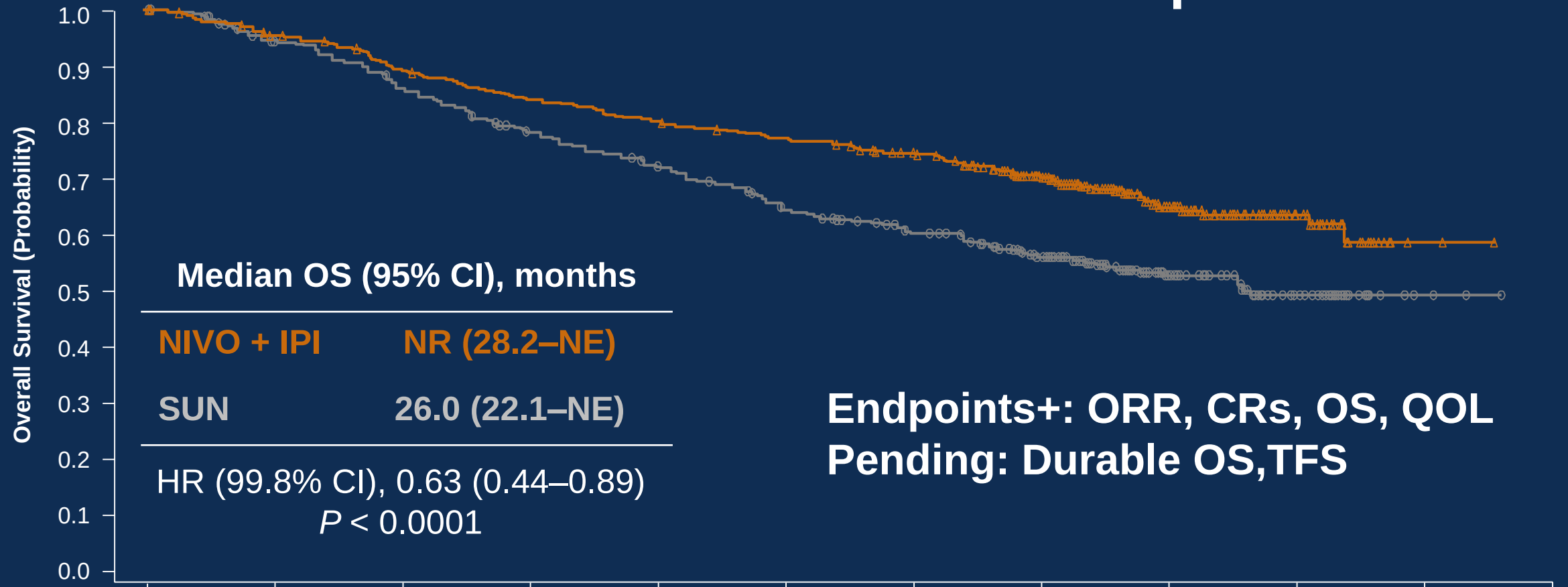
Median PFS, months (95% CI)	
NIVO + IPI	11.6 (8.7–15.5)
SUN	8.4 (7.0–10.8)

Hazard ratio (99.1% CI), 0.82 (0.64–1.05)
***P* = 0.0331**



No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

PD-1 + CTLA-4 Blockade (CM-214)
Overall Survival: IMDC intermediate/poor risk



Median OS (95% CI), months

NIVO + IPI	NR (28.2–NE)
SUN	26.0 (22.1–NE)

HR (99.8% CI), 0.63 (0.44–0.89)
P < 0.0001

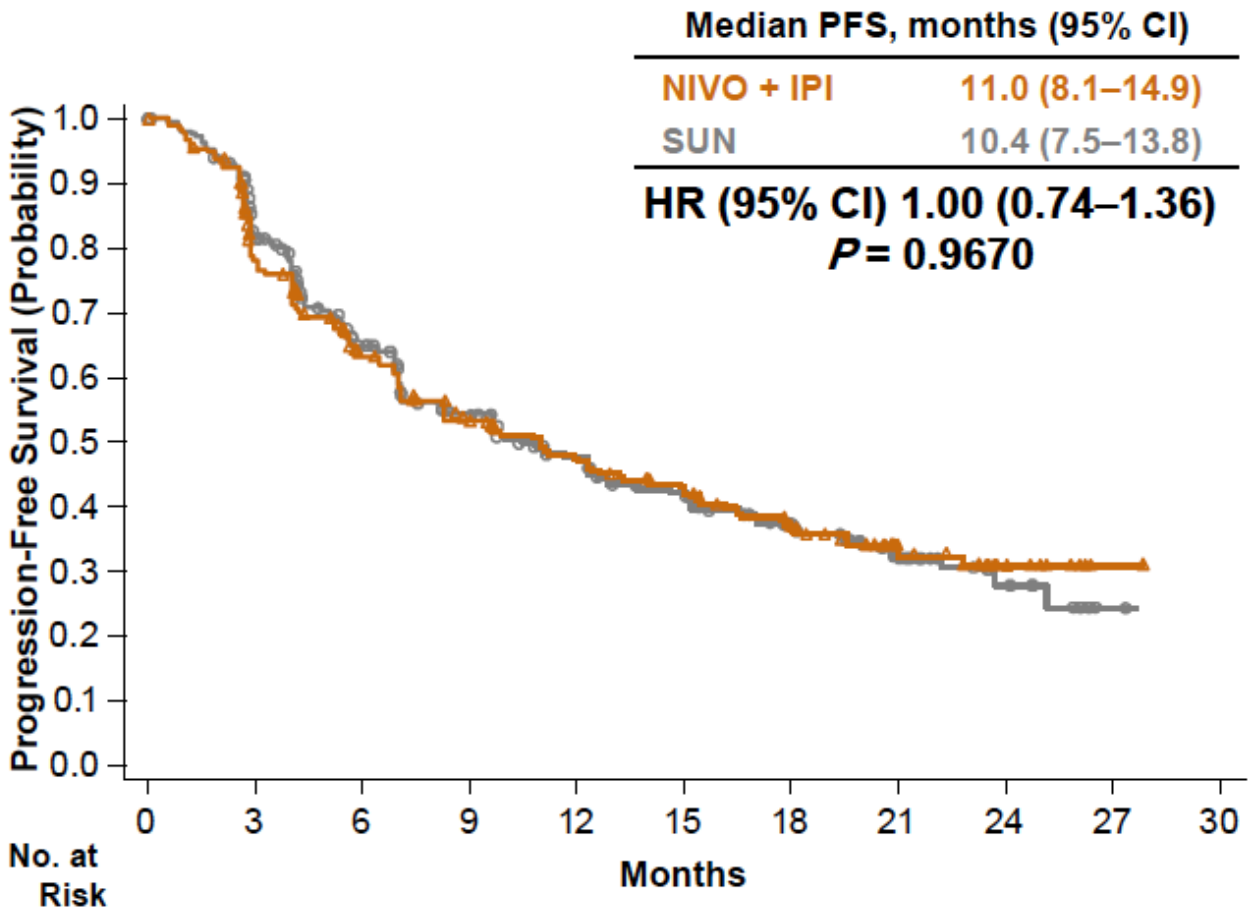
Endpoints+: ORR, CRs, OS, QOL
Pending: Durable OS,TFS

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

Motzer RJ et al. SITC 2016. Abst O38

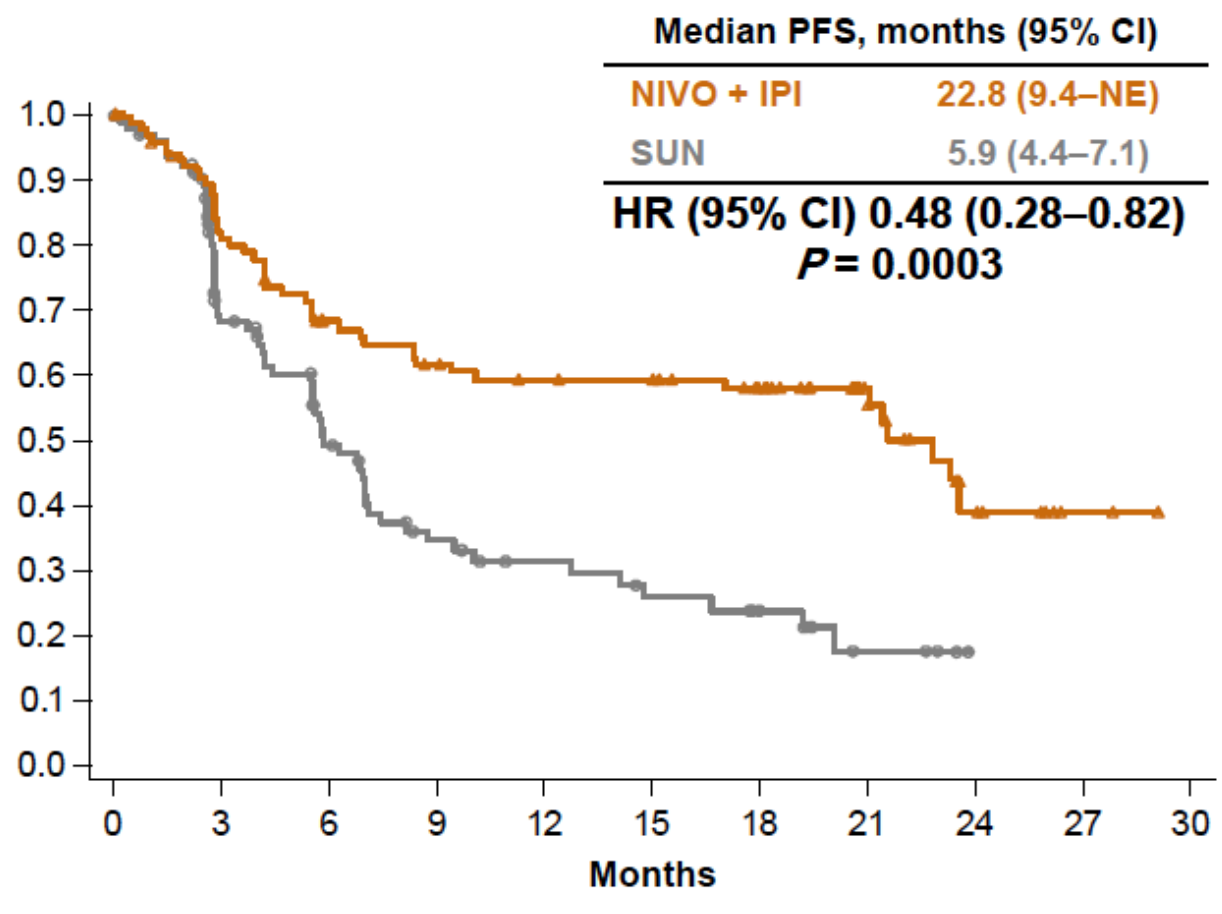
PFS by PD-L1 expression: IMDC intermediate/poor risk

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

Immune-mediated adverse events: All treated patients

	NIVO + IPI N = 547	
Category, %	Any grade	Grade 3–4
Rash	17	3
Diarrhea/colitis	10	5
Hepatitis	7	6
Nephritis and renal dysfunction	5	2
Pneumonitis	4	2
Hypersensitivity/infusion reaction	1	0
Hypothyroidism	19	<1
Hyperthyroidism	12	<1
Adrenal insufficiency	8	3
Hypophysitis	5	3
Thyroiditis	3	<1
Diabetes mellitus	3	1

- 60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event
- Secondary immunosuppression with infliximab (3%) and mycophenolic acid (1%) was reported

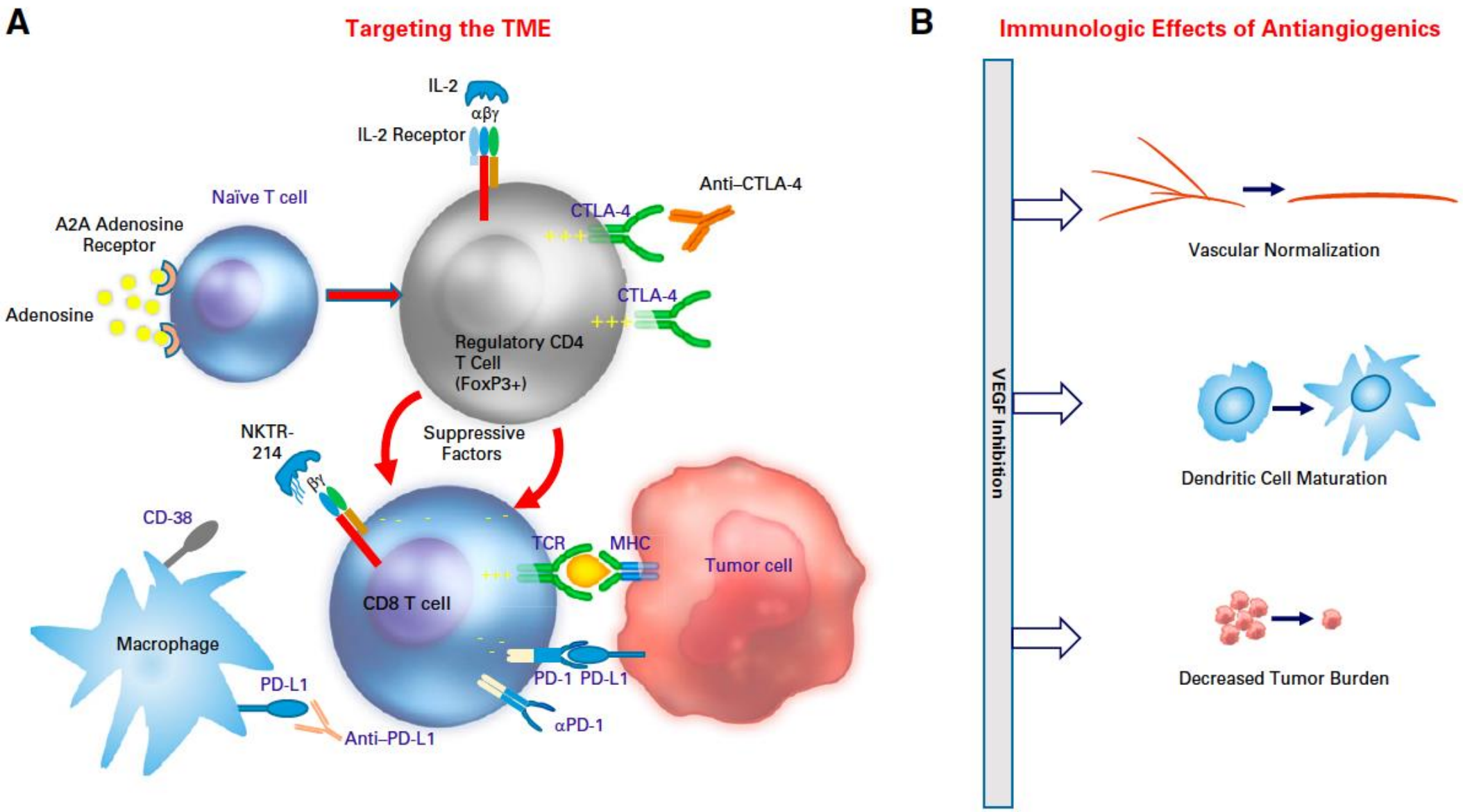
Summary and conclusions

- In **IMDC intermediate/poor risk treatment-naïve aRCC**, CheckMate 214 demonstrated
  - Significantly improved ORR with NIVO + IPI versus SUN
    - 9.4% complete response rate
    - Durable responses, with median duration of response not reached
  - Median PFS improvement of >3 months with NIVO + IPI versus SUN
  - Significant OS benefit with NIVO + IPI versus SUN
    - Median OS: not reached (NIVO + IPI) and 26.0 months (SUN); HR 0.63; *P* = 0.00003
- Exploratory analysis of patients with tumor PD-L1 ≥1% demonstrated a higher ORR and improved PFS with NIVO + IPI versus SUN

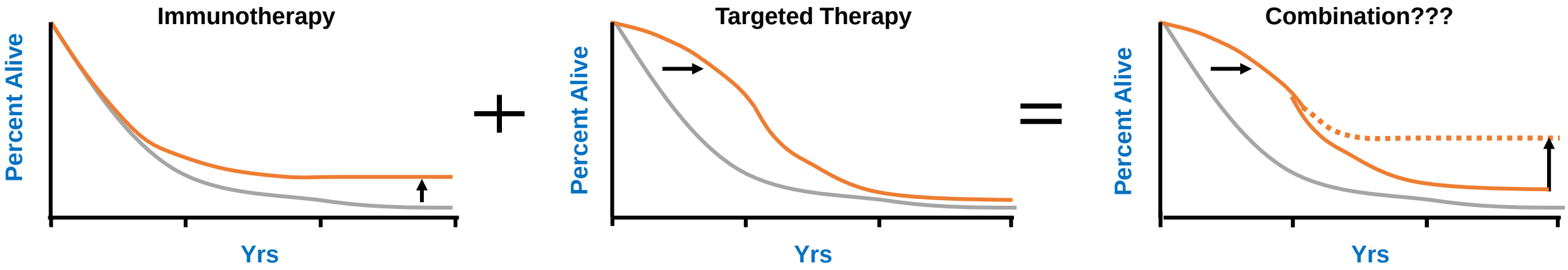
Summary and conclusions

- **The safety profile of NIVO + IPI was manageable** and consistent with previous studies
  - More high-grade treatment-related adverse events were observed with SUN, although more patients had treatment-related adverse events leading to treatment discontinuation with NIVO + IPI
  - Patients in the NIVO + IPI arm experienced greater symptomatic improvement versus SUN
  - Throughout the course of the study, patients in the NIVO +IPI arm reported better symptom control relative to those in the SUN arm
- These results suggest that NIVO + IPI is a potential first-line treatment option for patients with aRCC, **with intermediate or poor IMDC risk, especially in those with PD-L1 expression ≥1%**

Rationale for Combination of Immune Checkpoint Inhibitor and Anti-Angiogenesis



Combining VEGF and PD-1 Blockade



Slide courtesy of T RIbas

Pembrolizumab and Axitinib in RCC

- RCC is susceptible to antiangiogenic and immunotherapeutic approaches
- Both the anti–PD-1 monoclonal antibody pembrolizumab and the VEGFR-TKI axitinib and have shown antitumor activity as monotherapy in the first-line advanced RCC setting[1,2]
  - Pembrolizumab (phase 2 study): 38% ORR, 8.7-month median PFS[1]
  - Axitinib (phase 3 study): 32% ORR, 10.1-month median PFS[2]
- Data from patients with RCC suggest antiangiogenic agents can enhance antitumor immunity[3-7] and that adding immune checkpoint inhibitors may augment these effects[7]
- Pembrolizumab plus axitinib demonstrated a high ORR, promising PFS, and a manageable safety profile as first-line therapy for advanced RCC in a phase 1b study[8]

1. McDermott DF et al. *J Clin Oncol* 2018;36(suppl):abstr 4500. 2. Hutson TE et al. *Lancet Oncol* 2013;14:1287-94.
3. Ko JS et al. *Clin Cancer Res* 2009;15:2148-57. 4. Adotevi O et al. *J Immunother* 2010;33:991-8.
5. Desar IM et al. *Int J Cancer* 2011;129:507-12. 6. Sharpe K et al. *Clin Cancer Res* 2013;19:6924-34.
7. Wallin JJ et al. *Nat Commun* 2016;7:12624. 8. Atkins MB et al. *Lancet Oncol* 2018;19:405-15.

KEYNOTE-426 Study Design

Key Eligibility Criteria

- Newly diagnosed or recurrent stage IV clear-cell RCC
- No previous systemic treatment for advanced disease
- Karnofsky performance status ≥70
- Measurable disease per RECIST v1.1
- Provision of a tumor sample for biomarker assessment
- Adequate organ function

Stratification Factors

- IMDC risk group (favorable vs intermediate vs poor)
- Geographic region (North America vs Western Europe vs ROW)

R (1:1)

N = 432 → Pembrolizumab 200 mg IV Q3W for up to 35 cycles + Axitinib 5 mg orally twice daily[a]

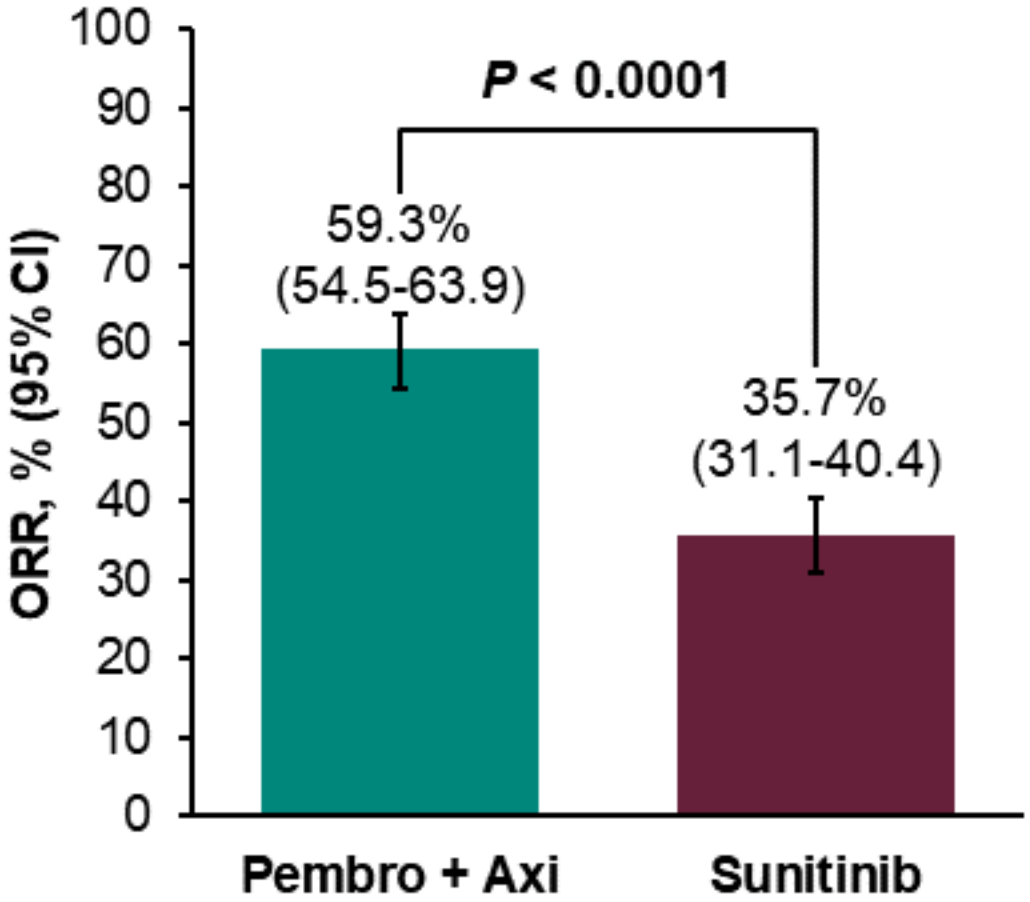
N = 429 → Sunitinib 50 mg orally once daily for first 4 wks of each 6-wk cycle[b]

End Points

- **Dual primary:** OS and PFS (RECIST v1.1, BICR) in ITT
- **Key secondary:** ORR (RECIST v1.1, BICR) in ITT
- **Other secondary:** DOR (RECIST v1.1), PROs, safety

[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

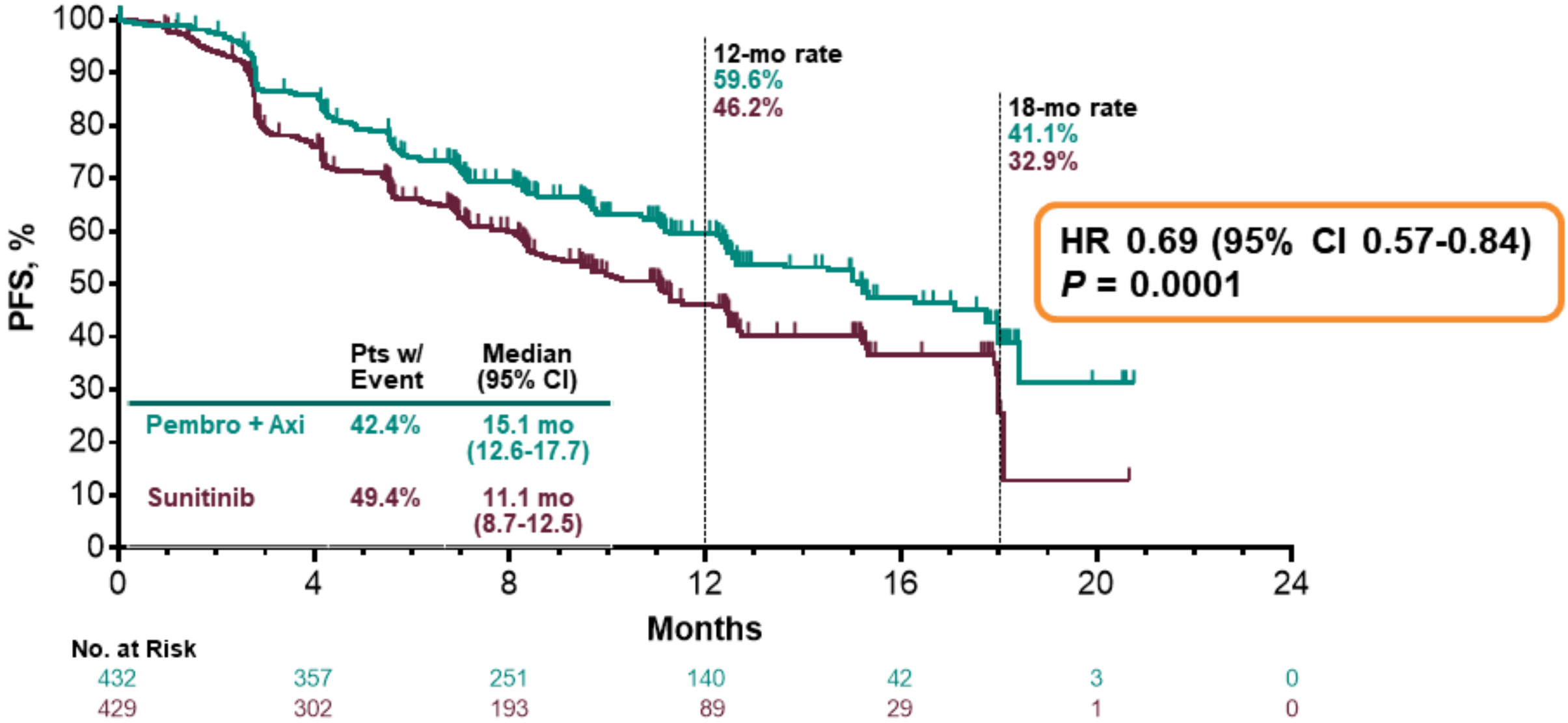
Confirmed Objective Response Rate



Best Response	Pembro + Axi N = 432	Sunitinib N = 429
CR	25 (5.8%)	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	47 (10.9%)	73 (17.0%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

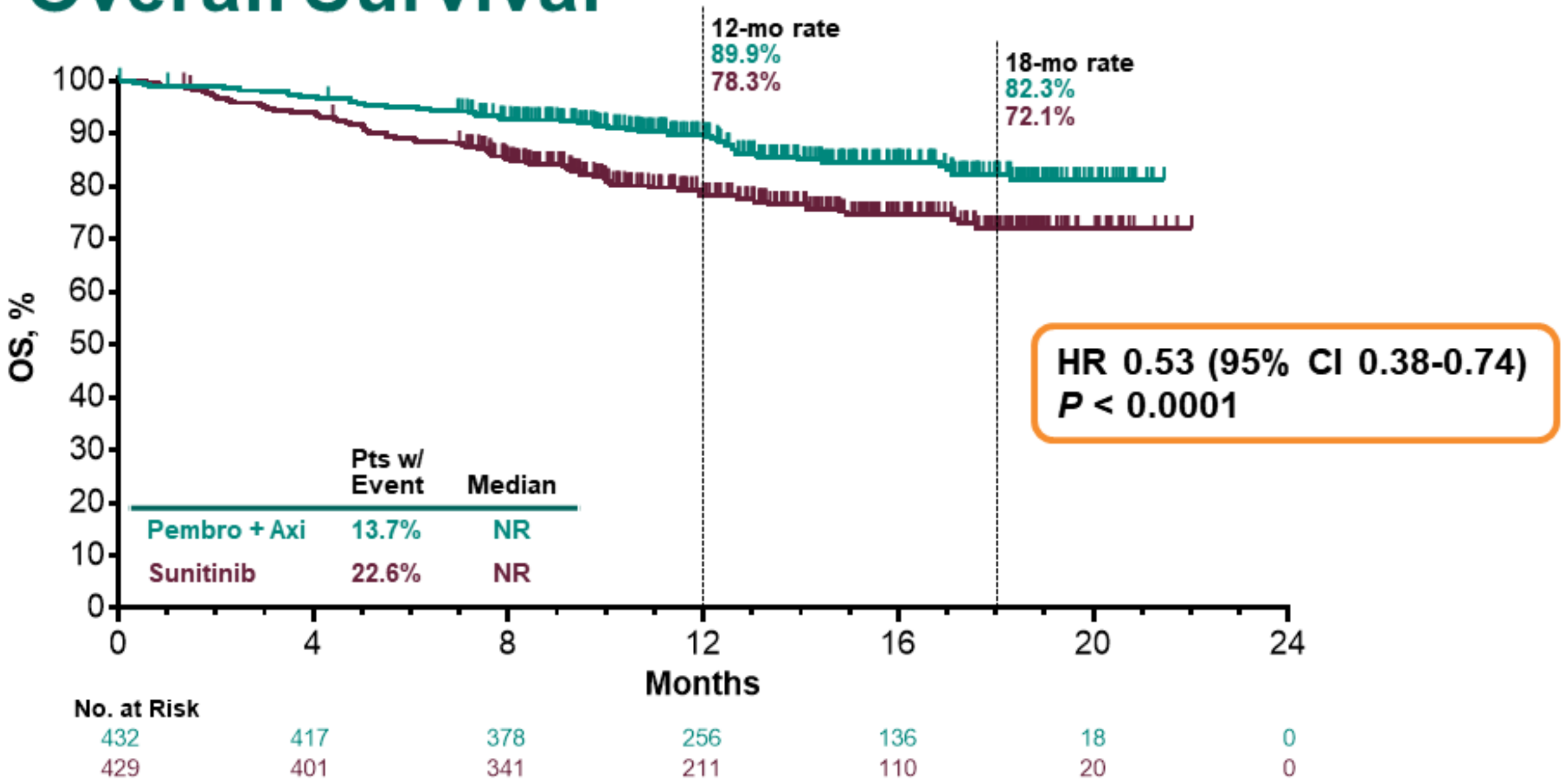
[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Data cutoff date: Aug 24, 2018.

