Update on Renal Cancer

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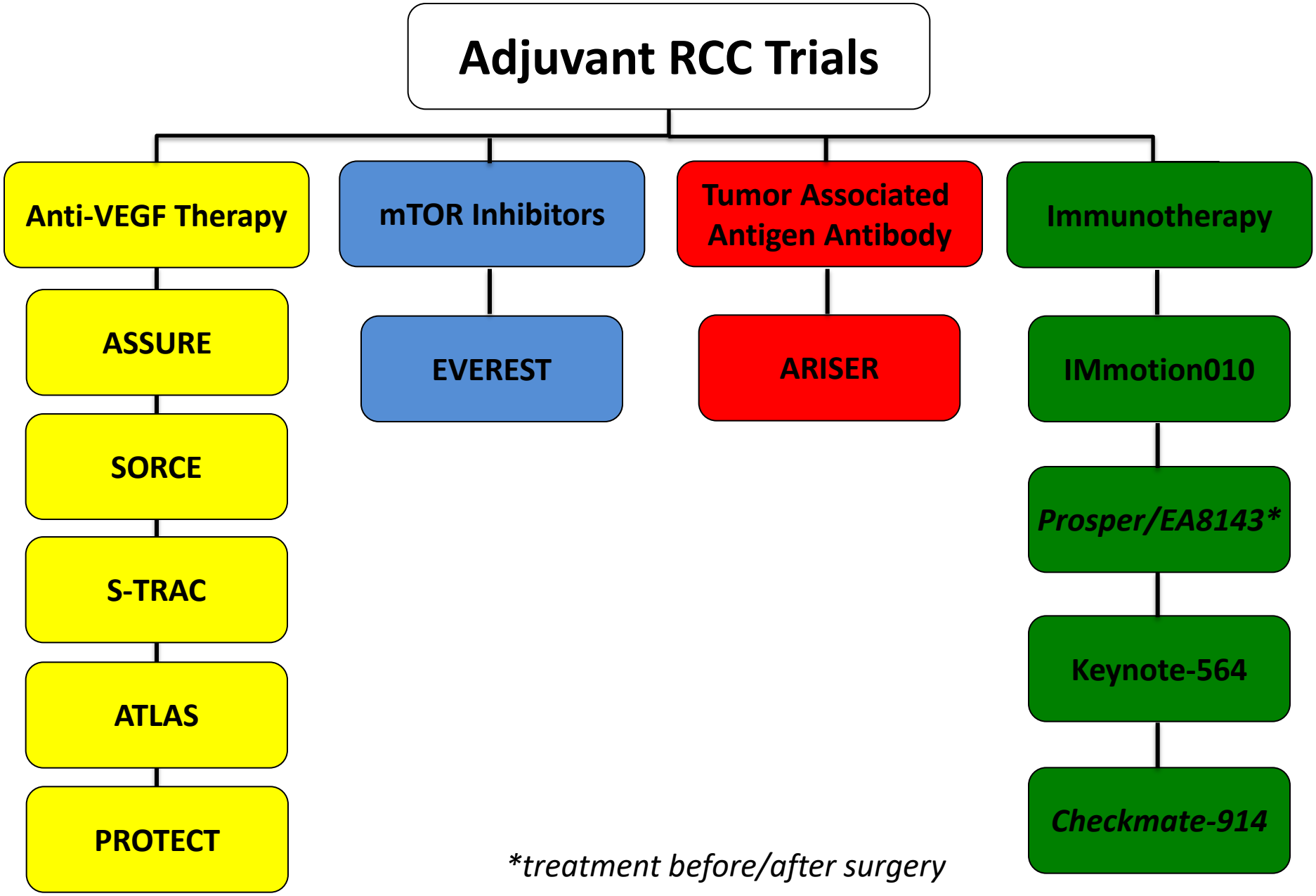
Organization

- Current status of adjuvant/neoadjuvant therapy
- Evolving role of cytoreductive nephrectomy

