Why perioperative therapy might cure kidney cancer

October 11, 2019

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Directory of Abramson Cancer Center Kidney and Prostate Cancer Clinical Trial Programs

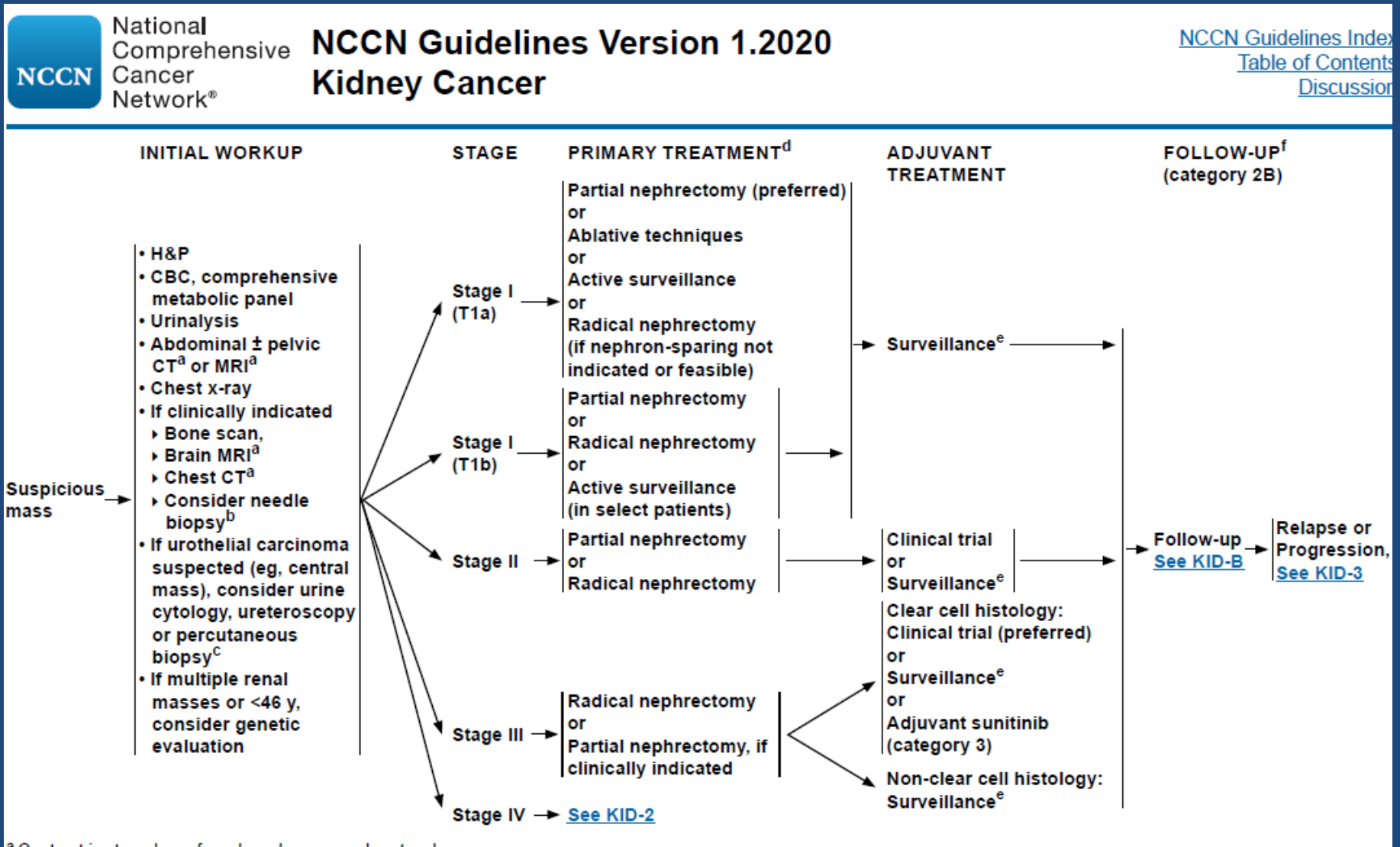
My Disclosures

- Pfizer- correlative and clinical trial support for E2805
- Merck- advisory board
- Roche- consultant

What is perioperative therapy?

- Additional treatment before, during or after surgery
- Usually in the case of kidney cancer limited to the kidney area

Guidelines that Doctors and Nurses Use for treating your cancer



Surveillance

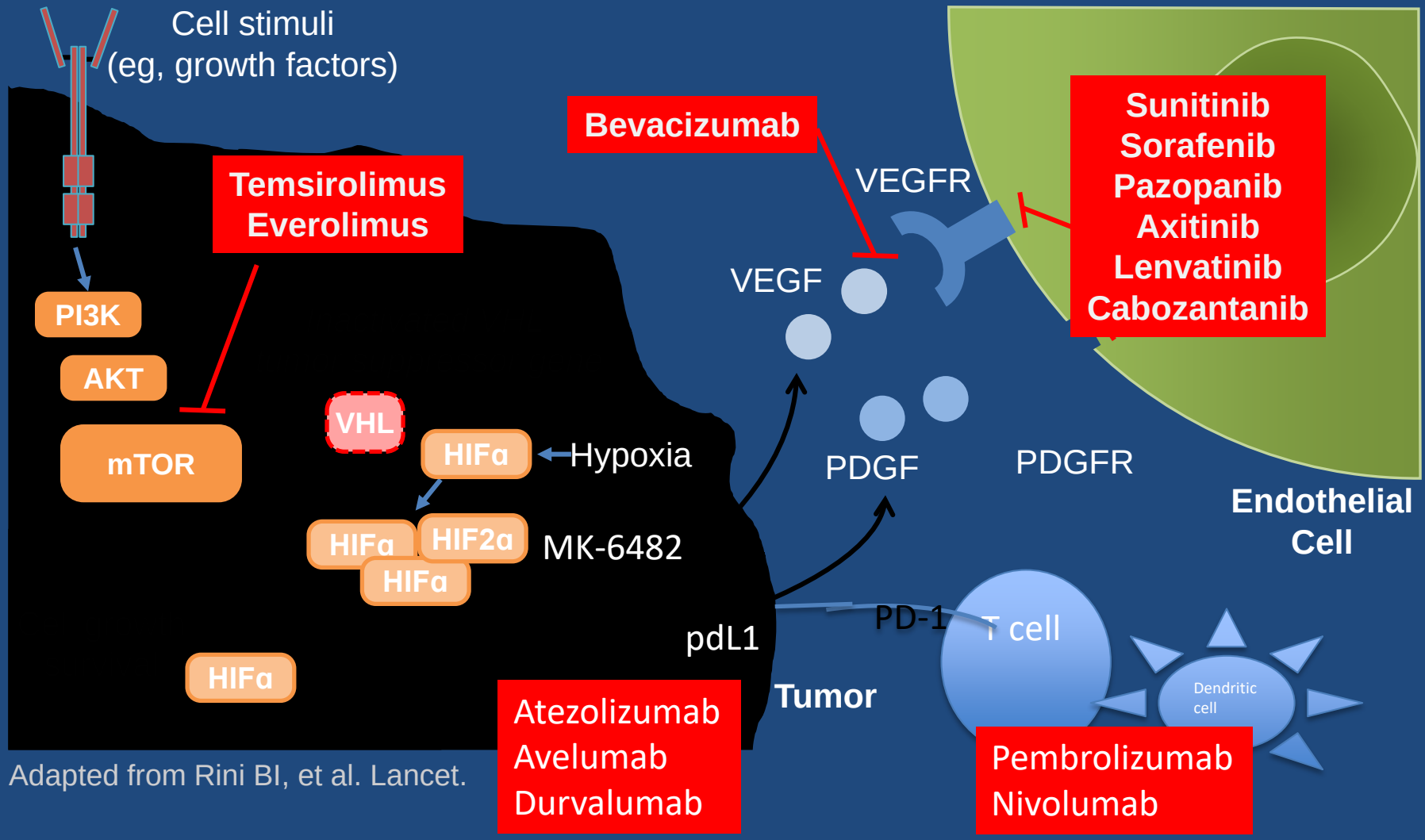
- Stage I- every 6 months for year one, then annually for up to 5 years
- Stage II- every 3-6 months for 3 years, then annually for at least 2 more years
- Preferred imaging is CT or MRI of abdomen and CT of chest

The drugs we have used in perioperative clinical trials

- VEGF TKIs (Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitors)
  - Sunitinib (Sutent)
  - Axitinib (Inlyta)
  - Pazopanib (Votrient)
  - Sorafenib (Nexavar)
- Immune Checkpoint Inhibitors
  - Ipililumab (Yervoy) +Nivolumab (Opdivo)
  - Nivolumab (Opdivo)
  - Pembrolizumab (Keytruda)
  - Atezolizumab (Tecentriq)

Metastatic RCC Therapy:

