Perioperative Systemic Therapy for Localized Renal Cell Carcinoma: To Treat or Not to Treat

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- **Stock: PTC therapeutics**

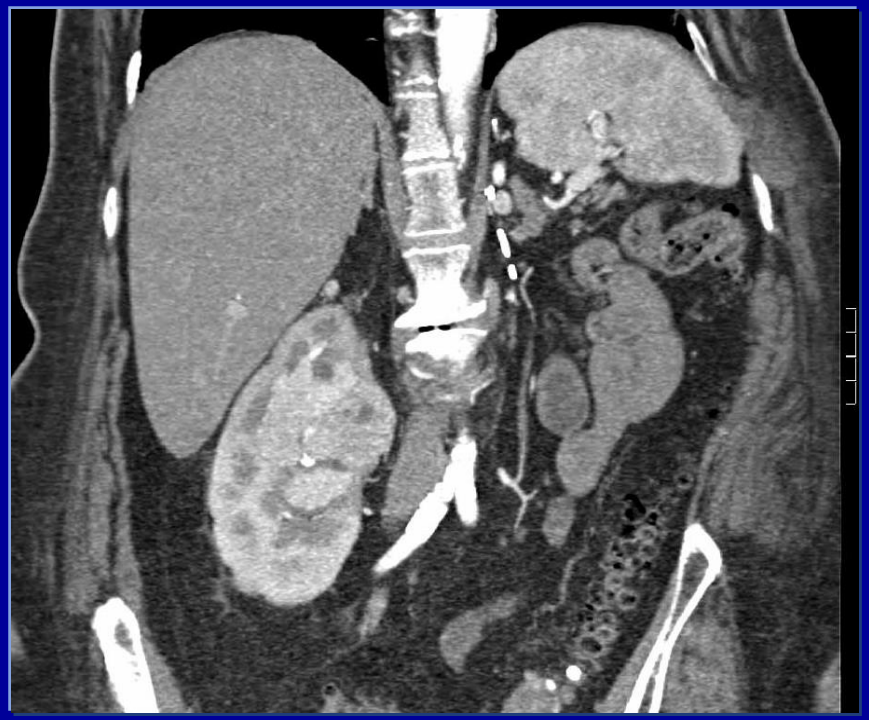
*Last 36 months

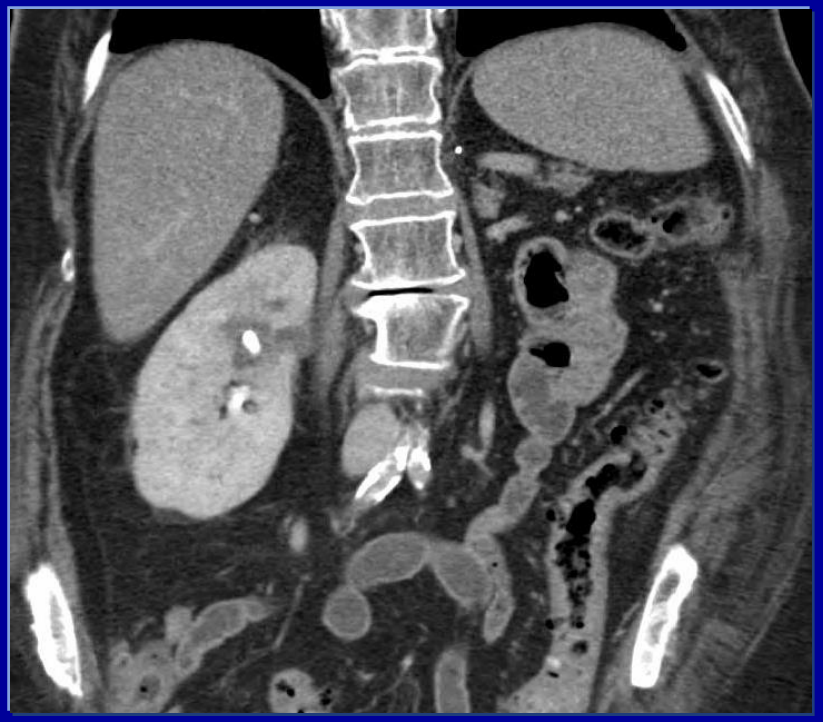
Perioperative Systemic Therapy in RCC

- Neoadjuvant therapy
  - VEGF TKI
  - I/O ongoing trials
- Adjuvant therapy
  - VEGF TKI results to date
  - S-TRAC in more depth
  - I/O ongoing trials

Pre-surgical VEGF-Targeted Therapy in RCC

Approach	Patient population	No. of pts/tumors with primary tumor shrinkage	Amount of primary tumor shrinkage	
Sunitinib (CCF)	'Unresectable' RCC; 50mg continuous (n=29)	80%	22%	1.2 cm
Sorafenib (UNC)	≥T2 RCC; sorafenib 400 mg BID x 4–8 weeks prior to nephrectomy (n=25)	64%	9%	0.8 cm
Pazopanib (CCF)	Localized RCC to enable partial nephrectomy; 8 weeks (n=28)	93%	25%	1.8 cm
Axitinib (MDACC)	Localized RCC; 12 weeks (n=24)	100%	28%	3.1 cm





PADRES (Prior Axitinib as a Determinant of Outcome of REnal Surgery)

1)Imperative indication for nephron sparing surgery (preexisting CKD or solitary kidney/anatomically functionally solitary kidney or bilateral synchronous disease); and