Importance of Adjuvant Therapy

- Classically 30% of patients will recur despite "Curative nephrectomy"
- To date no prior studies have demonstrated any effective adjuvant therapy improves <u>overall survival</u>

Trial Overview



**treatment before/after surgery*

ASSURE ADJUVANT TRIAL

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1˚ Outcome
ASSURE	III	1923	Sorafenib Sutent	PO	1-Placebo 2-Sorafenib-9 cycles 3- Sutent-9 cycles	All exept collecting duct or medullary	T1b, G3-4 T2,3,4 N+	DFS

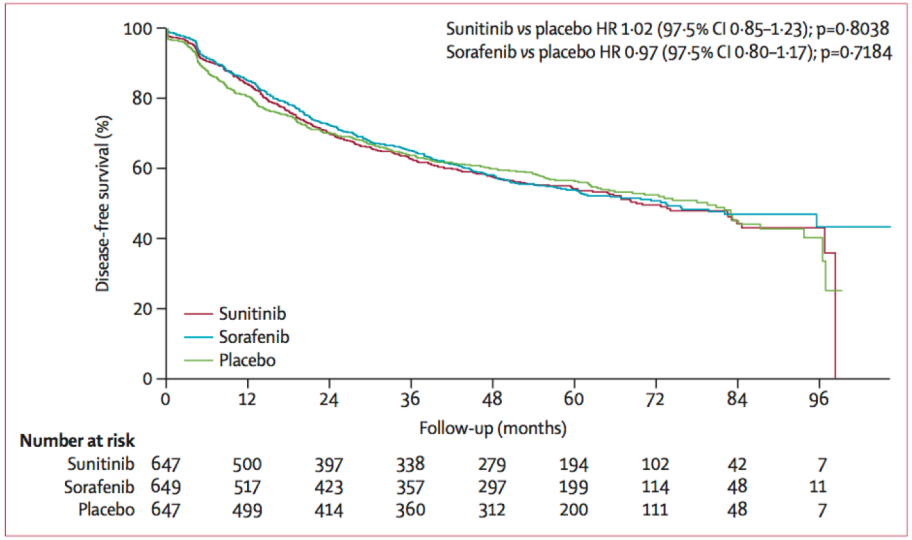


Figure 2: **Disease-free survival**
HR=hazard ratio.

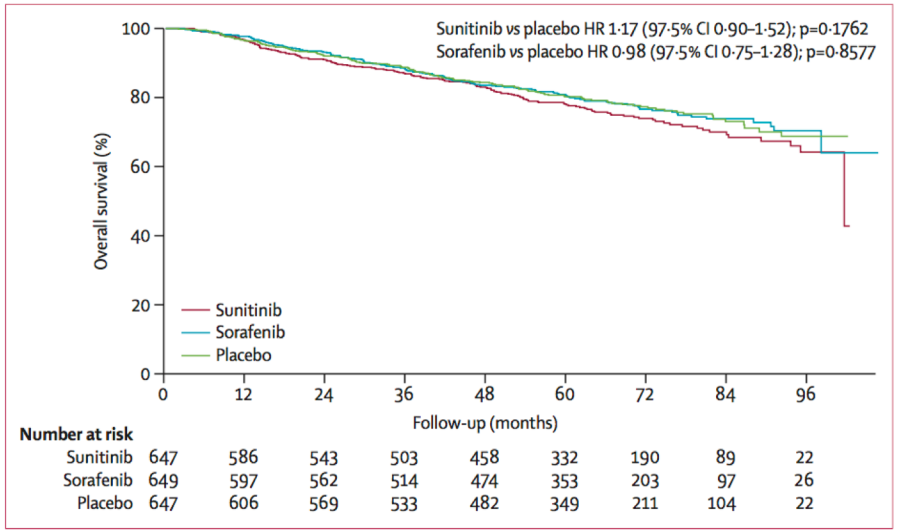


Figure 3: **Overall survival**
HR=hazard ratio.

Haas, N. B., et al. (2016). Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805)*Lancet*, *387*(10032), 2008–2016.