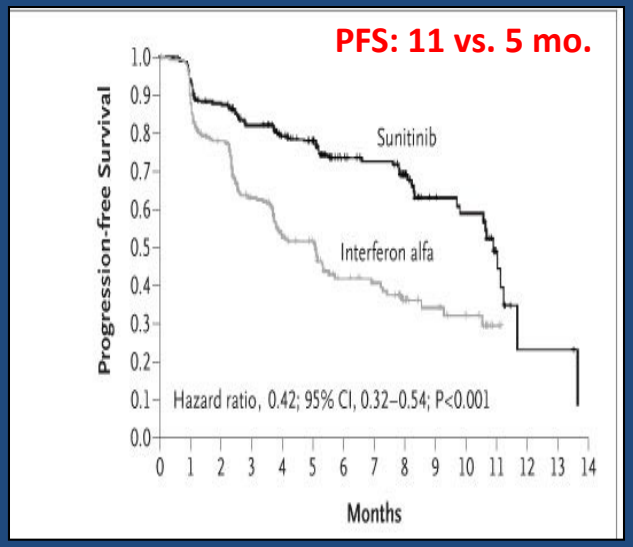
Mechanisms:
Angiogenesis
Metabolism
Immunomodulation
Epigenetics



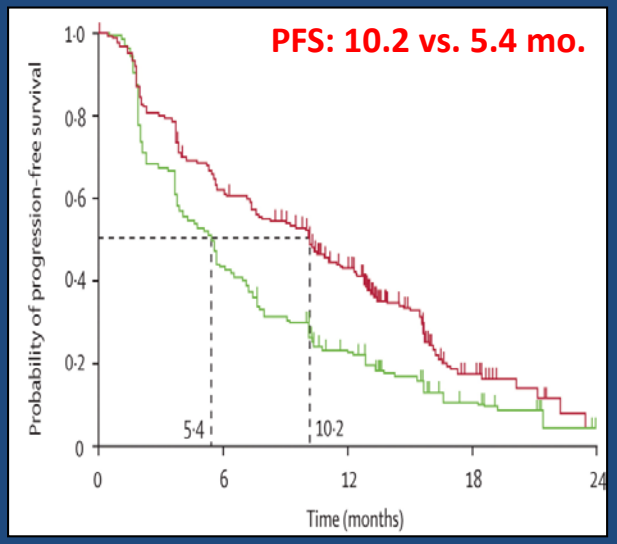
Adapted from Rini BI, et al. Lancet.

VEGF-TKIs are very active in kidney cancer that has spread

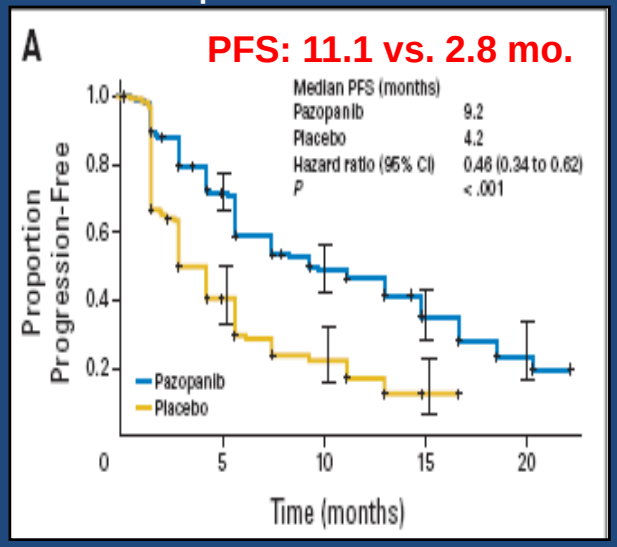
Sunitinib vs. IFN-α



Bevacizumab + IFN-α



Pazopanib vs. BSC/P



- Broadly efficacious: 80% achieve clinical benefit in metastatic disease
- Little data about best sequence
- However, not a panacea: ~20% non-responders

Motzer J Clin Oncol 2007, Escudier Lancet 2007, Sternberg J Clin Oncol 2010, Rini Lancet 2009

But the use of VEGF TKIs is controversial in the adjuvant setting

One trial of the 5 conducted has shown improved in DFS.
No improvement in OS in any of the 5 VEGF Adjuvant trials

1yr sunitinib, sorafenib,pcb

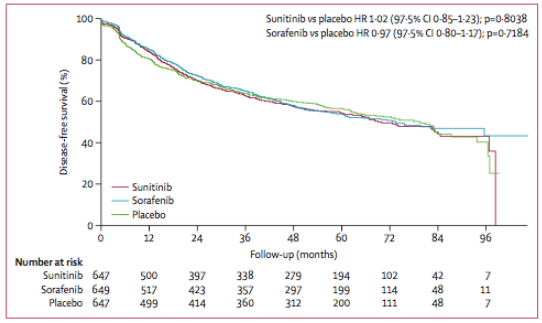


Figure 2: Disease-free survival
HR=hazard ratio.

ASSURE
Haas,
Lancet 2016

1 yr sunitinib , pcb

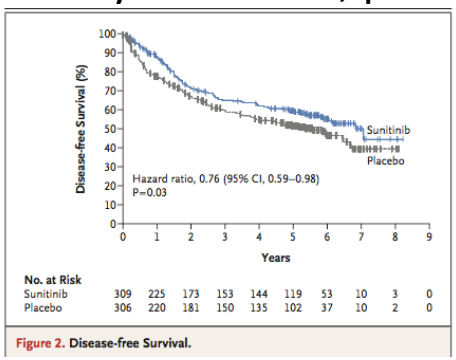


Figure 2. Disease-free Survival.

S-TRAC Ravaud
NEJM 2016

1 yr pazopanib, pcb

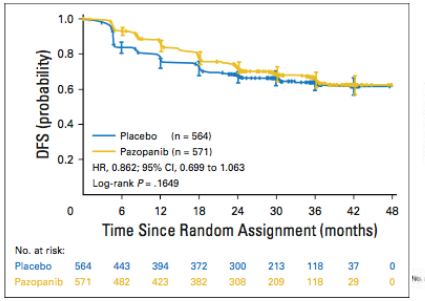
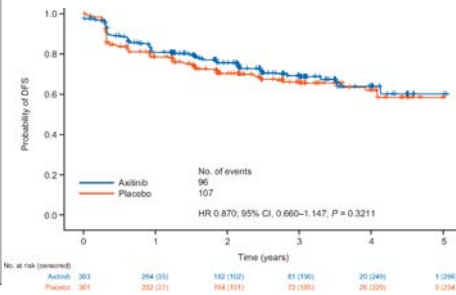


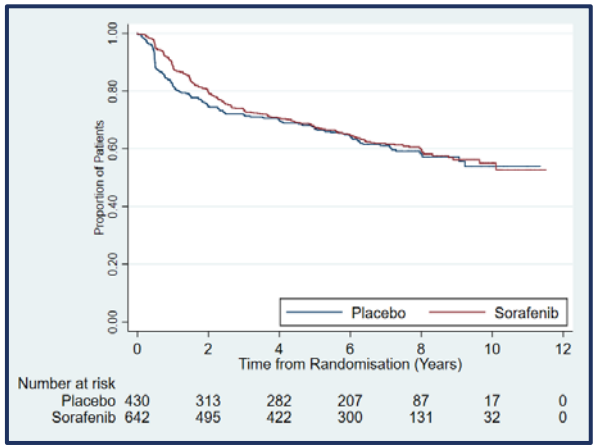
Fig 2. Disease-free survival (DFS) in the intent-to-treat pazopanib 600 mg (ITT_{600mg}) group. HR, hazard ratio.