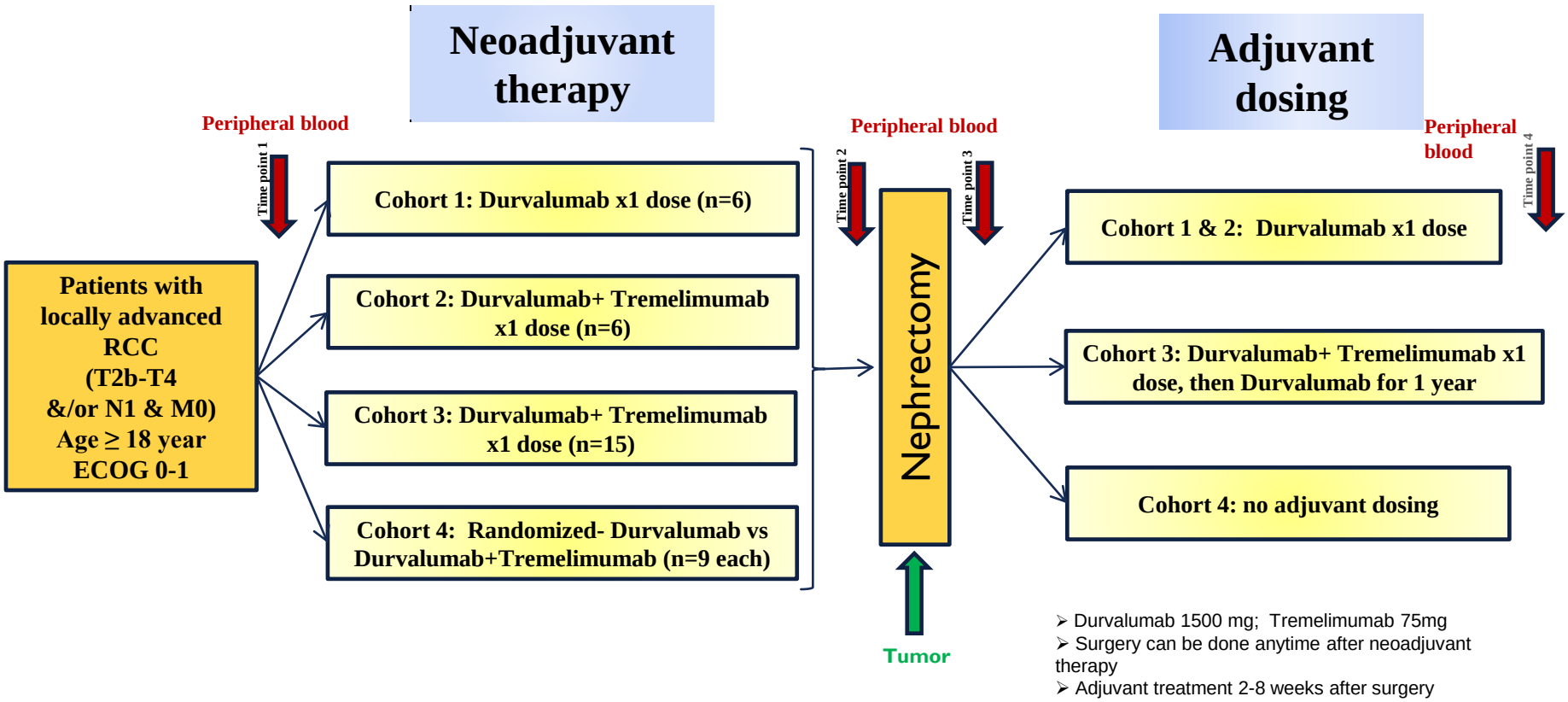
2) complex renal lesion defined as RENAL score ≥10 or proximity to renal hilum, defined as <2 mm away from at least 2 renal hilar vessels-the main artery/vein or first order branches); and

3) radical nephrectomy would place patient on dialysis or leave patient with severe CKD (> stage IIIb)

Axitinib-5 mg po BID x 8 weeks (with titration to 7mg BID as tolerated at 4 weeks), then re-staging

