

Predictive Biomarkers for VEGF Inhibitors in RCC

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First-line therapy for clear cell mRCC

Risk	Preferred	Other recommendations	Other circumstances
Favorable	<ul style="list-style-type: none"> • axitinib+prembro • pazopanib • sunitinib 	<ul style="list-style-type: none"> • ipi+nivo • cabozantinib • axitinib+avelumab 	<ul style="list-style-type: none"> • active surveillance • axitinib • high-dose IL2
Intermediate/Poor	<ul style="list-style-type: none"> • ipi+nivo • axitinib+pembro • cabozantinib 	<ul style="list-style-type: none"> • pazopanib • sunitinib • axitinib+avelumab 	<ul style="list-style-type: none"> • axitinib • high-dose IL2 • temsirolimus

Subsequent lines

Preferred	Other recommendations	Other circumstances
<ul style="list-style-type: none"> • cabozantinib • nivolumab • ipi+nivo 	<ul style="list-style-type: none"> • axitinib • lenvatinib+everolimus • axitinib+pembro • everolimus • pazopanib • sunitinib • axitinib+avelumab 	<ul style="list-style-type: none"> • bevacizumab • sorafenib • high-dose IL2 • temsirolimus

NCCN 2019

ORR and PFS based on phase II–III trials for first-line treatment of metastatic RCC

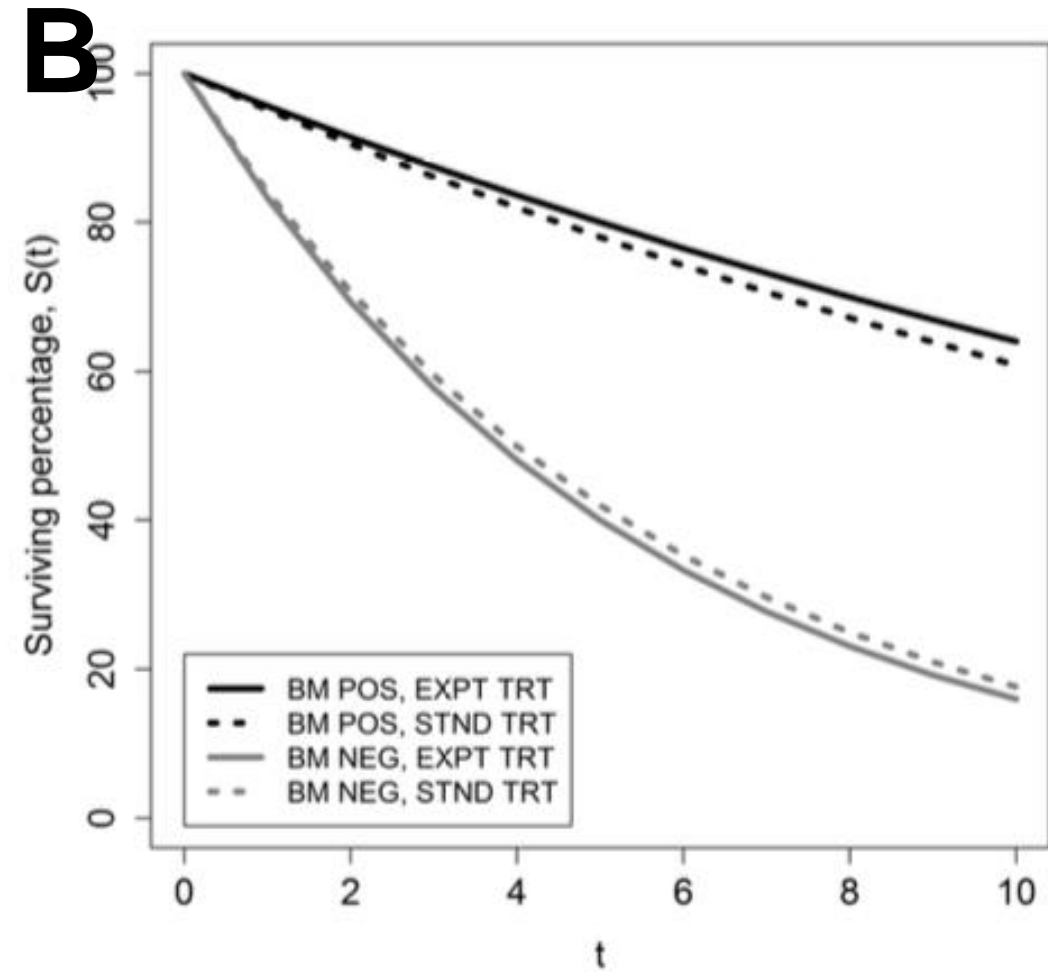
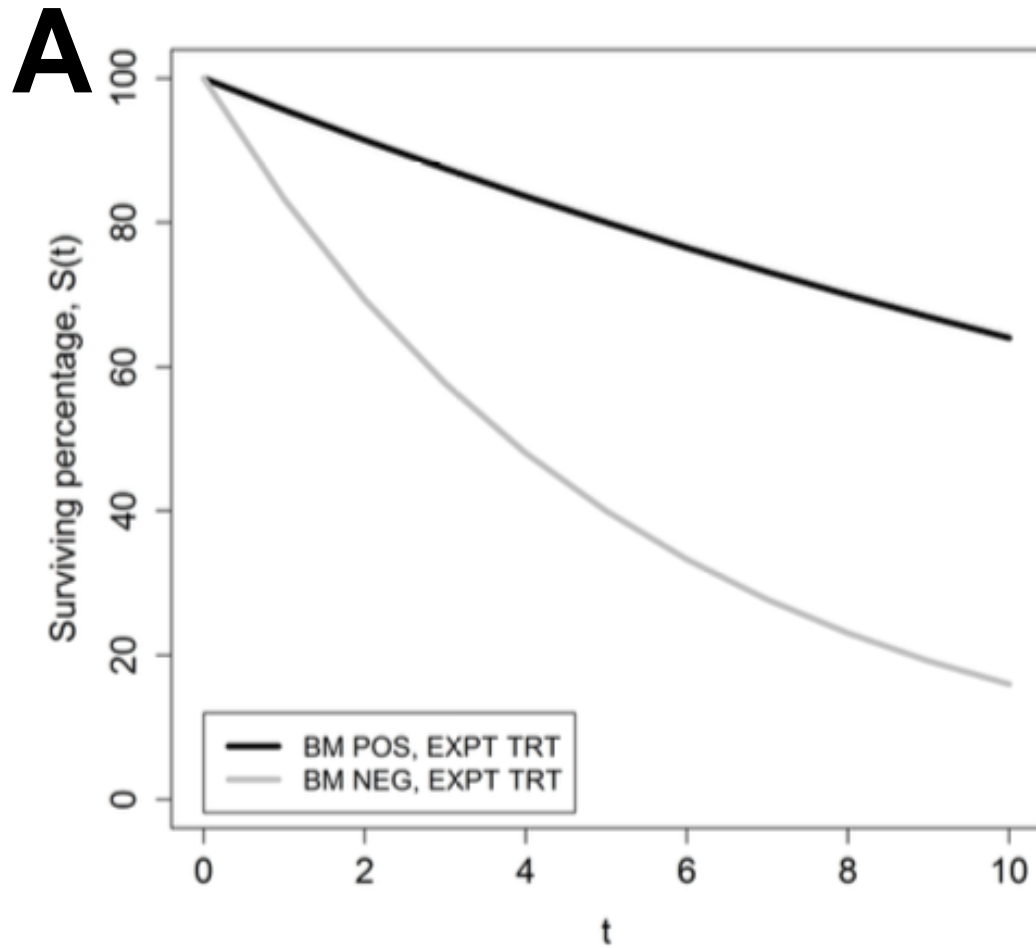
Agents	ORR	PFS
Pazopanib	30%	9.2 mo
Sunitinib	31%	11.0 mo
Cabozantinib	46%	8.2 mo
Axitinib	32%	10.1 mo
Bevacizumab+IFN	31%	10.2 mo
	26%	8.5 mo