Treatment Discontinuation in ASSURE

- After 12 weeks, only 30-40% of patients could receive full treatment dose

Supplemental Table 2. Dose Administration

Factor	Dose (g)	Sunitinib	Sorafenib	Placebo
Patients		647	649	647
Proportion of Patients Receiving Full Dose at Cycle 3	No	367(58·3)	437(69·4)	73(11·5)
	Yes	262(41·7)	193(30·6)	560(88·5)
	Unknown/Missing /Withdrew Before Treatment	18	19	14

to address toxicity issues, the starting doses were amended to 37.5 mg for sunitinib or 400 mg for sorafenib for the first one or two cycles of therapy.

Haas, N. B., Manola, J., Uzzo, R. G., Flaherty, K. T., Wood, C. G., Kane, C., et al. (2016). Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*.

S-TRAC Trial

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1˚ Outcome
S-TRAC	III	720	Sutent	PO	1-Placebo 2-Sutent-1 yr	Predominant clear cell	UISS High risk	DFS

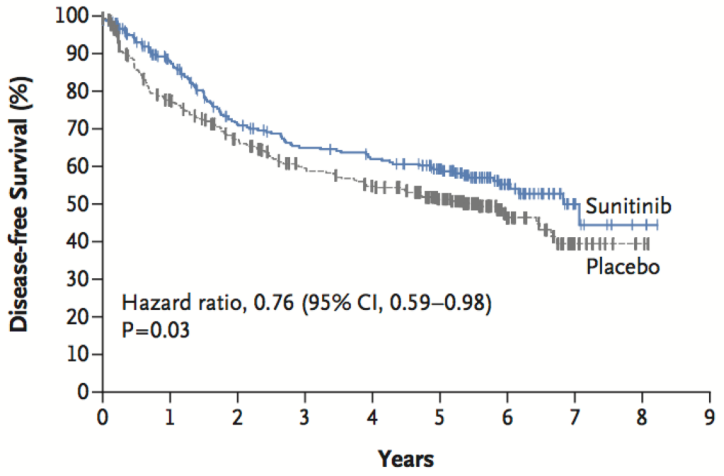


Figure 2. Disease-free Survival.
The median duration of disease-free survival according to independent central review was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group. At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group.

HR was 0.76 (p=0.003)

Median DFS (yrs)- 6.8 (5.8-NR) vs 5.6 (3.8-6.6)

Improvement in DFS for Central Path review (not investigator review)

1˚ end point was the duration of disease-free survival= first tumor recurrence, the occurrence of metastasis or a secondary cancer, or cancer death

S-TRAC Trial Safety/Tolerability

Table 3. Adverse Events (Safety Population).*

Event	Sunitinib (N=306)			Placebo (N=304)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	305 (99.7)	148 (48.4)	37 (12.1)	269 (88.5)	48 (15.8)	11 (3.6)
Diarrhea	174 (56.9)	12 (3.9)	0	65 (21.4)	1 (0.3)	0
Palmar–plantar erythrodysesthesia	154 (50.3)	46 (15.0)	3 (1.0)	31 (10.2)	1 (0.3)	0
Hypertension	113 (36.9)	24 (7.8)	0	36 (11.8)	3 (1.0)	1 (0.3)
Fatigue	112 (36.6)	13 (4.2)	2 (0.7)	74 (24.3)	4 (1.3)	0
Nausea	105 (34.3)	6 (2.0)	0	42 (13.8)	0	0
Dysgeusia	103 (33.7)	0	0	18 (5.9)	0	0
Mucosal inflammation	103 (33.7)	14 (4.6)	0	25 (8.2)	0	0
Dyspepsia	82 (26.8)	4 (1.3)	0	19 (6.3)	0	0
Stomatitis	81 (26.5)	5 (1.6)	2 (0.7)	13 (4.3)	0	0
Neutropenia	72 (23.5)	23 (7.5)	3 (1.0)	2 (0.7)	0	0
Asthenia	69 (22.5)	11 (3.6)	0	37 (12.2)	2 (0.7)	1 (0.3)
Hair-color change	68 (22.2)	0	0	7 (2.3)	0	0
Thrombocytopenia	64 (20.9)	15 (4.9)	4 (1.3)	5 (1.6)	1 (0.3)	0
Decreased appetite	59 (19.3)	2 (0.7)	0	16 (5.3)	0	0
Rash	59 (19.3)	2 (0.7)	0	29 (9.5)	0	0
Vomiting	58 (19.0)	7 (2.3)	0	20 (6.6)	0	0
Headache	57 (18.6)	2 (0.7)	0	36 (11.8)	0	0
Hypothyroidism	56 (18.3)	0	0	4 (1.3)	0	0
Epistaxis	55 (18.0)	0	0	9 (3.0)	0	0