Progression-Free Survival



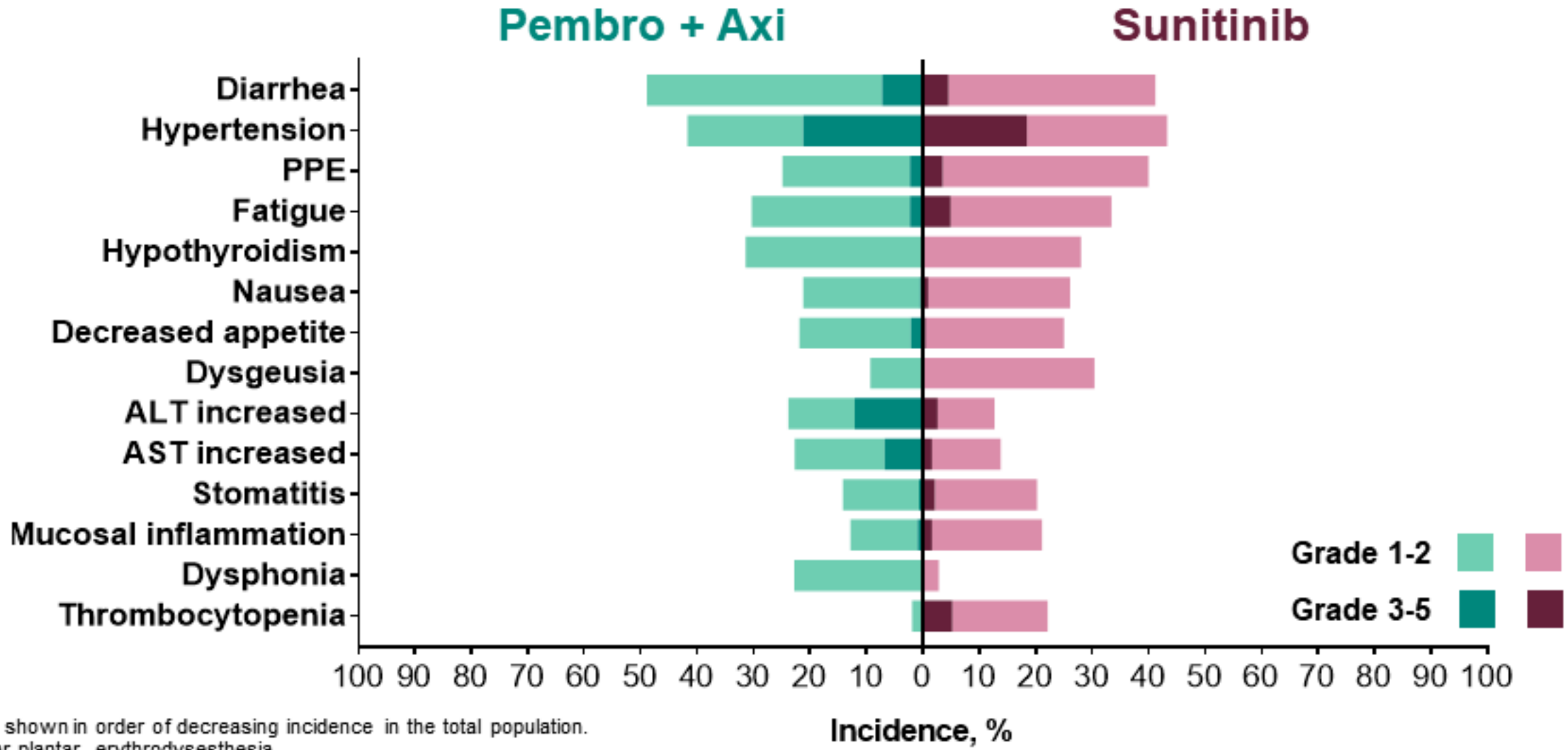
Data cutoff date: Aug 24, 2018.

Overall Survival



Data cutoff date: Aug 24, 2018.

Treatment-Related Adverse Events: Incidence ≥20%

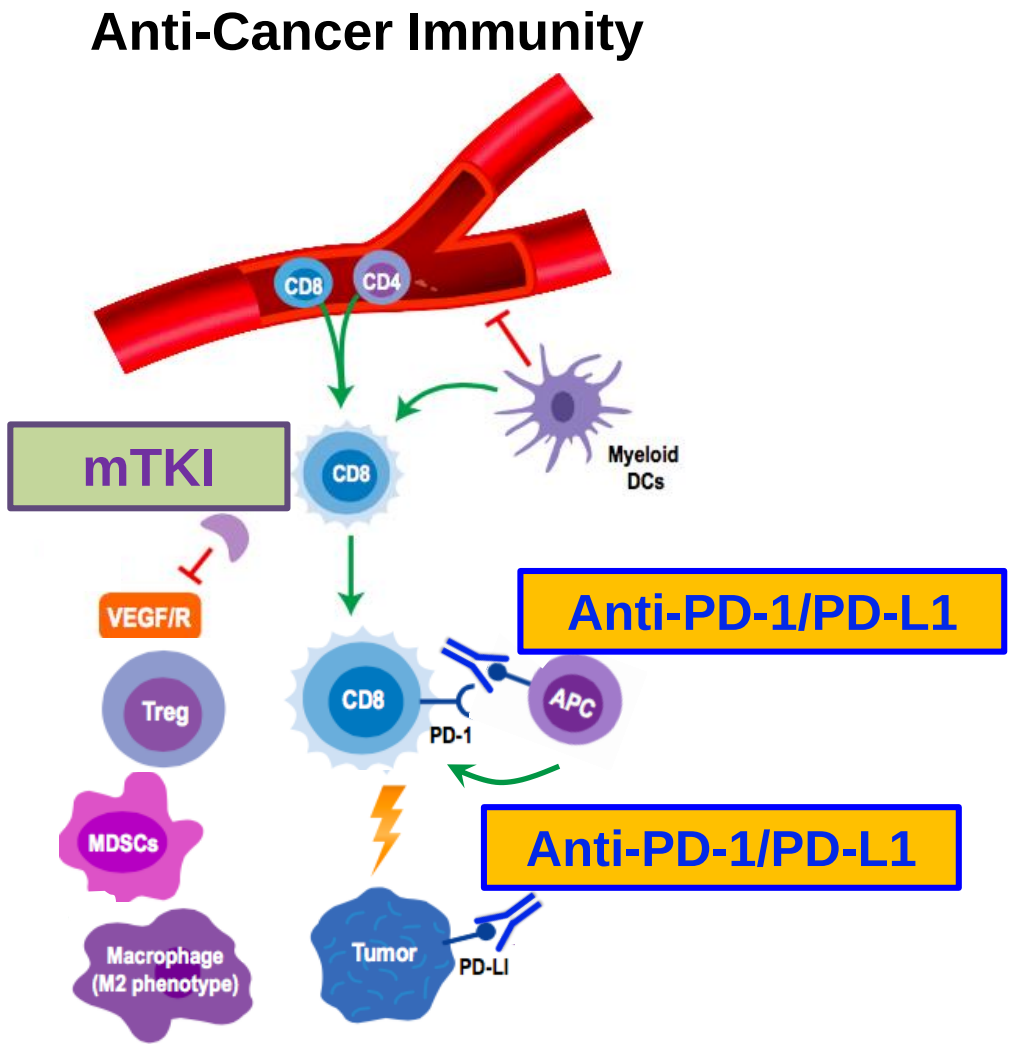


Events are shown in order of decreasing incidence in the total population.
PPE, palmar-plantar erythrodysesthesia.
Data cutoff date: Aug 24, 2018.

Summary and Conclusions

- Pembrolizumab plus axitinib demonstrated superior efficacy compared with sunitinib in patients with previously untreated, locally advanced or metastatic clear-cell RCC
  - OS: HR 0.53, $P < 0.0001$; 12-mo rate 89.9% vs 78.3%
  - PFS: HR 0.69, $P = 0.0001$; median 15.1 mo vs 11.1 mo
  - ORR: 59.3% vs 35.7%, $P < 0.0001$
  - DOR: median not reached vs 15.2 mo
- Benefit was observed across all subgroups, including IMDC favorable, intermediate, and poor risk groups and PD-L1–expressing and non-expressing tumors
- Overall toxicity was comparable between arms, with manageable AE profiles
- Pembrolizumab plus axitinib should be a new standard of care for first-line treatment of patients with advanced clear-cell RCC

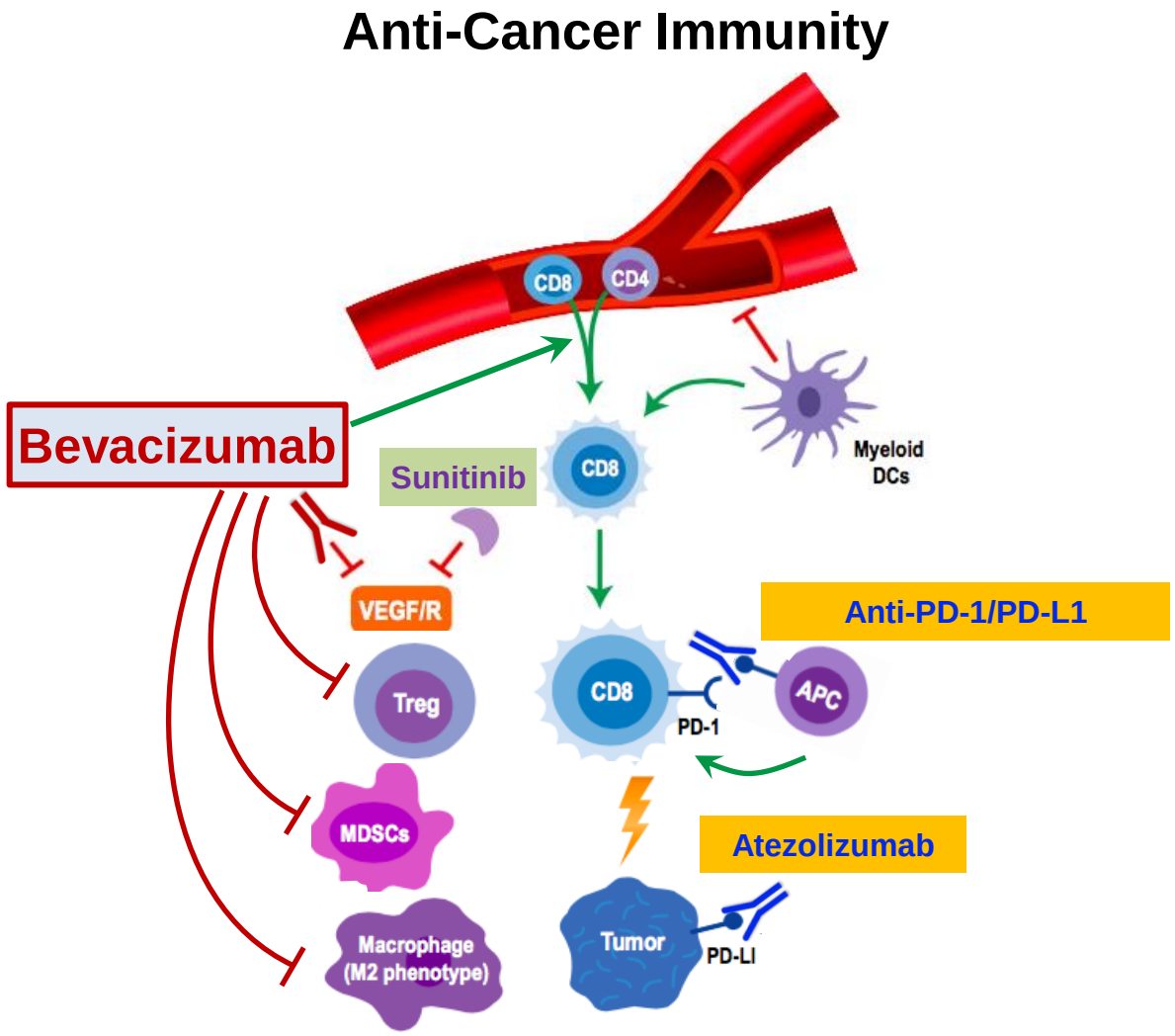
Shifting the Balance Toward Anti-Cancer Immunity With Combined VEGF/PD-L1 Blockade



PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.
Finke, *Clin Cancer Res*. 2008; McDermott, *J Clin Oncol*. 2016; Wallin. *Nat Commun*. 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Shifting the Balance Toward Anti-Cancer Immunity With Combined VEGF/PD-L1 Blockade



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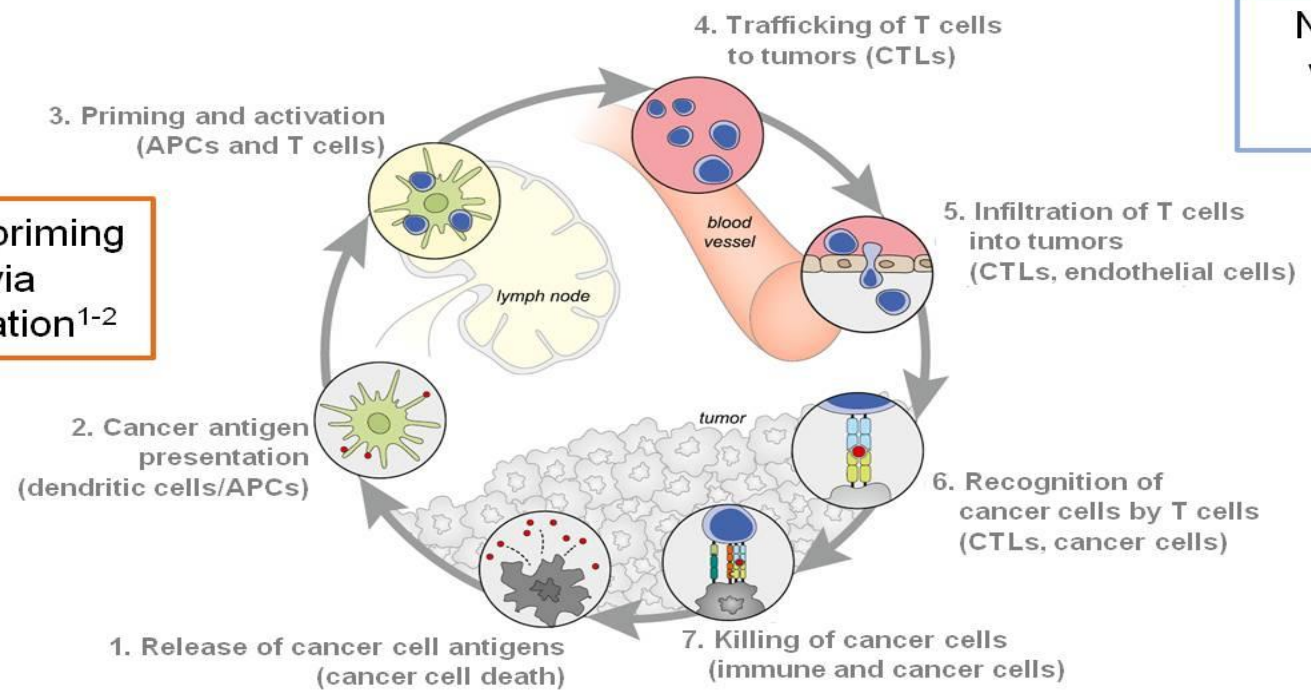
McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Rationale for Combining Atezolizumab + Bevacizumab

Normalization of the tumor vasculature for increased T-cell tumor infiltration[3-6]

Promotion of T-cell priming and activation via dendritic cell maturation[1-2]

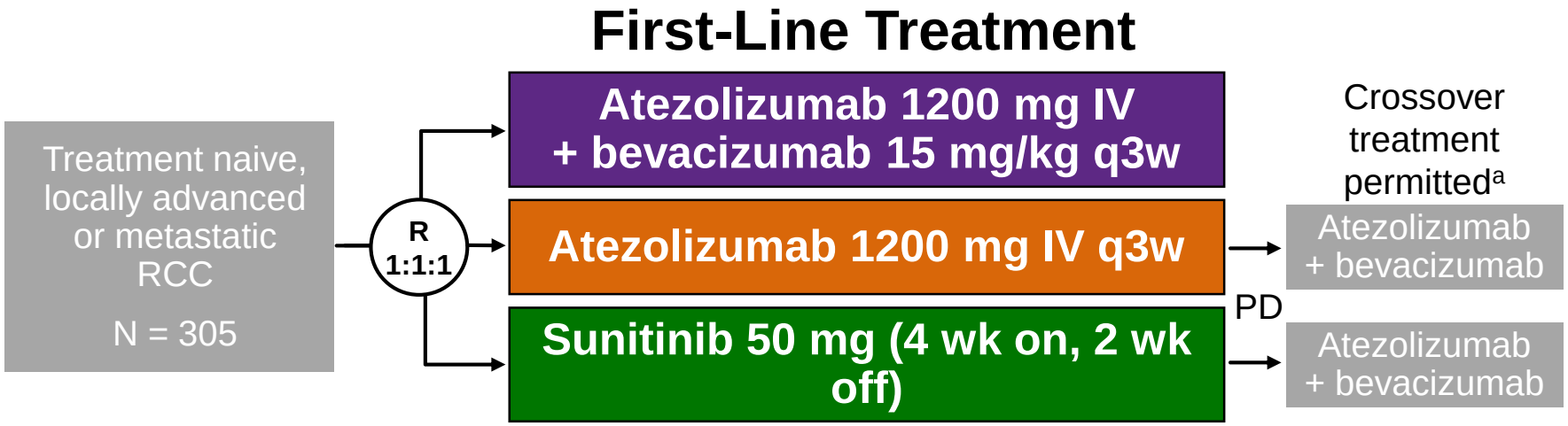


Establishing an immune-permissive tumor microenvironment by decreasing MDSC and Treg populations[6-10]

- Atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression

1. Gabrilovich DI, et al. *Nat Med*, 1996. 2. Oyama T, et al. *J Immunol*, 1998. 3. Goel S, et al. *Physiol Rev*, 2011. 4. Motz GT, et al. *Nat Med*, 2014. 5. Hodi FS, et al. *Cancer Immunol Res*, 2014. 6. Wallin JJ, et al. *Nat Commun*, 2016. 7. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*, 2009. 8. Roland CL, et al. *PLoS One*, 2009. 9. Facciabene A, et al. *Nature*, 2011. 10. Voron T, et al. *J Exp Med*, 2015.
Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.

IMmotion150 (Phase II) Trial Design



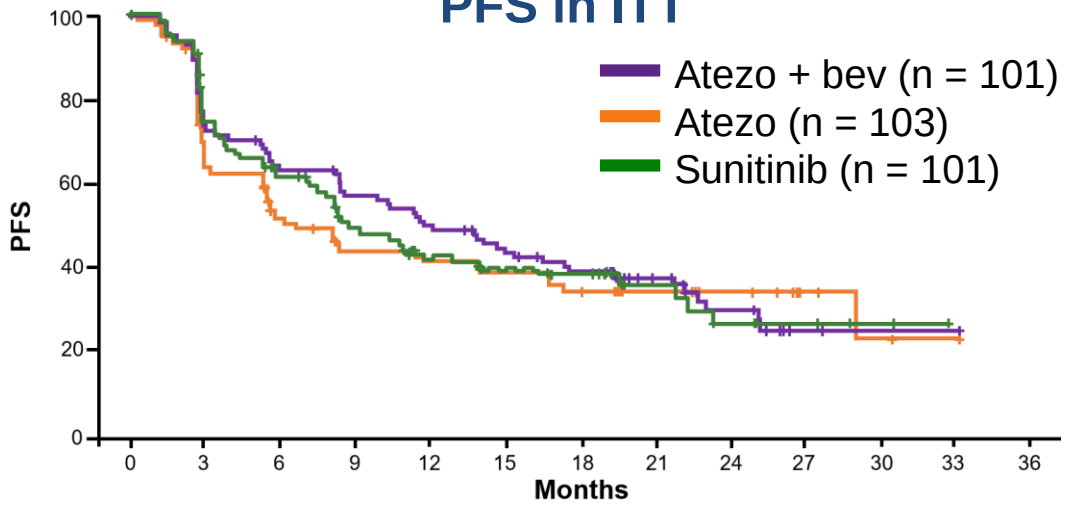
- IMmotion150 was designed to be hypothesis generating and inform the Phase III study IMmotion151
- Coprimary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with ≥ 1% of IC expressing PD-L1
- Exploratory endpoints included interrogation of the association between outcome and TME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

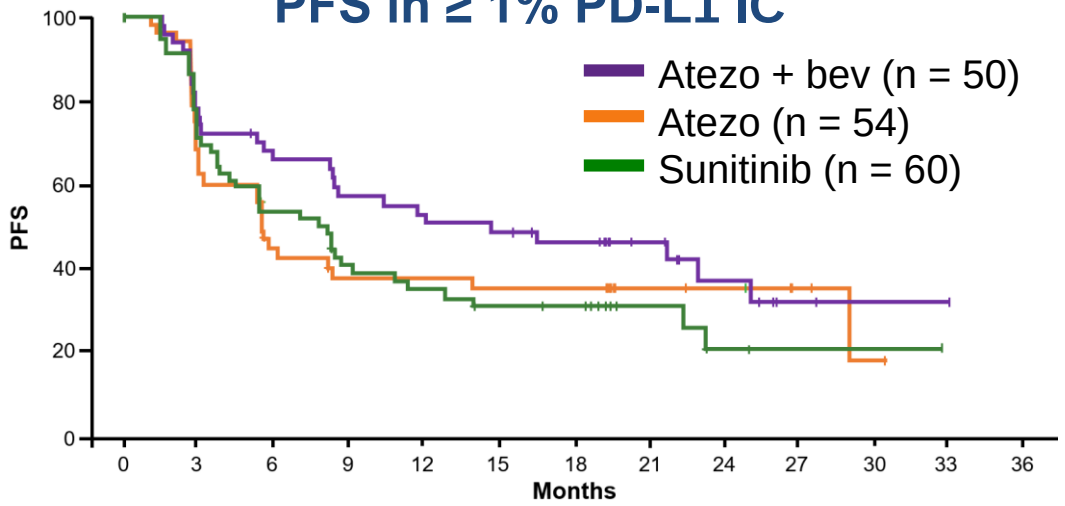
McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Encouraging Efficacy by PFS of Atezolizumab + Bevacizumab vs Sunitinib in Patients With IC PD-L1 Expression

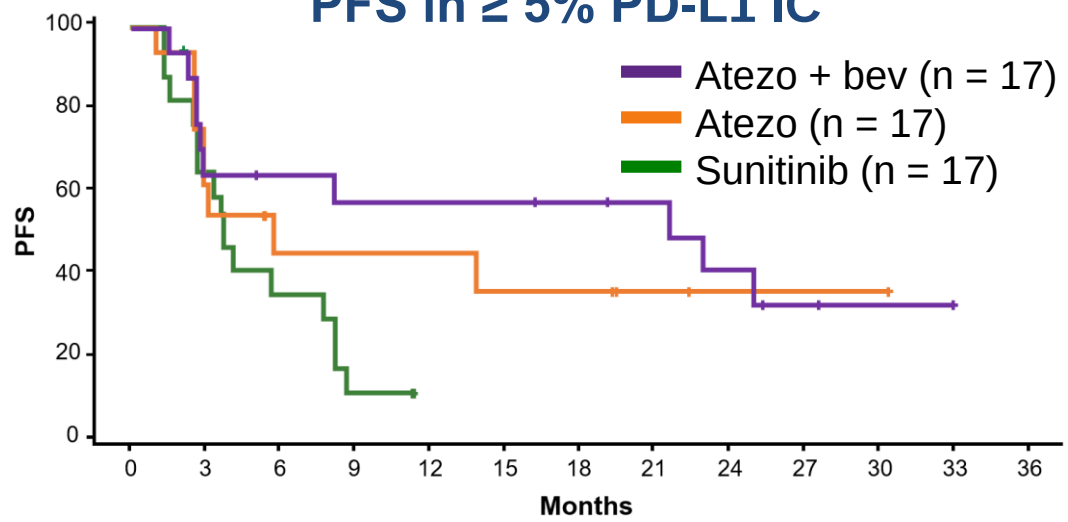
PFS in ITT



PFS in ≥ 1% PD-L1 IC



PFS in ≥ 5% PD-L1 IC



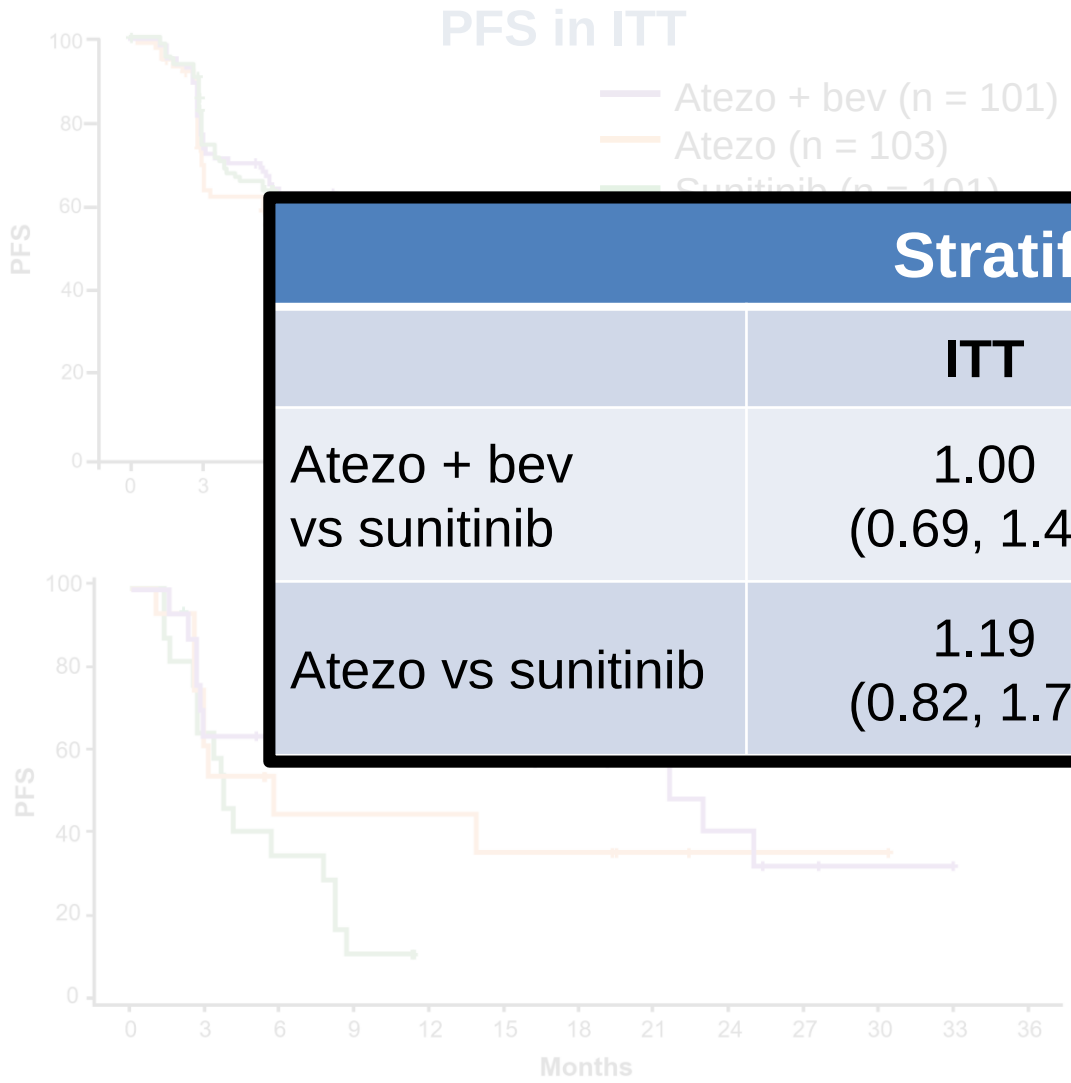
Stratified HR (95% CI)			
	ITT	**≥ 1% PD-L1 IC**	**≥ 5% PD-L1 IC**
Atezo + bev vs sunitinib	1.00 (0.69, 1.45)	**0.64 (0.38, 1.08)**	**0.34 (0.13, 0.91)**
Atezo vs sunitinib	1.19 (0.82, 1.71)	1.03 (0.63, 1.67)	**0.64 (0.27, 1.54)**

- Responses were observed in both patients with tumors expressing < 1% PD-L1 on IC and ≥ 1% PD-L1 on IC

Atezo, atezolizumab; bev, bevacizumab. IRF-assessed PFS.
McDermott, ASCO GU 2017.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Encouraging Efficacy by PFS of Atezolizumab + Bevacizumab vs Sunitinib in Patients With IC PD-L1 Expression



Stratified HR (95% CI)			
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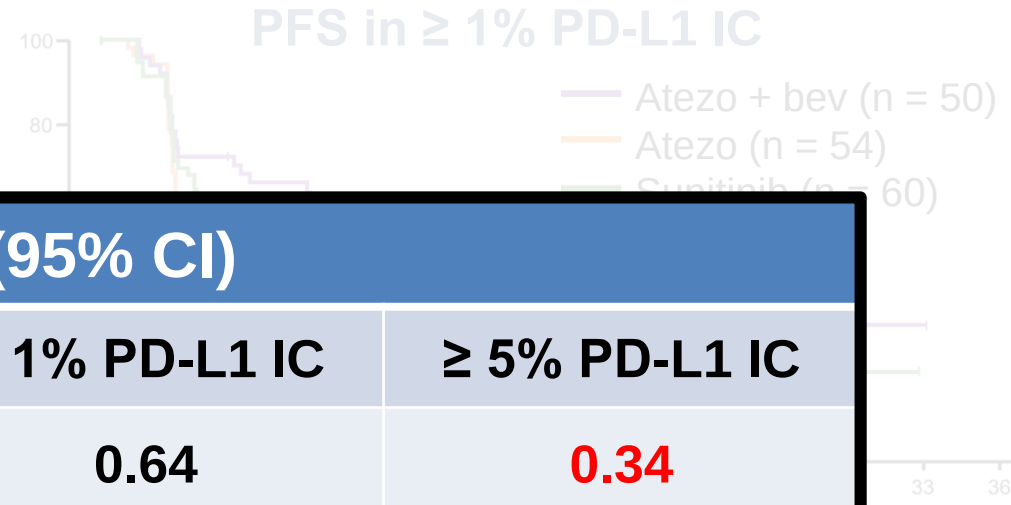

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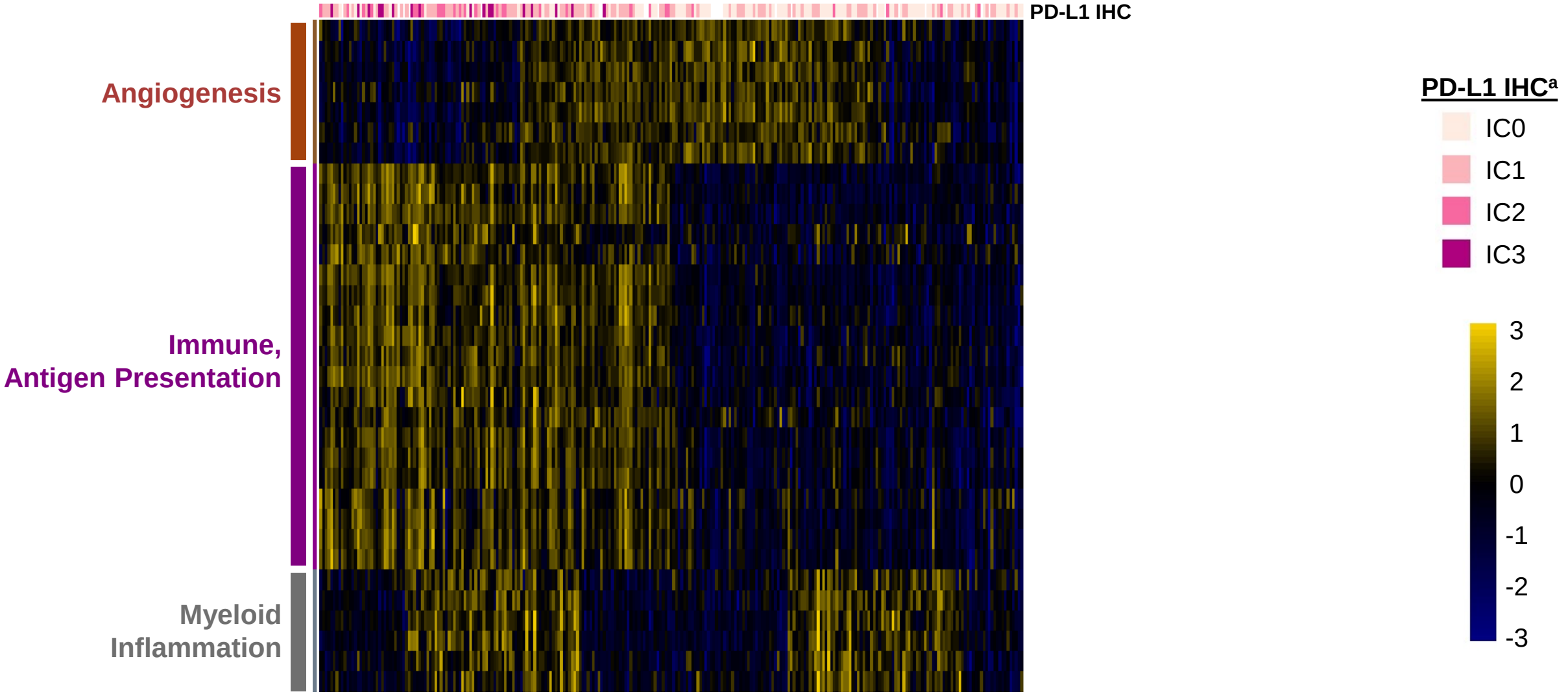
IRF-assessed PFS.
McDermott, ASCO GU 2017.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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