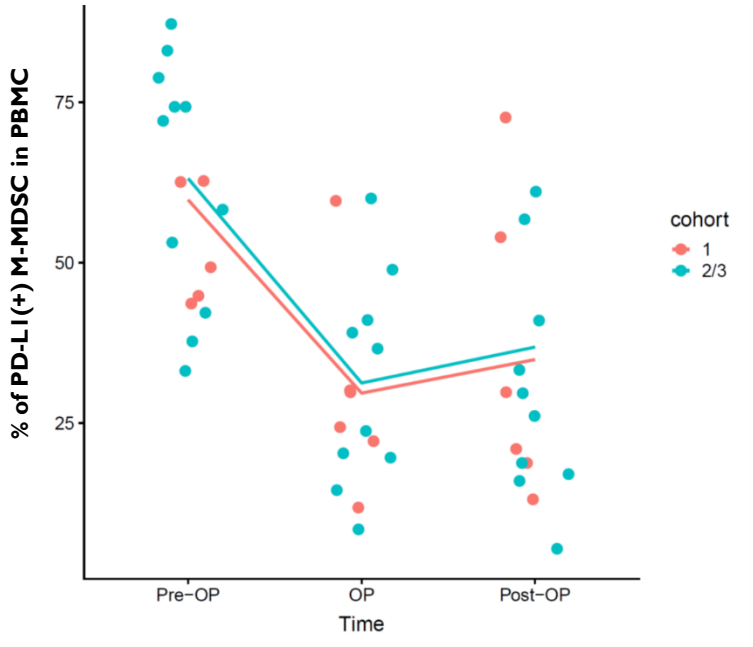
Outcome measures

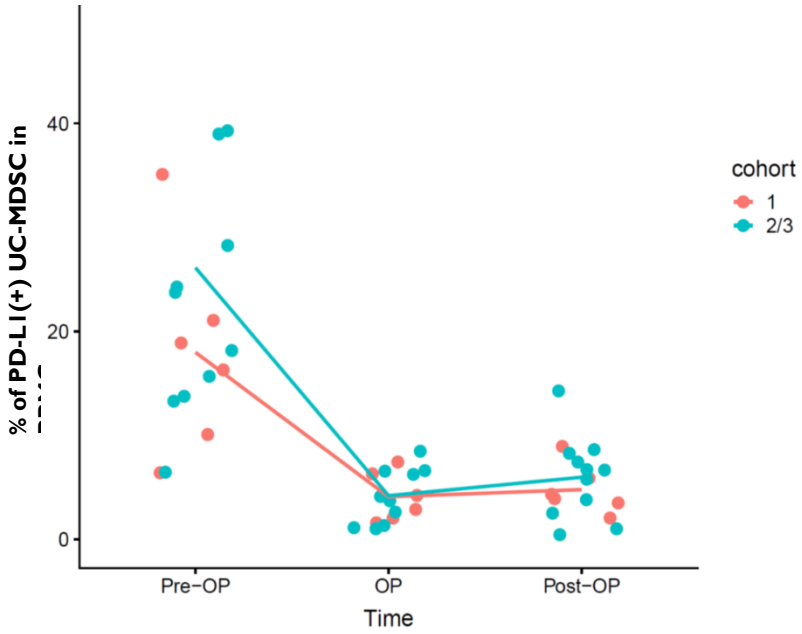
1) Assessment of Tumor Response (CT or MRI) after completion of axitinib therapy
   a) RECIST v1.1 response / change in maximal tumor diameter
   b) Change in R.E.N.A.L. Nephrometry Score
2) Ability to perform Partial Nephrectomy after TKI therapy with Negative Margins
3) Functional issues: avoidance of dialysis and severe CKD (stage 4, GFR <30 ml/min/1.73 m2)
4) Safety indices
a) avoidance of major Complications: Clavien ≥ 3
b) avoidance of need for multiple blood transfusion



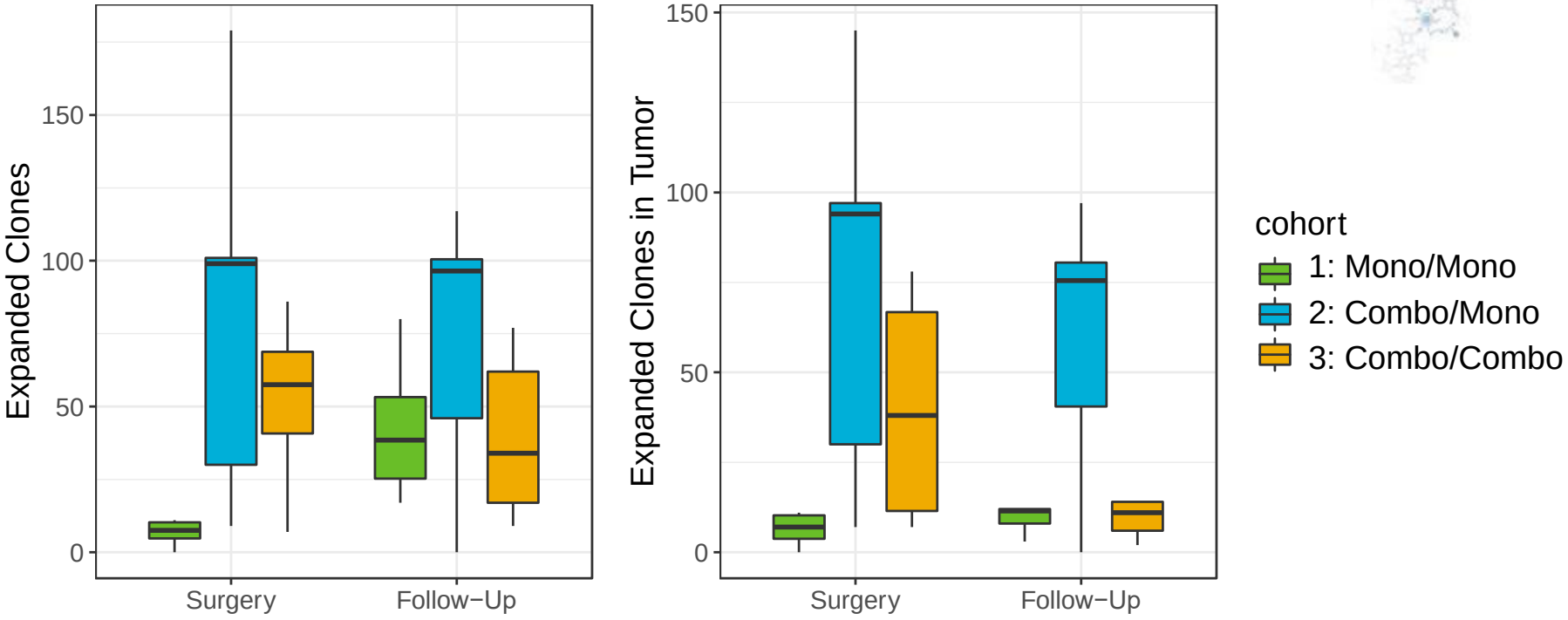
- Durvalumab 1500 mg; Tremelimumab 75mg
- Surgery can be done anytime after neoadjuvant therapy
- Adjuvant treatment 2-8 weeks after surgery

Frequencies of PD-L1 expression on M-MDSC and UC-MDSC in PBMC decreased significantly from pre- to post-neoadjuvant treatment ($p < 0.01$).