* Listed are adverse events that were reported in at least 15% of the patients in each group during treatment. Grade 5 events occurred in 5 patients (1.6%) in each group. Patients were counted once at the highest grade with respect to common terminology criteria during the study. A complete listing of adverse events is provided in Table S4 in the Supplementary Appendix.

Low grade 4 toxicities, expected toxicities such as HTN, fatigue, P.P.E

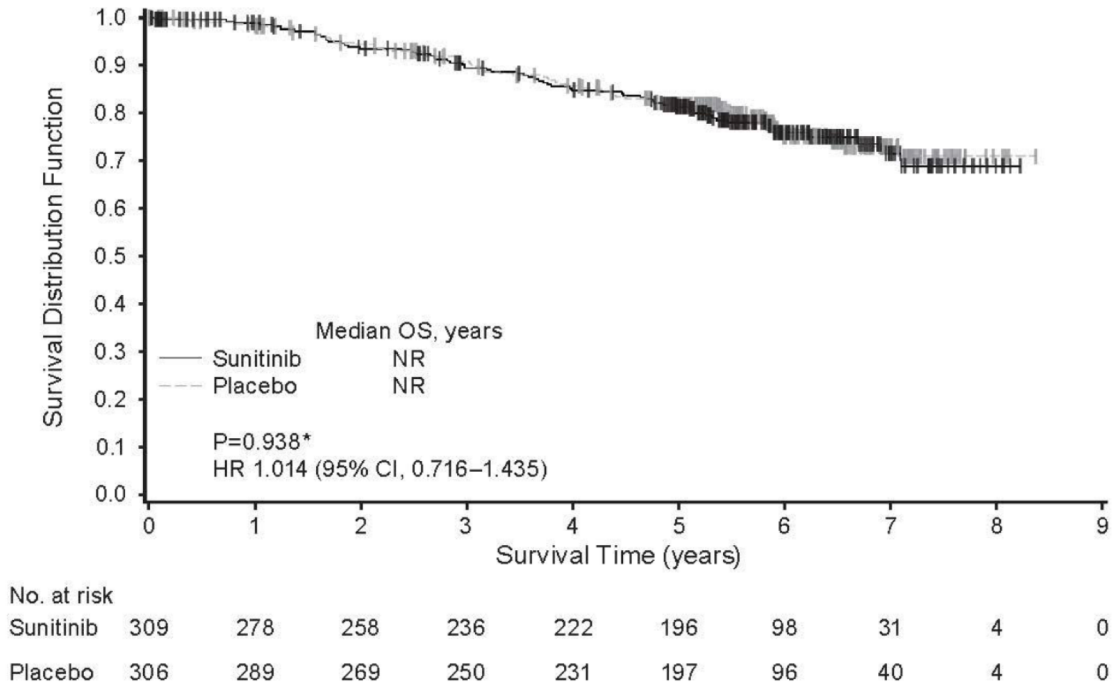
Patients given 50 mg sutent, no change in trial design

Among the patients in the sunitinib group, 54.2% maintained the starting dose; the median daily dose was 45.9 mg (range, 8.9 to 52.6) in the sunitinib group and 50 mg (6.7 to 52.8) in the placebo group.