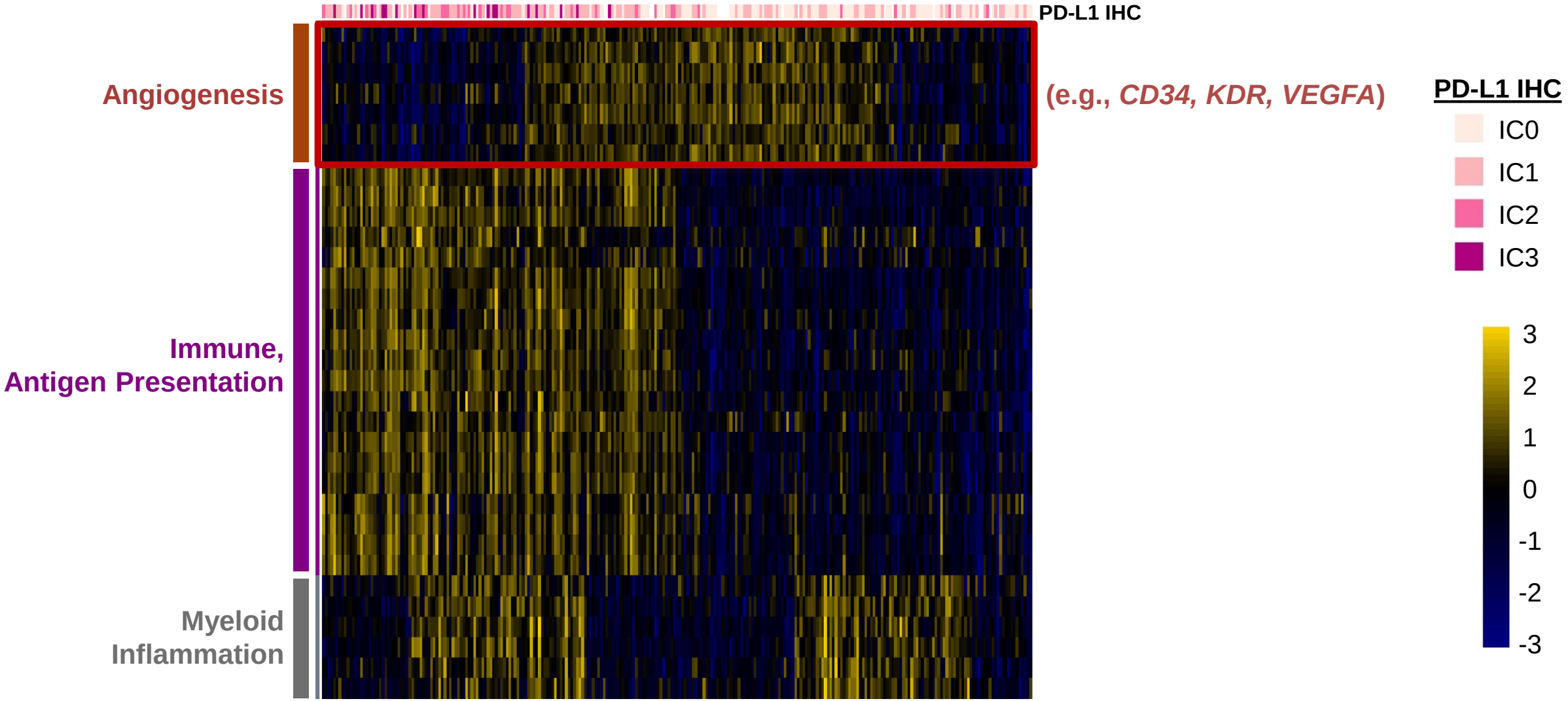


Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

[a] PD-L1 expression scored as IC3 (≥ 10%), IC2 (≥ 5% and < 10%), IC1 (≥ 1% and < 5%) or IC0 (< 1%).

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

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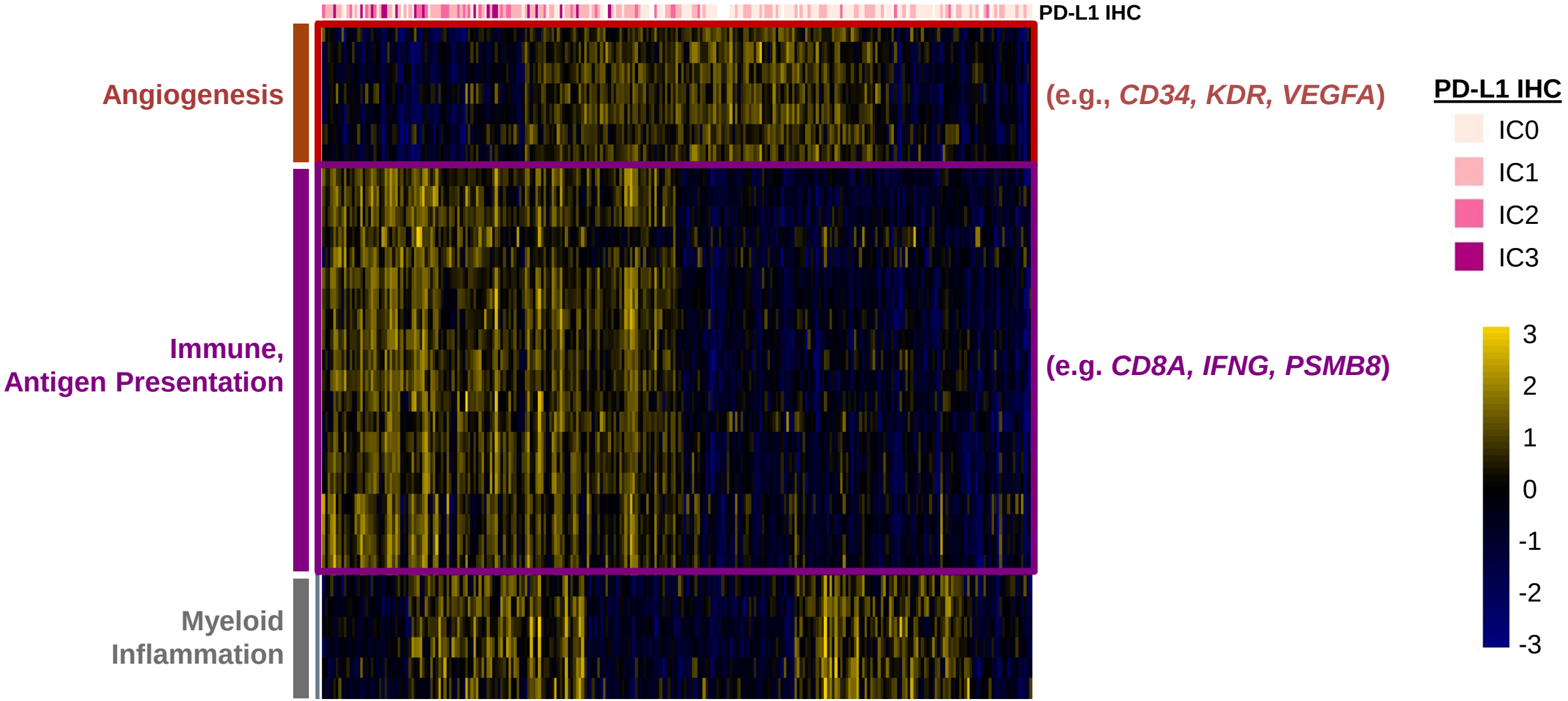
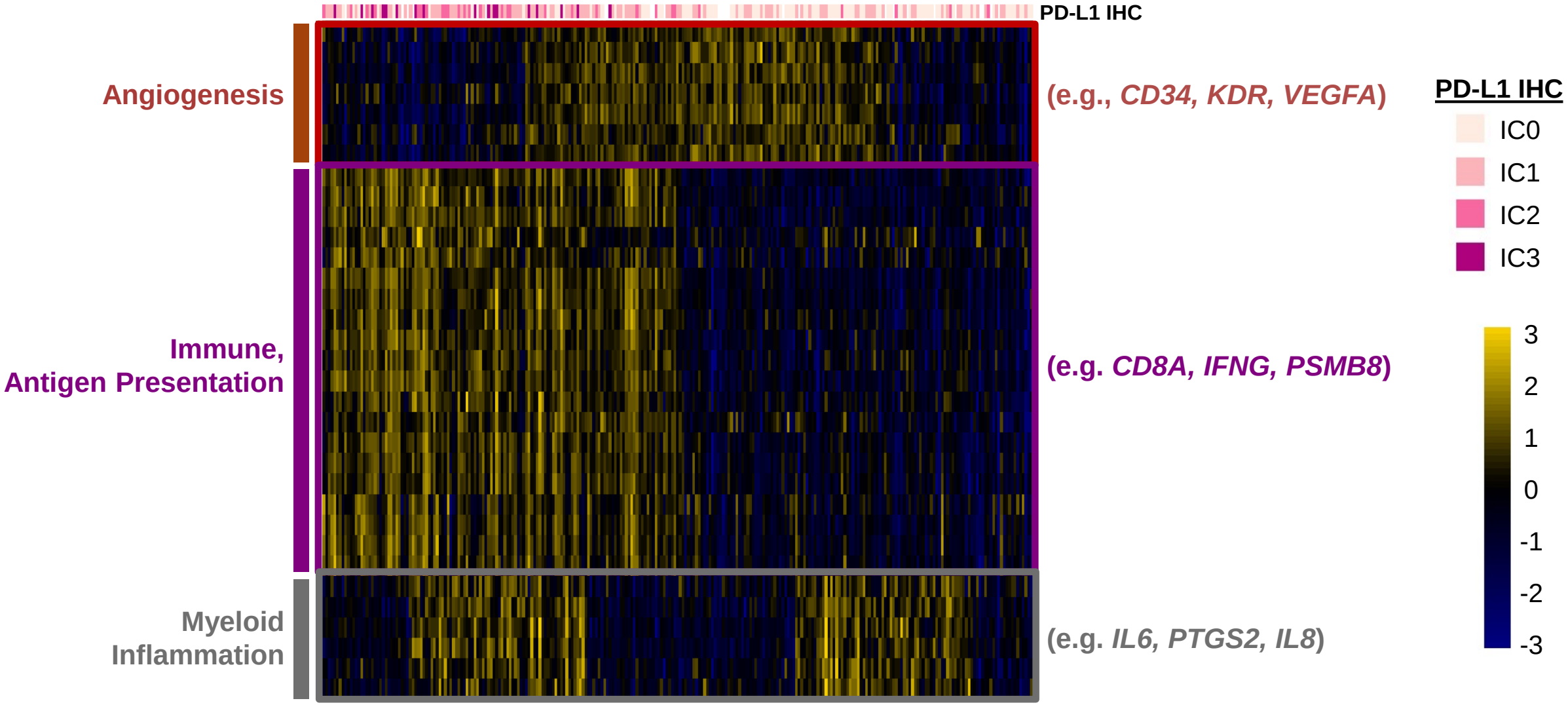


Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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

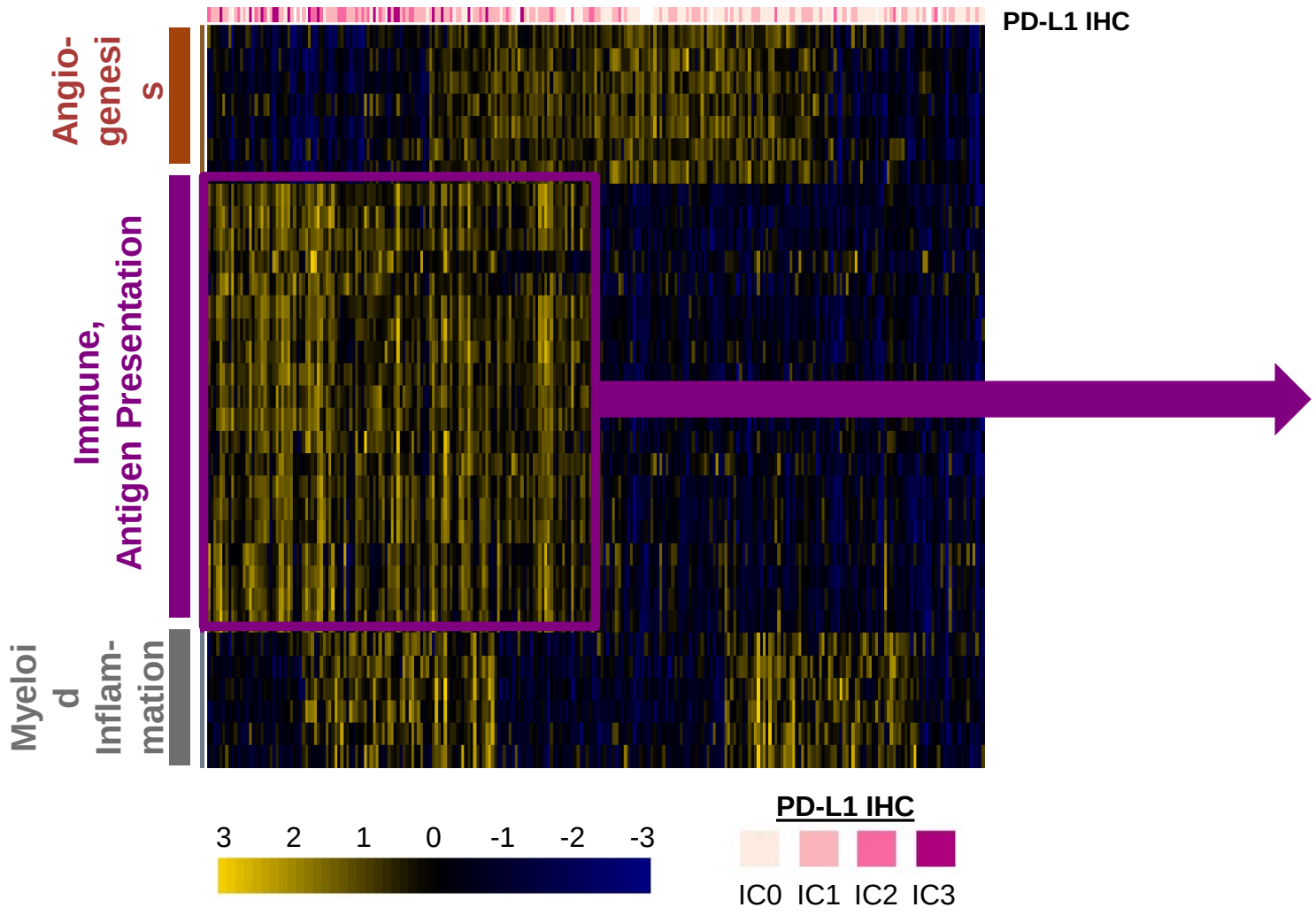


Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

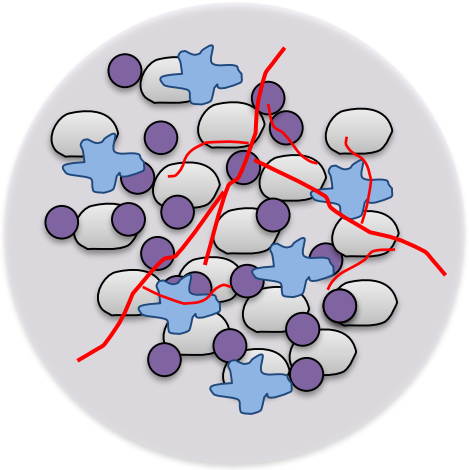
McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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

Immune



T-effector^{High}



Tumor cells

T-effector cells

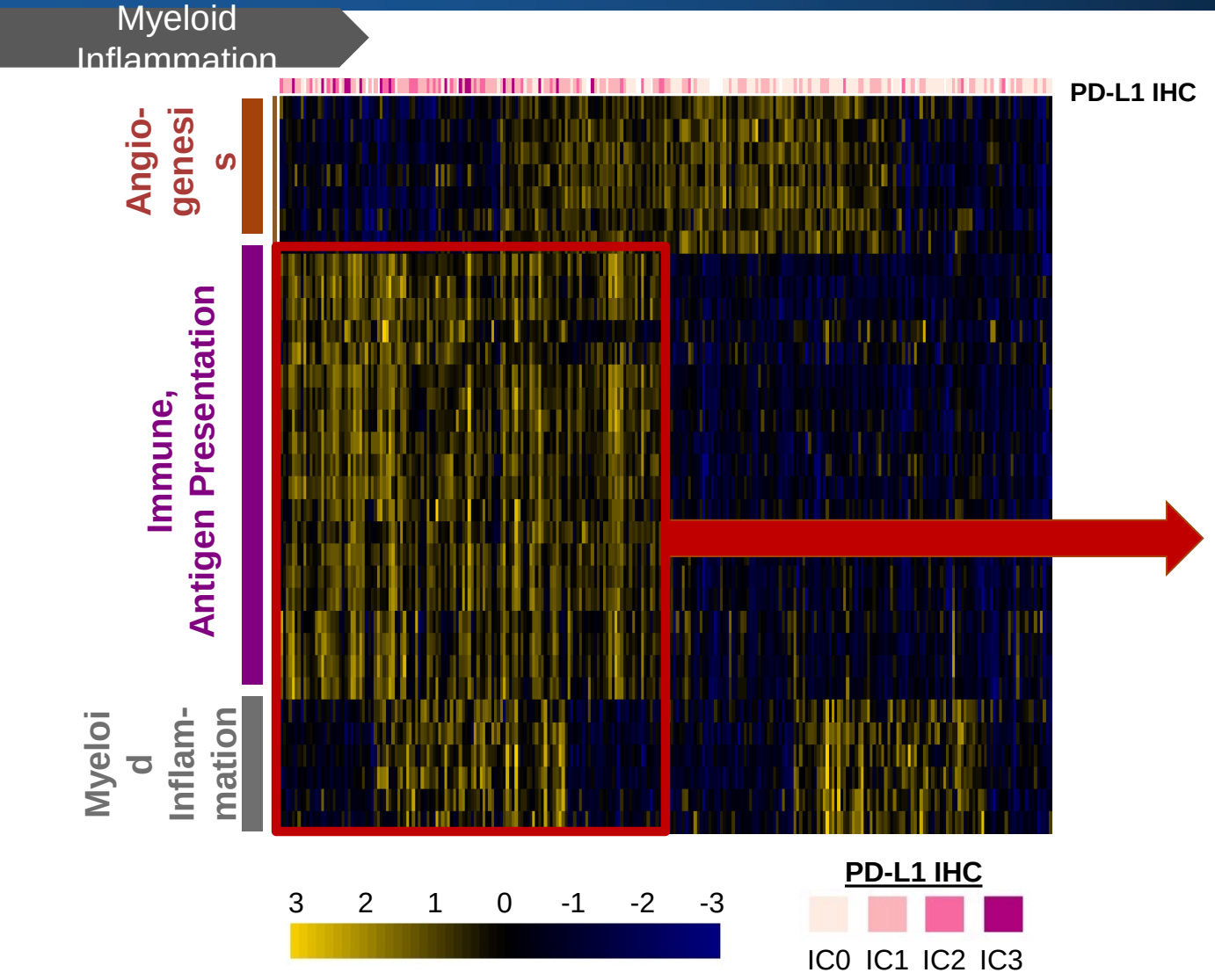
Myeloid cells

Vasculature

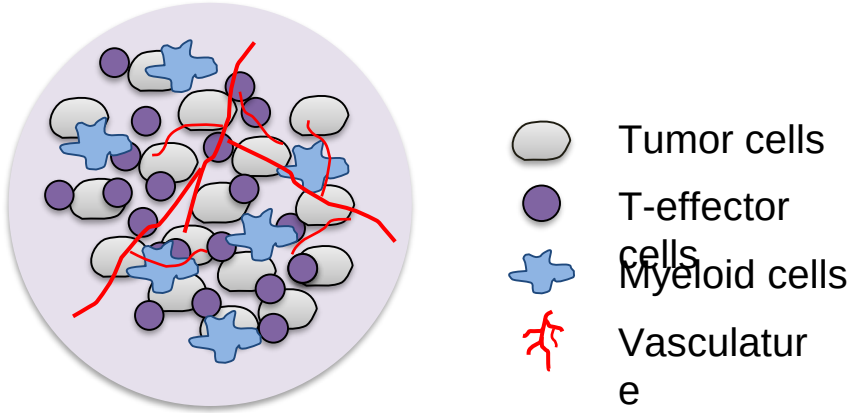
Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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



T-effector^{High} Subpopulation

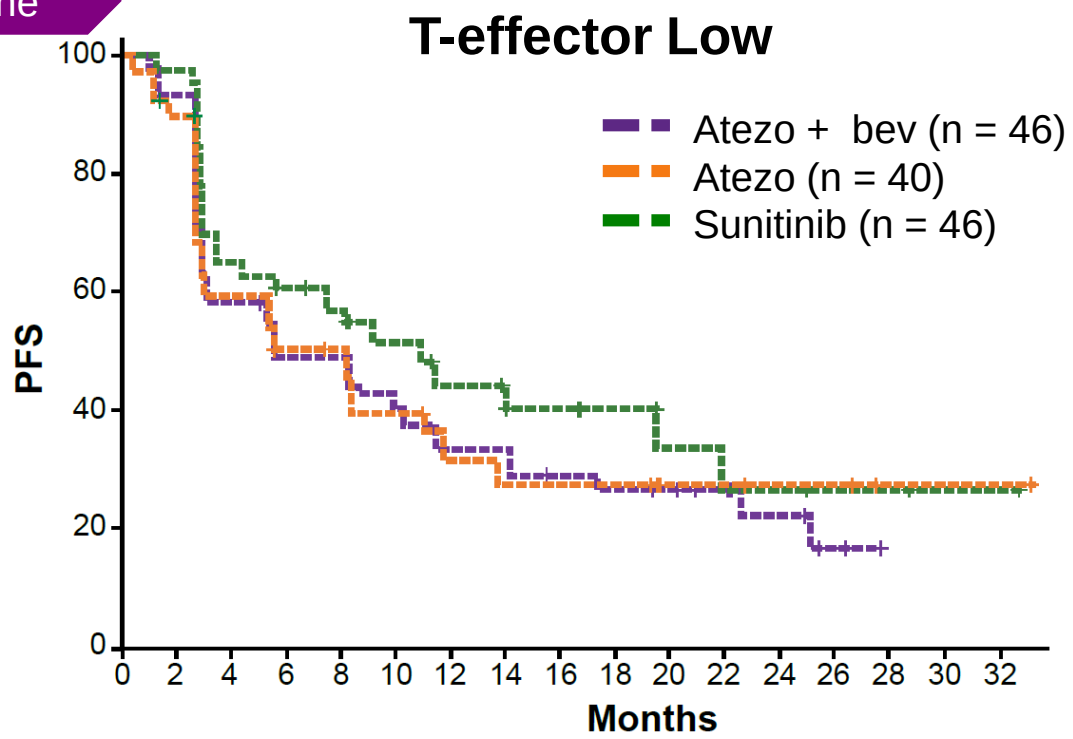


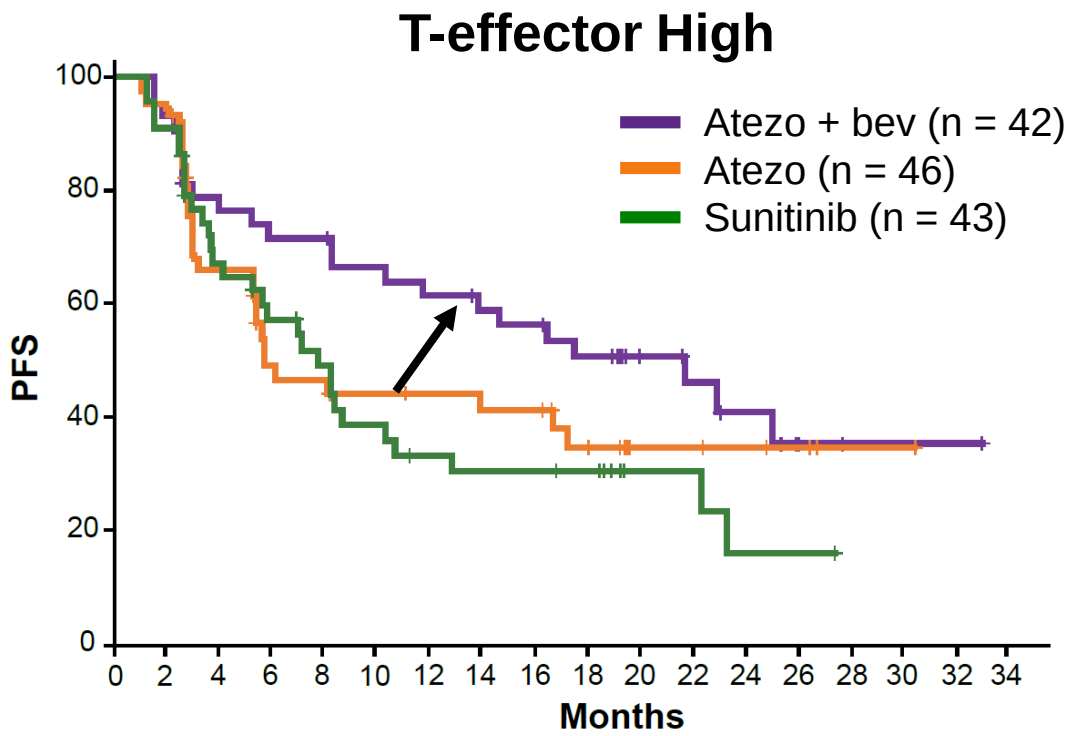
Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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

Immune



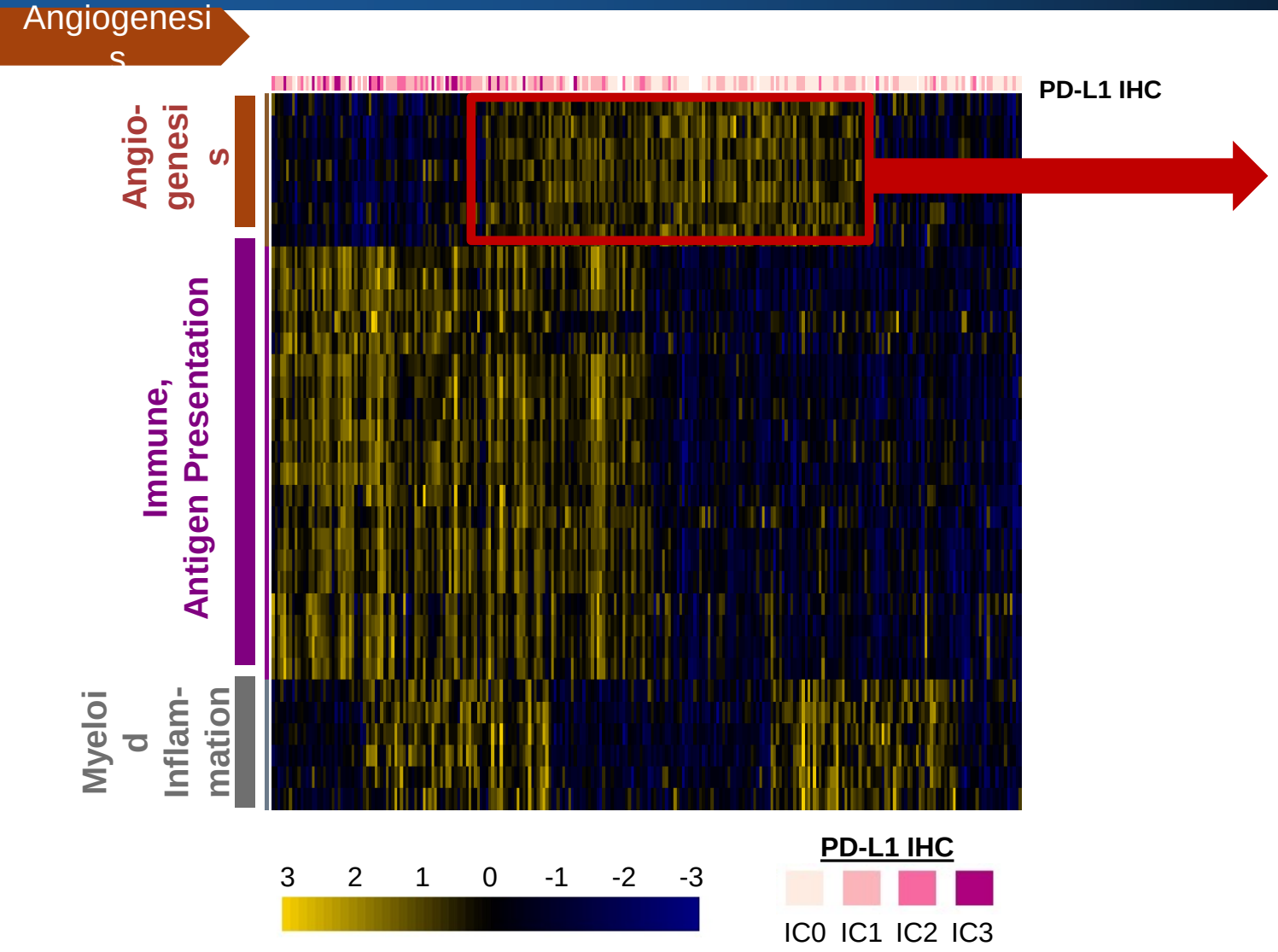


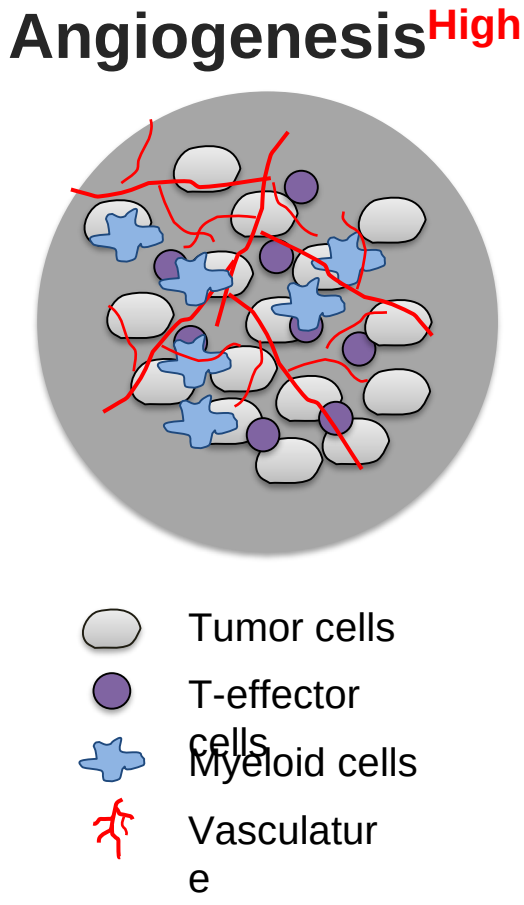
HR (95% CI)		
	T-effector Low	**T-effector High**
Atezo + bev vs sunitinib	1.41 (0.84, 2.36)	**0.55 (0.32, 0.95)**
Atezo vs sunitinib	1.33 (0.76, 2.33)	0.85 (0.50, 1.43)