PROTECT
Motzer JCO
2017

<3 yr axitinib, pcb

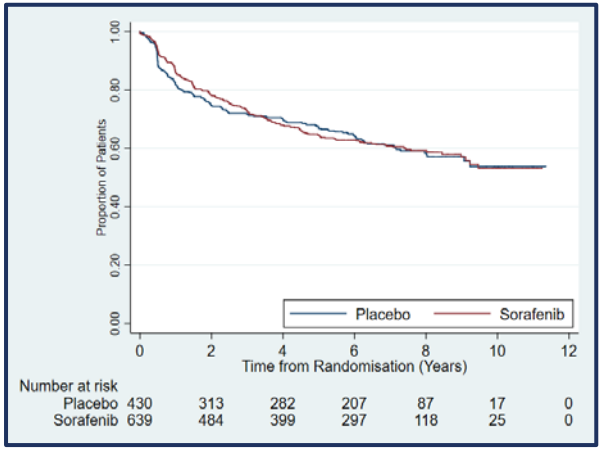


ATLAS Quinn
Annals
Oncol 2018



Sorafenib, pcb

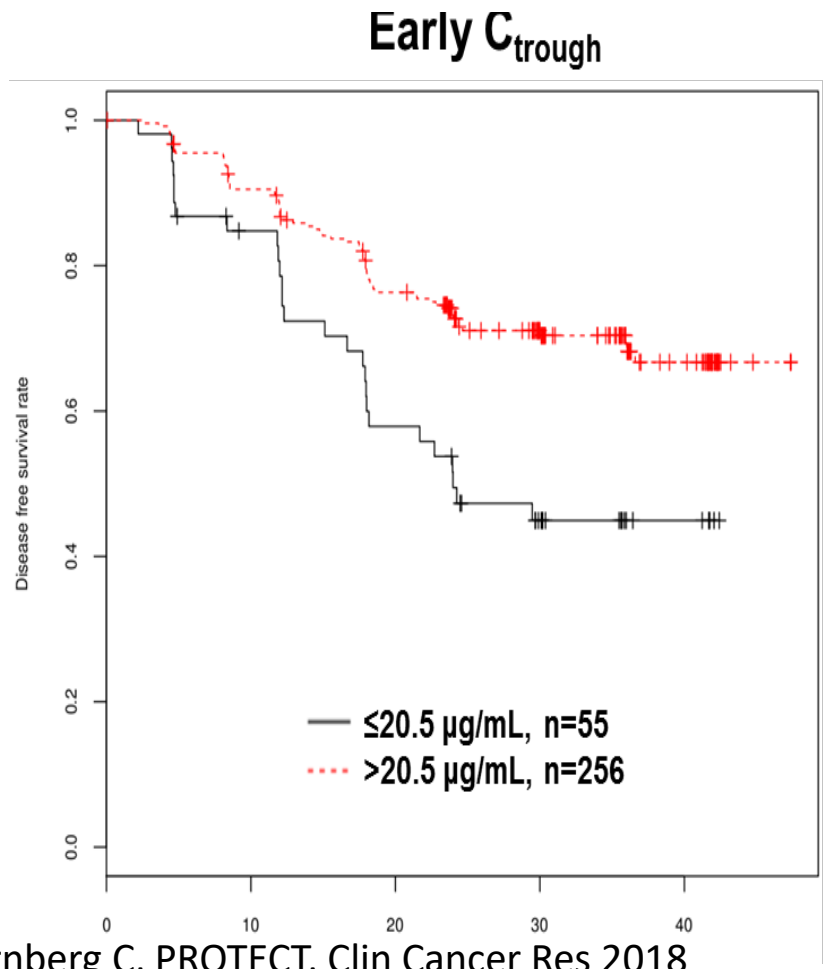
SORCE
3y
Eisen
ESMO 2019

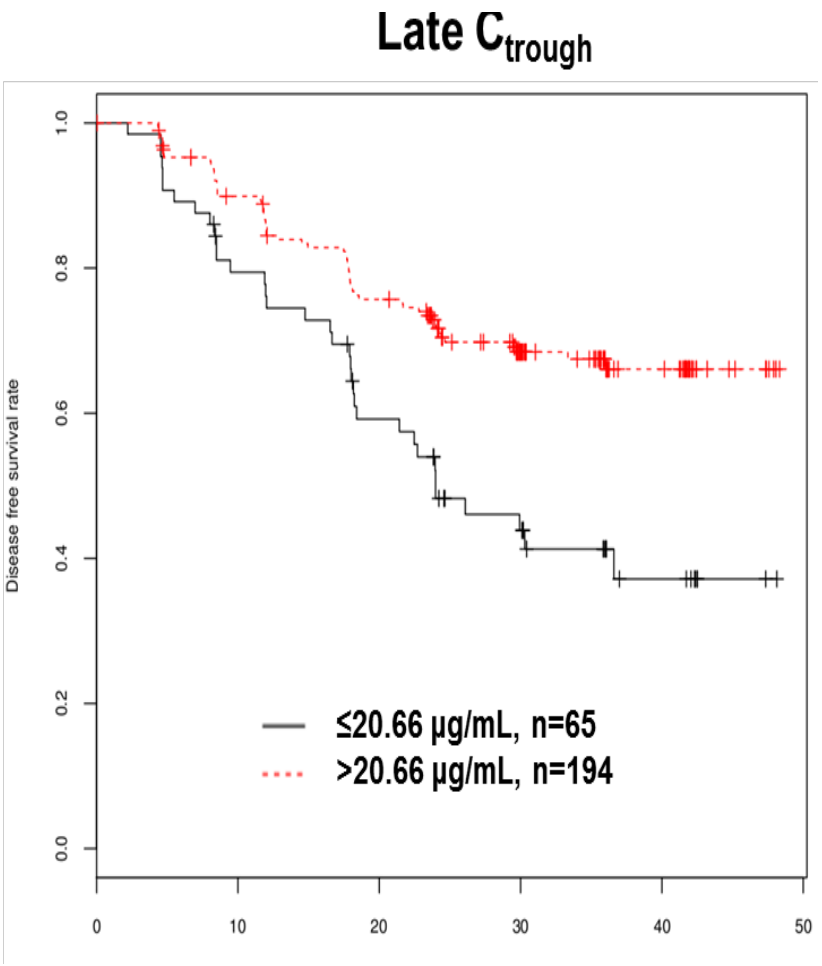


SORCE
1y
Eisen
ESMO 2019

PROTECT

Patients who have higher drug levels of pazopanib in their bodies might benefit but it is difficult to determine who those patients might be





Sternberg C, PROTECT, Clin Cancer Res 2018

Patients on the adjuvant VEGF TKI trials had worse (or less well tolerated) side effects than those patients who participated in clinical trials for advanced disease

Toxicity Grade % pts with side effects	**>3**	**>3**	**>3**
	Sunitinib	Sorafenib	Placebo
ASSURE (all)	63%	70%	24%
S-TRAC (all)	56.9%		19.4%
	Pazopanib		Placebo
PROTECT (600 mg dose)	60%		21%
	Axitinib		Placebo
ATLAS (all)	61%		30%
SORCE (all)		57%	20%

What Is Being Tested in the remaining VEGF TKI trials?

Current/Recent Adjuvant RCC Trials	Design / risk criteria Different Populations!	Reporting?
EVEREST (SWOG)	Can an mTor inhibitor for 1 year cure kidney cancer (cc and non ccRCC)? Everolimus vs placebo	2020?

What Is Being Tested in the Immune Checkpoint Inhibitor Perioperative trials?

- Does leaving the kidney tumor in, when immune therapy is started, make the Immune checkpoint inhibition therapy work better?
- Does Immune checkpoint inhibition cure high risk kidney cancer?
- Does immune checkpoint inhibition cure low volume resected metastatic disease?
- Does immune checkpoint inhibition delay relapse of cancer?
- Can we identify immune or other profiles which could predict benefit to these agents?

Completed Phase 3 RCC single agent IO Adjuvant Studies

IMmotion010

- High risk or limited M1 NED
- Post nephrectomy ≤12 wks
- Clear cell or sarcomatoid

- Stratification Factors:

-T2/T3a vs. >T3b
-PD-L1 (IC0 vs IC1/2/3
-Region (US/Can vs ROW)

→ Randomize

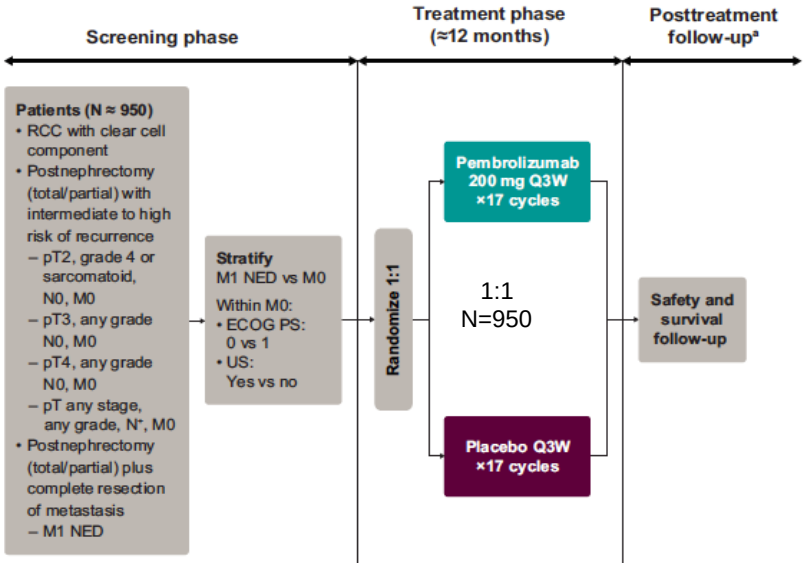
Atezolizumab 1200mg IV Q3 wks x 16 cycles