S-TRAC Trial

SUPPLEMENTARY FIGURES

Figure S1. Overall survival



No. at risk

Sunitinib	309	278	258	236	222	196	98	31	4	0
Placebo	306	289	269	250	231	197	96	40	4	0

Data for overall survival, a 2˚ end point, were not mature at the time of the data cutoff, with deaths reported in 64 patients (20.7%) in the sunitinib group and 64 (20.9%) in the placebo group. The median overall survival was not reached in either group

However median survival already 5+ years…..

ASSURE ADJUVANT TRIAL Differences?: Highest Risk Individuals

Figure 1. CONSORT Diagram of Participant Selection

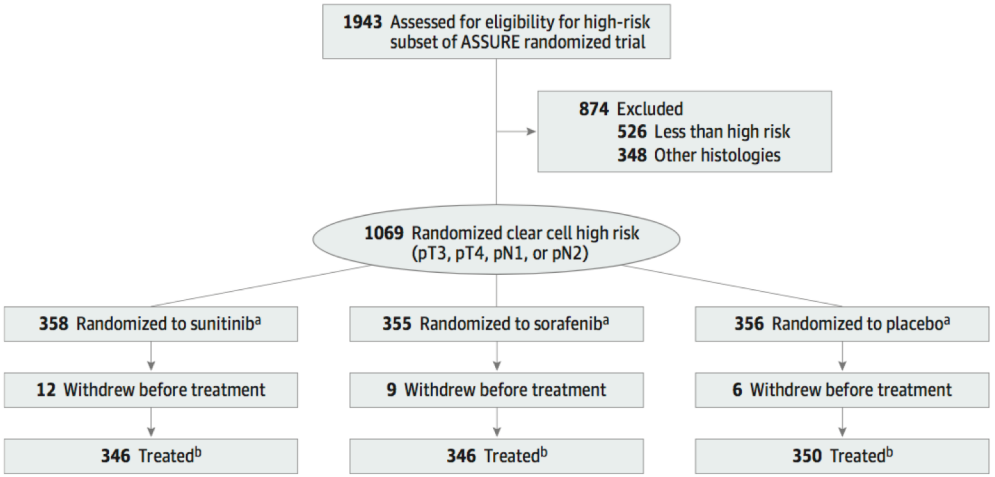
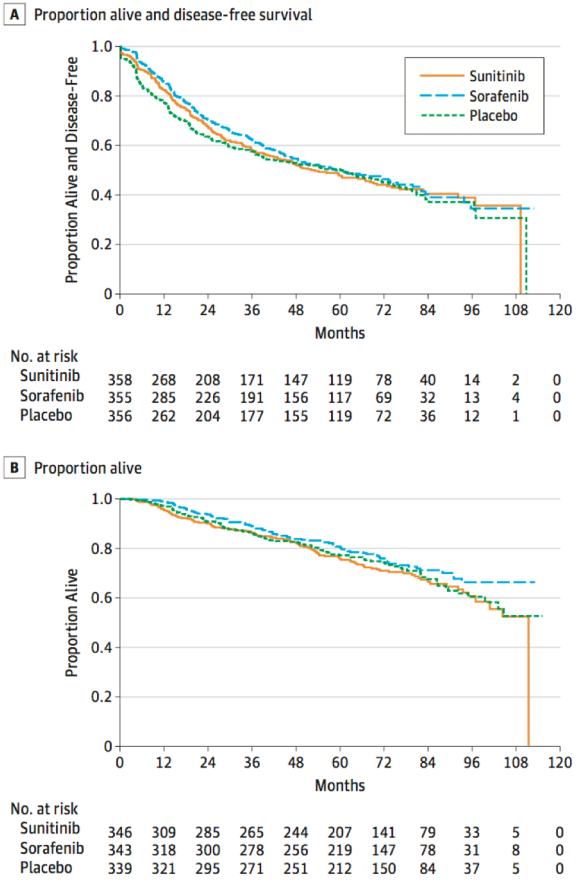


Figure 2. Disease-Free and Overall Survival by Treatment Arm in the High-Risk Clear Cell Cohort