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

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



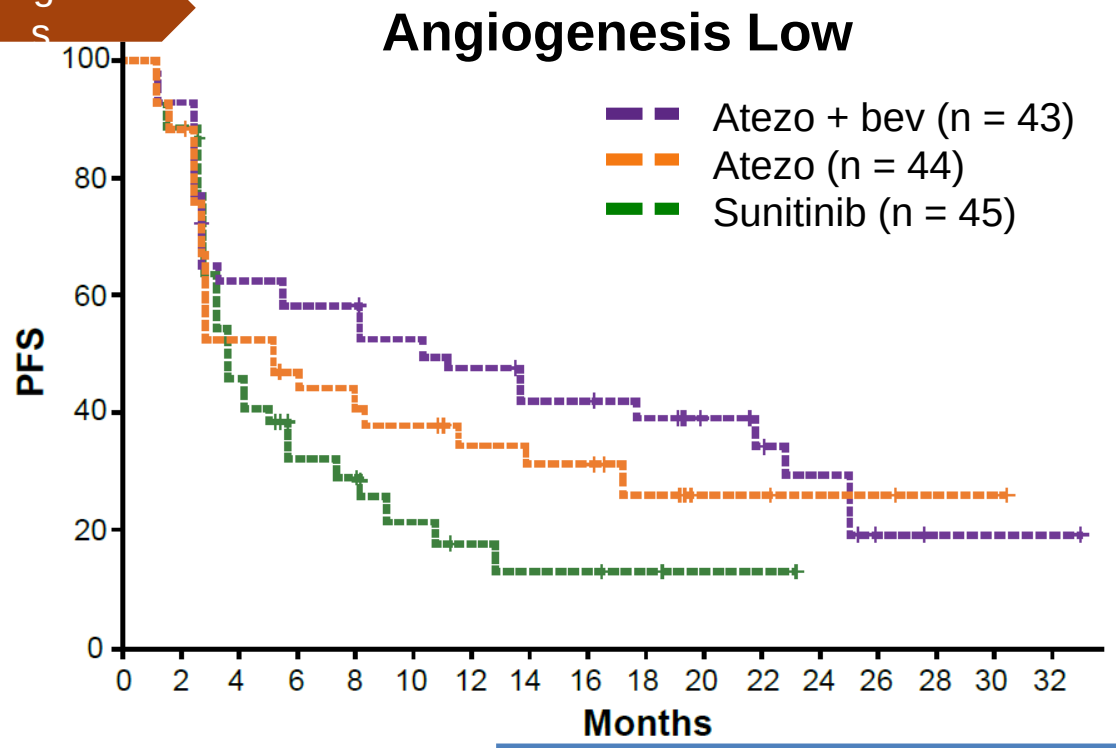


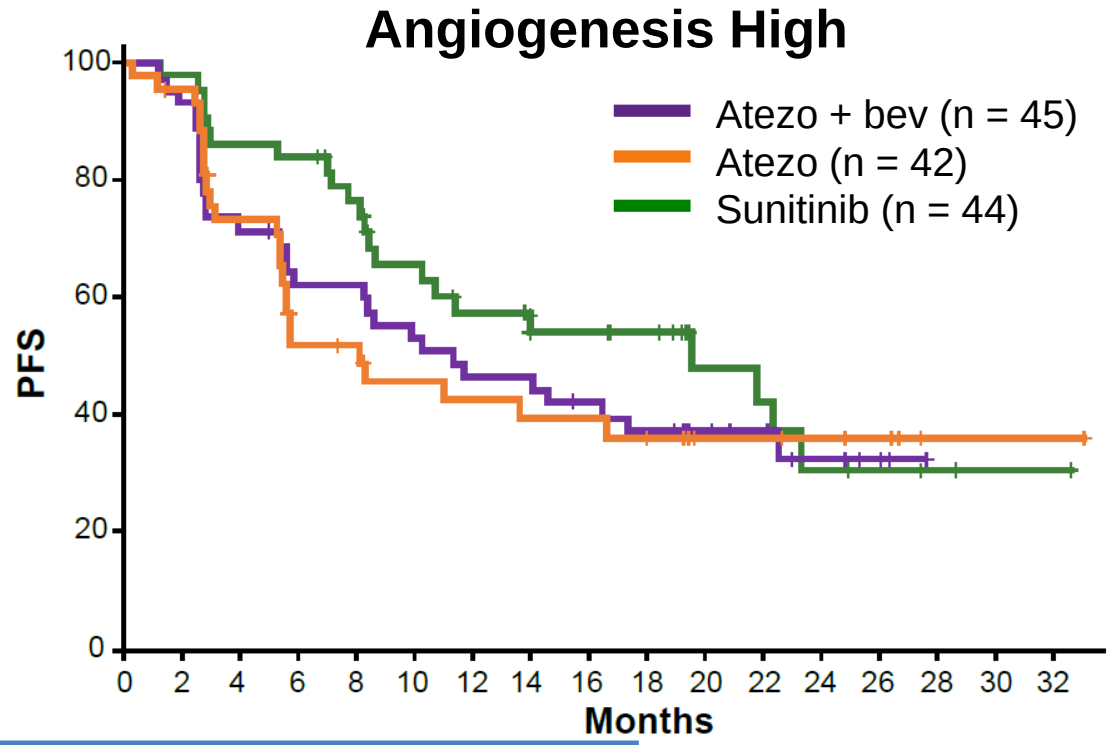
Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Atezolizumab + Bevacizumab Demonstrated Improved PFS vs Sunitinib in the Angiogenesis^{Low} Subset

Angiogenesis



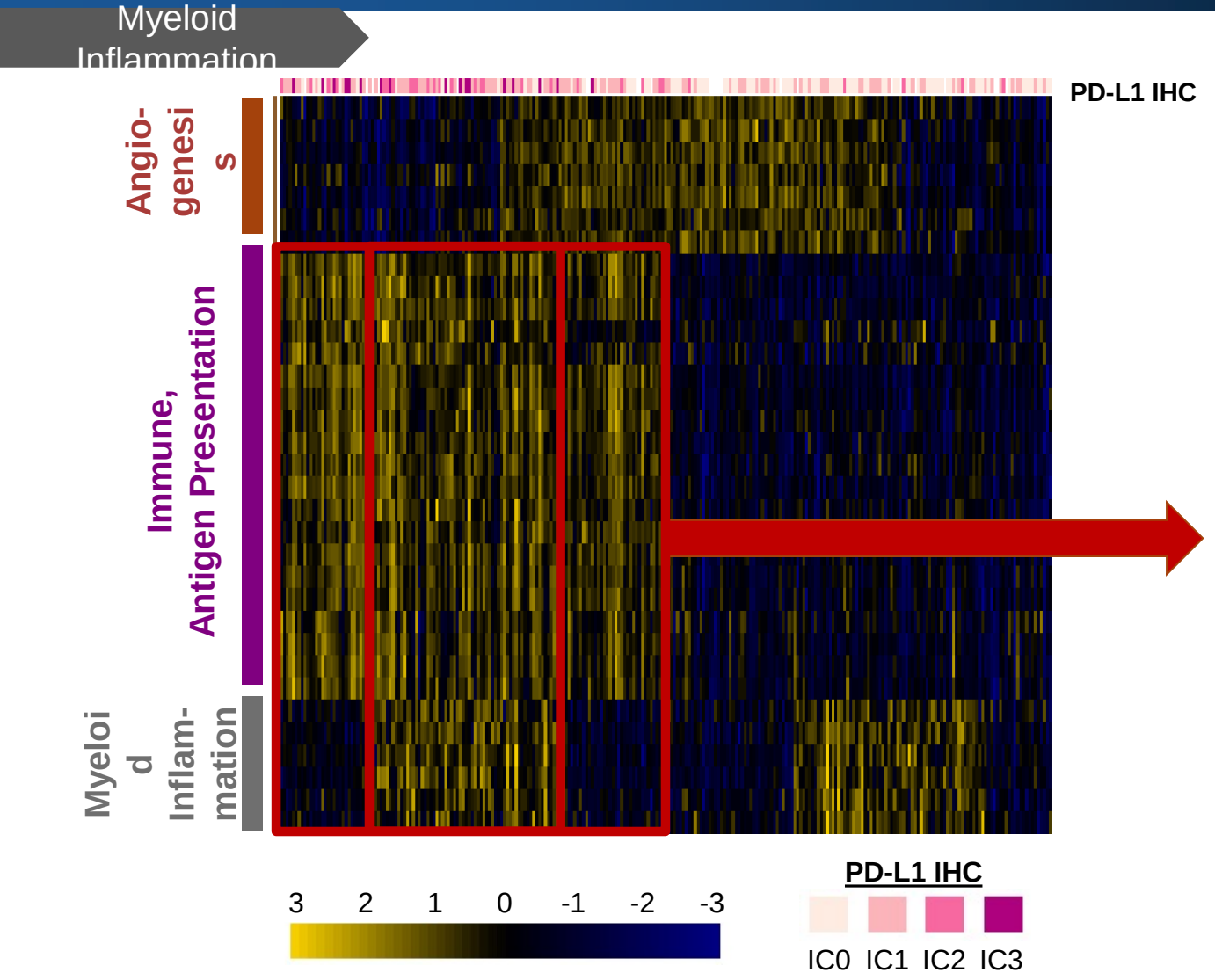


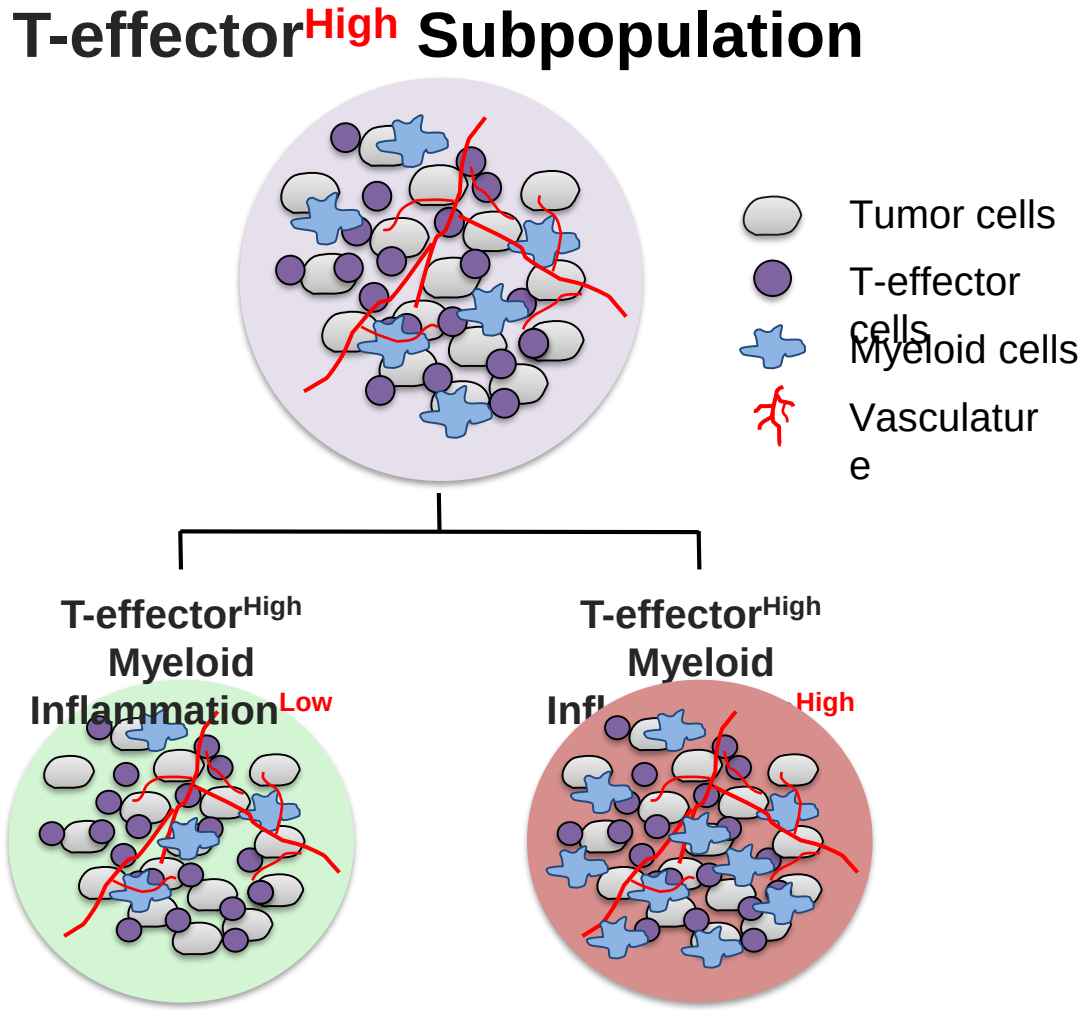
HR (95% CI)		
	Angiogenesis Low	**Angiogenesis High**
Atezo + bev vs sunitinib	**0.58 (0.35, 0.98)**	1.36 (0.78, 2.36)
Atezo vs sunitinib	**0.75 (0.45, 1.25)**	1.45 (0.81, 2.60)

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

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





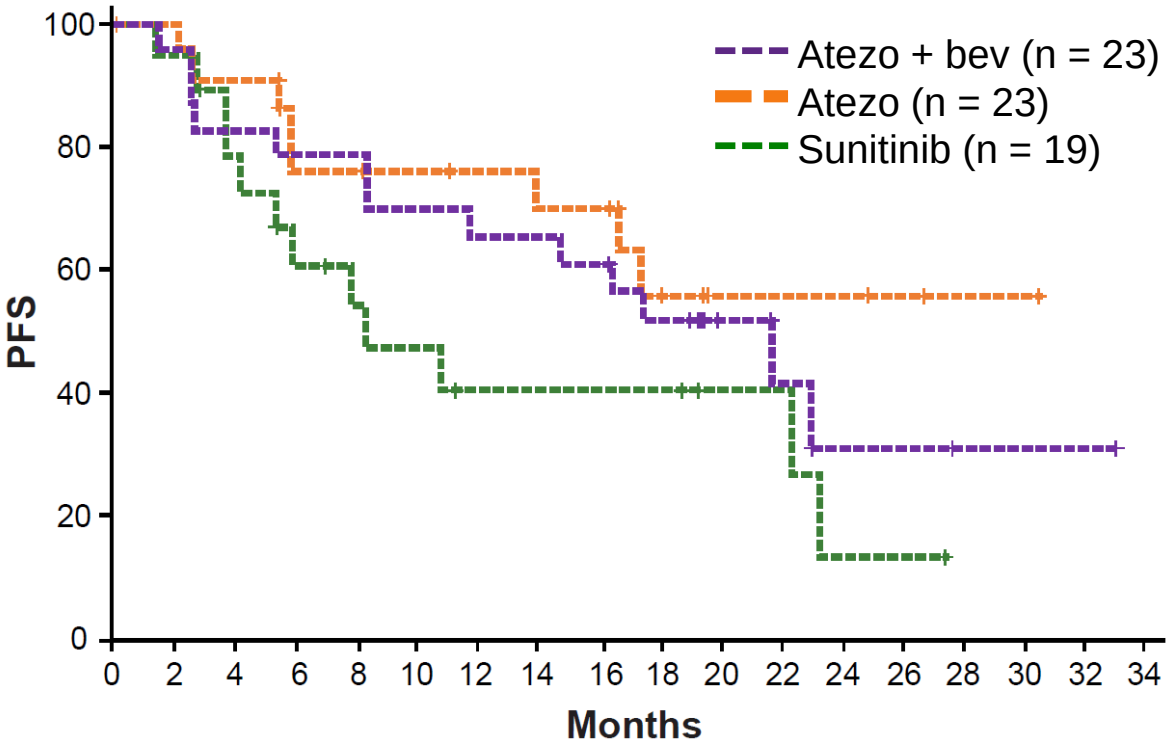
Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

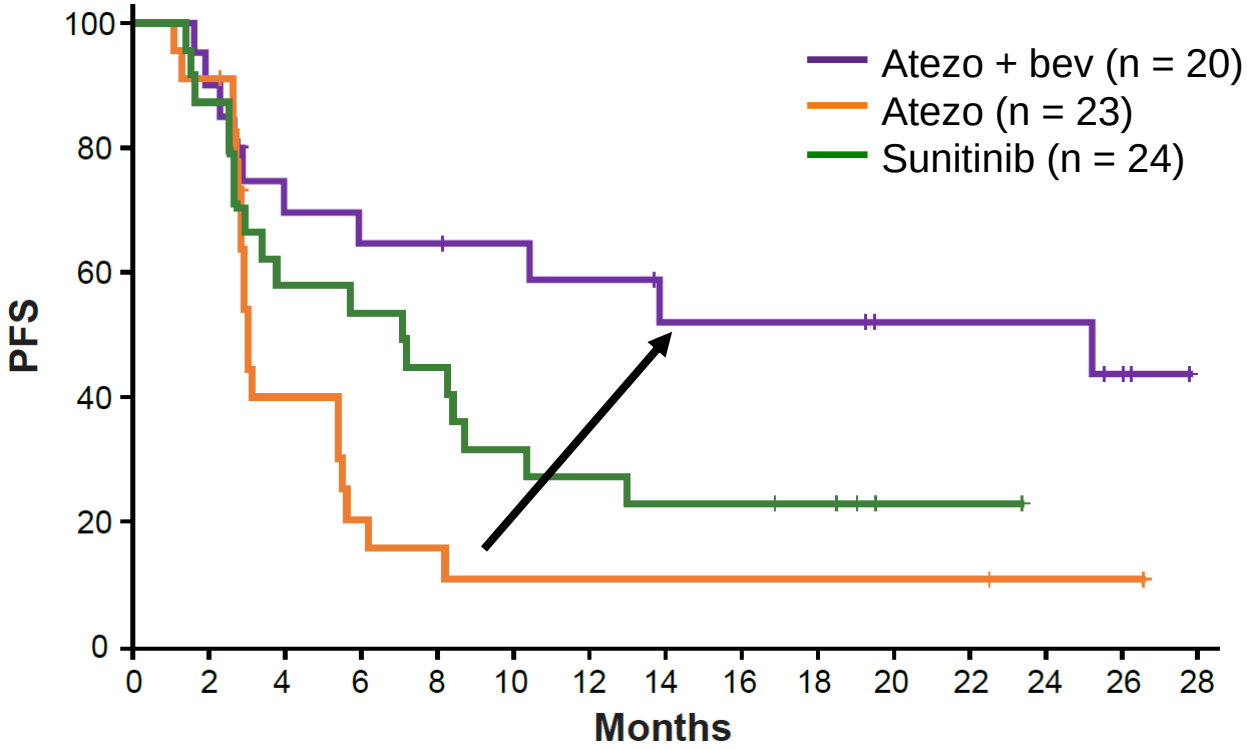
Addition of Bevacizumab to Atezolizumab is Associated With Improved Benefit in T-effector^{High}/Myeloid Inflammation^{High} Subgroup

Myeloid Inflammation

T-effector^{High}Myeloid^{Low}



T-effector^{High}Myeloid^{High}

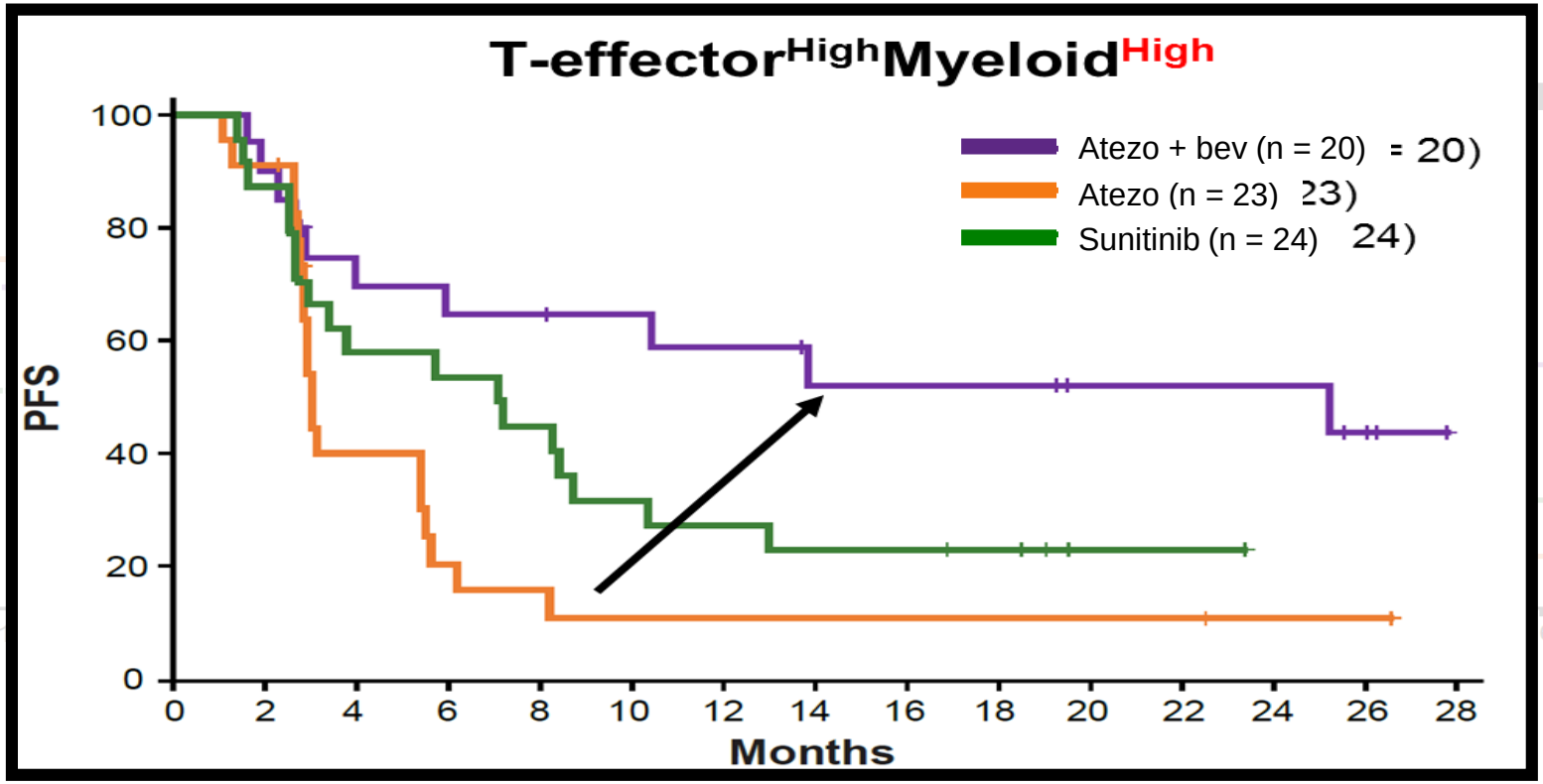


T-effector Gene Signature: *CD8A, EOMES, PRF1, IFNG, CD274*.
High: ≥ median expression, Low: < median expression.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Addition of Bevacizumab to Atezolizumab is Associated With Improved Benefit in T-effector^{High}/Myeloid Inflammation^{High} Subgroup

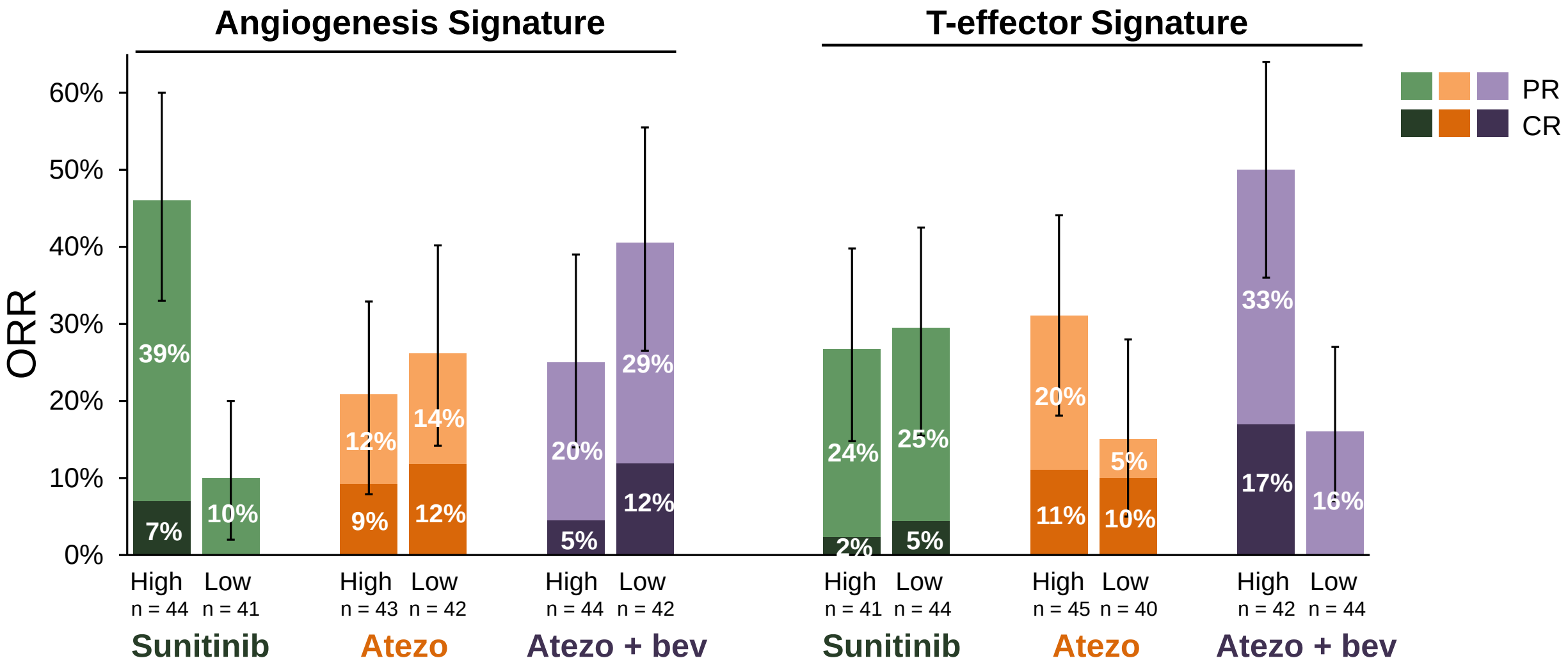
Myeloid Inflammation



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

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

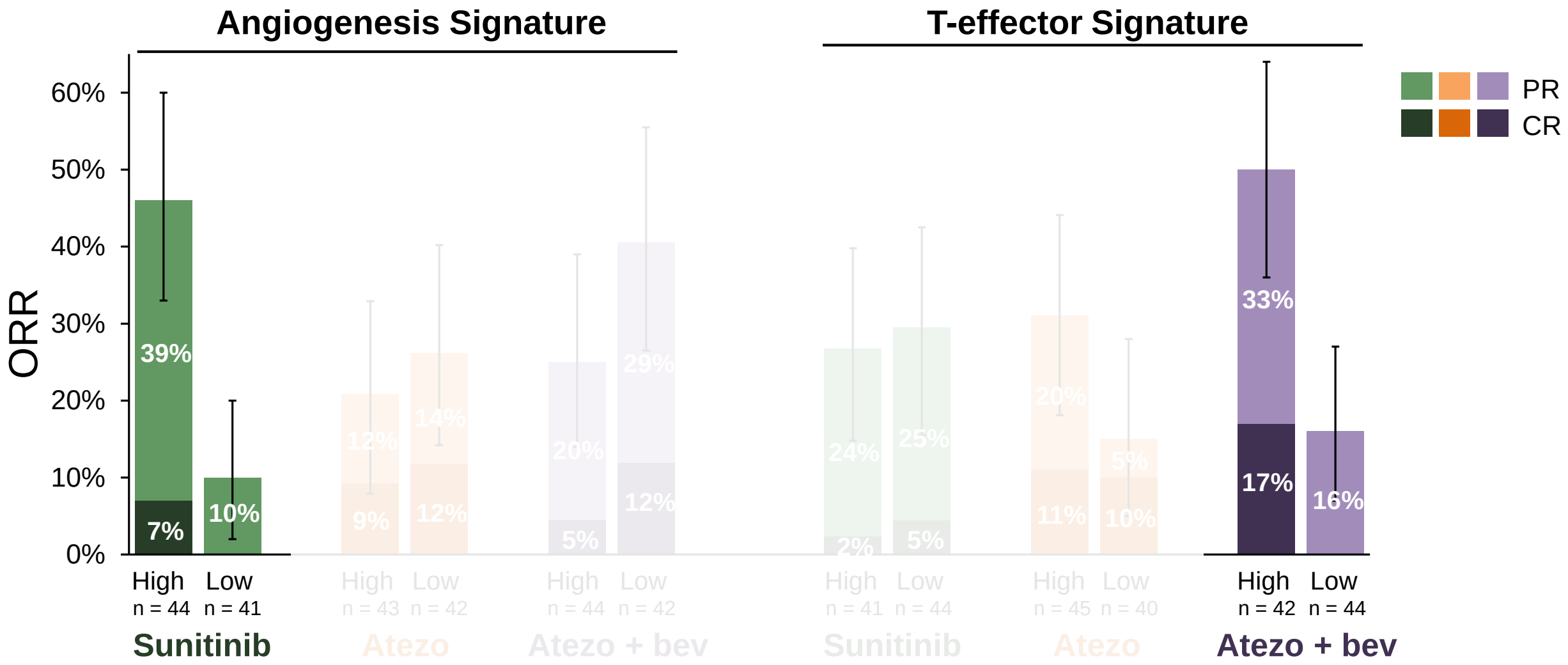
ORR Correlates With PFS in Gene Expression Subgroups



Confirmed IRF-assessed ORR.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

ORR Correlates With PFS in Gene Expression Subgroups



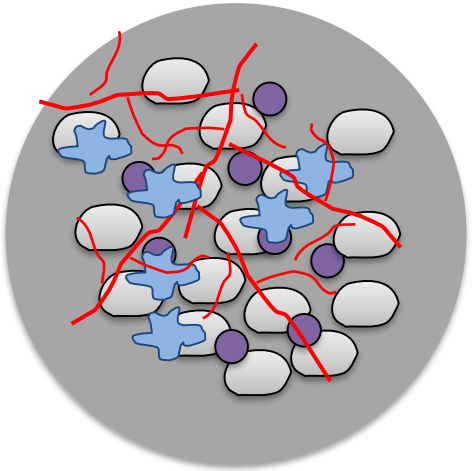
Confirmed IRF-assessed ORR.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



Angiogenic

Clinical Activity

Sunitinib

Tumor cells

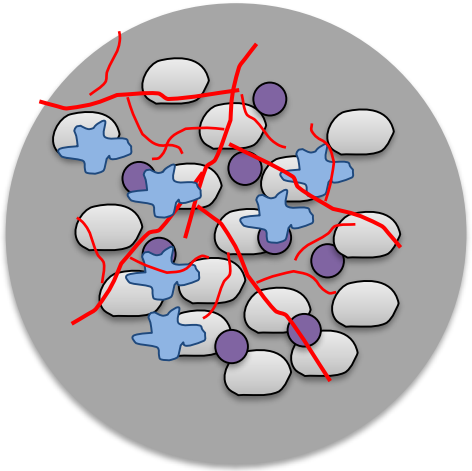
T-effector cells

Myeloid cells

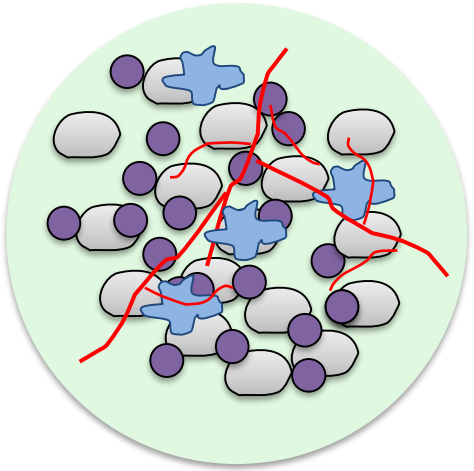
Vasculature

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

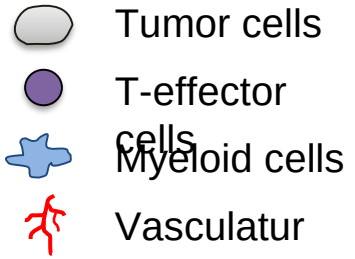
Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