Predictive biomarker

A biomarker is predictive if the treatment effect is different for the biomarker-positive patients compared with the biomarker-negative patients

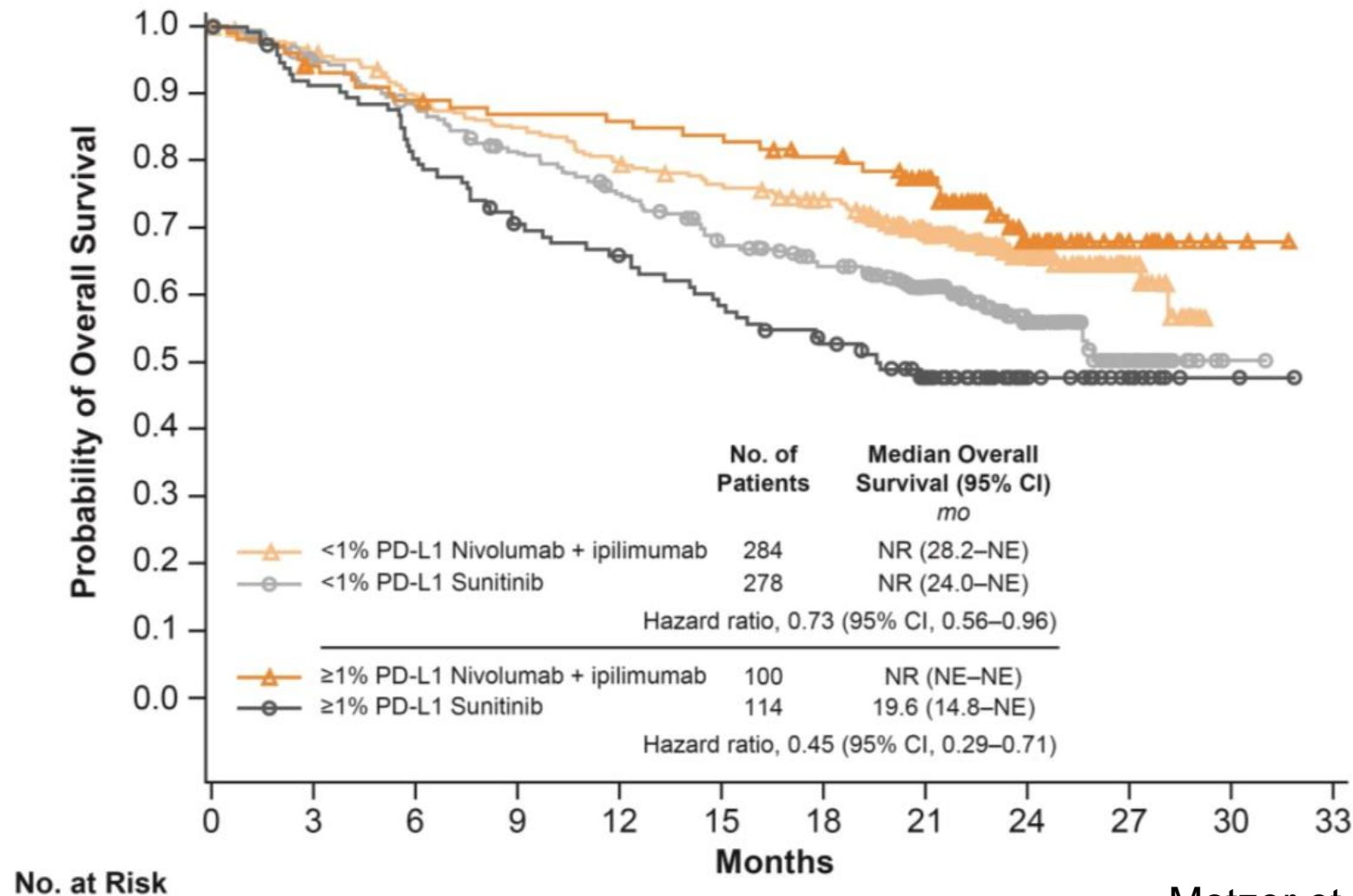
Hayes et al. JNCI 1996
Simon et al. JNCI 2009
Ballman JCO 2015