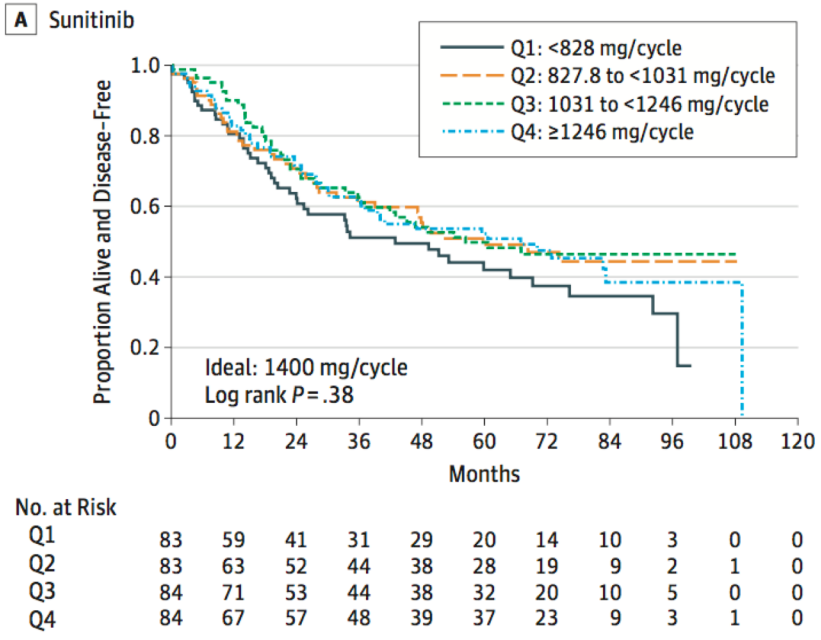
An Analysis of HIGHEST Risk Individuals was performed

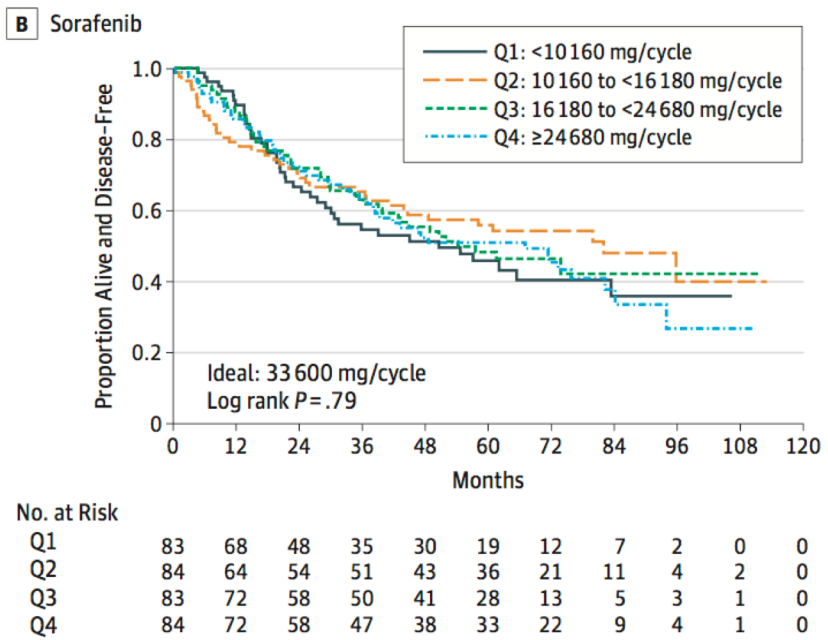
No improvement in DFS or OS

Haas, N. B., et al. (2017). Adjuvant Treatment for High-Risk Clear Cell Renal Cancer: Updated Results of a High-Risk Subset of the ASSURE Randomized Trial. *JAMA Oncology*. 6

ASSURE ADJUVANT TRIAL Differences?: Highest Risk Individuals

Figure 3. Disease-Free Survival by Quartile of Average Dose Received per 6-Week Cycle





No differences in outcome with dose intensity (evaluation between dosing quartiles)