Angiogenic



T-effector^{High}
Myeloid Inflammation^{Low}



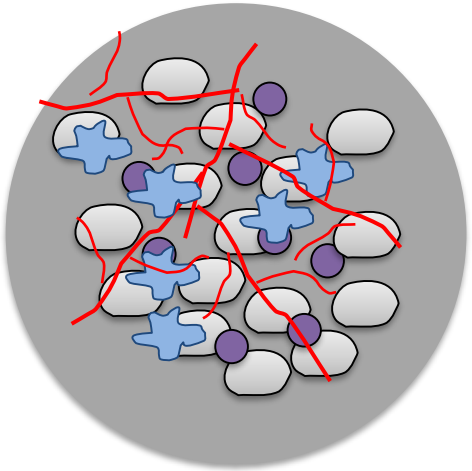
Clinical Activity

Sunitinib

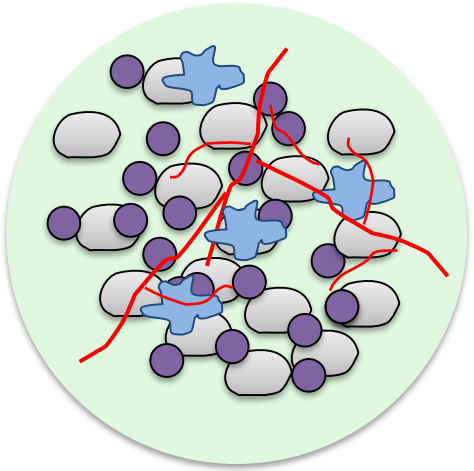
Atezolizumab

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

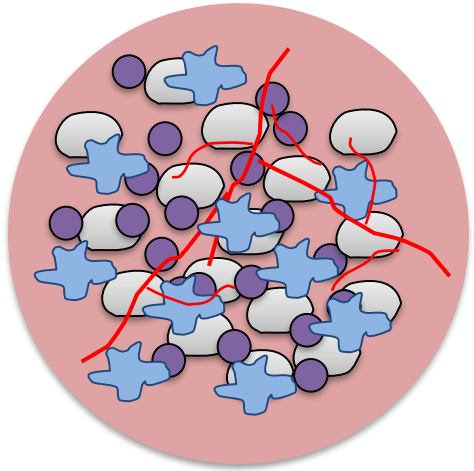
Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



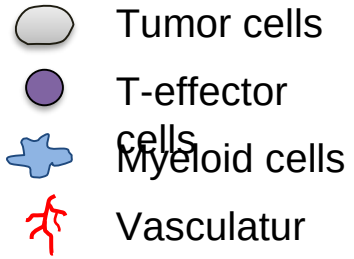
Angiogenic



T-effector^{High}
Myeloid Inflammation^{Low}



T-effector^{High}
Myeloid Inflammation^{High}
Immune Suppressed



Clinical Activity

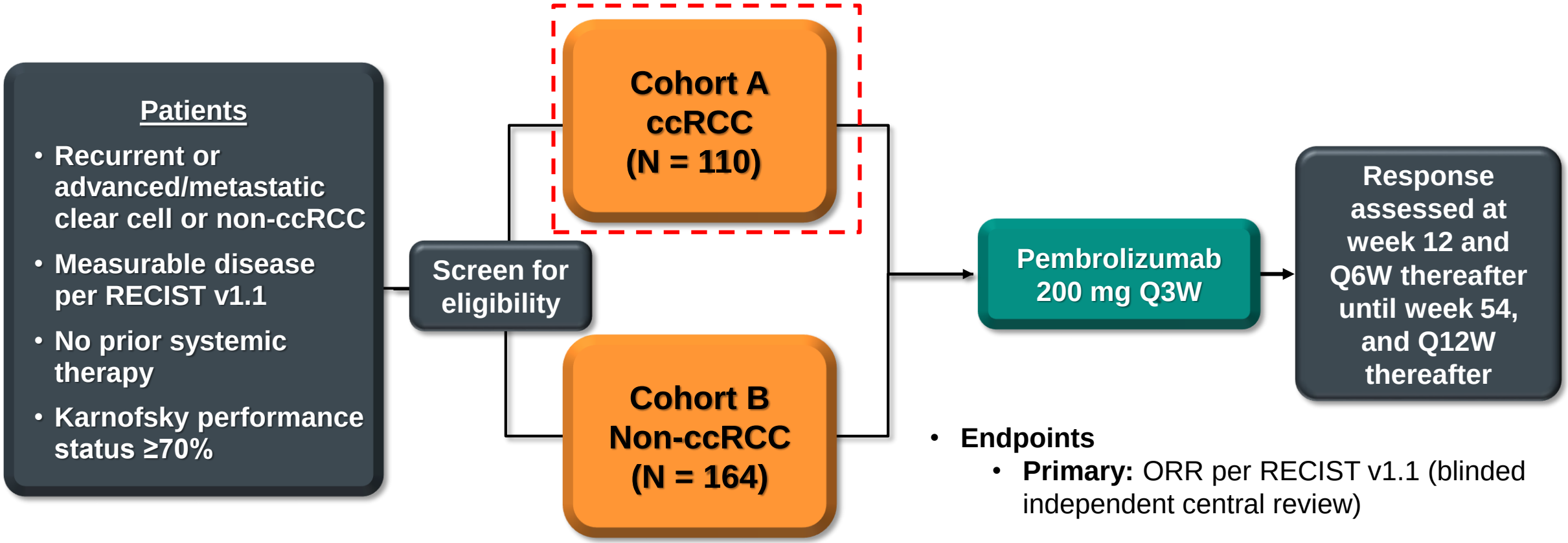
Sunitinib

Atezolizumab

Atezolizumab + Bevacizumab

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

KEYNOTE-427: (NCT02853344)



- **Endpoints**
  - **Primary:** ORR per RECIST v1.1 (blinded independent central review)
  - **Secondary:** DOR, DCR, PFS, OS, safety, and tolerability
  - **Exploratory:** tissue based biomarkers (e.g. IHC, RNA sequencing)

PD-1/PD-L1 Checkpoint Inhibitors in RCC

- PD-1/PD-L1–based combination regimens are being evaluated as first line RCC therapy
  - Nivolumab + ipilimumab was recently approved by the FDA[1,2] for the treatment of patients with IMDC intermediate- or poor risk, previously untreated advanced RCC (aRCC)
  - Atezolizumab + bevacizumab met the primary end point of PFS in patients with PD-L1–positive tumors by investigator review[3]
  - Pembrolizumab + axitinib, pembrolizumab + lenvatinib, avelumab + axitinib, and nivolumab + cabozantinib are being evaluated in phase 3 studies
- Atezolizumab monotherapy displayed encouraging antitumor activity in treatment-naive patients in a randomized phase 2 study[4]
- Less is known about the activity of single-agent PD-1 blockade in treatment-naive patients with clear cell RCC (ccRCC)

IMDC, International Metastatic RCC Database Consortium.

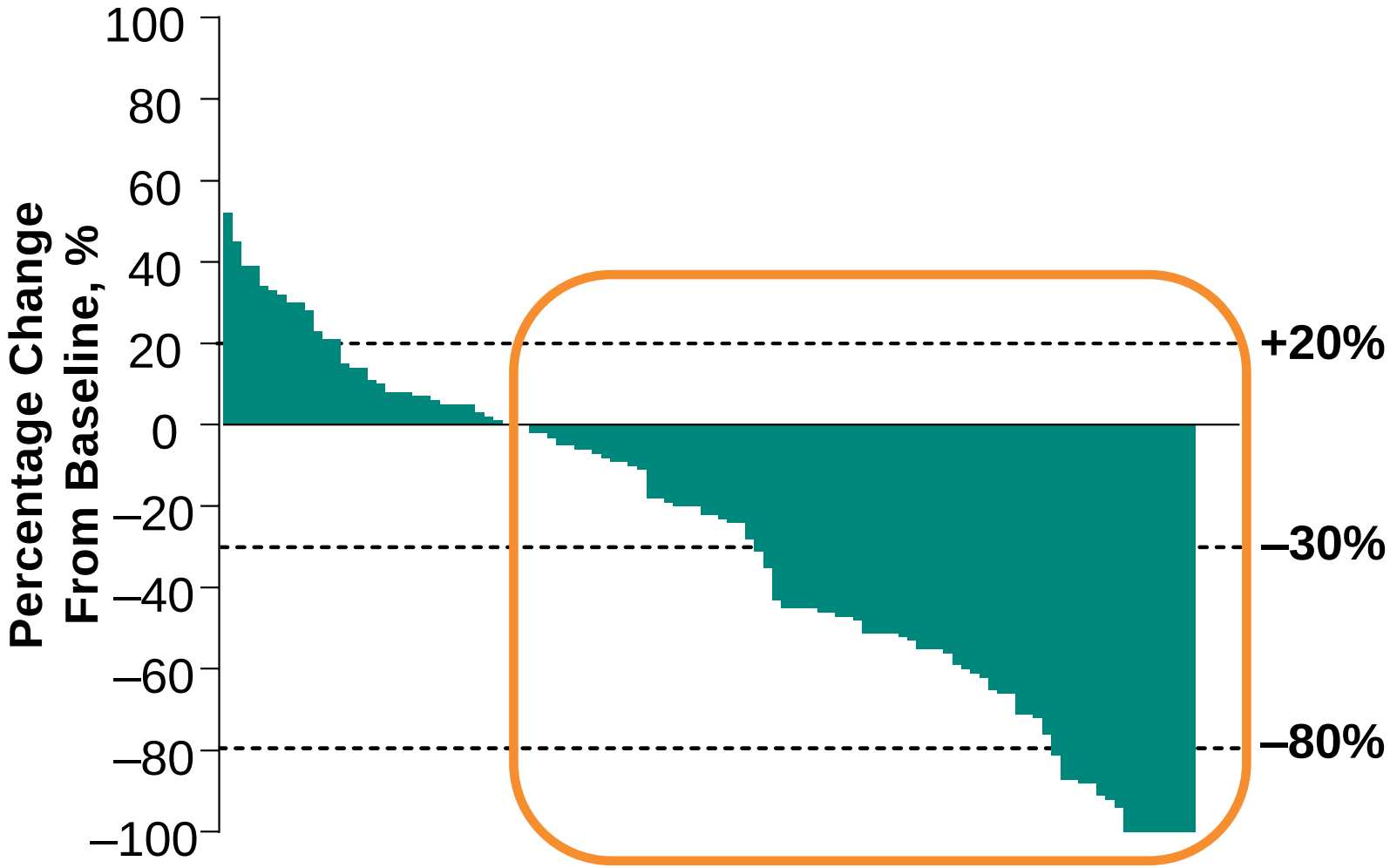
1. OPDIVO [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; April 2018. 2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): kidney cancer (Version 4.2018). 2018. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed May 31, 2018. 3. Motzer RJ et al. *J Clin Oncol.* 36(6 suppl):578-578. 4. Atkins MB et al. *J Clin Oncol.* 2017;35(suppl):4505.

Confirmed ORR by Blinded Independent Central Review

	N = 110		
	n	**%**	**95% CI**
ORR	**42**	**38.2**	**29.1-47.9**
DCR (CR + PR + SD ≥6 months)	**65**	**59.1**	**49.3-68.4**
Best overall response			
CR	3	2.7	
PR	39	35.5	
SD	35	31.8	
PD	31	28.2	
No assessment	2	1.8	

Database cutoff: March 12, 2018.

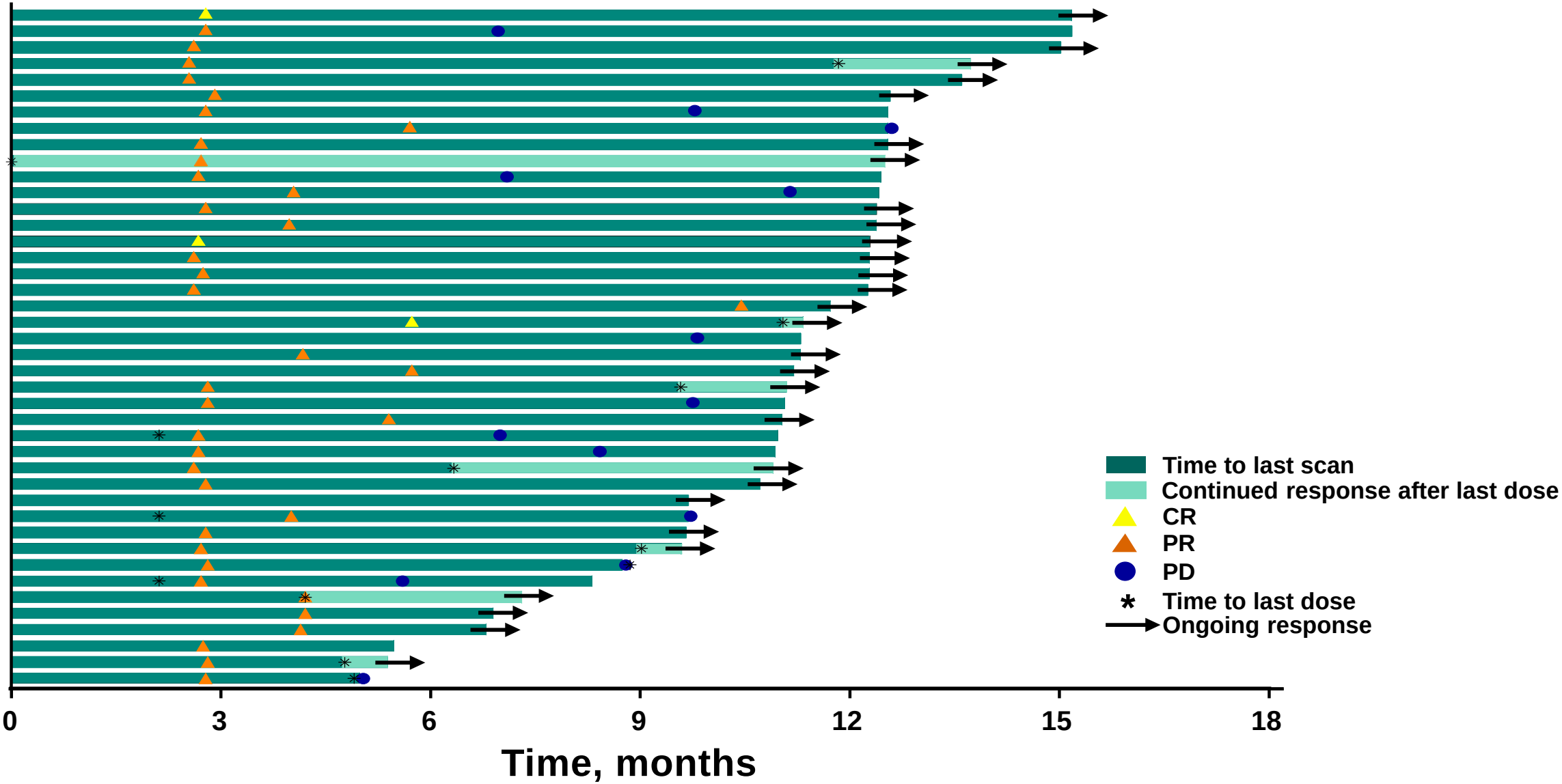
Maximum Change From Baseline in Target Lesions by Central Review



- 74 of 110 (67.3%) patients experienced a reduction in tumor burden
- 16 of 110 patients (14.5%) experienced a tumor burden reduction ≥80%
- 8 of 110 patients (7.3%) experienced 100% tumor burden reduction

Includes patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and had a postbaseline assessment (n = 108).
Database cutoff: March 12, 2018.

Time to Response and Response Duration



Database cutoff: March 12, 2018.

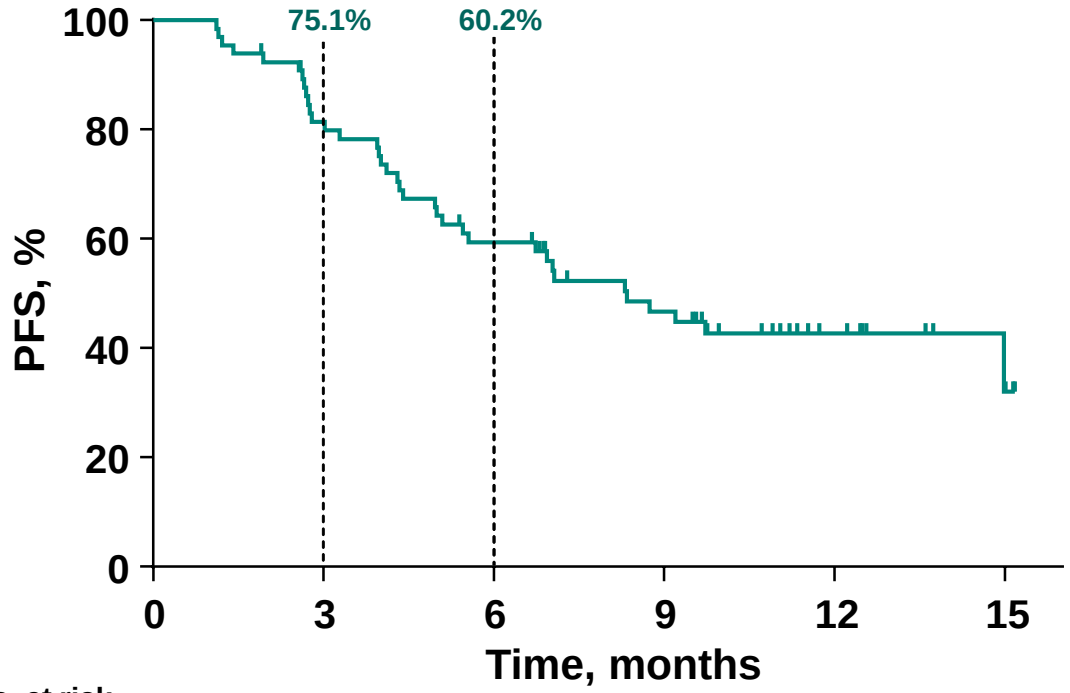
ORR by PD-L1 Expression

	CPS ≥1 n = 46	CPS <1 n =53	Missing n = 11
Confirmed ORR, % (95%CI)	**50.0 (34.9-65.1)**	**26.4 (15.3-40.3)**	**45.5 (16.7-76.6)**
DCR, % (95%CI)[a]	**67.4 (52.0-80.5)**	**49.1 (35.1-63.2)**	**72.7 (39.0-94.0)**
Confirmed BOR, %			
CR	6.5	0	0
PR	43.5	26.4	45.5
SD	26.1	35.8	36.4
PD	23.9	34.0	18.2
NA	0	3.8	0

[a]DCR = CR + PR + SD ≥6 months.
Database cutoff: March 12, 2018.

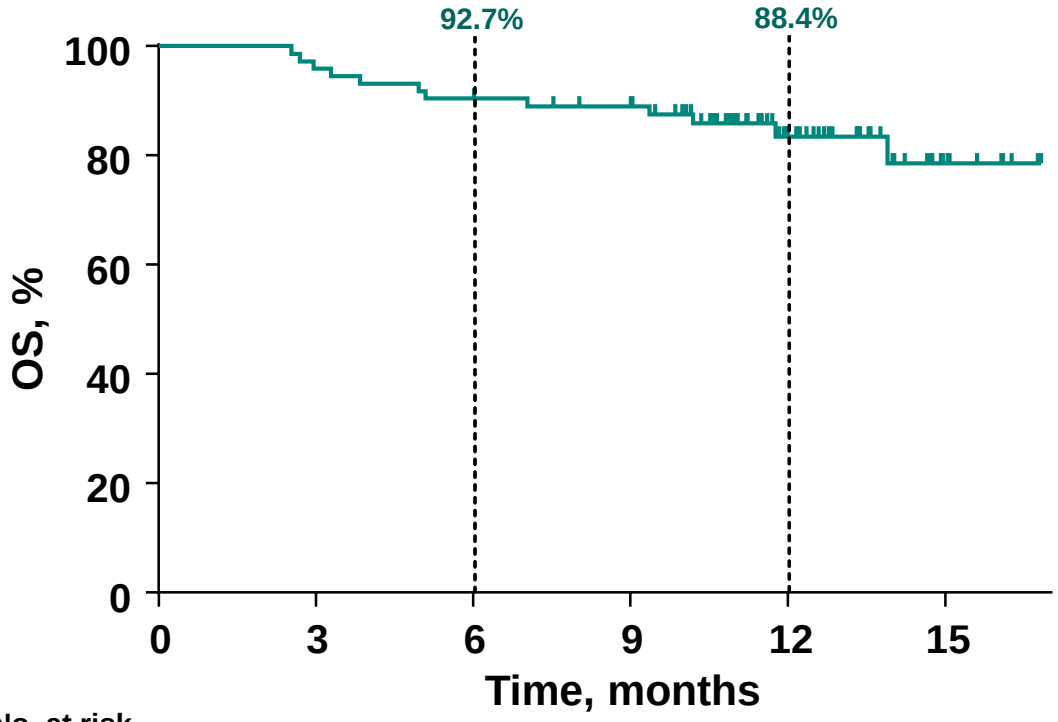
Progression-Free Survival and Overall Survival

Median PFS
8.7 months (95% CI, 6.7-12.2 months)



No. at risk						
Cohort A	110	81	62	47	21	0

Median OS
NR (95% CI, NR)



No. at risk						
Cohort A	110	107	102	98	57	0

Database cutoff: March 12, 2018.

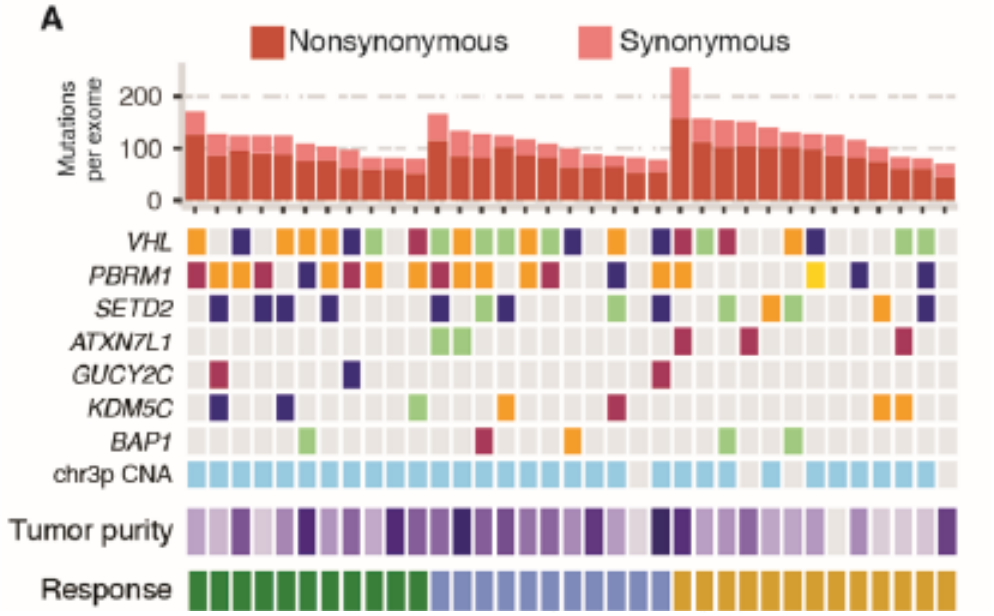
Adverse Events of Special Interest[a]

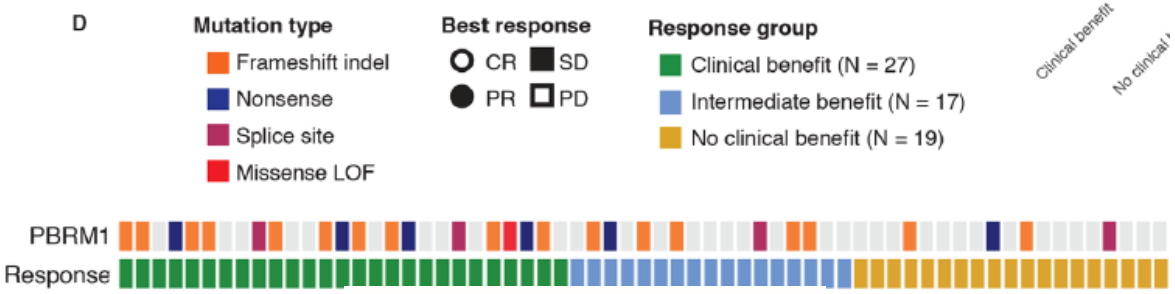
n (%) N = 110	Any Grade ≥2 Patients	Grade 3-5
Hypothyroidism	12 (10.9)	0 (0)
Hyperthyroidism	5 (4.5)	0 (0)
Pneumonitis	5 (4.5)	1 (0.9)[b]
Colitis	3 (2.7)	3 (2.7)
Hepatitis	2 (1.8)	2 (1.8)
Severe skin reaction	2 (1.8)	2 (1.8)
Myositis	2 (1.8)	1 (0.9)

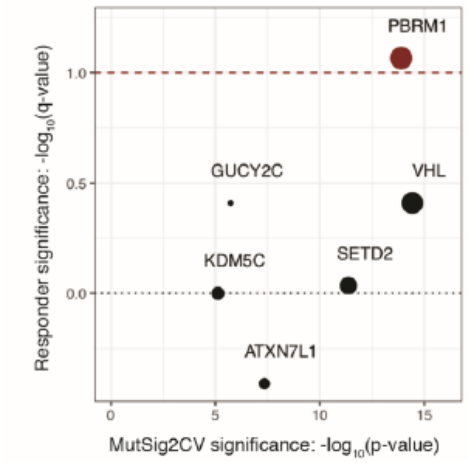
[a]Based on a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included.
[b]Grade 5 pneumonitis
Database cutoff: March 12, 2018.

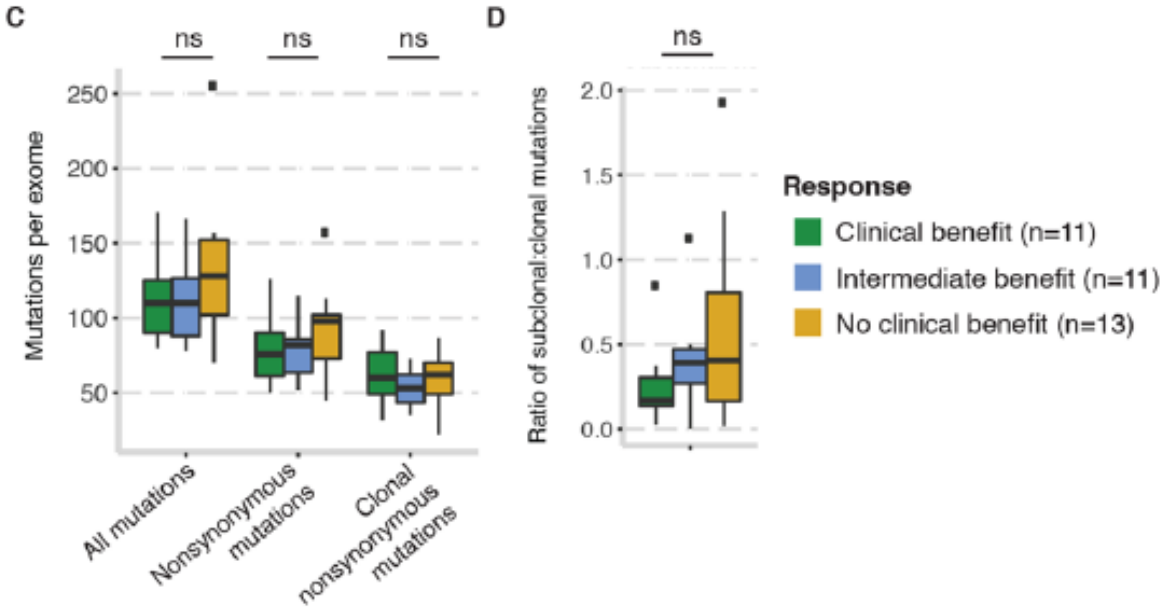
Conclusions

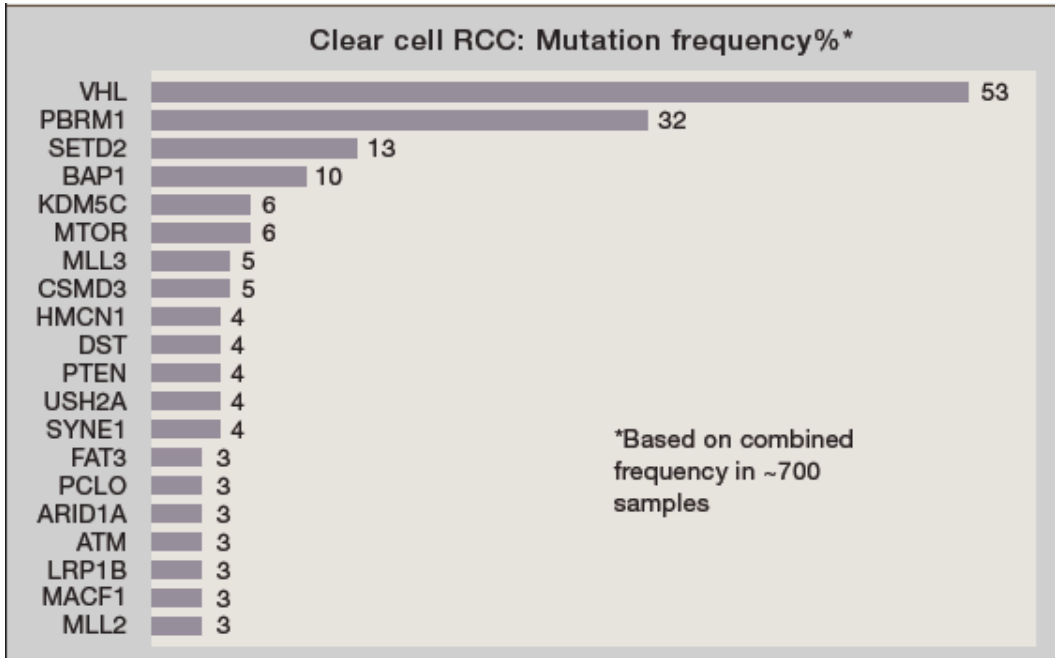
- Pembrolizumab has shown promising antitumor activity as monotherapy in first-line ccRCC across IMDC risk groups, with ORR 38%
  - Encouraging activity was also observed in key subgroups, such as IMDC intermediate/poor risk (ORR, 42%) and patients with PD-L1–positive tumors (ORR, 50%)
  - ORR of 32% in patients with IMDC favorable risk
- Safety profile in KEYNOTE-427 cohort A was similar to the previously described safety profile of pembrolizumab in other tumor types
- Cohort B of KEYNOTE-427, to explore the role of pembrolizumab monotherapy in non-ccRCC patients, is ongoing
- Results presented herein provide support for the exploration of pembrolizumab in the adjuvant setting (KEYNOTE-564 NCT03142334, currently enrolling) and will allow investigators to put the benefit of anti–PD-1–based combination therapies in better context