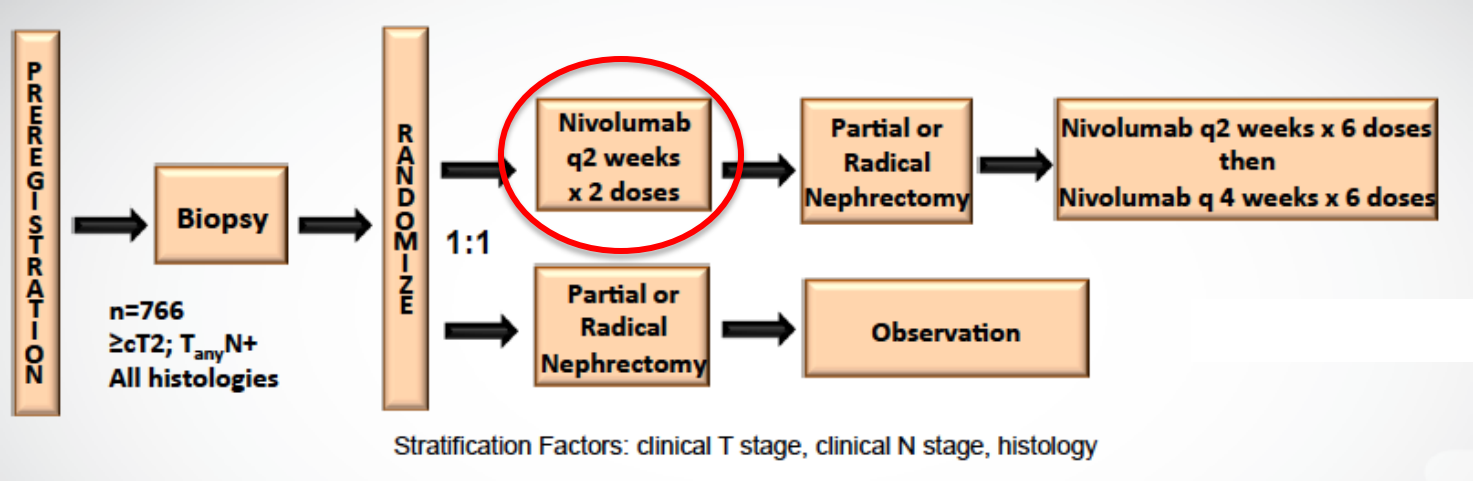


Cohort 2 and 3 have the Most Peripheral Clonal Expansion, And Cohort 2 Maintains Expansion of Tumor Clones



- Both cohort 2 and 3 show the most clonal expansion at Surgery. All 3 cohorts have greater than 75% of expanded clones being present in the tumor.
- At Follow-up cohort 2 has the most expansion overall and maintains expansion of TIL clones.
- Statistically only expanded clones at surgery shows a significant p-value between groups (Kruskal Wallis test p=0.04)

EA8143 PROSPER RCC: Neo/Adjuvant Therapy



NCT03055013

- Need the trifecta: presurgical priming with PD-1 blockade necessary for enhanced efficacy
- 2 neoadjuvant doses may not be sufficient→ further engage with adjuvant administration
- Biopsy will allow critical insights into tumor response and resistance mechanisms as well of proof of RCC

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

Neoadjuvant Therapy in RCC

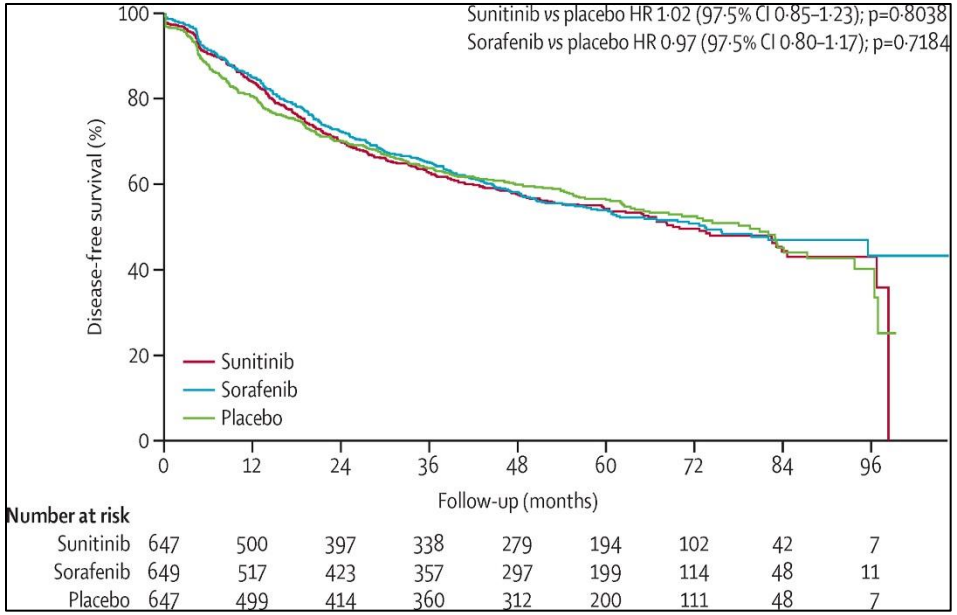
- Neoadjuvant TKI can shrink tumors and is potentially useful is specific clinical circumstances (e.g. hilar tumor in a solitary kidney)

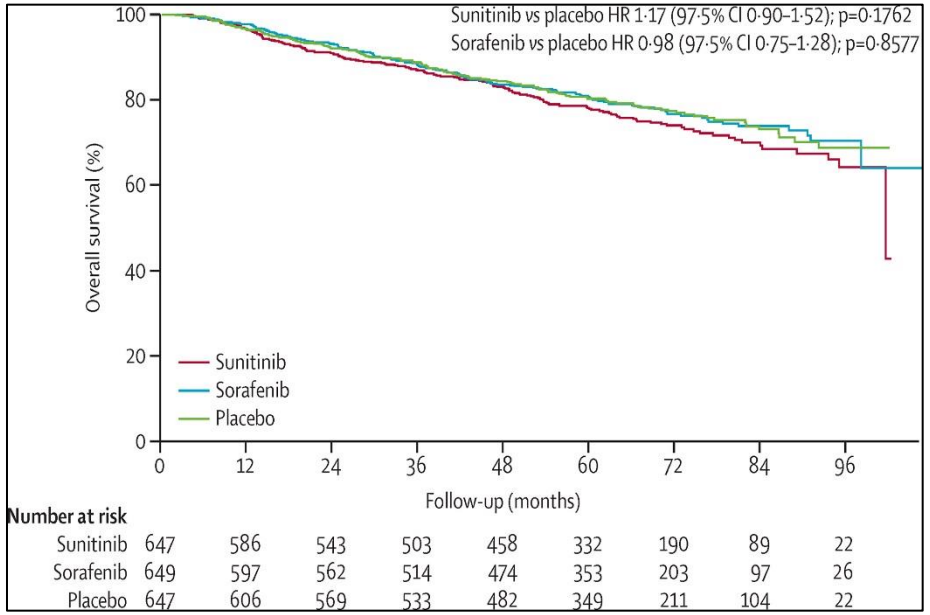
- Neoadjuvant IO is an opportunity for correlate science