1:1
N=664

Placebo IV Q3 wks x 16 cycles

NCT03024996

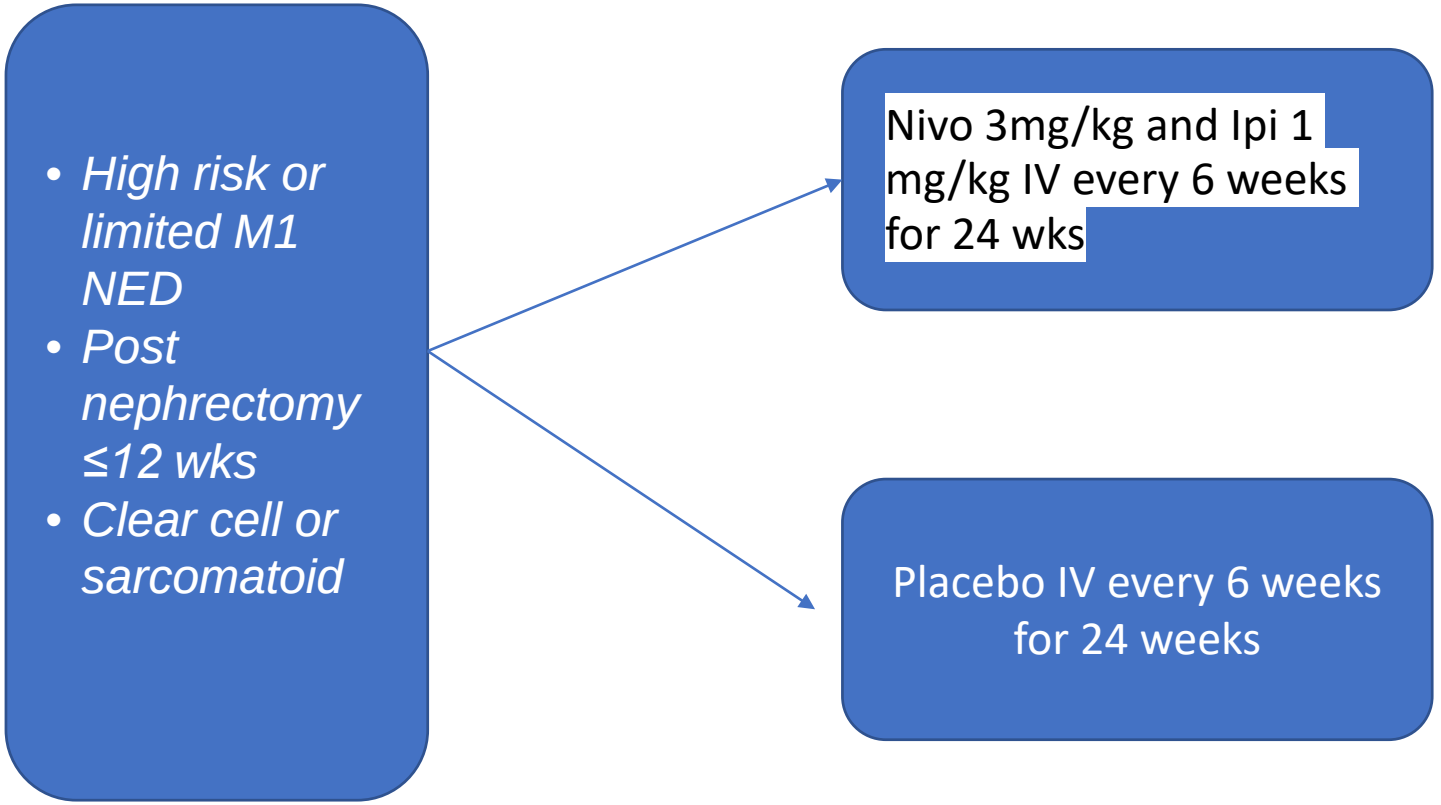
KEYNOTE 564



NCT03142334

Allow limited resectable M1 disease that would be rendered NED

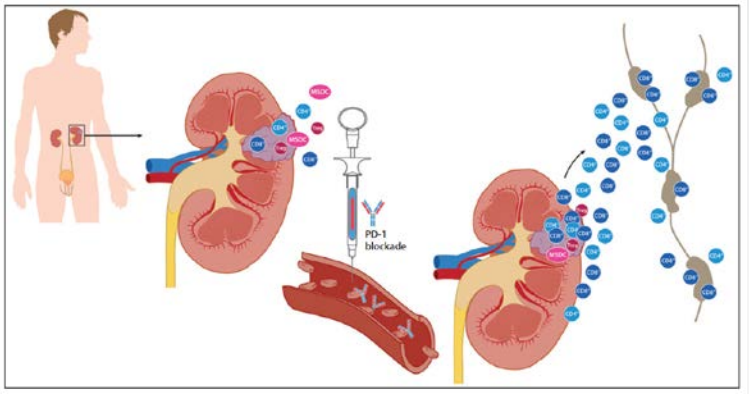
Ongoing
Checkmate -914(BMS)
Nivolumab + Ipilimumab vs Placebo

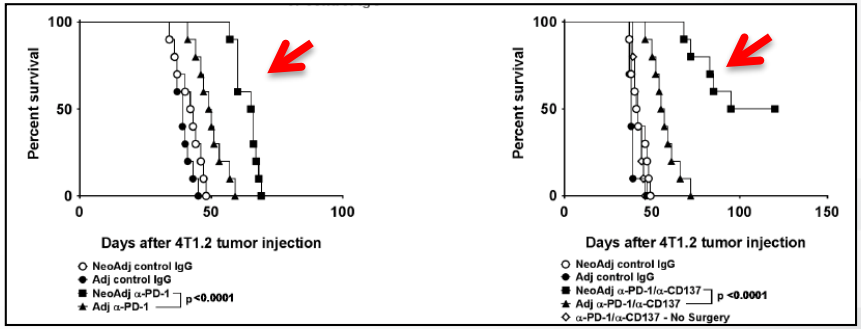


Open at LHV Allentown
And MSKCC

Disrupting Practice: Pre-surgical Priming with anti-PD-1

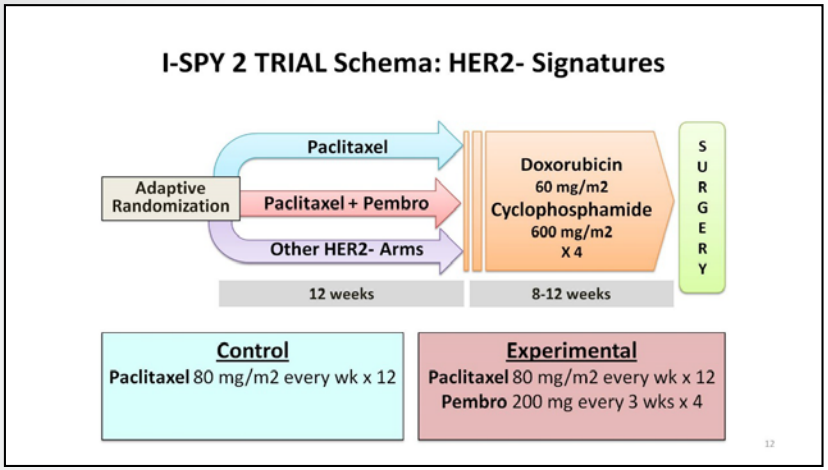
- Ongoing but unsuccessful anti-tumor T cell response in the primary tumor, tumor ME, and draining nodes
- Post-PD-1 blockade anti-tumor CD8 T cells may preferentially expand in these areas and traffic to distant sites and develop into memory cells (mice)
- Nephrectomy may remove the majority of these effector cells and cytokines→ less potent response?
- Short course of neoadjuvant immunotherapy increased survival compared to adjuvant …in MICE
  - Primary tumor required for T cell expansion
- Two ongoing phase 2 studies of neoadjuvant nivolumab in M0 RCC: safe, no surgical delays, target is hit





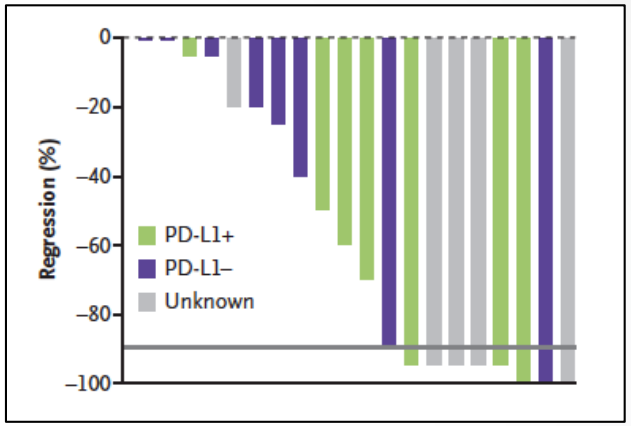
Woo…Drake Cancer Res 2012, MacFarlane CIR 2013, Liu Cancer discovery, Harshman Kidney 2017

Proof of efficacy in other solid tumors: TNBC & Lung Cancer



Nanda ASCO 2017

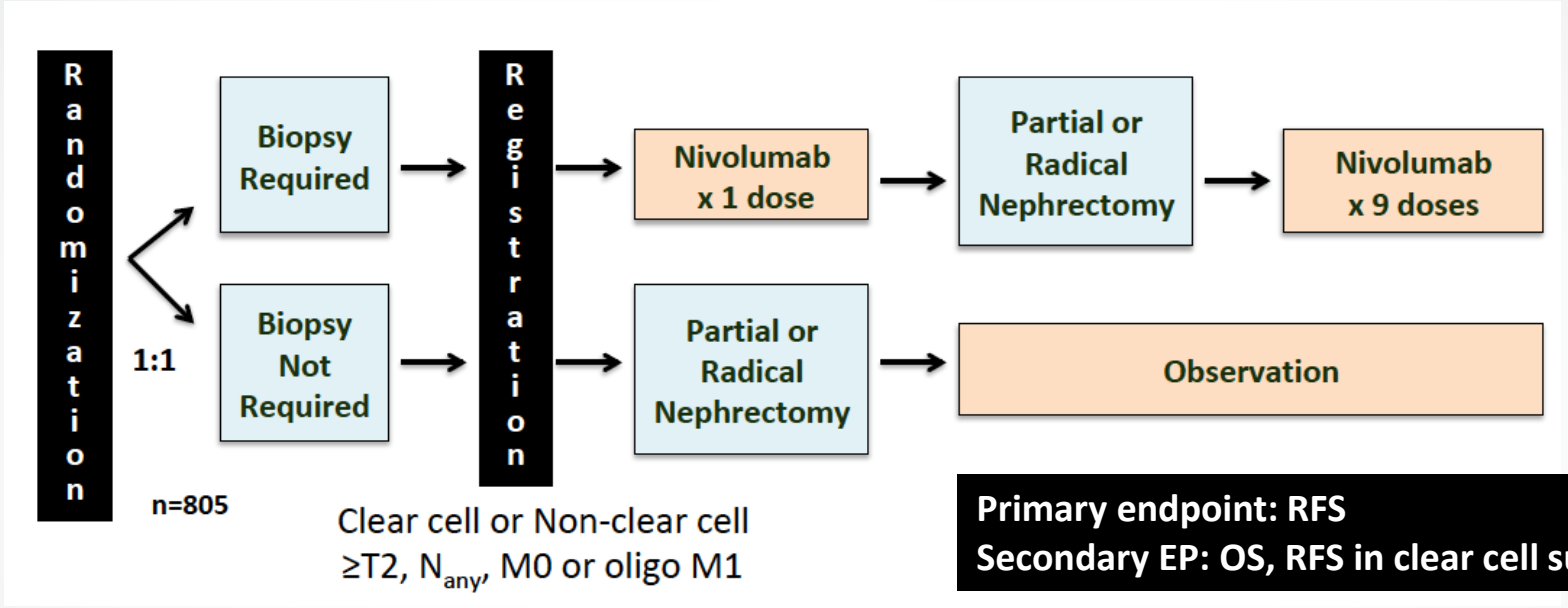
- Tripling of estimated pCR rate in TNBC: 60 vs. 20%
- Near tripling in HR+/HER2 neg: 34 vs. 13%