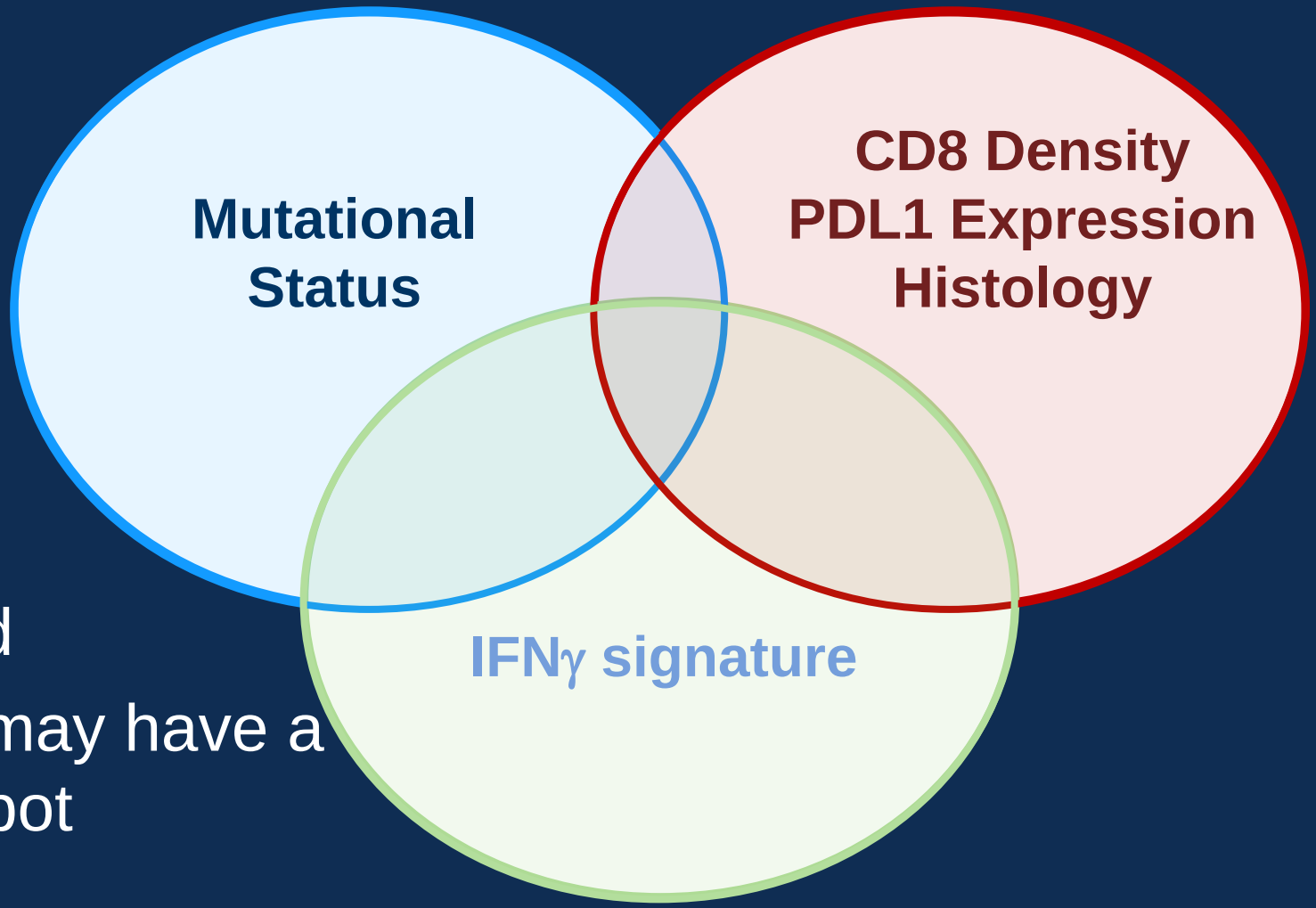






PBRM1 LOF and Response to anti-PD-1 immunotherapy

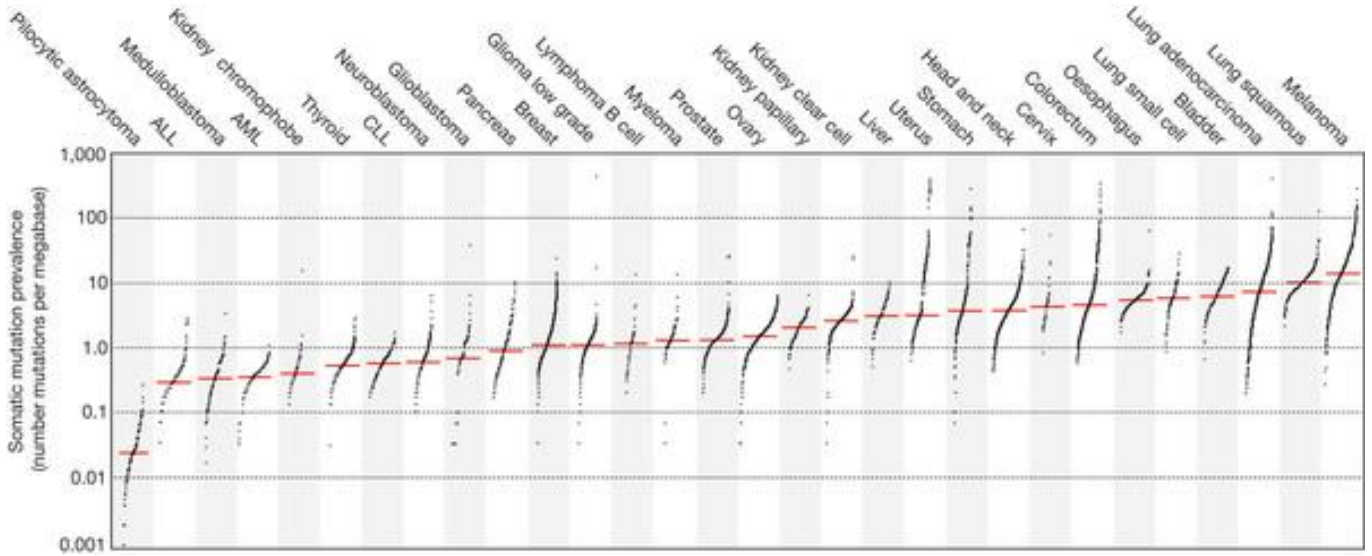
Biomarker Model



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

Biomarkers for Immune Checkpoint Inhibitors

Genetics: Overall Tumor Mutation Burden

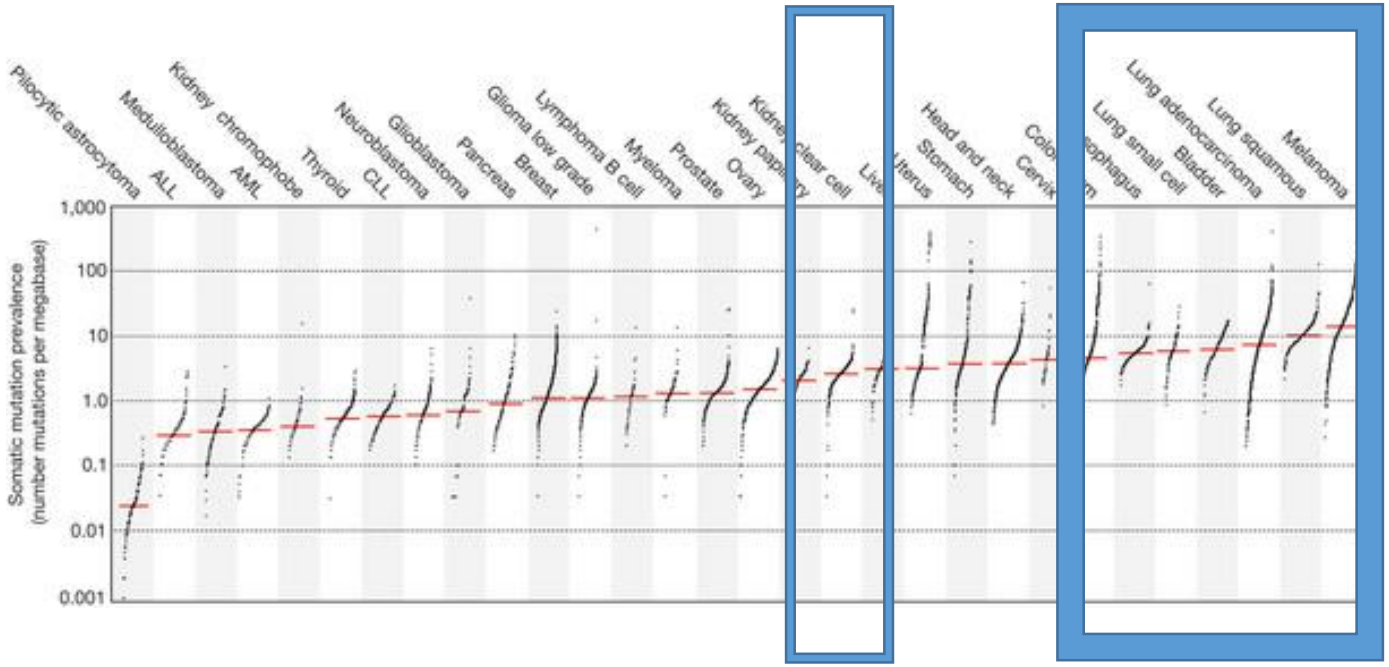


Alexandrov et al, Nature 2013

Biomarkers for Immune Checkpoint Inhibitors

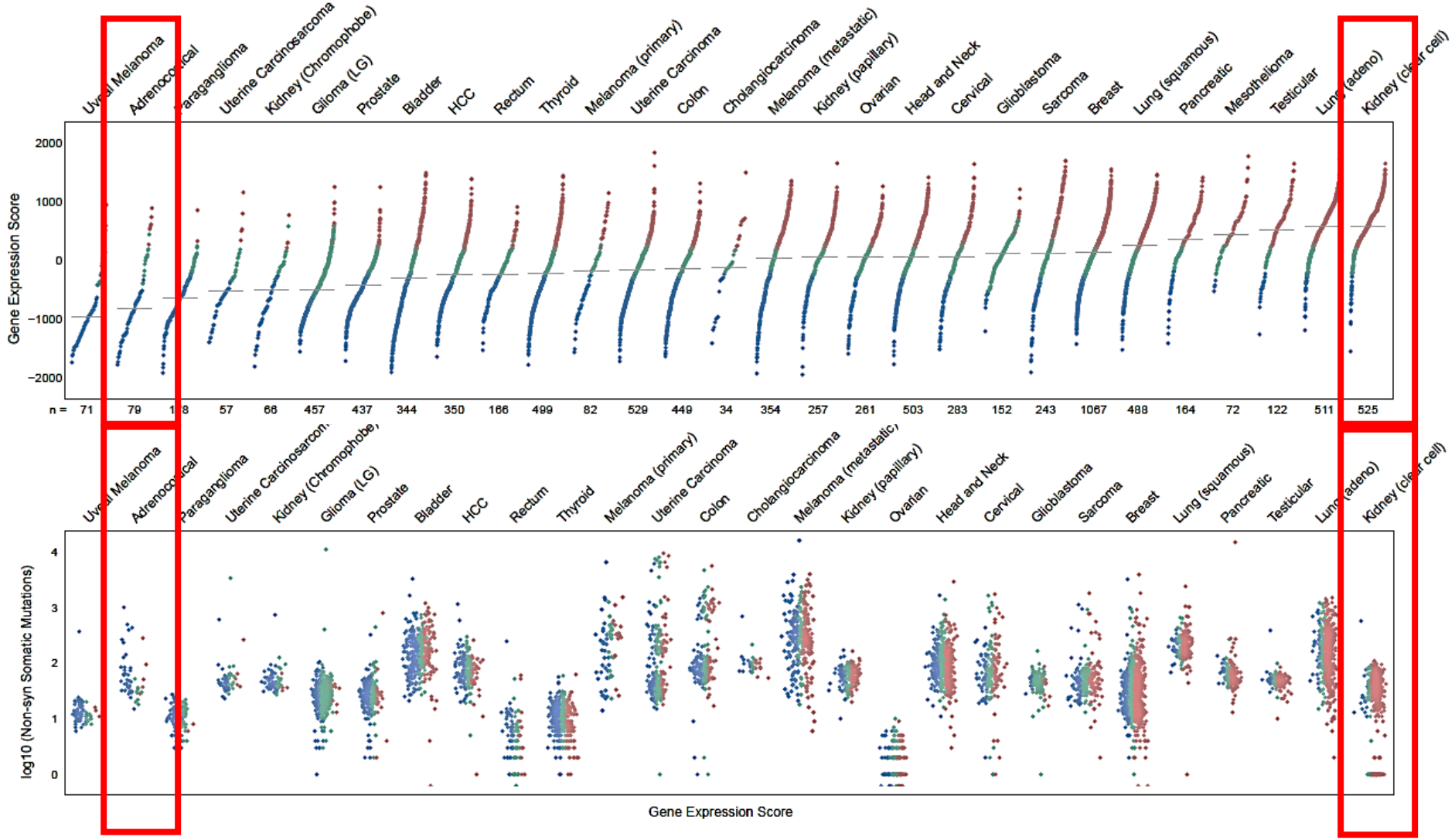
Genetics: Overall Tumor Mutation Burden

- Melanoma has the highest mutation rate of any cancer



Alexandrov et al, Nature 2013

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



Urothelial Cancer and Immune Checkpoint Therapy with anti-PD-1/PD-L1

Overview with Significant Evolving Literature

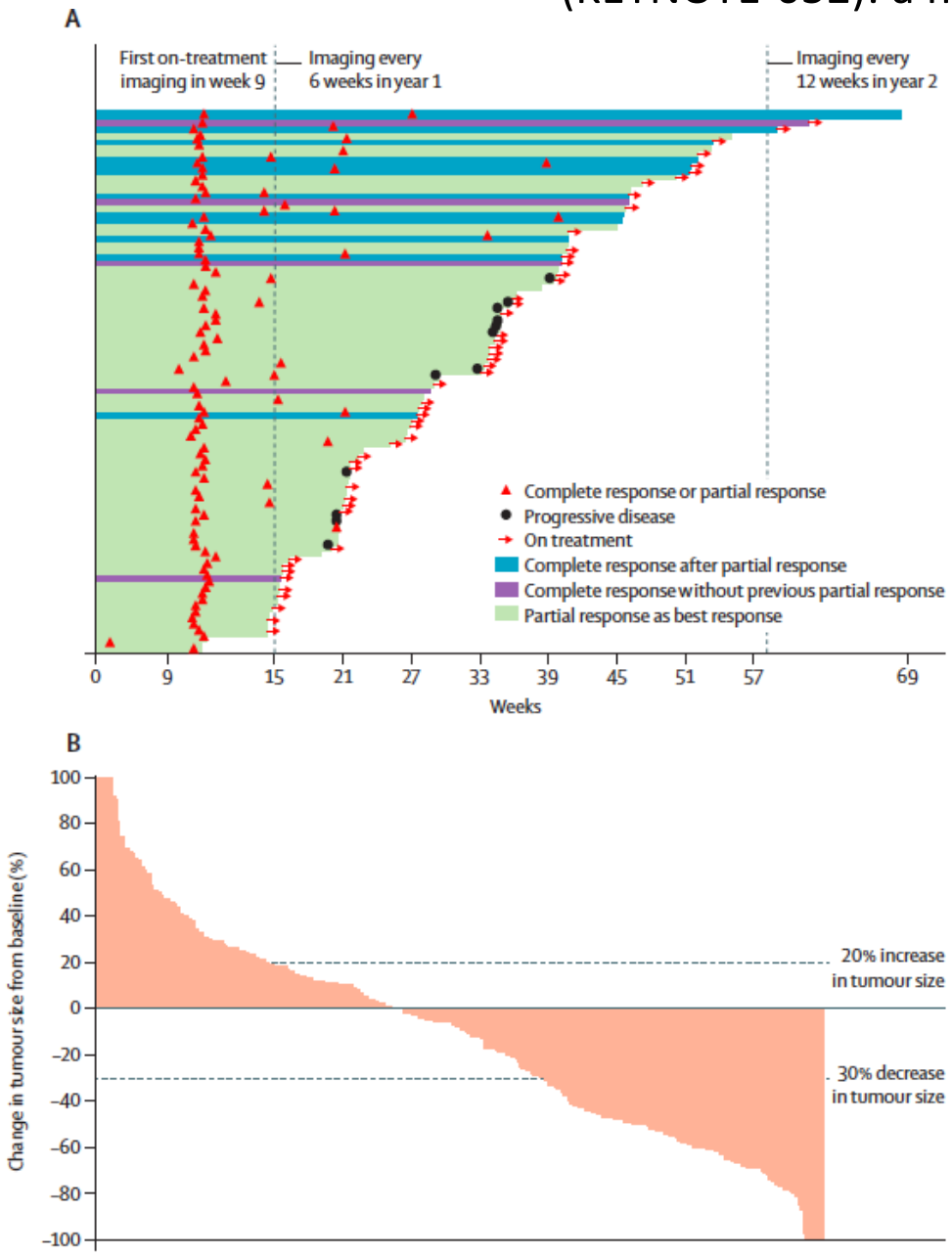
First-line **pembrolizumab** in cisplatin-ineligible patients with advanced urothelial cancer (KEYNOTE-052): a multicenter, single-arm, phase 2 study

	All treated patients (n=370)	Patients enrolled at least 4 months before data cutoff (n=307)
Objective response	89 (24%, 20–29)	83 (27%, 22–32)
Complete response	17 (5%, 3–7)	17 (6%, 3–9)
Partial response	72 (19%, 16–24)	66 (21%, 17–27)
Stable disease	84 (23%, 19–27)	57 (19%, 14–23)
Progressive disease	156 (42%, 37–47)	130 (42%, 37–48)
No assessment*	31 (8%, 6–12)	28 (9%, 6–13)
Not evaluable†	10 (3%, 1–5)	9 (3%, 1–6)

Data are n (%, 95% CI). Only confirmed responses are included. *Patients with no assessment had no post-baseline imaging. †Patients who were not evaluable had post-baseline imaging, but images were not of sufficient quality to determine response.

Table 2: **Centrally assessed objective tumour response to pembrolizumab as per Response Evaluation Criteria in Solid Tumors (version 1.1)**

First-line **pembrolizumab** in cisplatin-ineligible patients with advanced urothelial cancer (KEYNOTE-052): a multicenter, single-arm, phase 2 study



	Responders/ total in subgroup	Objective response (%)
Age		
<65 years	17/57	30% (95% CI 18–43)
≥65 years	66/250	26% (95% CI 21–32)
ECOG performance status		
0 or 1	49/179	27% (95% CI 21–35)
2*	34/128	27% (95% CI 19–35)
Primary tumour location		
Upper urinary tract	13/59	22% (95% CI 12–35)
Lower urinary tract	70/247	28% (95% CI 23–34)
Metastases location		
Lymph node only	20/43	47% (95% CI 31–62)
Visceral disease	61/260	23% (95% CI 18–29)
Liver metastases		
Present	11/64	17% (95% CI 9–29)
Absent	72/243	30% (95% CI 24–36)
Reason for cisplatin ineligibility		
ECOG performance status 2	25/97	26% (95% CI 17–36)
Renal dysfunction	41/154	27% (95% CI 20–34)
ECOG performance status 2 and renal dysfunction	7/24	29% (95% CI 13–51)
Other reasons†	10/32	31% (95% CI 16–50)

Only confirmed responses are included. ECOG=Eastern Cooperative Oncology Group. *One patient had an ECOG performance status of 3. †Other reasons include New York Heart Association Class III heart failure, grade 2 or worse peripheral neuropathy, and grade 2 or worse hearing loss.

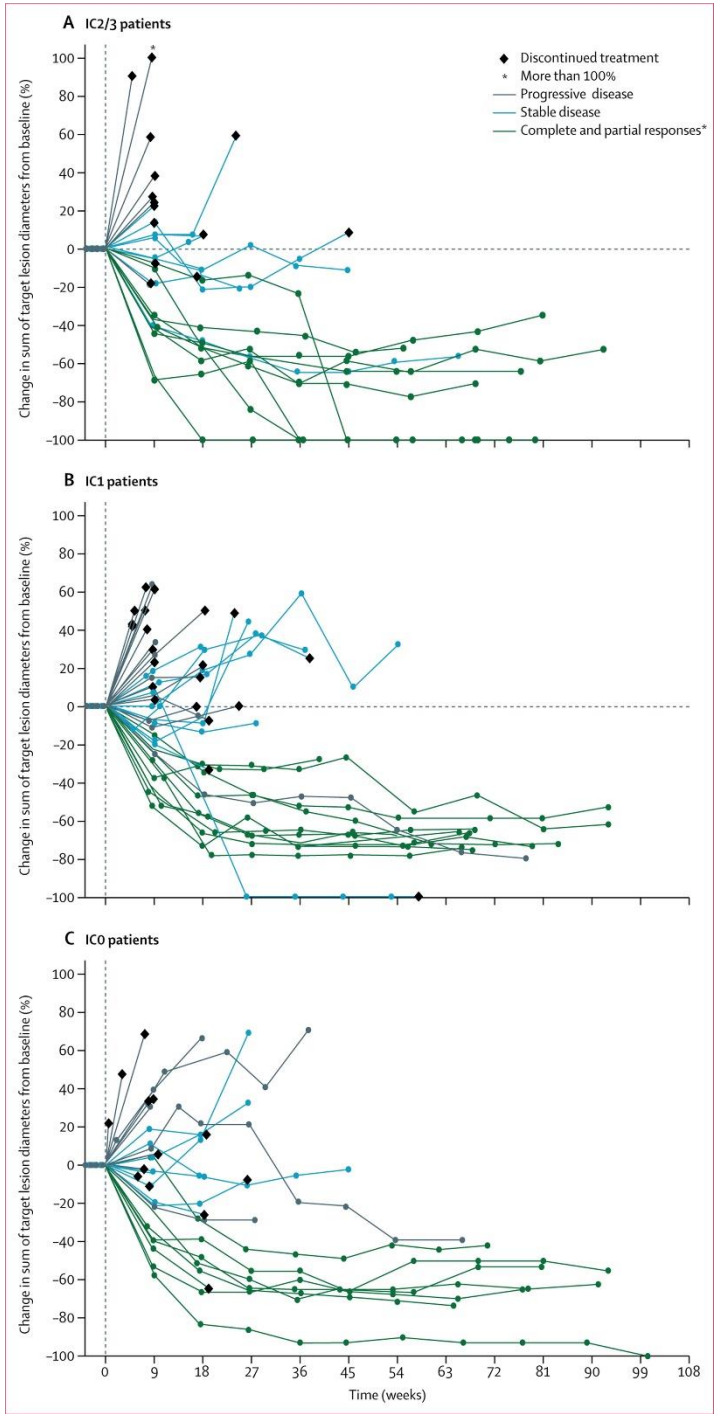
Table 3: **Tumour response to pembrolizumab in patients enrolled at least 4 months before data cutoff, by subgroup**

Atezolizumab as first-line treatment in cisplatin-ineligible patients with advanced urothelial carcinoma: a single-arm, multicentre, phase 2 trial

	Patients	Complete response	Partial response	Objective response, n (% [95% CI])*	Median duration of response (95% CI)
	119	11	16	27 (23% [16–31])	NE (14·1–NE)
IC2/3	32	4	5	9 (28% [14–47])	NE (11·1–NE)
IC1/2/3	80	8	11	19 (24% [15–35])	NE (NE–NE)
IC1	48	4	6	10 (21% [10–35])	NE (NE–NE)
IC0	39	3	5	8 (21% [9–36])	NE (12·8–NE)

Data cutoff was July 4, 2016. PD-L1=programmed death-ligand 1. IC=tumour-infiltrating immune cell. NE=not estimable. *Includes objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (independent review facility).

Table 2: **Objective response by PD-L1 status on tumour-infiltrating immune cells**



	Patients	Objective response, n (% [95% CI])*
All patients	119	27 (23% [16–31])
Demographics and previous treatment		
Age ≥80 years	25	7 (28% [12–49])
Perioperative chemotherapy†	22	8 (36% [17–59])
Primary tumour sites‡		
Bladder or urethra	85	14 (17% [9–26])
Upper tract	33	13 (39% [23–58])
Metastatic sites at baseline		
Lymph node only	31	10 (32% [17–51])
Visceral§	78	11 (14% [7–24])
Liver	25	2 (8% [1–26])
Cisplatin ineligibility criteria		
Impaired renal function	83	21 (25% [16–36])
ECOG PS 2	24	6 (25% [10–47])
Hearing loss of ≥25 dB¶	17	2 (12% [2–36])
Peripheral neuropathy, grade ≥2	7	1 (14% [0–58])
Renal impairment and ECOG PS 2	8	2 (25% [3–65])
Bajorin risk factors‖		
0	35	12 (34% [19–52])
1	66	13 (20% [11–31])
2	18	2 (11% [1–35])

Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicenter, open-label, phase 3 randomized controlled trial

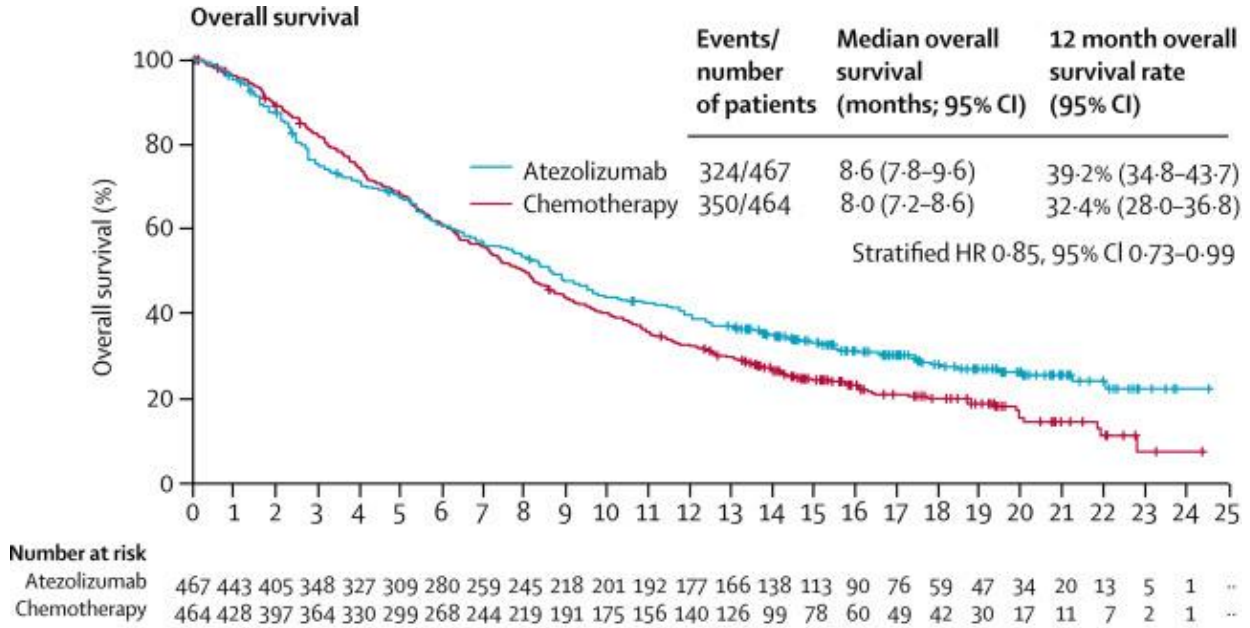
	IC2/3 population		ITT population	
	Atezolizumab group (n=116)	Chemotherapy group (n=118)	Atezolizumab group (n=467)	Chemotherapy group (n=464)
Progression-free survival				
Patients with event (%)*	93 (80%)	105 (89%)	407 (87%)	410 (88%)
Median (months; 95% CI)	2·4 (2·1–4·2)	4·2 (3·7–5·0)	2·1 (2·1–2·2)	4·0 (3·4–4·2)
Objective response†				
Number of evaluable patients	113	116	462	461
Number of patients with response (%, 95% CI)	26 (23·0%, 15·6–31·9)	25 (21·6%, 14·5–30·2)	62 (13·4%, 10·5–16·9)	62 (13·4%, 10·5–16·9)
Best overall response†				
Complete response	8 (7%)	8 (7%)	16 (3%)	16 (3%)
Partial response	18 (16%)	17 (15%)	46 (10%)	46 (10%)
Stable disease	23 (20%)	37 (32%)	92 (20%)	162 (35%)
Progressive disease	47 (42%)	30 (26%)	240 (52%)	150 (32%)
Missing or unevaluable	17 (15%)	24 (21%)	68 (15%)	87 (19%)
Duration of response†				
Patients with event (%)*	10/26 (38%)	20/25 (80%)	23/62 (37%)	49/62 (79%)
Median (months; 95% CI)	15·9 (10·4–NE)	8·3 (5·6–13·2)	21·7 (13·0–21·7)	7·4 (6·1–10·3)

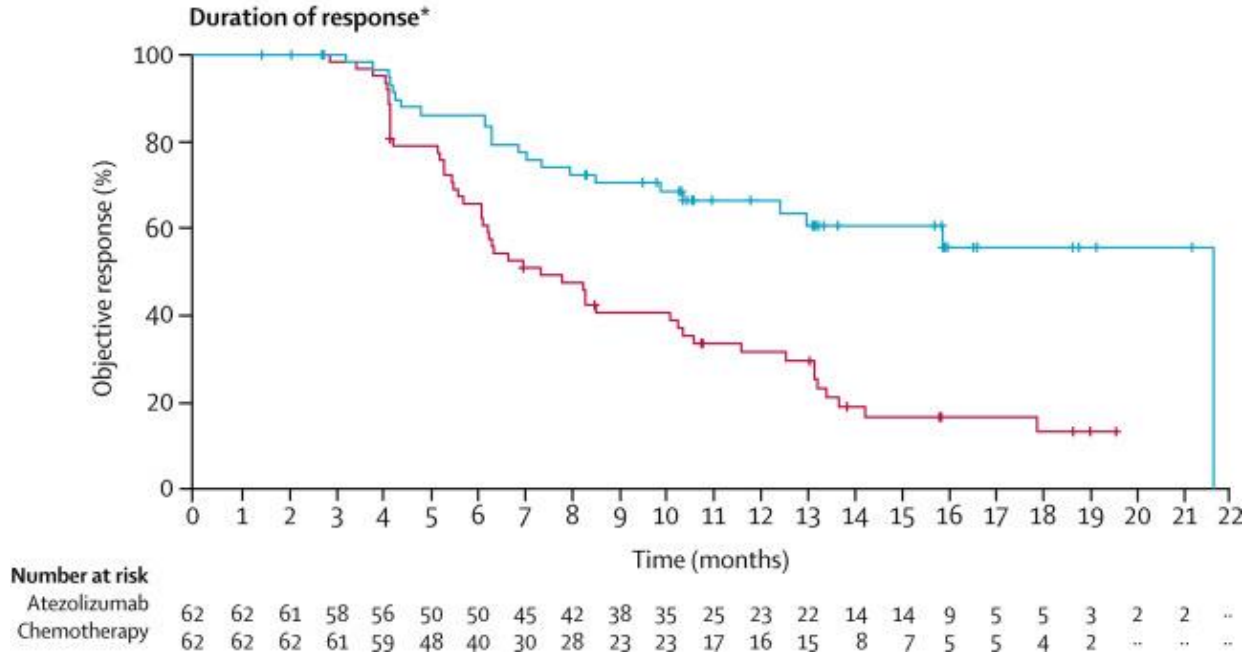
Data are n (%) or n/N (%), unless otherwise specified. IC2/3=patients with programmed death-ligand-1 expression on 5% or more of tumour-infiltrating immune cells. ITT=intention-to-treat. NE=not estimable. *Progressive disease or death. †Confirmed investigator-assessed objective responses.