Adjuvant Therapy in RCC

ASSURE

Sunitinib vs Sorafenib vs Placebo





Haas NB *et al* Lancet 2016

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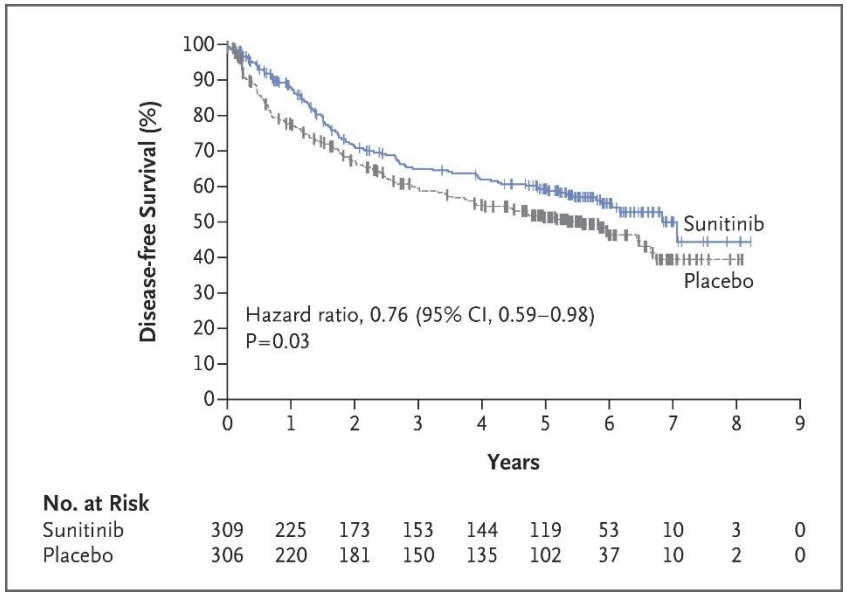
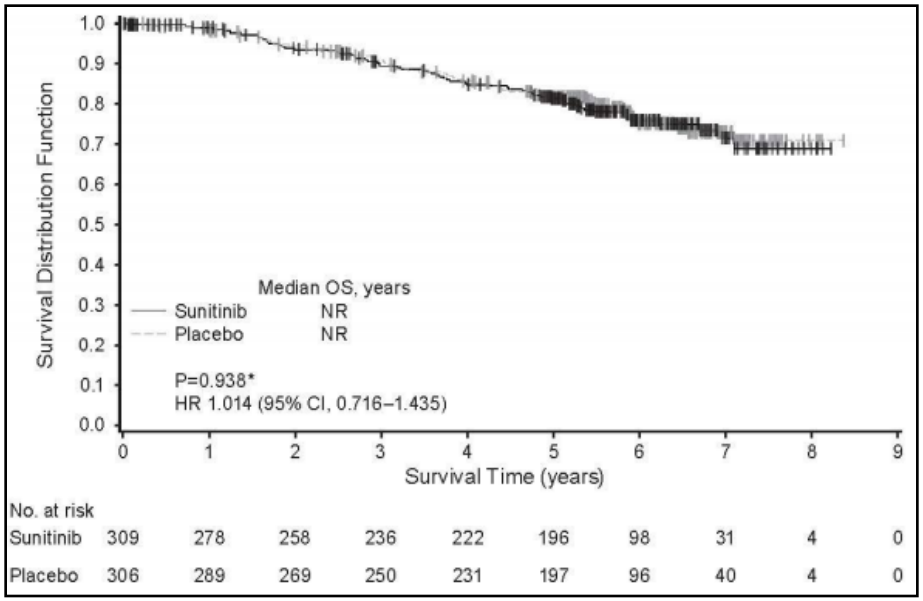
S-TRAC

Sunitinib vs Placebo





Ravaud A. *et al* New Engl J Med 2016

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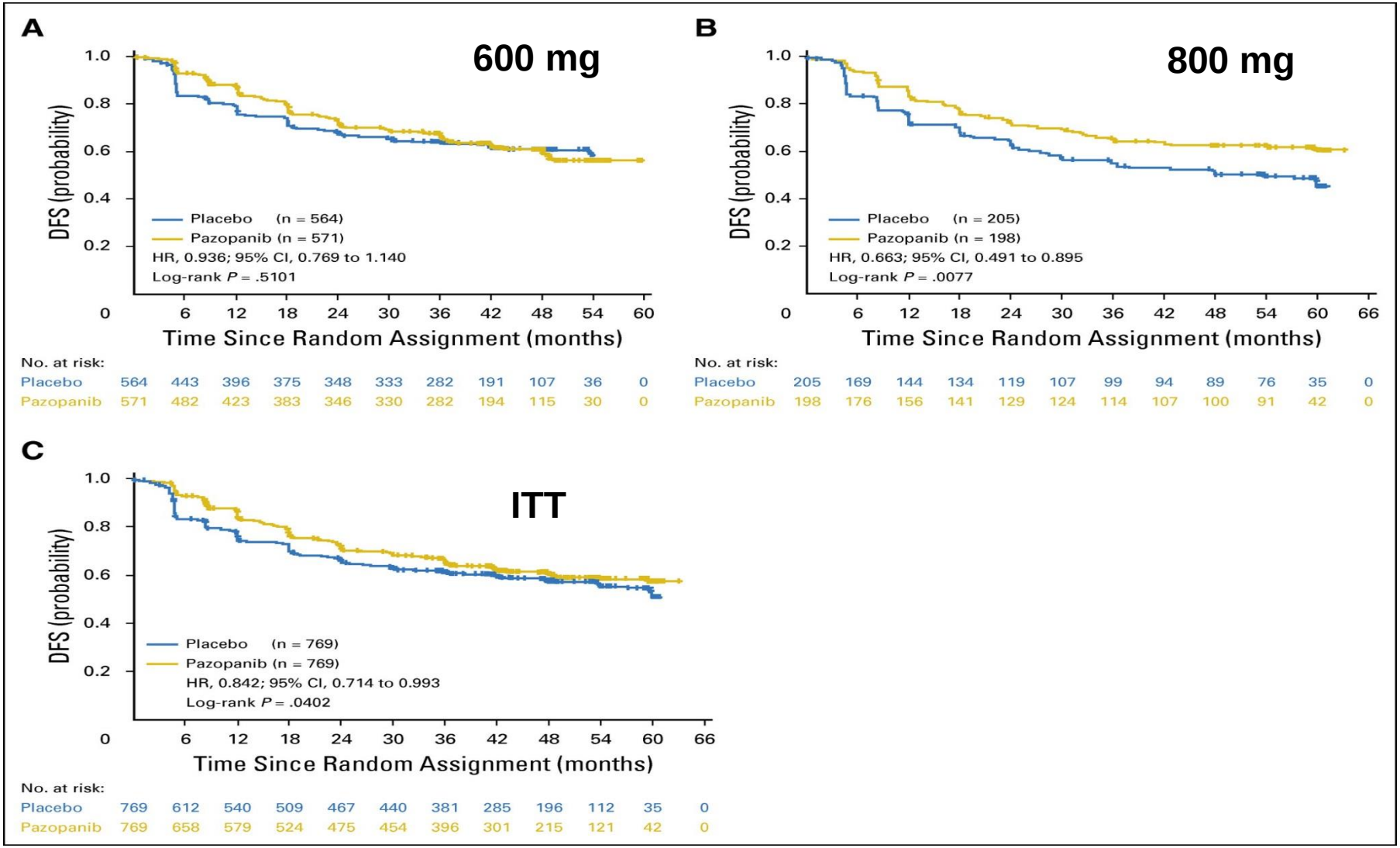
PROTECT