Predictive or prognostic?



FDA-NIH Biomarker Working Group, NIH 2016

From interaction to clinical utility



Motzer et al. N Engl J Med 2018

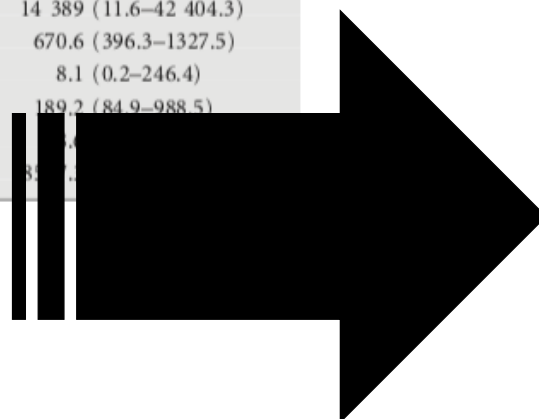
Predictive biomarkers for VEGF inhibitors

Study	Treatment	Predictive biomarker
Pena (2010)	Sorafenib vs. placebo	VEGF-A (PFS $P_{\text{interaction}}=0.02$)
Zurita (2011)	Sorafenib vs. sorfenib+IFN	VEGF-A (PFS $P_{\text{interaction}}=0.01$)
Zurita (2011)	Sorafenib vs. sorafenib+IFN	OPN, sCAIX, VEGF-A, TRAIL, ColIV, sVEGFR2 (PFS $P_{\text{interaction}}=0.0002$)
Zurita (2011)	Sorafenib vs. sorafenib+IFN	Osteopontin (PFS $P_{\text{interaction}}=0.004$)
Tran (2012)	Pazopanib vs. placebo	IL-6 (PFS $P_{\text{interaction}}=0.009$, OS $P_{\text{interaction}}=0.005$)
Nixon (2013)	Bev+IFN vs. IFN	IL-6 and HGF (PFS $P_{\text{interaction}}<0.0001$)
Xu (2011)	Pazopanib vs. placebo	IL-8 rs1126647 (PFS $P_{\text{interaction}}=0.04$)
McDermott (2018)	Atezo+bev vs. atezo vs. sunitinib	Angiogenesis, T-effector, Myeloid inflammation

Cytokines and angiogenic factors

Biomarkers	N	Mean (pg/ml)	Median (range), pg/ml
sCA9	69	103.7	47 (4.2–816.7)
Collagen IV ^a	69	127.8	110.3 (52.4–320.4)
CTACK	68	755.9	698.1 (332.8)
EGF	69	57.2	36.1 (0.3–2)
Eotaxin	68	76.2	47.5 (10.1–)
E-selectin	69	471 732.4	143 863.2 (39 64)
BFGF	68	18.1	15.9 (0.9–8)
G-CSF	68	22.8	21.8 (13.7–)
GM-CSF	68	37	14.6 (0–59)
GRO-alpha	68	79.6	75.6 (2.1–3)
HGF	68	438.6	413 (135.2)
IFN alpha-2	68	132	128.4 (77.6–)
IFN gamma	68	203.1	192.4 (46.6–)
IL-1 beta	68	1.3	0.5 (0–8.4)
IL-1ra	68	381.6	156.3 (53.1–)
IL-2	69	22.7	8.6 (0.2–6)
IL2-RA	68	134.7	128.1 (72.3–)
IL-3	69	68.3	57.9 (4.9–3)
IL-4	68	1.6	1.4 (0.5–3)
IL-5	69	2.5	1.8 (0–17)
IL-6	68	7	4.7 (0.1–8)
IL-7	68	3.1	1.9 (0.1–1)
IL-8	69	1.6	1.4 (0–6.2)
IL-9	68	33.8	21.8 (3.1–1)
IL-10	69	3.2	2 (0–19.4)
IL-12 p40	68	324.6	248.6 (22–2746.9)
IL-12 p70	68	11.6	2.1 (0–445.7)
IL-13	69	11.7	5.5 (0.1–149.4)
IL-16	68	358	204.1 (54.5–11 028.2)
IL-17	69	4.4	2.2 (0.2–53.7)
IL-18	68	60.7	54 (17.3–164.4)
IP-10	68	927.7	787.5 (124.5–4548.4)
MCP-1	69	22	20.4 (3.4–100.3)
MCP-3	68	52.1	44.5 (16.2–476.1)
M-CSF	68	17.7	14.4 (1.1–67.8)
MIF	68	259.6	195 (84.6–3691.1)
MIG	68	415.7	333.4 (110.2–2282.8)
MIP-1-alpha	68	8.1	8.1 (4–12.9)
MIP-1-beta	68	29.9	18.2 (2.5–393.9)
MMP-9	69	152 287	93 423 (6322.7–1 770 047.2)