Table 2: **Secondary and exploratory efficacy outcomes**

Atezolizumab vs chemotherapy in pts. with urothelial cancer platinum-treated (IMvigor211): Multicenter, open-label, phase 3 randomised controlled trial

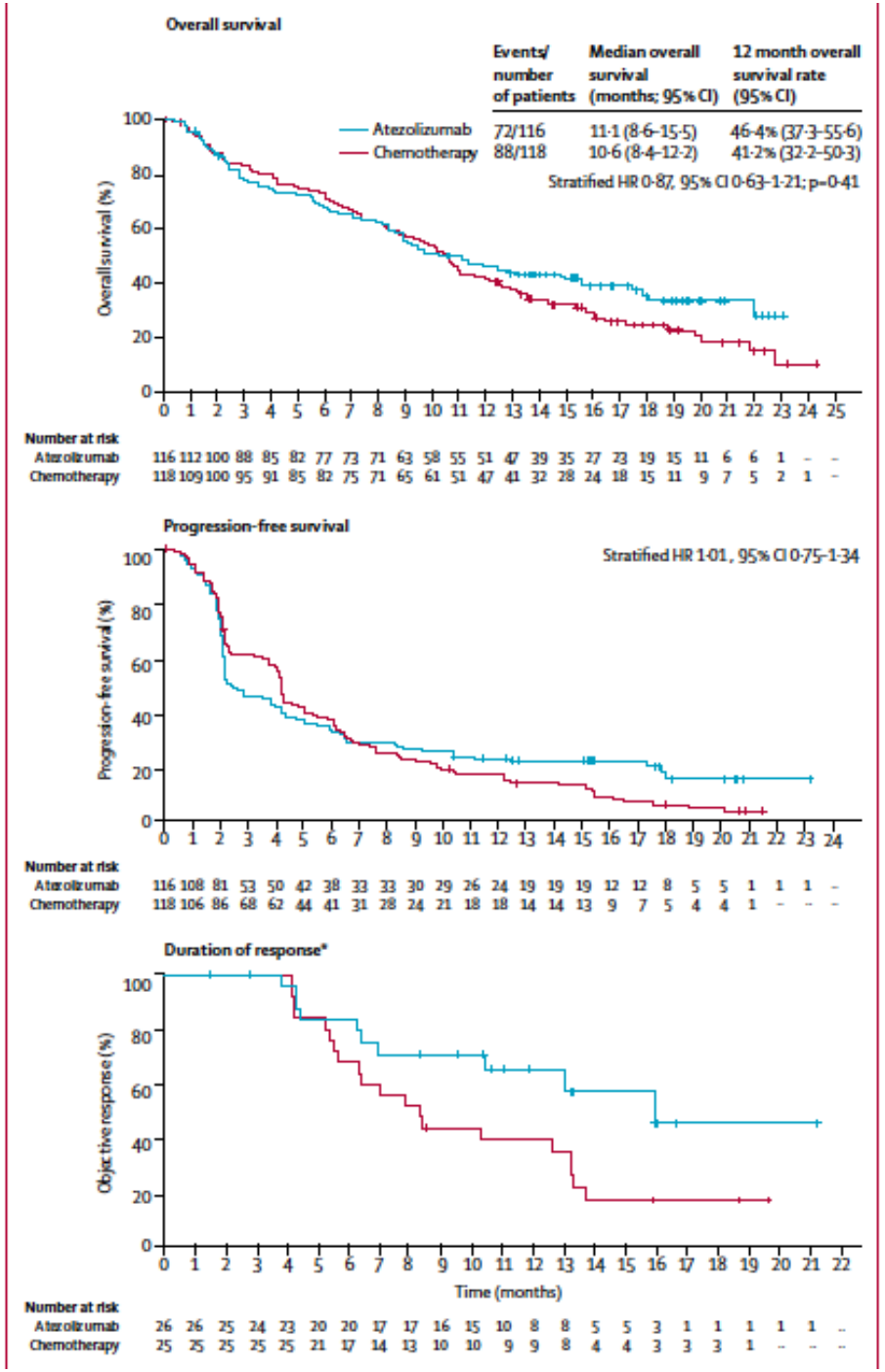
Intent-to-Treat patients enrolled with all patient cohorts



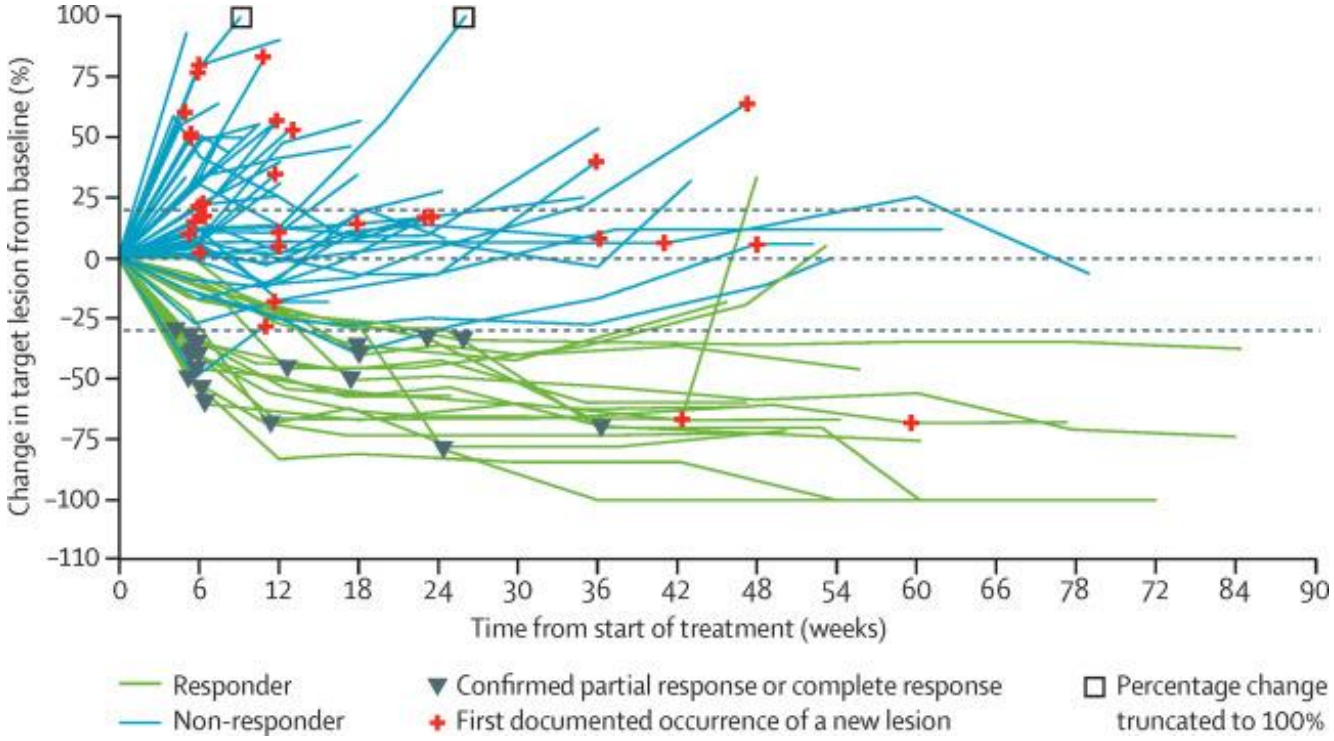


Atezolizumab vs chemotherapy in pts. with platinum-treated (IMvigor211): Multicenter, open-label, phase 3 randomised controlled trial

Efficacy outcomes in patients with PDL-1 expression on >5% tumor-infiltrating immune cells (IC2/3 population)



Nivolumab in recurrent metastatic urothelial cancer (CheckMate 032): a multicenter, open-label trial



	Nivolumab (n=78)	PD-L1 <1% (n=42)	PD-L1 ≥1% (n=25)
Confirmed objective response	19 (24·4%, 15·3–35·4)	11 (26·2%, 13·9–42·0)	6 (24·0%, 9·4–45·1)
Best overall response			
Complete response	5 (6%)	1 (2%)	4 (16%)
Partial response	14 (18%)	10 (24%)	2 (8%)
Stable disease	22 (28%)	11 (26%)	8 (32%)
Progressive disease	30 (38%)	18 (43%)	8 (32%)
Unable to establish	7 (9%)	2 (5%)	3 (12%)

Data are number (%, 95% CI) or number (%). Some percentages do not add up to 100 because of rounding.

Table 2: **Antitumour activity**

Nivolumab in recurrent metastatic urothelial cancer (CheckMate 032): a multicenter, open-label trial

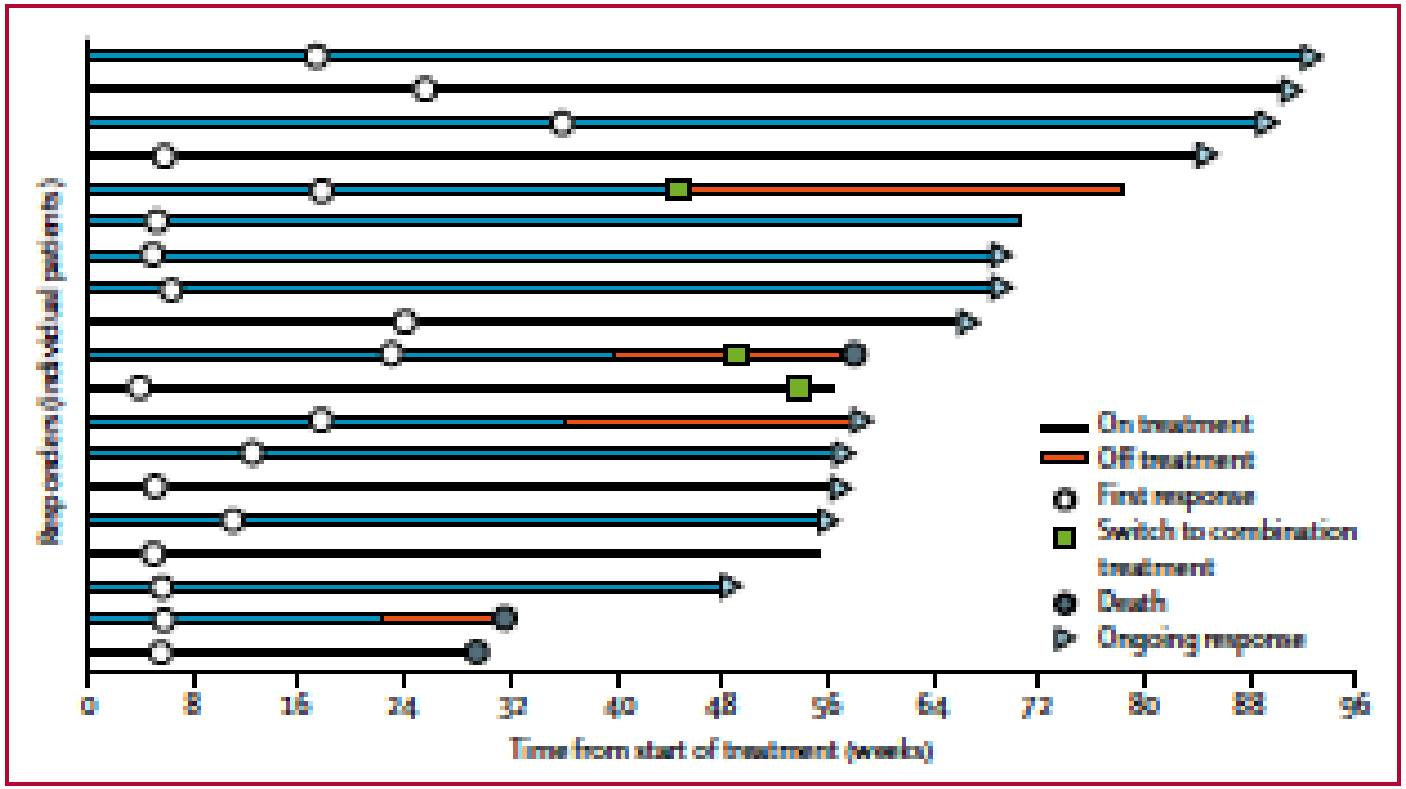


Figure 3: Time to and duration of response

Nivolumab in recurrent metastatic urothelial cancer (CheckMate 032): a multicenter, open-label trial

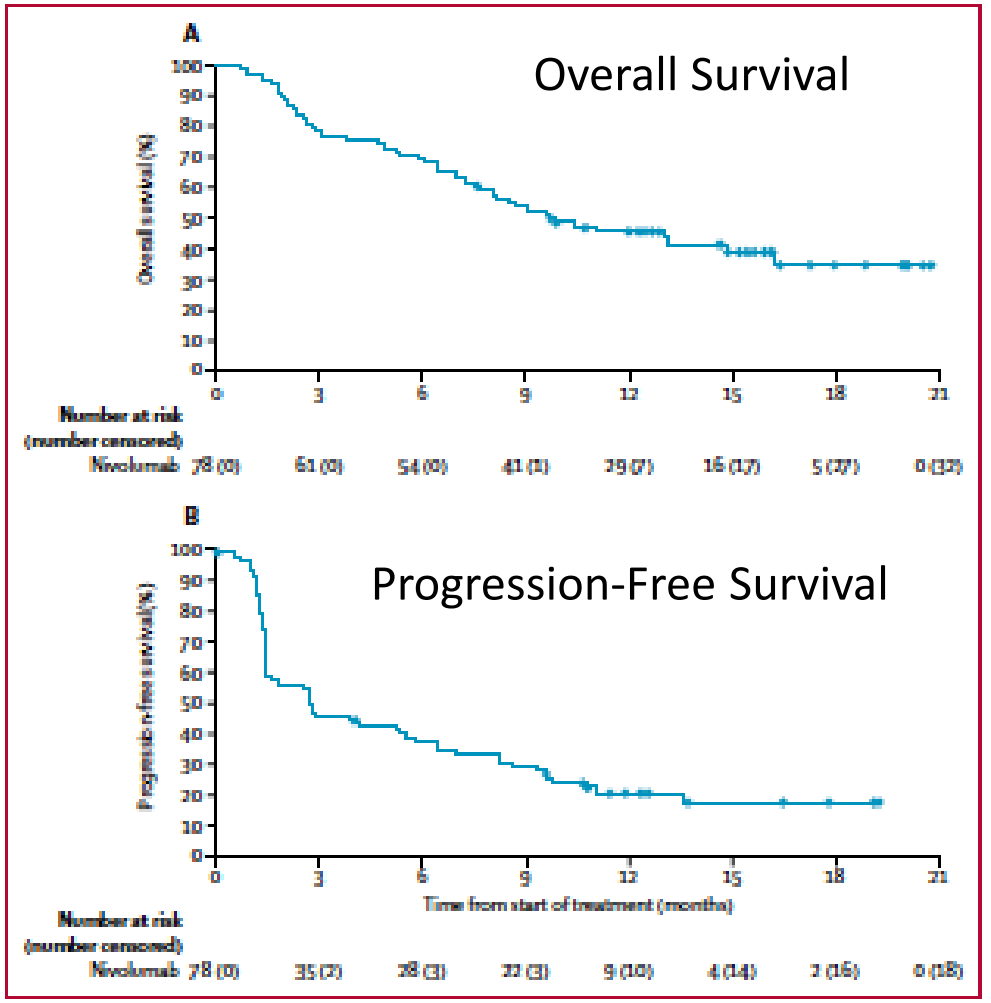
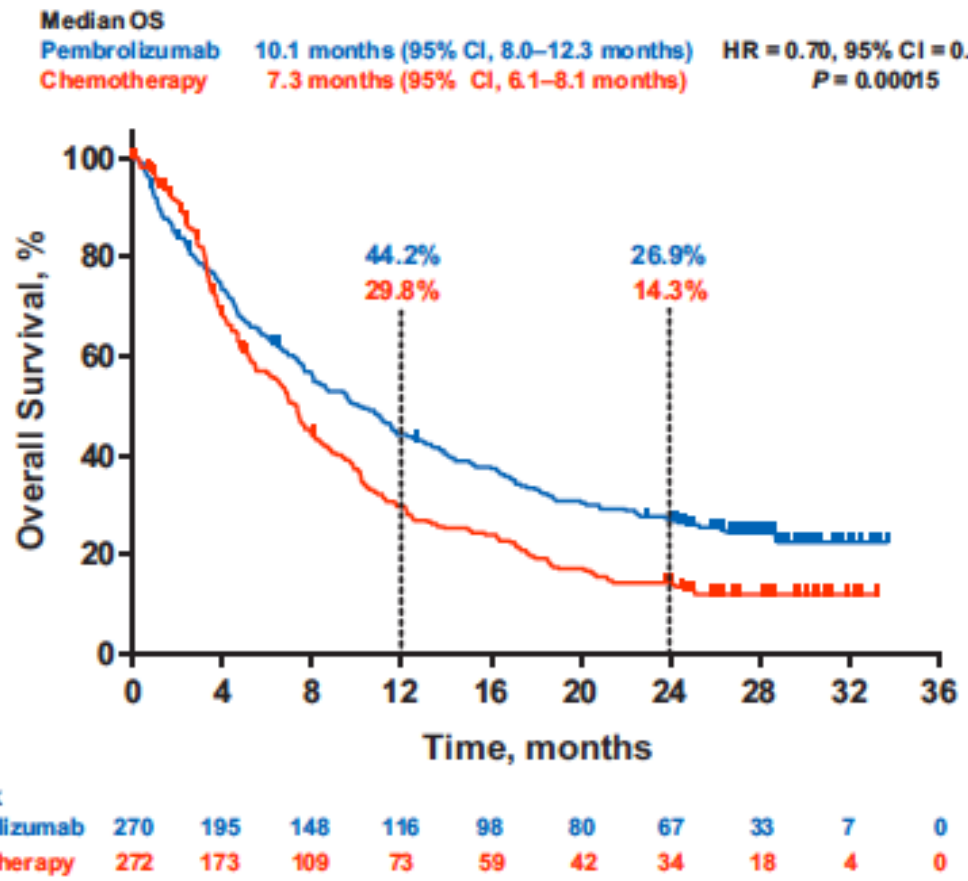
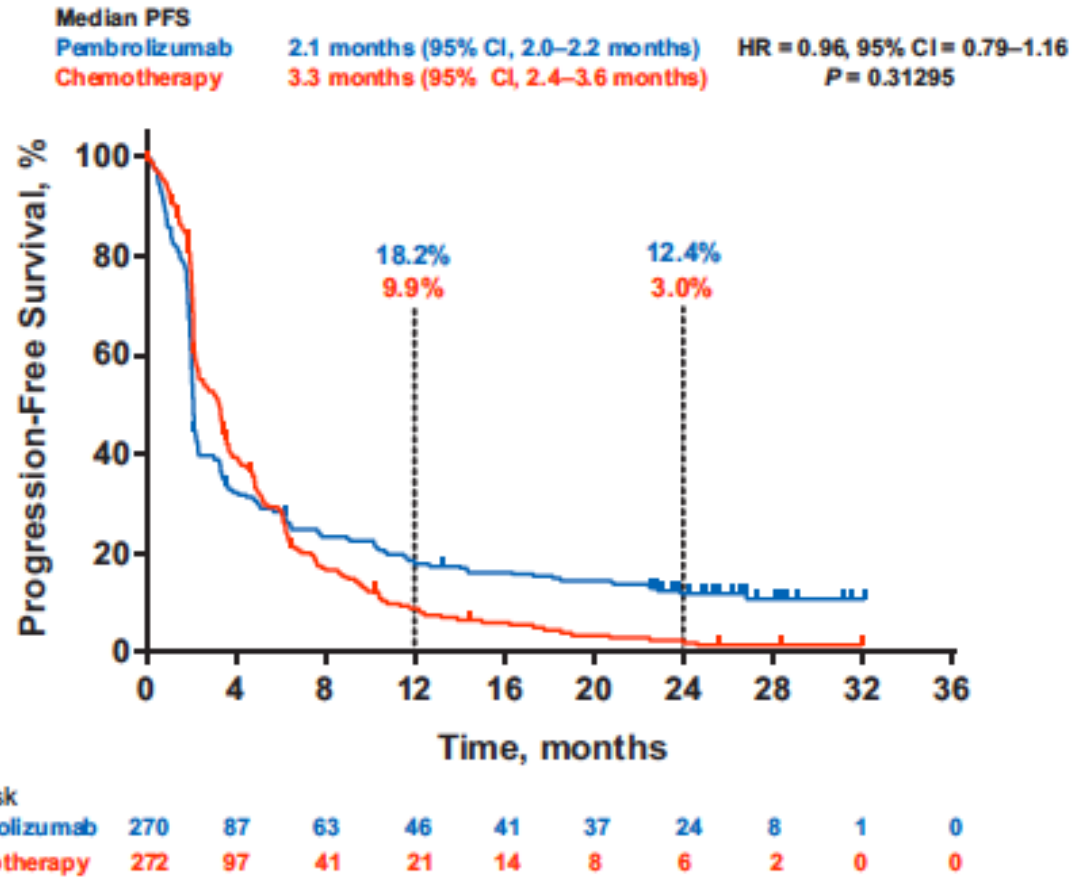


Figure 4: Kaplan-Meier curves of overall survival (A) and progression-free survival (B)
Circles are censored patients.

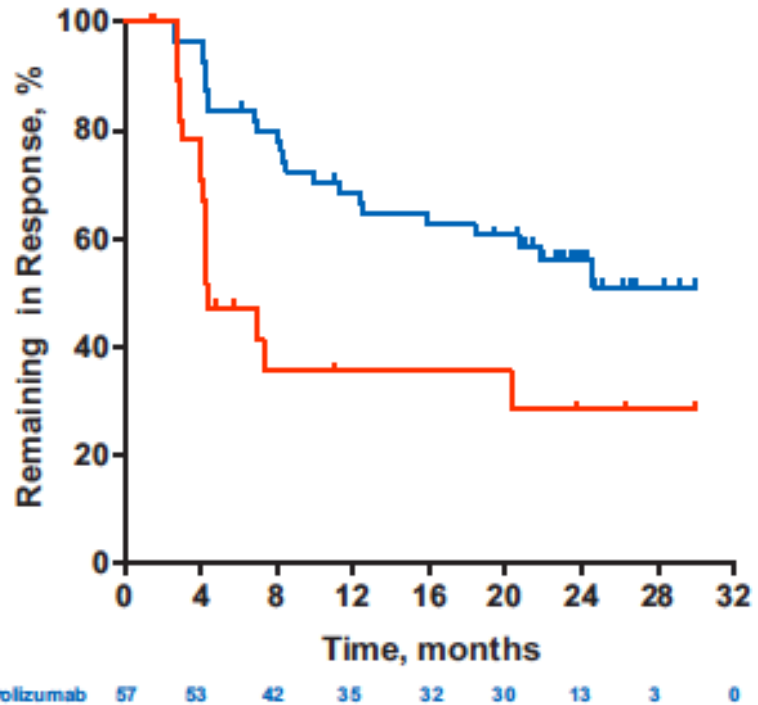
Randomized phase III KEYNOTE-045 trial of pembrolizumab vs chemotherapy in recurrent and advanced urothelial cancer: long term f/u





Randomized phase III KEYNOTE-045 trial of pembrolizumab vs chemotherapy in recurrent and advanced urothelial cancer: long term f/u

	Time to response, months Median (range)	Duration of response, months Median (range)
Pembrolizumab	2.1 (1.4–6.3)	NR (1.6+ to 30.0+)
Chemotherapy	2.1 (1.7–4.9)	4.4 (1.4+ to 29.9+)



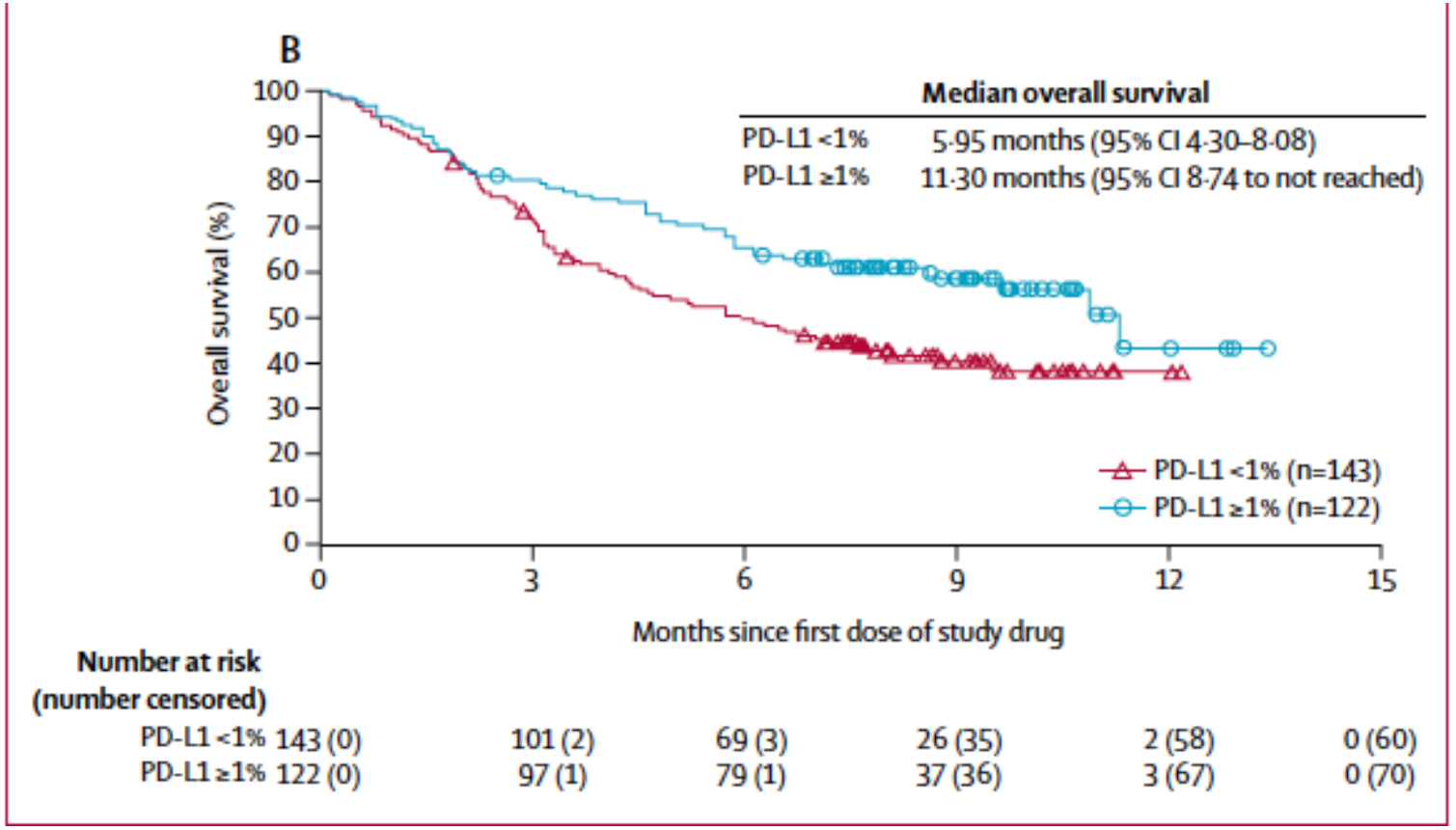
Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicenter, single-arm, phase 2 trial

	Total (n=265)*
Confirmed objective response†	52 (19·6%; 95% CI 15·0–24·9)
Best overall response‡	
Complete response	6 (2%)
Partial response	46 (17%)
Stable disease	60 (23%)
Progressive disease	104 (39%)
Unable to determine	49 (18%)
Time to response, months§	1·87 (1·81–1·97)
Duration of response, months§	NR (7·43–NR)

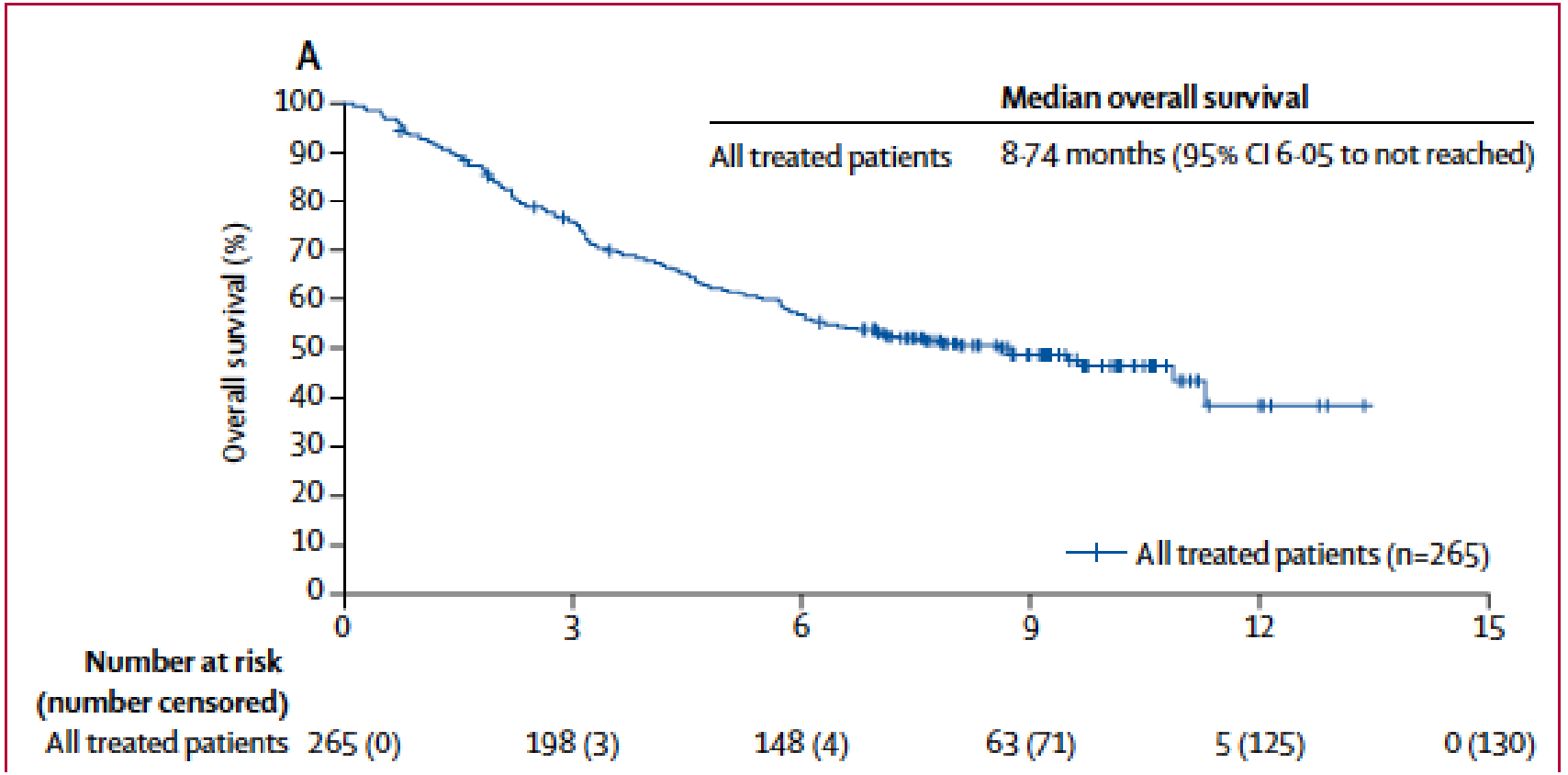
Data are n (%) or median (IQR) unless otherwise specified. Responses were determined by a blind independent review committee. NR=not reached. RECIST=Response Evaluation Criteria In Solid Tumors. *Treated patients from Japan enrolled after main enrolment period are not included because they had not met the minimum of 6 months' follow-up. †Complete response plus partial response; 95% CI based on the Clopper and Pearson method. ‡RECIST v1.1; confirmation of response required. §Measured in the 52 people who responded to treatment.