Forde NEJM 2018

- 2 doses of preoperative nivolumab in M0 NSCLC
- 45% experienced major pathologic response (MPR ≤10% viable tumor cells)
- Primary tumors with MPR: increased infiltrating lymphocytes and macrophages consistent with immune mechanism of response
- PD-L1 expression didn't predict response

EA8143 PROSPER RCC: Adjuvant Therapy with a Twist



- Need the trifecta: presurgical priming with PD-1 blockade necessary for enhanced efficacy
- 1 neoadjuvant dose may not be sufficient→ further engage with adjuvant therapy
- No Placebo—patients really do care about this!

Urology PI: Allaf; PIs: Harshman/McDermott, MANY OTHERS

Conclusions

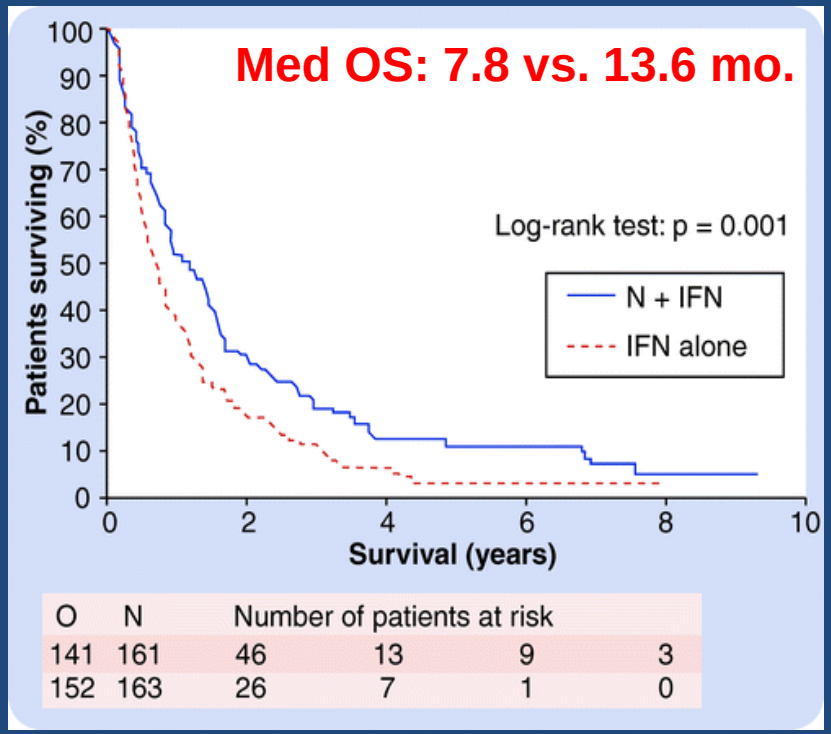
- No OS benefit in any of the 5 reported adjuvant VEGF trials
- No DFS benefit in 4 large adjuvant VEGF TKI trials/ DFS Benefit in 1 trial led to FDA approval of adjuvant sunitinib
- Adjuvant VEGF TKI inhibitors are associated with severe side effects in more than half of all patients so we need to really understand who should be offered this therapy
- Pharmacokinetic/ pharmacogenomic analyses may help to determine benefit to VEGF TKI adjuvant therapy
- Current immune checkpoint inhibitor trials are ongoing and we are hopeful
- Surveillance Clinical trial participation or adjuvant sunitinib remain choices for patient with kidney cancer at high risk for recurrence

Role of Cytoreduction

- Benefit for nephrectomy in the metastatic setting?

- 5.8 month overall survival benefit in the immunotherapy era
  - Combined analysis: SWOG 8949 and EORTC 30947
  - No difference in response
  - Acceptable toxicity

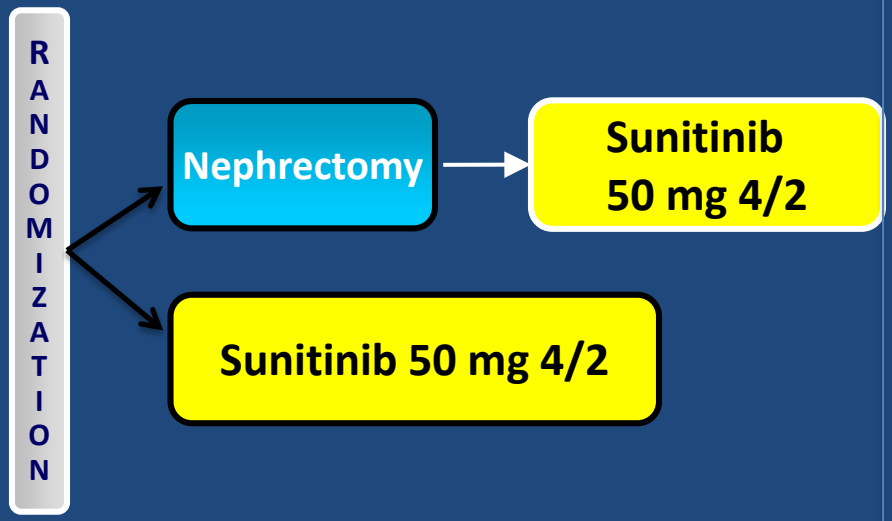
- True for targeted agents?
  - Need? (can shrink primary tumor)
  - Toxicity?



Harshman Future Drugs 2007, Adapted from Flanigan J Urol 2004

Cytoreductive Nephrectomy in the Targeted Therapy Era

Nephrectomy needed?

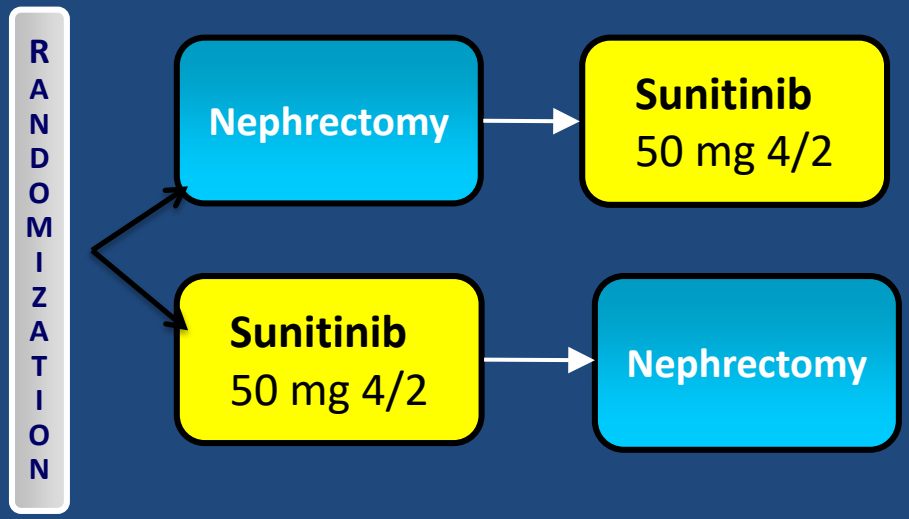


N=576

CARMENA Trial

- Non-inferiority trial
- **Primary Objective: OS**

Sequence?



N=440

EORTC Trial

- Nephrectomy after sunitinib only if no PD in metastatic dz
- **Primary Objective: PFS**

Cytoreductive Nephrectomy in the Targeted Therapy Era

Nephrectomy needed?