Biomarkers	N	Mean (pg/ml)	Median (range), pg/ml
Beta-NGF	69	2.3	2.3 (0.2–5)
Osteopontin ^a	69	93.5	51 (0–461)
PIGF	69	15.8	8 (0.3–71.4)
PDGF BB	68	767.7	311.1 (43.6–24 285.5)
RANTES	69	215.3	168 (17.2–1284.4)
SCF	68	73.1	61.1 (20.5–373.3)
SCGF-beta	68	16 039.9	14 389 (11.6–42 404.3)
SDF-1 alpha	68	691.7	670.6 (396.3–1327.5)
TNF-a	68	21	8.1 (0.2–246.4)
TRAIL	68	218.1	189.2 (84.9–988.5)
VEGF	69	45.8	45.8 (0.2–246.4)
sVEGFR-2	69	8796.5	8796.5 (0.2–246.4)

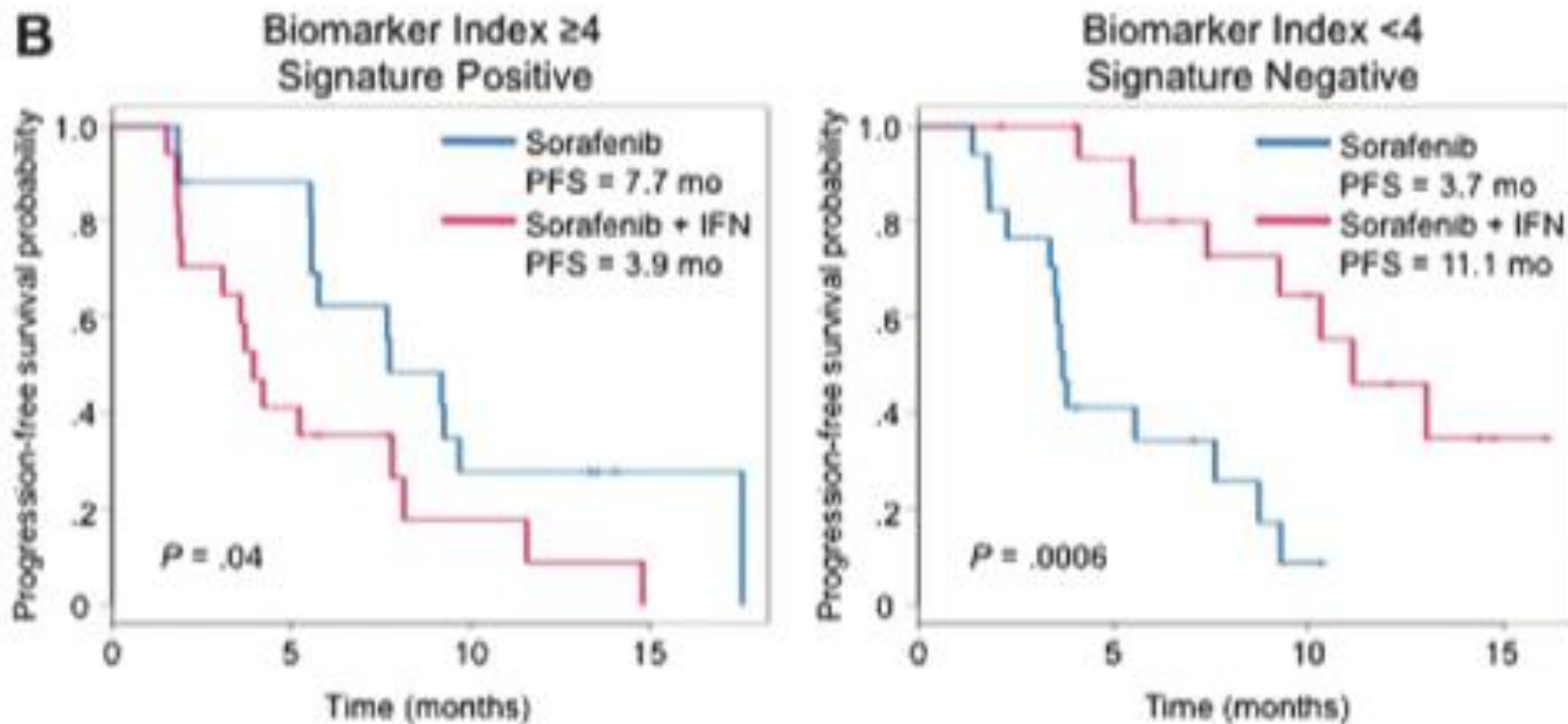


Biomarker expression index:

1. Osteopontin
2. sCA9
3. VEGF
4. Tumor-necrosis factor related apoptosis inducing ligand (TRAIL),
5. ColIV
6. sVEGFR2

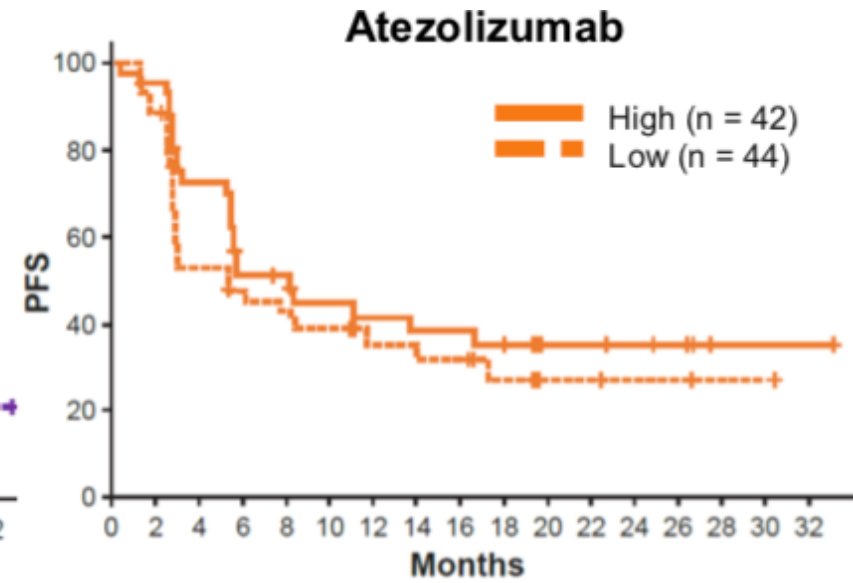
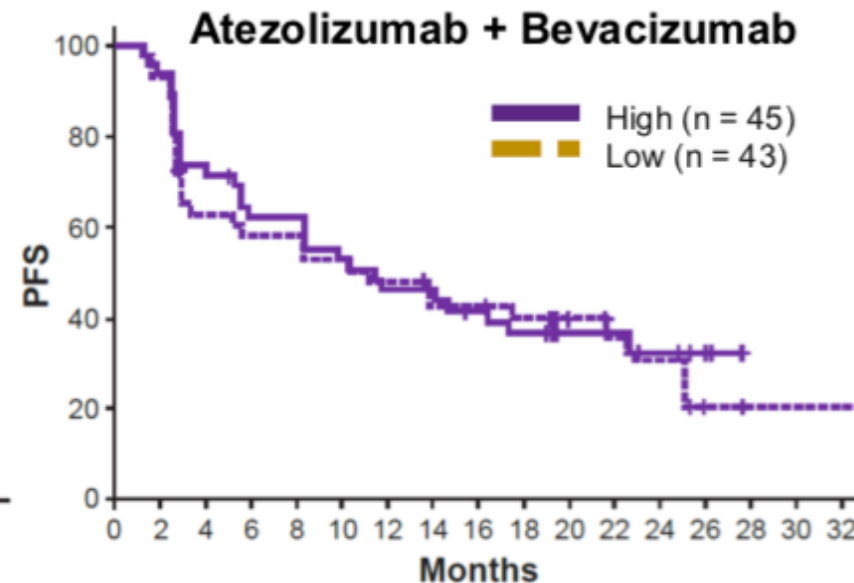
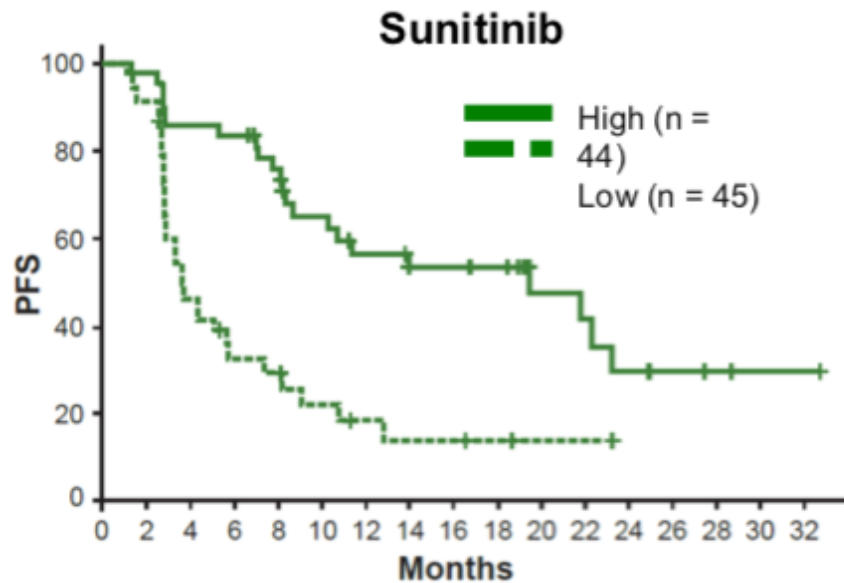
$P_{interaction}=0.0002$ (signature positive vs. negative) and treatment (combination versus single-agent)