Table 2: **Objective response, time to response, and duration of response in all treated patients**

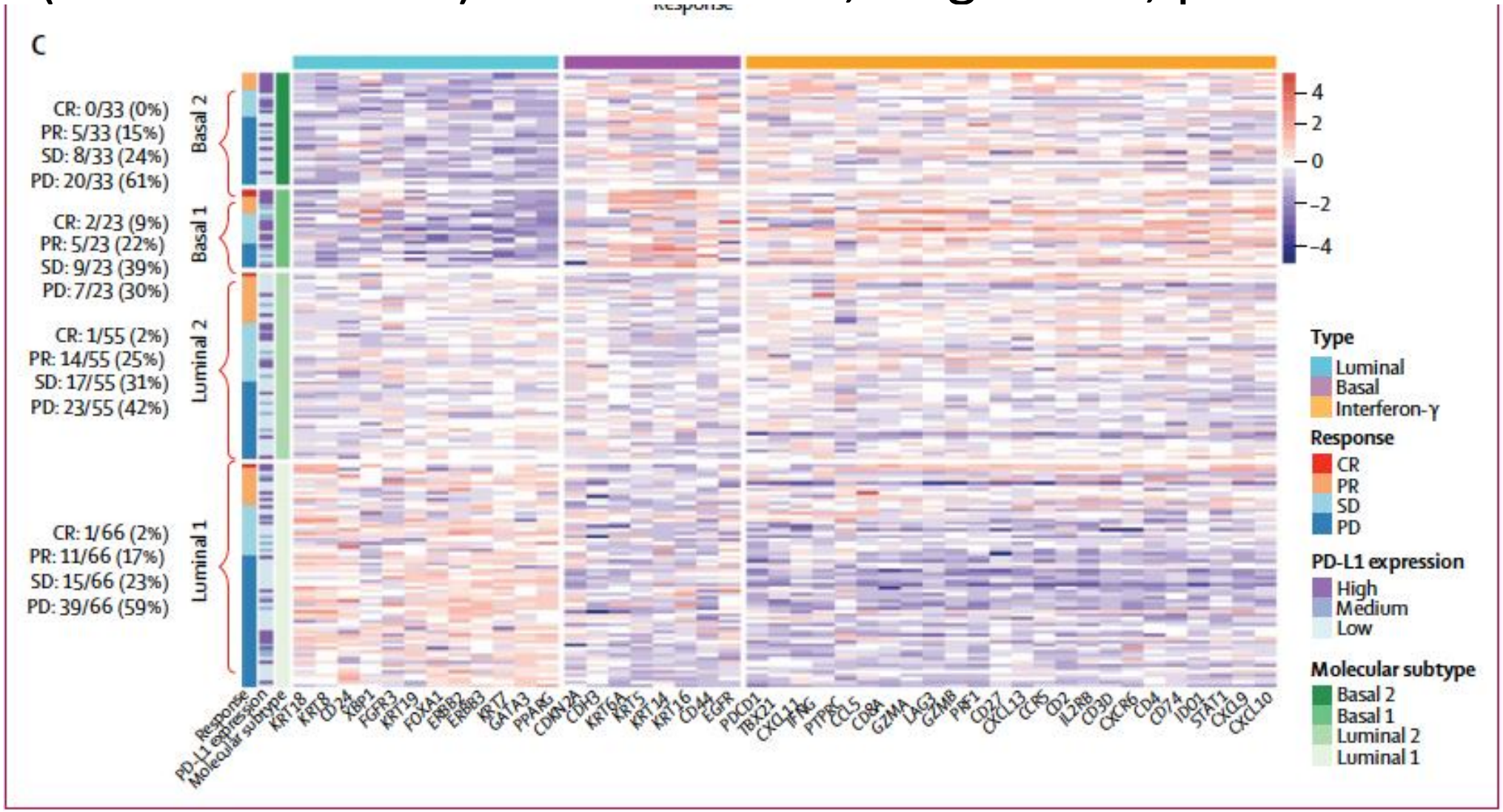
Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicenter, single-arm, phase 2 trial



Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicenter, single-arm, phase 2 trial



Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicenter, single-arm, phase 2 trial



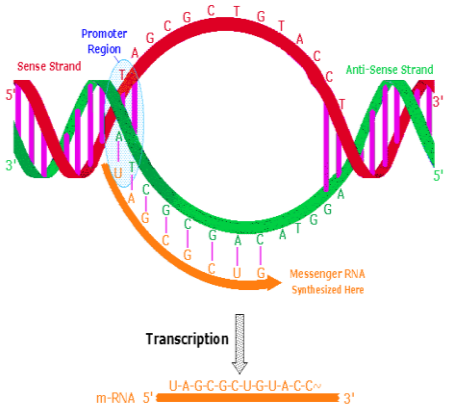
Conclusions for Bladder Cancer and Immune Checkpoint Inhibitors

- Nivolumab monotherapy provided meaningful clinical benefit, irrespective of PD-L1 expression, and was associated with an acceptable safety profile in *previously treated* patients with metastatic or surgically unresectable urothelial carcinoma.

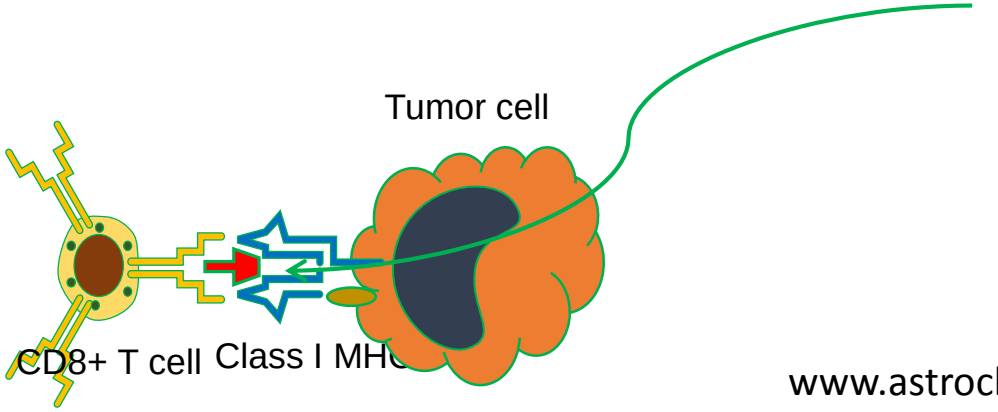
- KEYNOTE-52 First-line pembrolizumab has antitumour activity and acceptable tolerability in *cisplatin-ineligible untreated* urothelial patients with urothelial cancer, most of whom were elderly, had poor prognostic factors, or had serious comorbidities.
- KEYNOTE-045 study of Pembrolizumab improved survival, safety, and quality-of-life compared with chemotherapy in *recurrent* Urothelial cancer

- Atezolizumab showed encouraging durable response rates, survival, and tolerability, supporting its therapeutic use in *cis-platin ineligible* <u>*untreated*</u> metastatic urothelial cancer.
- Atezolizumab was not associated with significantly longer overall survival than chemotherapy in patientswith platinum-refractory metastatic urothelial carcinoma overexpressing PD-L1 (IC2/3).

Why Does Mutational Load Matter?



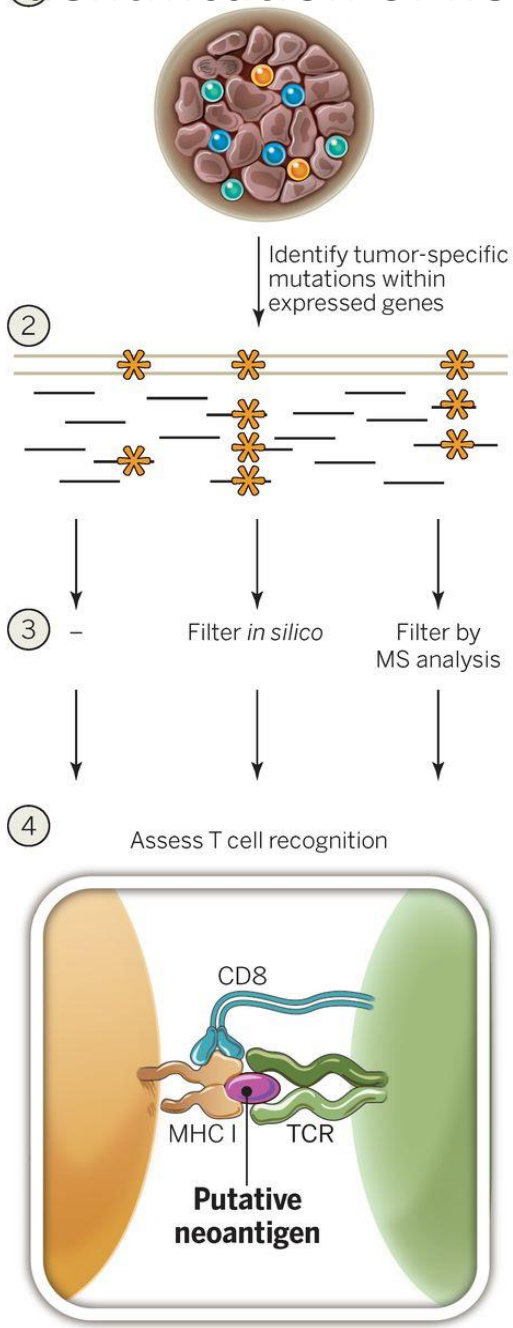
DNA **RNA** **PROTEIN**



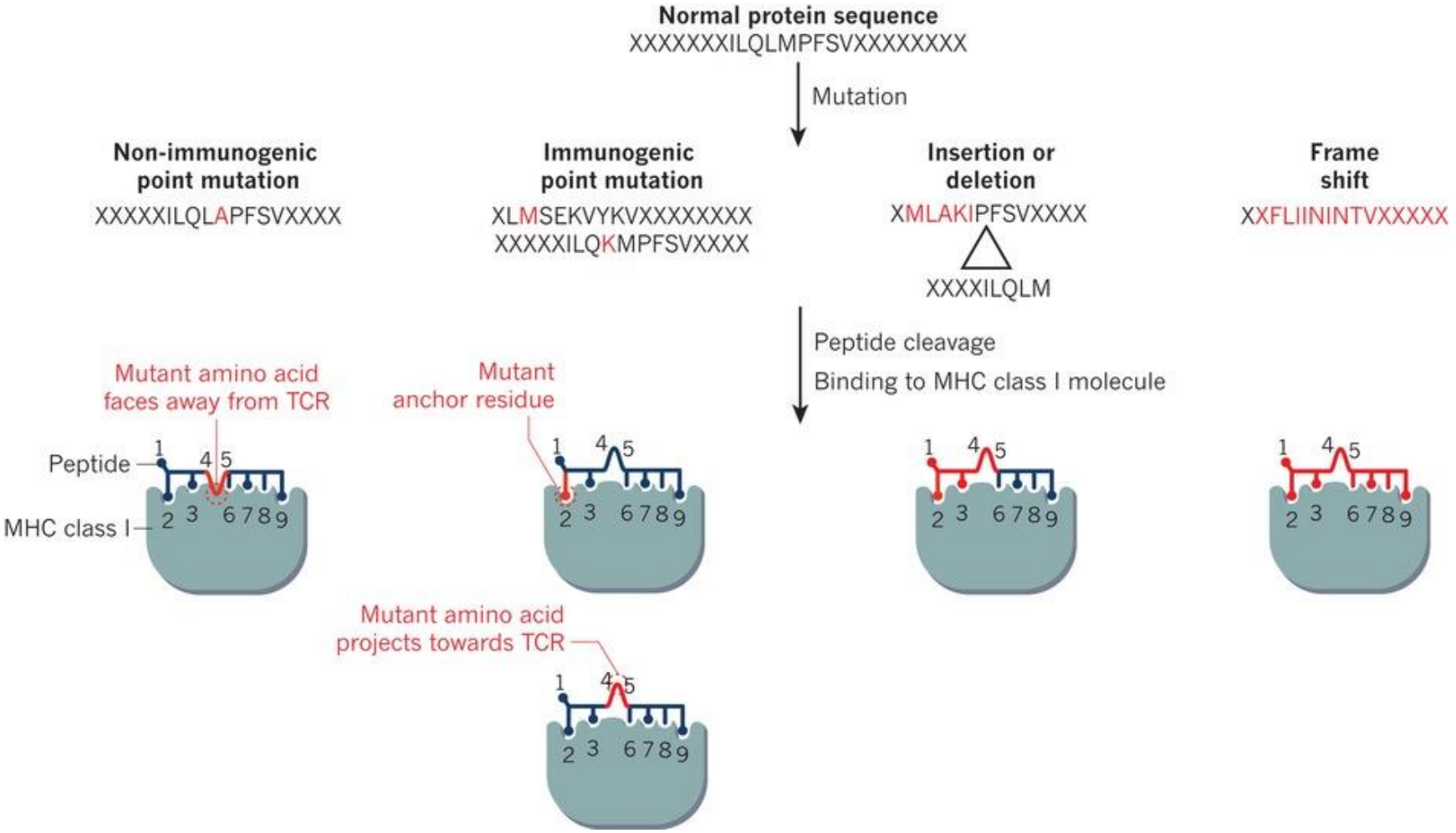
www.astrochemo.org,
www2.chemistry.msu.edu,
http://fineartamerica.com

Presented by: Alexandra Snyder, M.D.

Cancer exome–based identification of neoantigens.

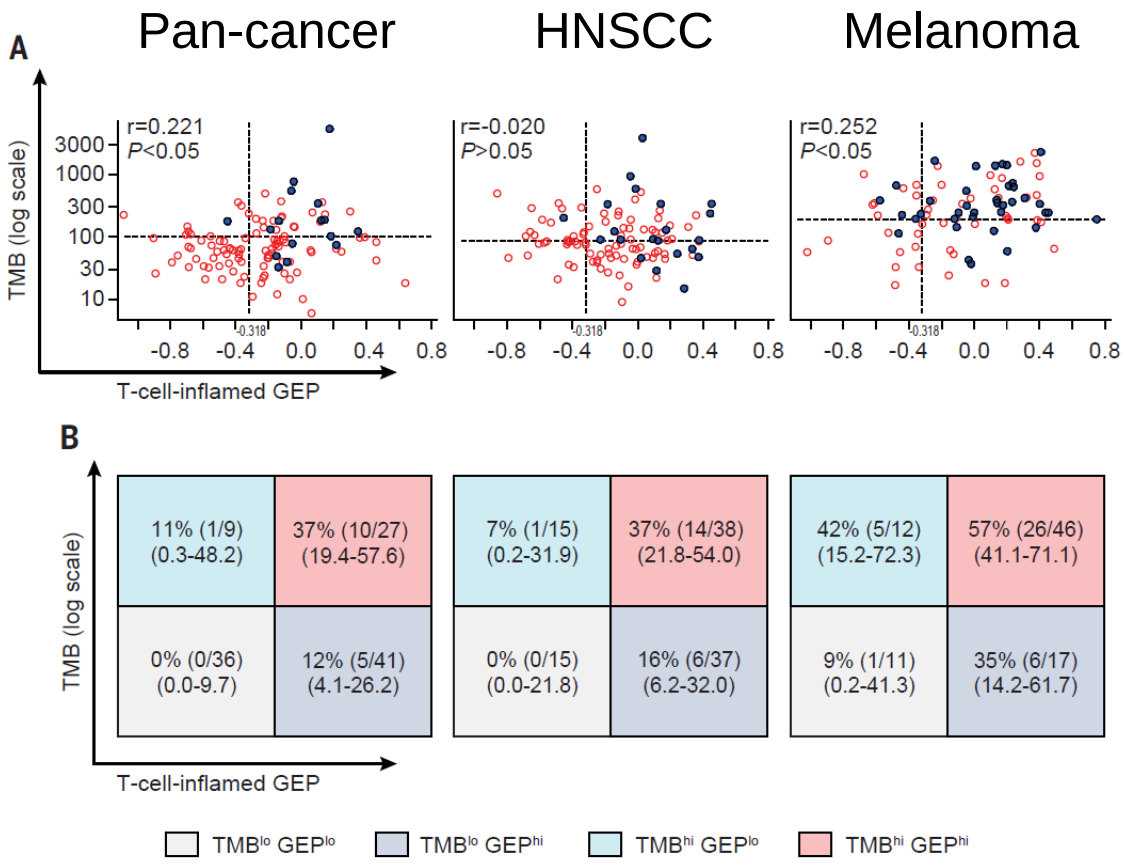


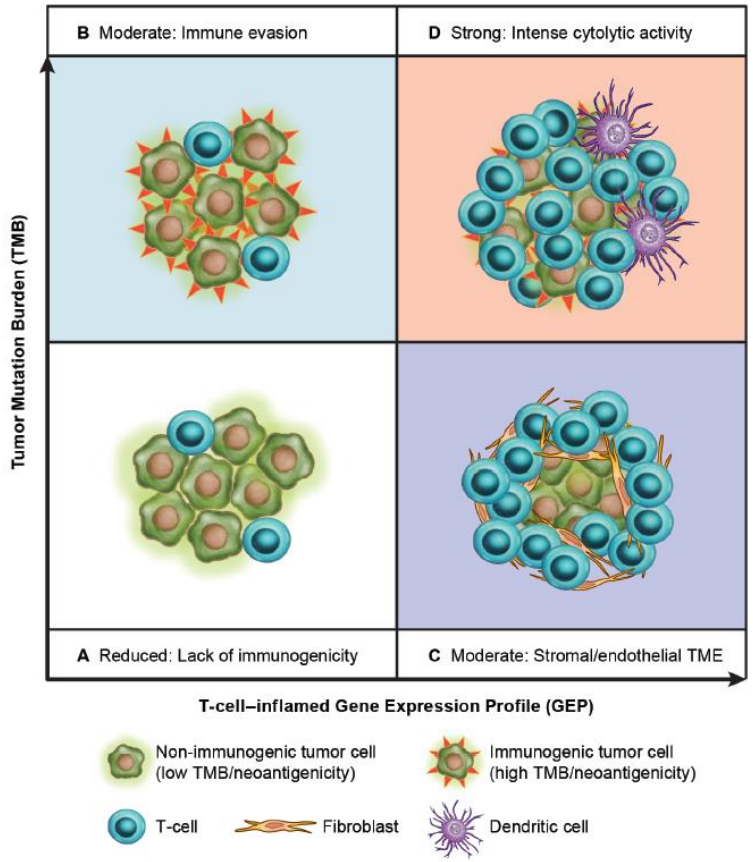
Cancer mutations, neoantigens, and immunogenicity



Chen and Mellman, Nature 2017

How can this information help select patients for PD-1 blockade therapy?



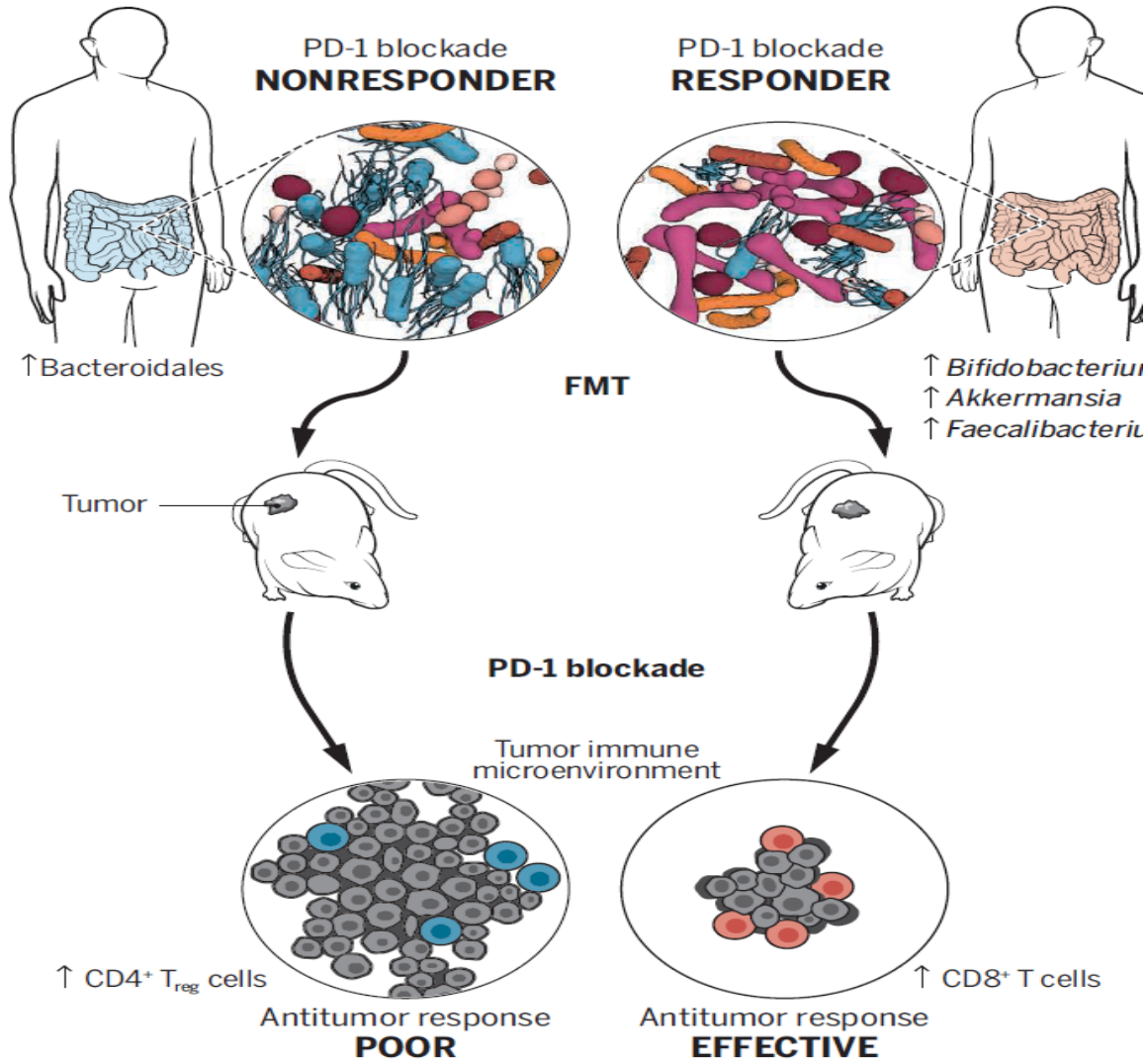


- **TMB**: Tumor mutational burden measured by whole exome sequencing (WES)
- **18 gene T-cell inflamed gene expression profiling (GEP)**: *CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PDL2), PSMB10, STAT1,* and *TIGIT*, measured by RNASeq

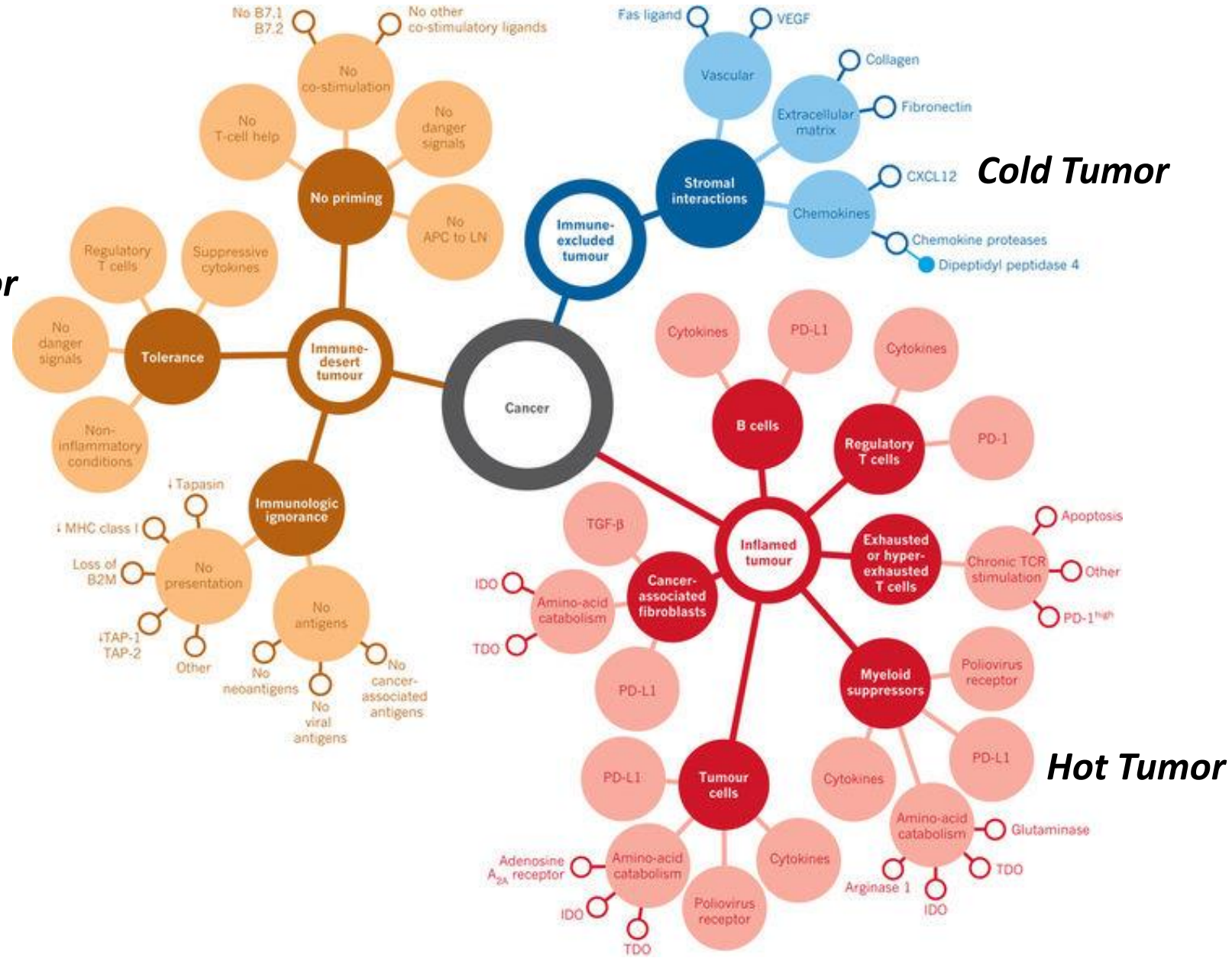
Cristescu et al., Science 362, 197, 12 October 2018

The intestinal microbiota influences the efficacy of PD-1 blockade

The enrichment of specific microbial taxa in intestines correlates with response to PD-1 blockade in cancer patients. FMT from responders into tumor-bearing mice improved responses to anti–PD-1 therapy and correlated with increased antitumor $CD8^+$ T cells in the tumors. Mice receiving FMT from nonresponders did not respond to anti–PD-1 therapy, and tumors had a high density of immunosuppressive $CD4^+$ T_{reg} cells.



Geography and Climate of the Tumor Microenvironment



Desert Tumor

Cold Tumor

Hot Tumor

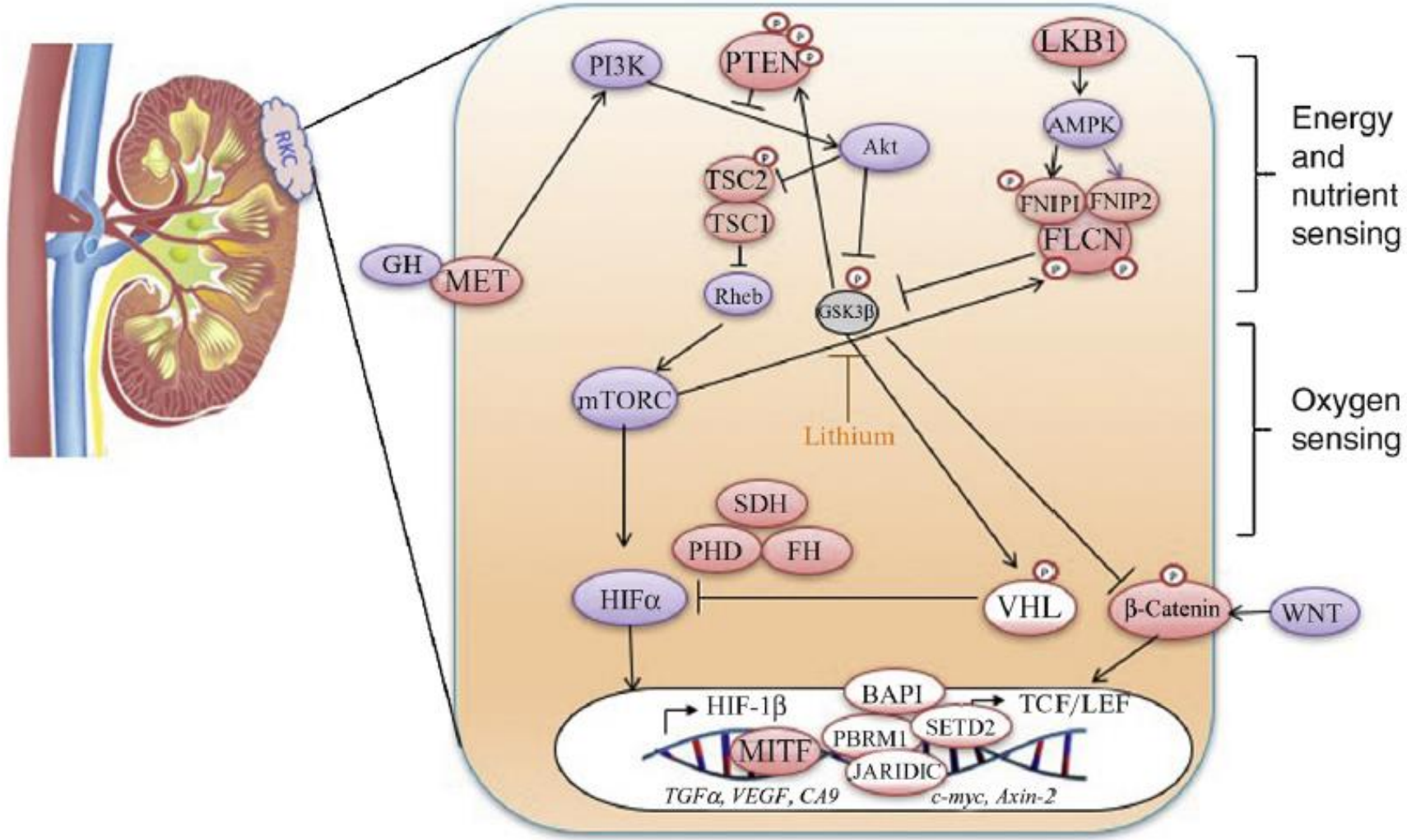


Fig. 1 – Pathways driving most subtypes of RCCs converge on nutrient- and/or oxygen-sensing pathways in the renal cell. Pink circles indicate proteins whose genes are mutated in rare kidney cancers (RKCs), and clear circles indicate genes mutated in clear-cell RCCs. RCC = renal cell carcinoma.

Where are the best targets in RCC?

- One answer: the vHL Pathway

- Why?
  - Tumor suppressor gene
  - Commonly inactivated in clear cell RCC (70%)
  - Inactivation induces hypoxia-regulated genes
  - Promoting angiogenesis and tumor growth

Study Design

Key Eligibility:

- Treatment-naive advanced or metastatic RCC
- Clear cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumor tissue available for PD-L1 staining

Stratification:

- MSKCC risk score
- Liver metastases
- PD-L1 IC IHC status (< 1% vs ≥ 1%)[a]

N = 915

R 1:1

Atezolizumab 1200 mg IV q3w[b] + Bevacizumab 15 mg/kg IV q3w[b]

Sunitinib 50 mg/day orally (4 wk on, 2 wk off)

[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.