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Motzer R *et al* J Clin Oncol 2017

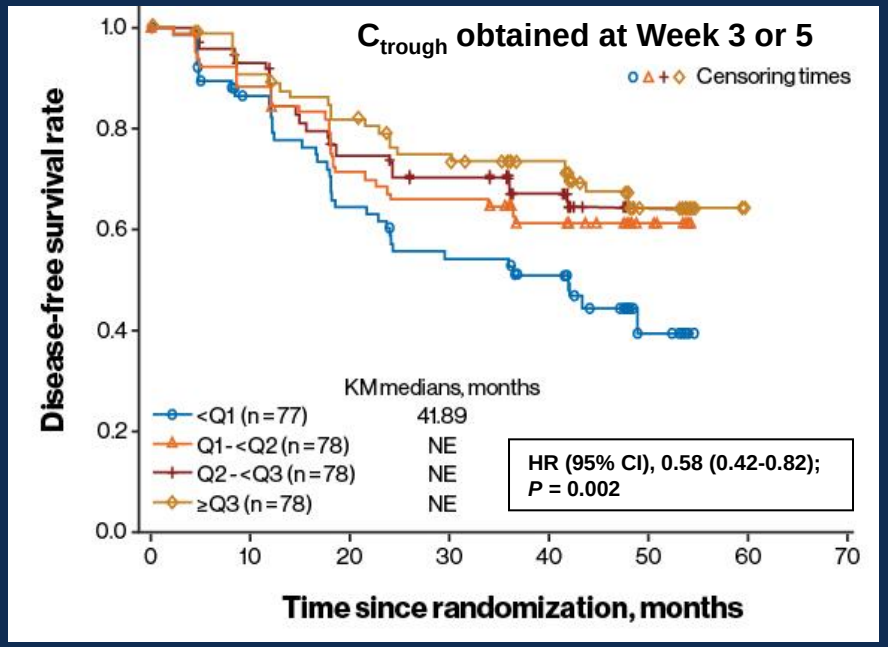
TKI Adjuvant Trials: Analysis

	Therapy	N	Histology	Stage	Starting Dose	Minimum Dose	DFS	OS
ASSURE	Sunitinib Sorafenib Placebo	1943	**79% ccRCC**	≥pT1b, G3-4, or N+	50 or 37.5 mg (Su) **100% / 75%**	25mg **50%**	No	No
S-TRAC	Sunitinib Placebo	615	99% ccRCC	≥pT3b or N+	50mg **100%**	37.5mg **75%**	Yes	No
PROTECT	Pazopanib Placebo	1538	ccRCC or mostly ccRCC	pT2 (3-4), or ≥pT3, or N+	600mg **75%**	400mg **50%**	No	No

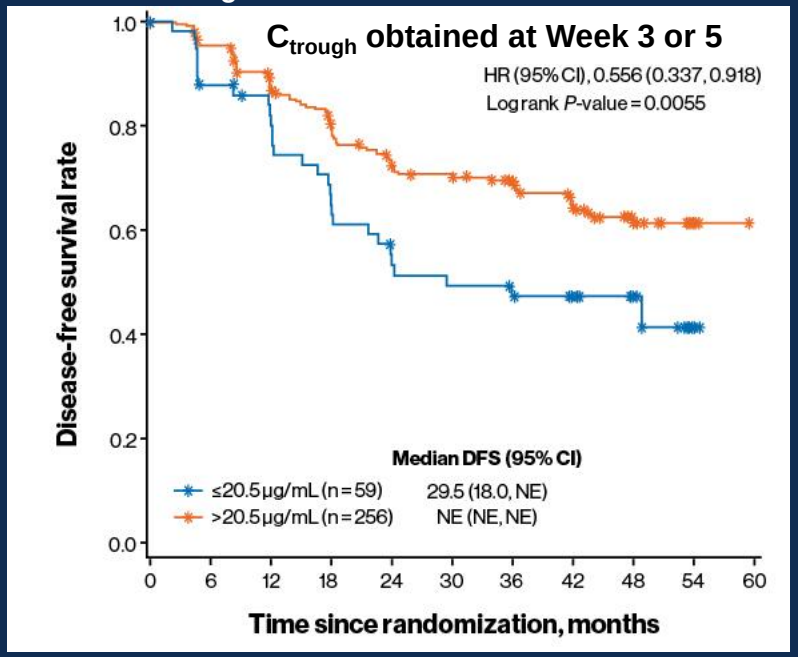
Ravaud A. NEJM 2016; Haas NB Lancet 2016; Motzer R JCO 2017

Pazopanib Concentrations for 600 mg Starting Dose

DFS by C_{trough} Quartiles



DFS by C_{trough} >20.5 µg/mL or ≤20.5 µg/mL



- Longer DFS was observed in patients achieving higher C_{trough} quartiles and those achieving C_{trough} >20.5 µg/mL