Cytokines and angiogenic factors



Zurita et al. Ann Oncol 2012

Angiogenesis, T-effector/IFN- γ response, and myeloid inflammatory gene expression signatures (IMmotion150)



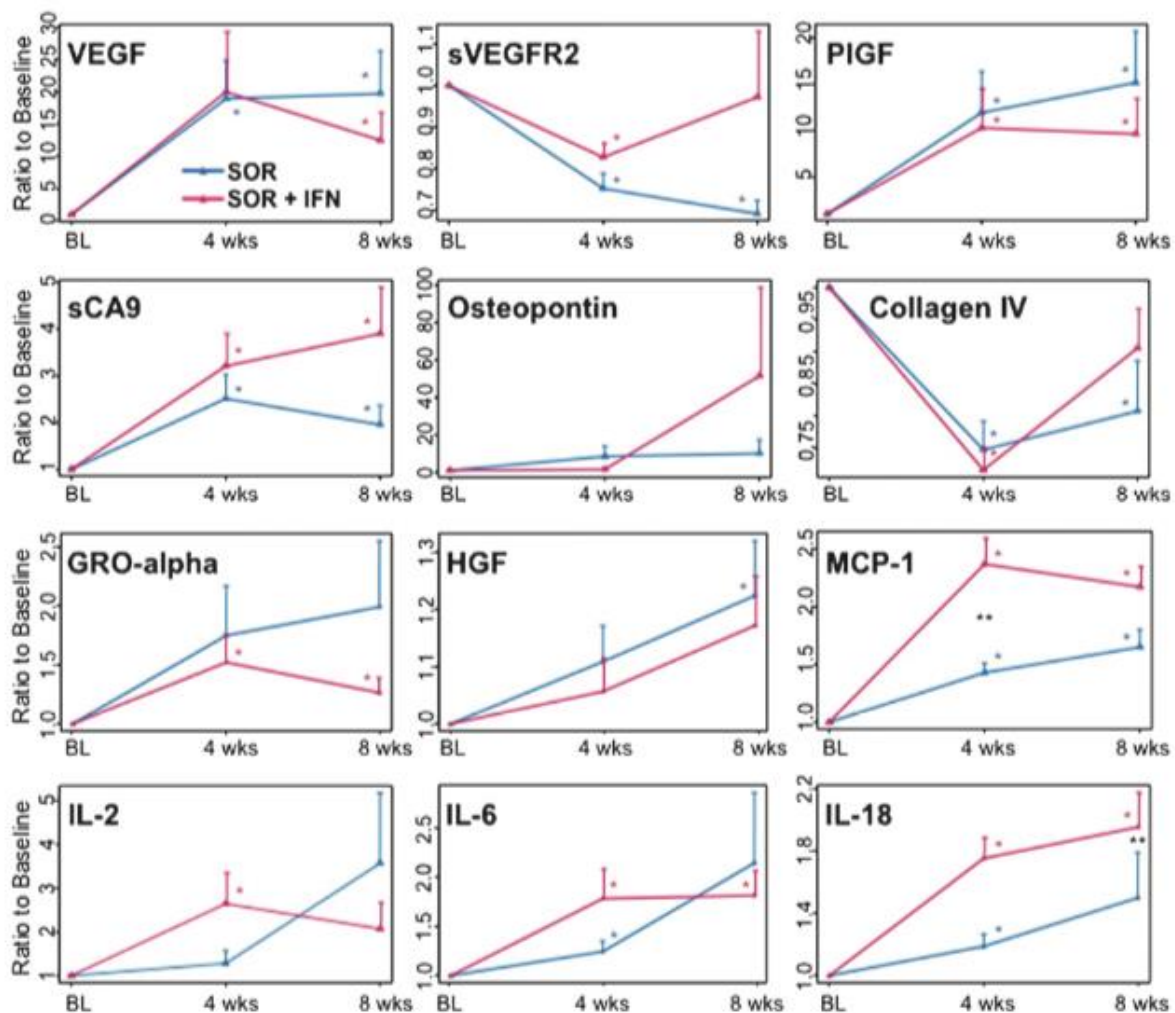
McDermott et al. AACR 2017
McDermott et al. Nat Med 2018

Angiogenesis, T-effector/IFN- γ response, and myeloid inflammatory gene expression signatures (IMmotion150)

Biomarker subgroups	HR (95% CI)	
	Atezo+bev vs. sun	Atezo vs. sun
Angiogenesis		
Low	0.59 (0.35–0.98), P=0.042	0.75 (0.46–1.25), P=0.270
High	1.36 (0.78–2.36), P=0.283	1.46 (0.81–2.60), P=0.206
T-eff		
Low	1.41 (0.85–2.36), P=0.188	1.33 (0.76–2.33), P=0.319
High	0.55 (0.32–0.95), P=0.033	0.85 (0.50–1.43), P=0.537
T-eff High		
Myeloid-Low	1.29 (0.57–2.90), P=0.546	2.14 (0.92–4.98), P=0.077
Myeloid-High	0.25 (0.10–0.60), P=0.002	0.55 (0.28–1.09), P=0.086