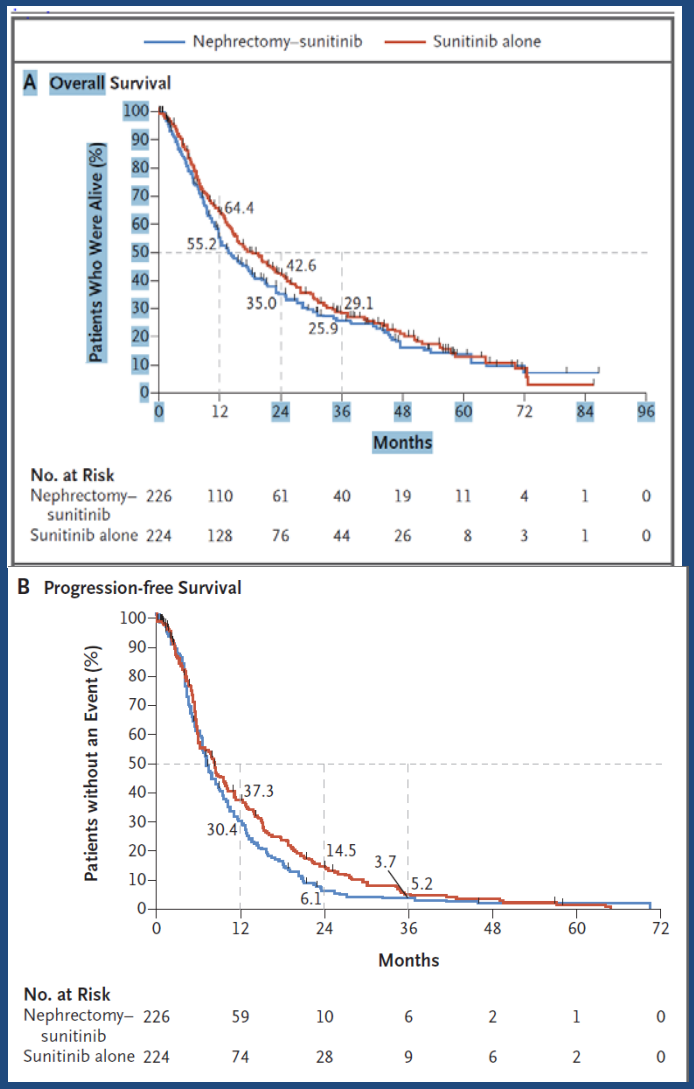
RANDOMIZATION

- **Nephrectomy** → **Sunitinib 50 mg 4/2**
- **Sunitinib 50 mg 4/2**

N=576

CARMENA Trial

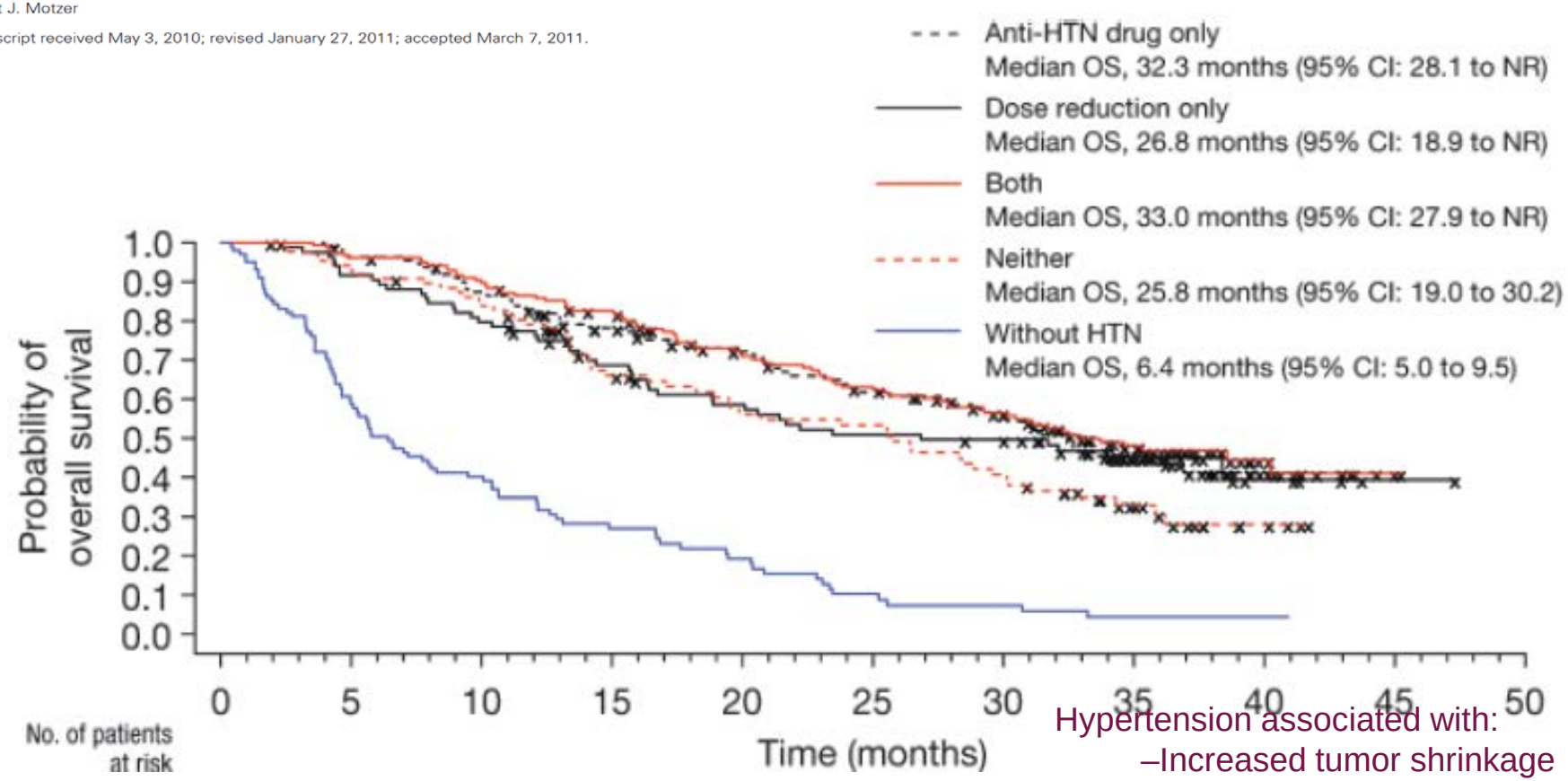
- Non-inferiority trial
- **Primary Objective: OS**



Hypertension as a Biomarker of Efficacy in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib

Brian I. Rini, Darrel P. Cohen, Dongrui R. Lu, Isan Chen, Subramanian Hariharan, Martin E. Gore, Robert A. Figlin, Michael S. Baum, Robert J. Motzer

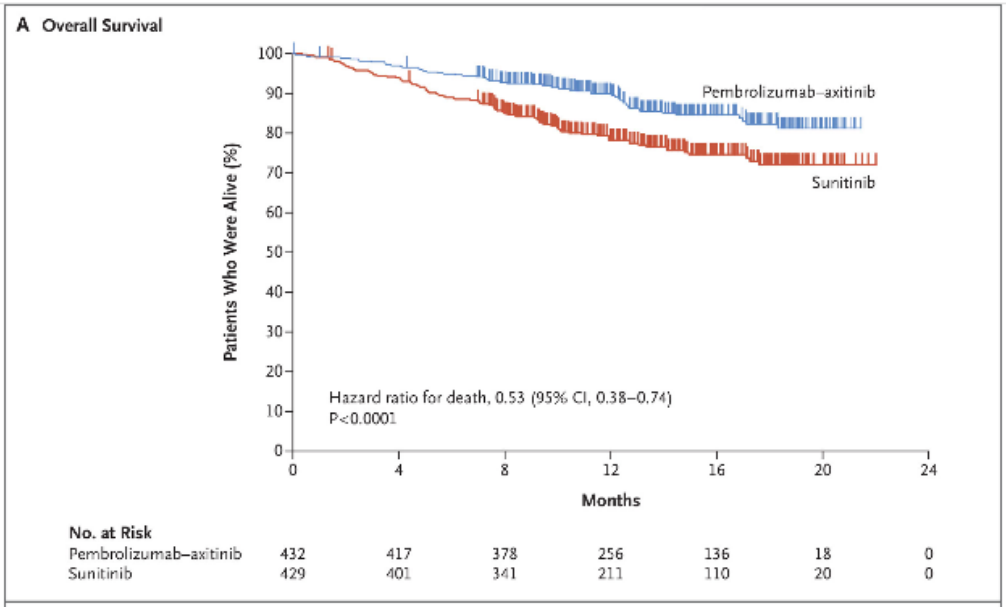
Manuscript received May 3, 2010; revised January 27, 2011; accepted March 7, 2011.