Sternberg CN, et al. ASCO 2017; abstr 4564

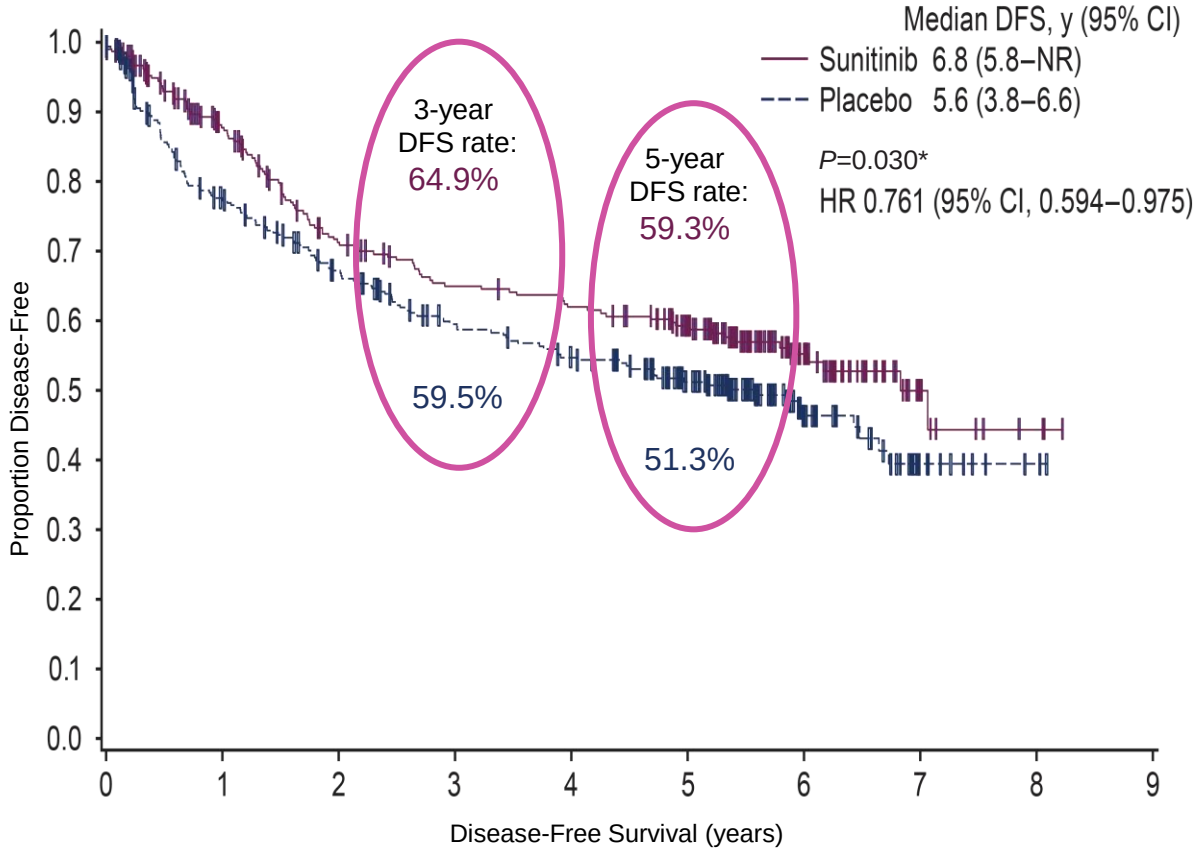
Adjuvant Sunitinib in RCC

Pros

- The standard of care is doing nothing which neither docs nor patients like.

Cons

Disease-Free Survival By Blinded Independent Central Review



No. at risk

Sunitinib	309	225	173	153	144	119	53	10	3	0
Placebo	306	220	181	150	135	102	37	10	2	0

* Two-sided *P* value from log-rank test stratified by UISS high-risk group.

Adjuvant Sunitinib in RCC

Pros

- The standard of care is doing nothing which neither docs nor patients like.
- There is a DFS benefit to sunitinib - which may be durable (?)

Cons

- The DFS benefit of sunitinib is relatively small (5% ish more pts disease-free or 1+ year of median benefit)

Common Treatment-Emergent Adverse Events*

	Sunitinib (n=306)			Placebo (n=304)		
Adverse Event, %	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any adverse event	99.7	48.4	12.1	88.5	15.8	3.6
Diarrhea	56.9	3.9	0	21.4	0.3	0
PPE	50.3	15.0	1.0	10.2	0.3	0
Hypertension	36.9	7.8	0	11.8	1.0	0.3
Fatigue	36.6	4.2	0.7	24.3	1.3	0
Nausea	34.3	2.0	0	13.8	0	0
Dysgeusia	33.7	0	0	5.9	0	0
Mucosal inflammation	33.7	4.6	0	8.2	0	0
Dyspepsia	26.8	1.3	0	6.3	0	0
Stomatitis	26.5	1.6	0.7	4.3	0	0
Neutropenia	23.5	7.5	1.0	0.7	0	0
Asthenia	22.5	3.6	0	12.2	0.7	0.3
Hair color change	22.2	0	0	2.3	0	0
Thrombocytopenia	20.9	4.9	1.3	1.6	0.3	0

* In ≥20% of patients. Grade 5 events occurred in 5 (1.6%) and 5 (1.6%) of patients in the sunitinib placebo arms; no grade 5 AEs in either arm were considered treatment-related.
PPE, palmar-plantar erythrodysesthesia syndrome