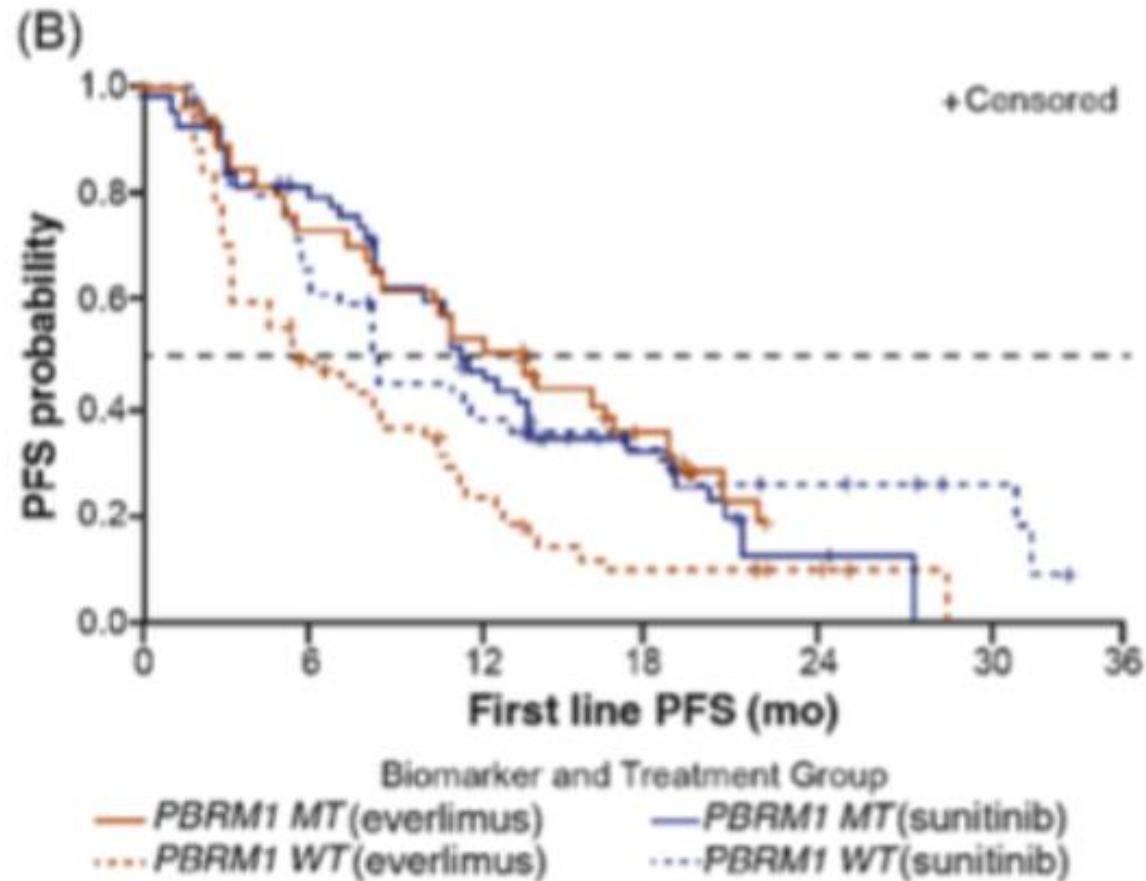
McDermott et al. Nat Med 2018

Cytokines and angiogenic factors



Zurita et al. Ann Oncol 2012

PBRM1 status



Wild-type PBRM1:

Sunitinib: 8.3 months (5.8 to 12.9)
Everolimus: 5.5 months (3.1 to 8.4)

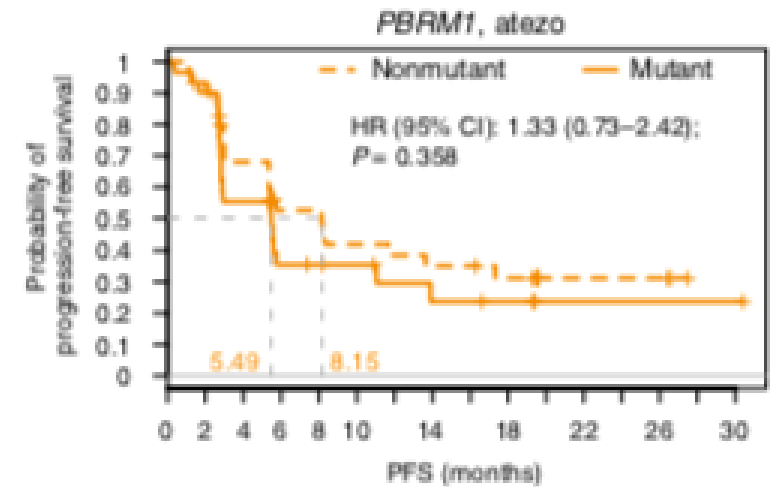
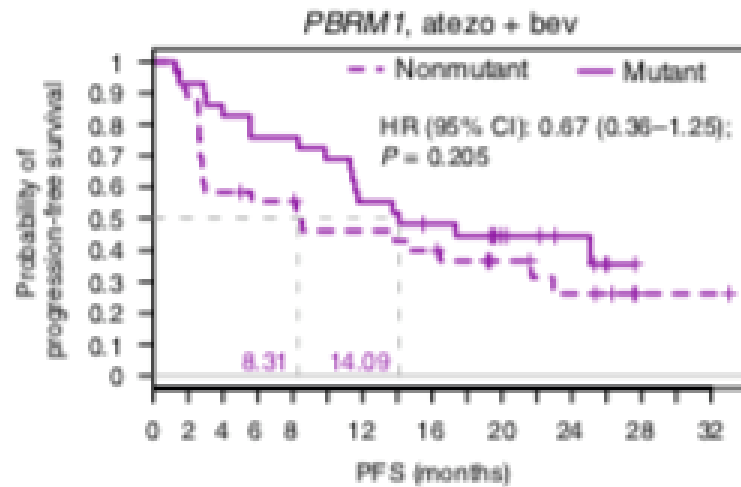
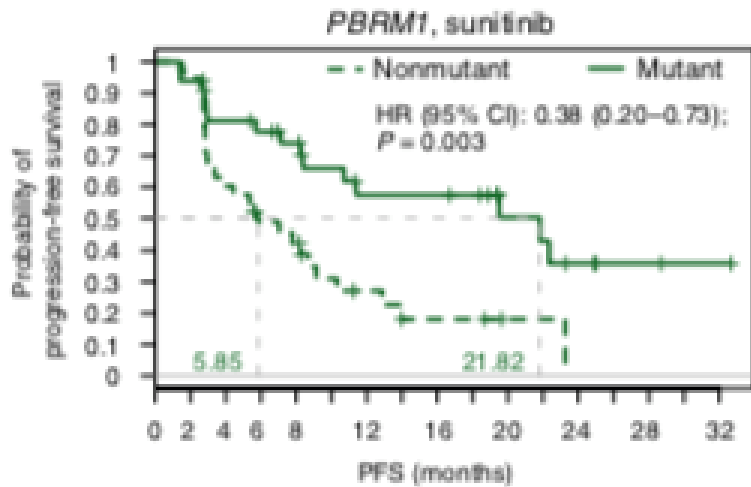
Mutant-type PBRM1:

Sunitinib: 11.0 months (8.3 to 13.8)
Everolimus: 12.8 months (8.1 to 18.3)

Hsieh et al. Eur Urol 2017

PBRM1 status

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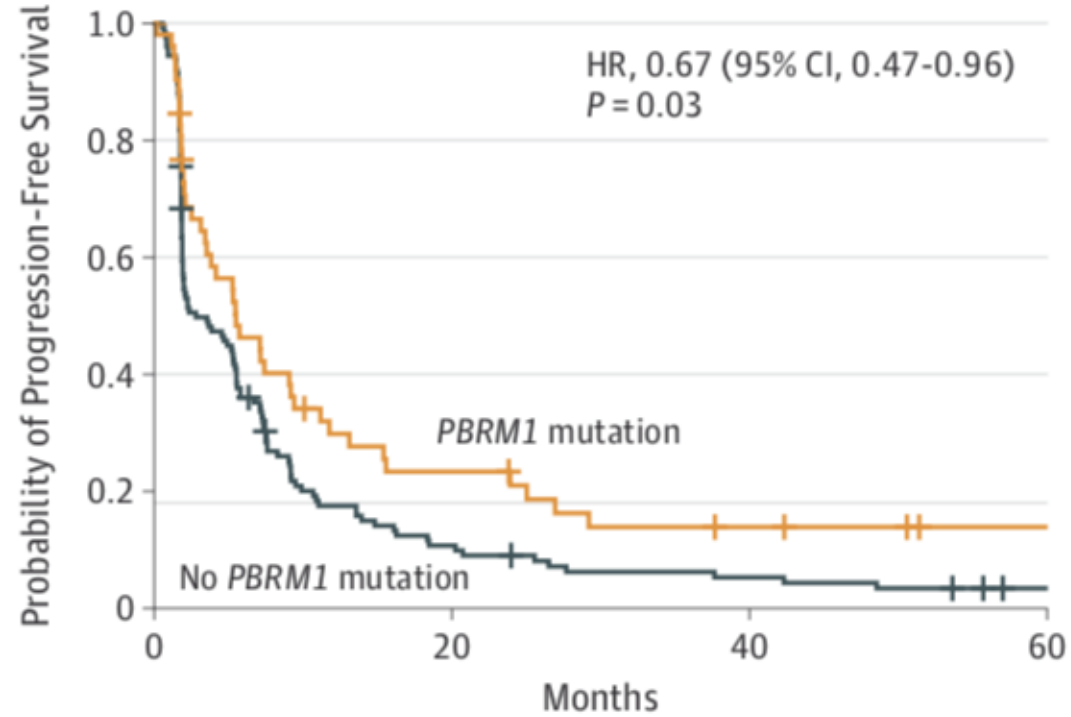


McDermott et al. Nat Med 2018

PBRM1 status

A Progression-free survival

	Median PFS (95% CI) Months	No. of Events
No <i>PBRM1</i> mutation	2.9 (2.0-5.6)	118
<i>PBRM1</i> mutation	5.6 (3.6-11.2)	42



No stratification

Braun et al. JAMA Oncol 2019

IMDC risk model

IMDC	ORR (%)		PFS	
	Nivo+Ipi	Sunitinib	Nivo+Ipi	Sunitinib
Intermediate/Poor-risk	42%	27%	11.6 months	8.4 months
Favorable risk	29%	52%	15.3 months	25.1 months

Motzer et al. N Engl J Med 2018

Summary

- Must continue our search for robust predictive biomarkers
- Candidate biomarkers should be validated
- Clinical utility