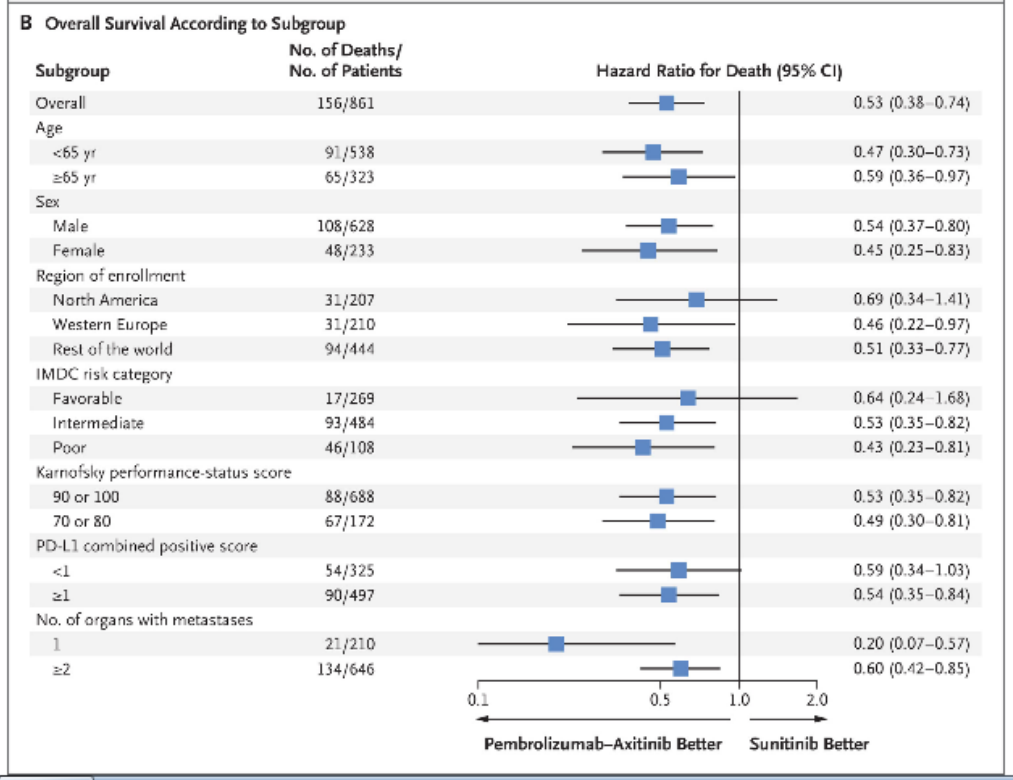


Hypertension associated with:
- –Increased tumor shrinkage
- –Prolonged time to progression
- –Increased overall survival

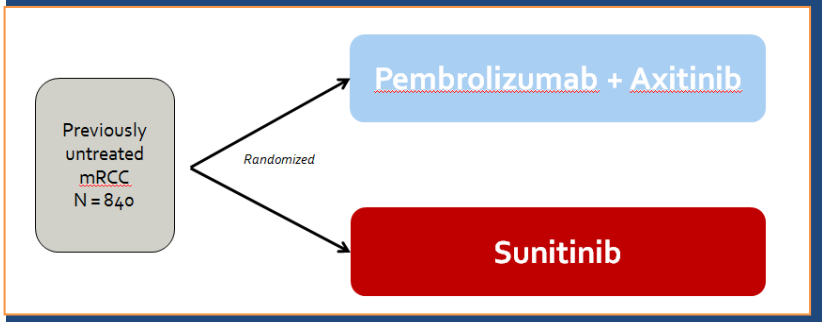
Controlling BP did not diminish effect

•On-therapy marker of effectiveness





Combination VEGF TKI and immune checkpoint inhibition has improved overall survival and led to first-line approval



Rini B, et al. NEJM 2018

Phase II Immotion 150:

305 pts
mccRCC
PFS
PDL1

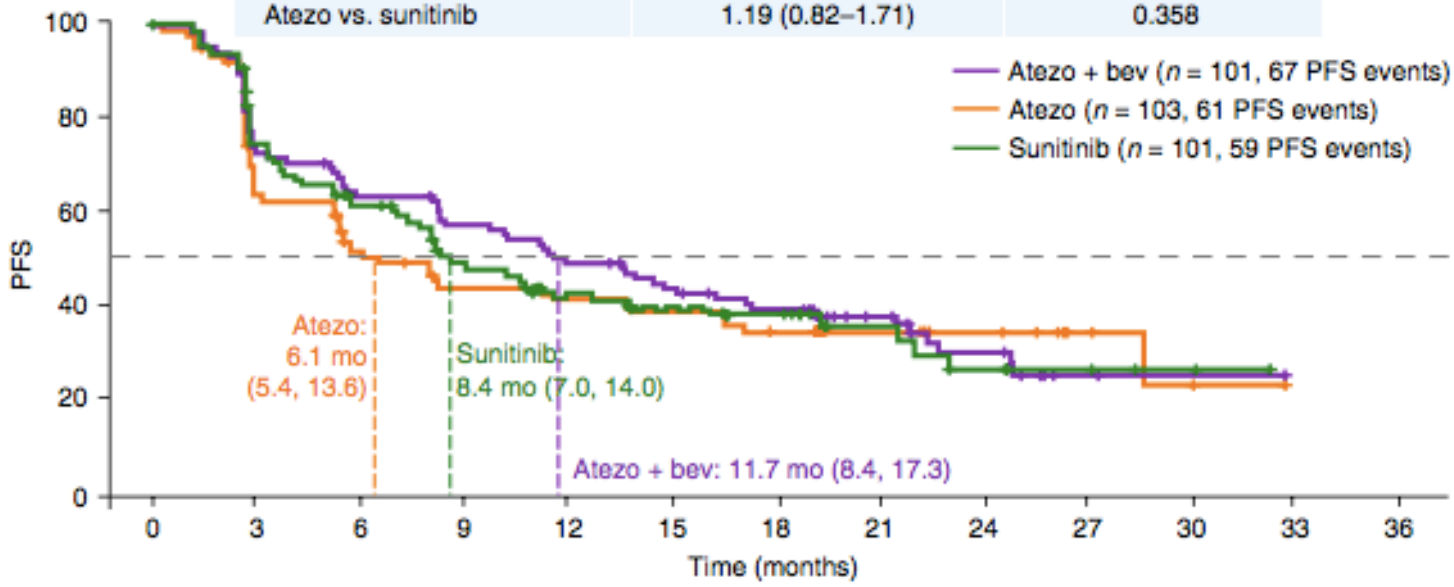
randomize

- Atezolizumab +bevacizumab
- Atezolizumab
- sunitinib

a

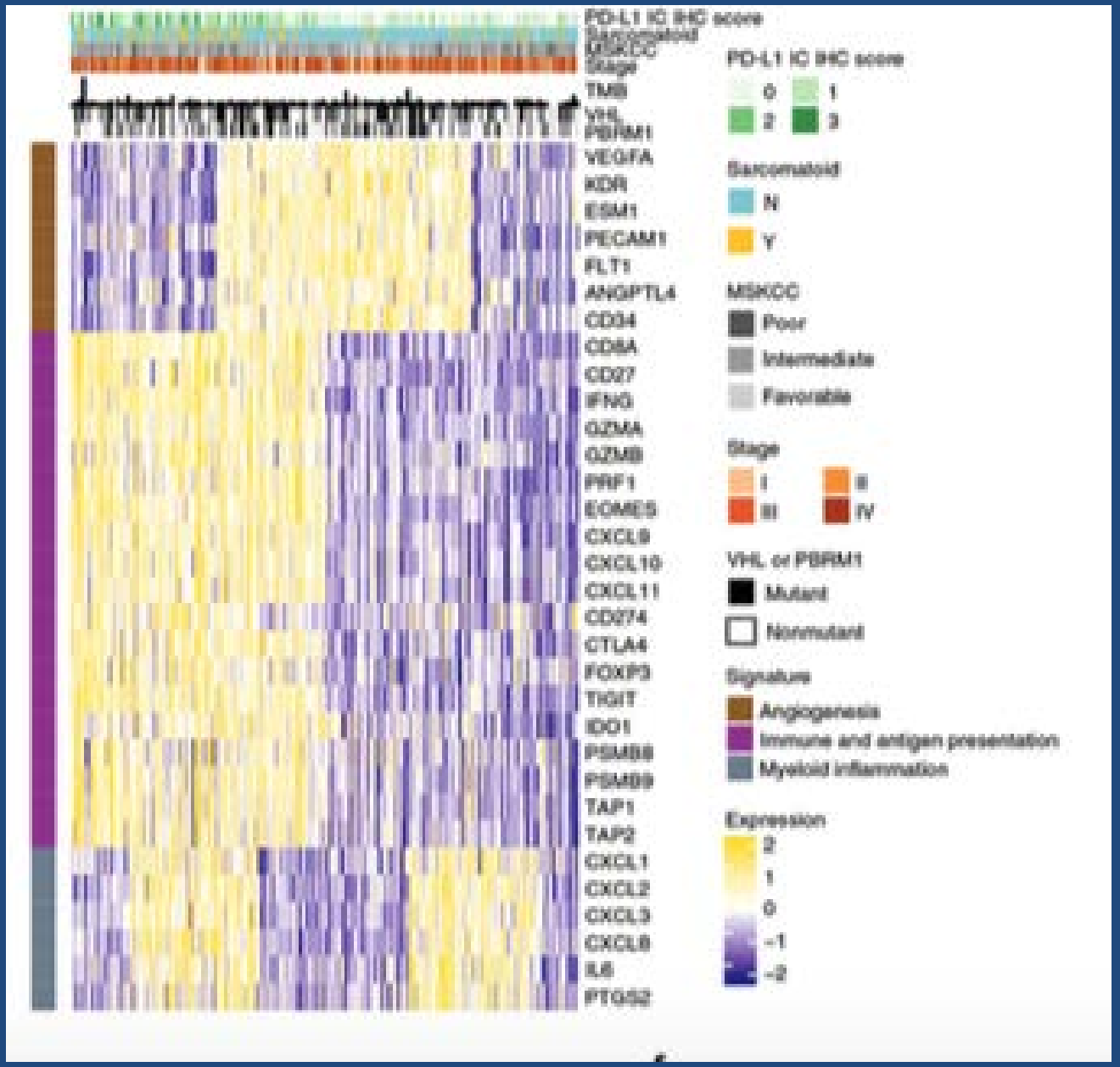
ITT

	Stratified HR (95% CI)	*P*
Atezo + bev vs. sunitinib	1.00 (0.69–1.45)	0.982
Atezo vs. sunitinib	1.19 (0.82–1.71)	0.358