Adjuvant Sunitinib in RCC

Pros

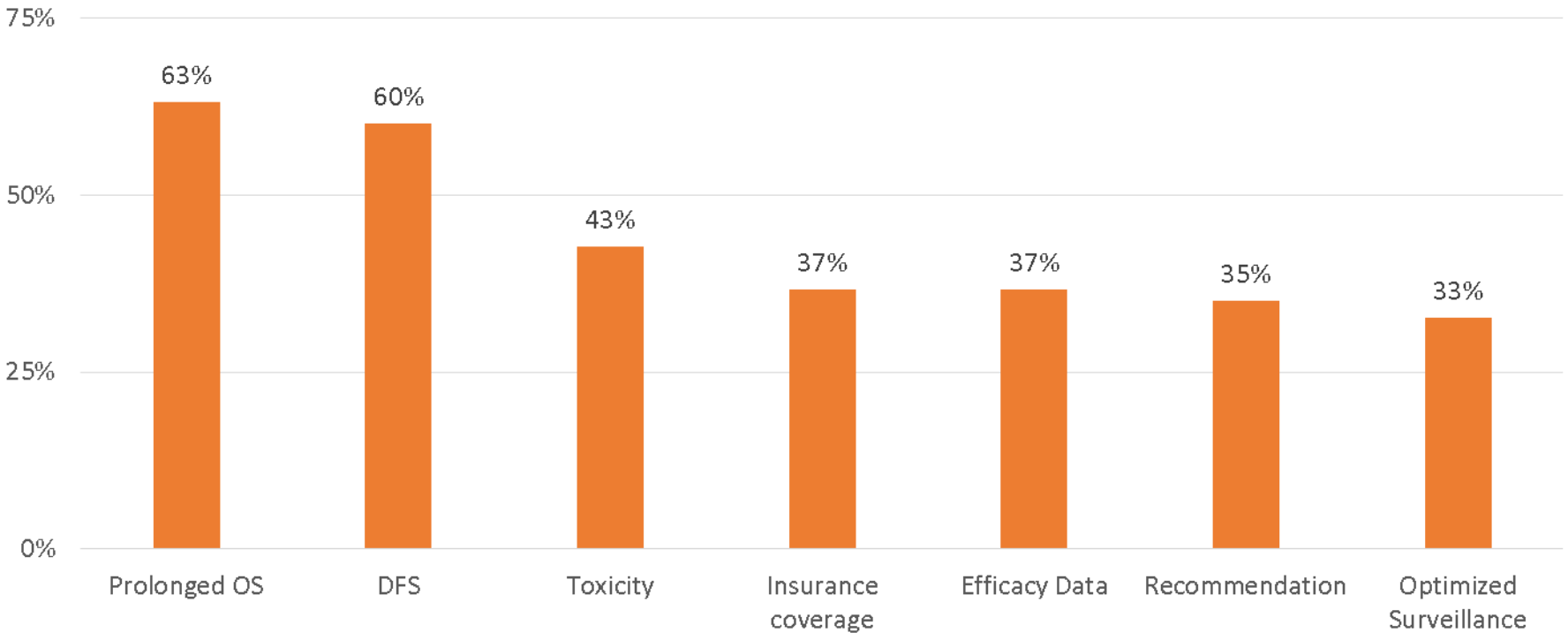
- The standard of care is doing nothing which neither docs nor patients like.
- There is a DFS benefit to sunitinib - which may be durable (?)
- There is likely an adequate window of exposure that balances benefit and risk.
- You can always discontinue drug for a particular patient.

Cons

- The DFS benefit of sunitinib is relatively small (5% ish more pts disease-free or 1+ year of median benefit)
- Adequate drug exposure is required - which can be associated with more toxicity

If you were able to get treatment to prevent recurrence of your kidney cancer, what would be important for you? (n=452)

kccure
Research Begins Here



Battle et al, JCO sup, Abs. #644, 2018

Targeted Therapy Adjuvant Trials

Study	Type of RCC	Risk of Recurrence (Assessment System)	Stratification by Risk?	Surgery	Eligibility
ASSURE (NCT00326898)	Clear cell or non clear cell RCC	Intermediate high/ very high risk (modified UISS)	Yes	Radical or partial nephrectomy with no evidence of residual macroscopic disease on postoperative CT scan	• pT1b N0 M0 G3-4 • pT2 N0 M0 G(any) • pT3 N0 M0 G(any) • pT4 N0 M0 G(any) • pT(any) N+(fully resected) M0 G(any)
S-TRAC (NCT00375674)	Clear cell RCC	High risk (UISS)	Yes	Kidney tumor removed with no evidence of residual macroscopic disease	• pT3-4 N0 M0 • pT4 N0 M0 • pT(any) N1 M0
PROTECT (NCT01235962)	Predominantly clear cell RCC	Intermediate-high/very high risk (modified UISS)	No	Radical or partial nephrectomy	• pT2 N0 M0 G3-4 • pT3-4 N0 M0 • pT(any) N1 M0
ATLAS (NCT01599754)	Predominantly clear cell RCC	high risk (UISS)	No	Kidney tumor removed with no evidence of residual macroscopic disease or metastatic disease	• pT3-4 N0 M0 PS 0-1 • pT3-4 Nx M0 PS 0-1 • pT(any) N1 M0
SORCE (NCT00492258)	Clear cell or nonclear cell RCC	Intermediate or high risk (SSIGN)	Unknown	Kidney tumor removed with no evidence of residual macroscopic disease on postoperative CT scan	• SSIGN score 3-11
EVEREST (NCT01120249)	Clear cell or nonclear cell RCC	Intermediate-high/very high risk (modified UISS)	Yes	Postnephrectomy with clear surgical margins and no evidence of residual disease	• pT1b N0 M0 G3-4 • pT2-4 N1-3 M0

I/O Adjuvant Trials

Trial	Intervention	N	Primary Endpoint
ECOG Prosper	Neo/adjuvant nivolumab vs BSC	766	DFS
ImMOTION 110	Atezolizumab vs placebo	664	DFS
KEYNOTE 564	Pembrolizumab vs Placebo	950	DFS/OS
BMS Checkmate	Ipi/Nivo vs. placebo	800	DFS/OS
RAMPART	Durva vs. Durva/Treme vs. observation	1,750	DFS/OS

Conclusions

- Neoadjuvant VEGF-targeted therapy has activity against primary clear cell RCC tumors and may lead to enhanced feasibility of resection, but is still investigational at present
  - Likely to be most useful in specific surgical circumstances yet to be defined
- Adequately dosed VEGF-targeted therapy can prolong DFS at a cost of toxicity in high risk patients.
- Neo/adjuvant I/O trials are ongoing and likely to change this landscape.