No. at risk

Atezo + bev	101	73	62	55	48	40	34	21	13	5	1	1
Atezo	103	59	43	35	31	29	24	14	10	4	2	1
Suntinib	101	69	53	37	30	26	22	11	7	4	2	


PD-L1 IC IHC score
Sarcomatoid
MSKCC
Stage
TMB
VHL
PBRM1
VEGFA
KDR
ESM1
PECAM1
FLT1
ANGPTL4
CD34
CD8A
CD27
IFNG
GZMA
GZMB
PRF1
EOMES
CXCL9
CXCL10
CXCL11
CD274
CTLA4
FOXP3
TIGIT
IDO1
PSMB8
PSMB9
TAP1
TAP2
CXCL1
CXCL2
CXCL3
CXCL8
IL6
PTGS2
PD-L1 IC IHC score
0
1
2
3
Sarcomatoid
N
Y
MSKCC
Poor
Intermediate
Favorable
Stage
I
II
III
IV
VHL or PBRM1
Mutant
Nonmutant
Signature
Angiogenesis
Immune and antigen presentation
Myeloid inflammation
Expression
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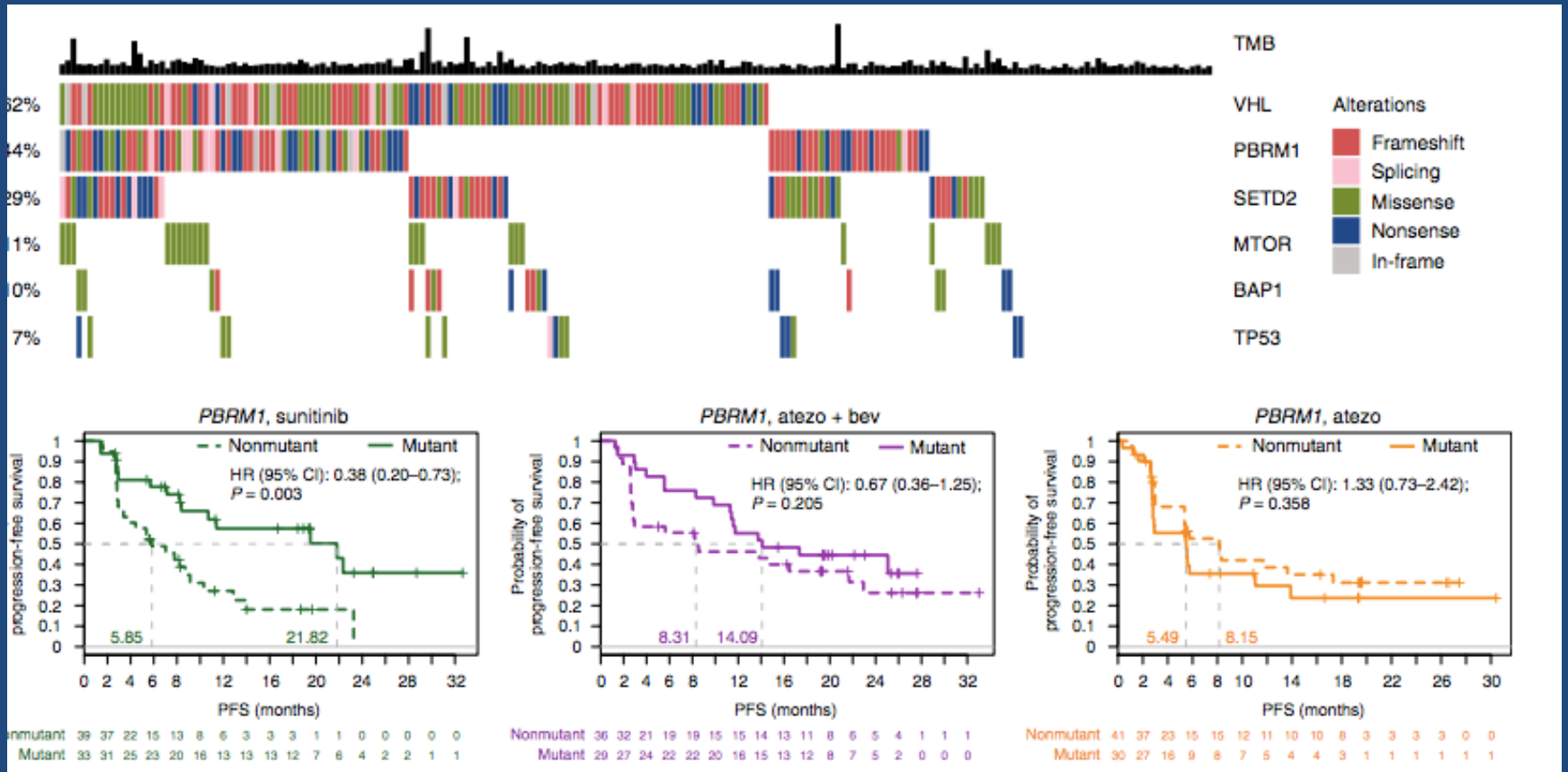
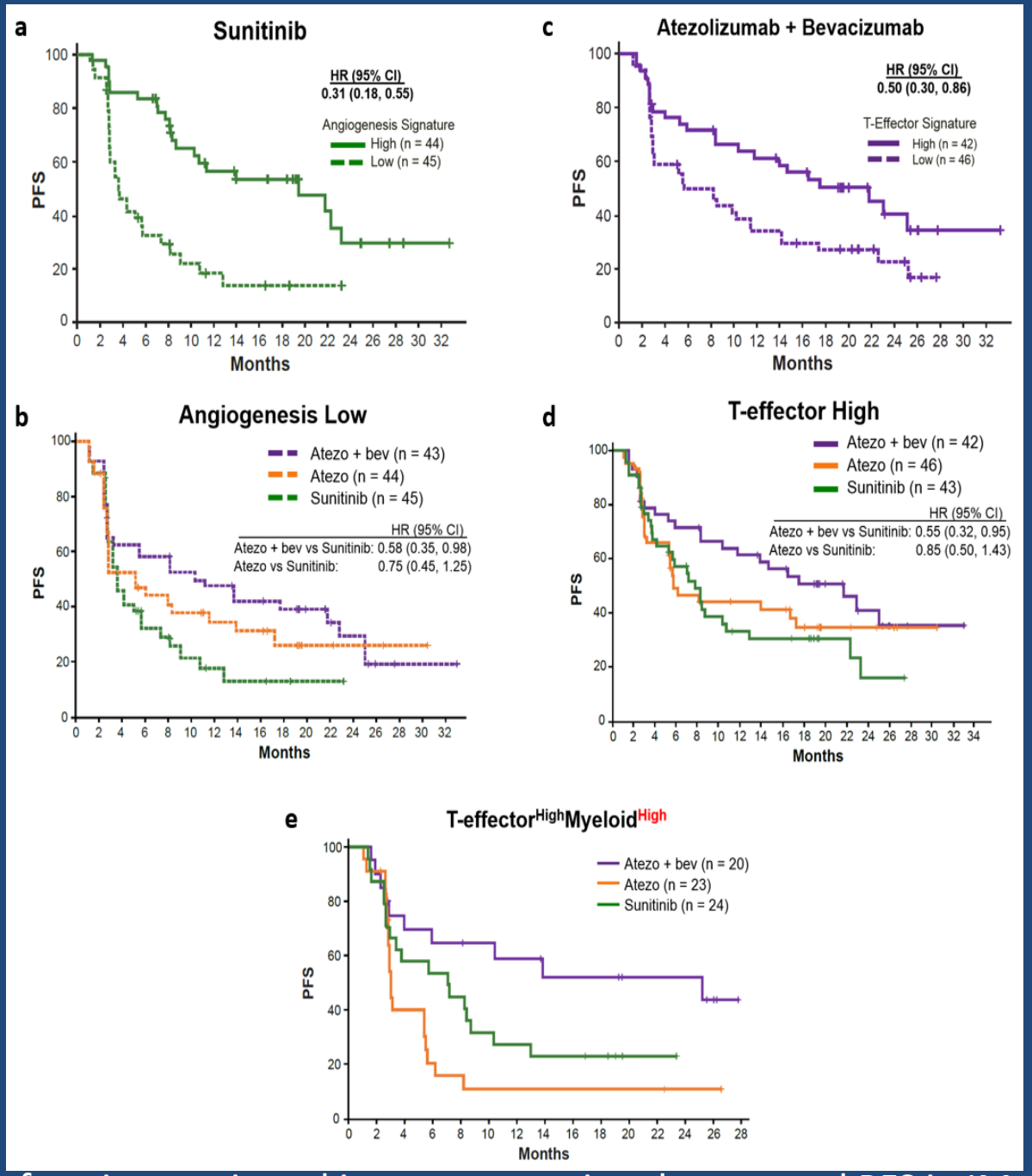
IMMOTION150



3 | Association between tumor mutations and clinical outcome. a, TMB and TNB are plotted by response group (CR and PR vs. SD (stable disease) PD (progressive disease)) for each treatment arm. No apparent difference was observed between response groups in the sunitinib (two-tailed *t*



Exploratory analyses of angiogenesis and immune-associated genes and PFS in IMmotion150.