Haas, N. B., et al. (2017). Adjuvant Treatment for High-Risk Clear Cell Renal Cancer: Updated Results of a High-Risk Subset of the ASSURE Randomized Trial. *JAMA Oncology*. 6

PROTECT

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1˚ Outcome
PROTECT	III	1500	Pazopanib	PO	1-Placebo 2- Pazopanib x 1 yr	Predominant clear cell	T2 (G3-4), T3, T4, N1	DFS

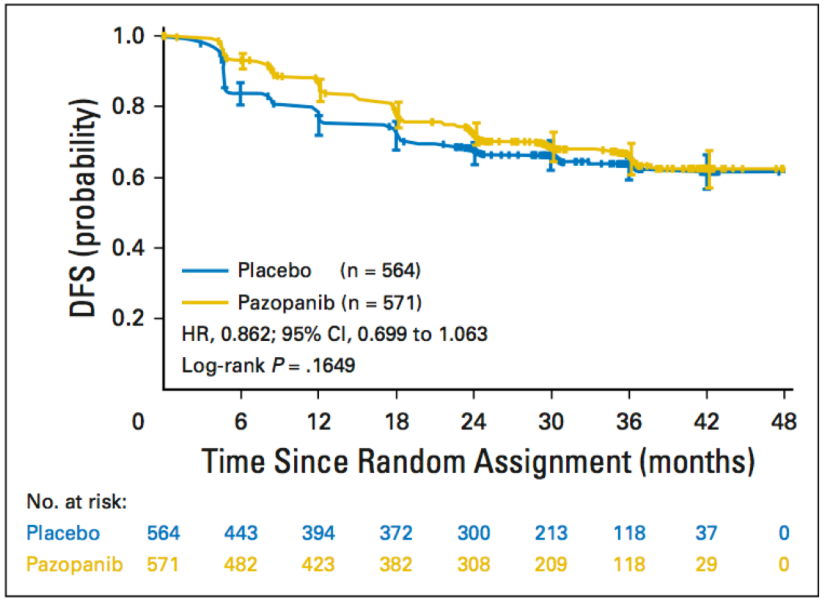
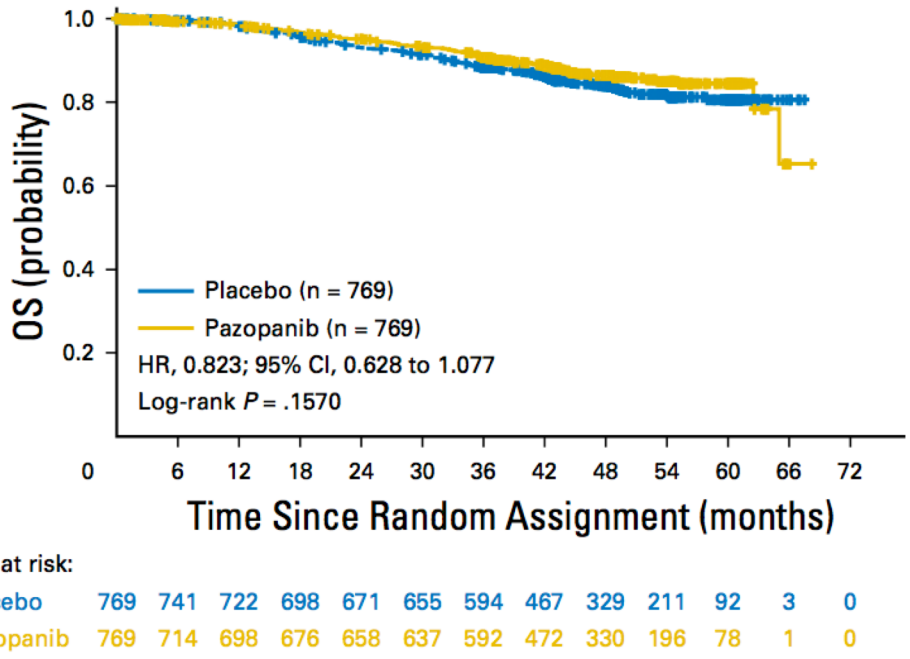


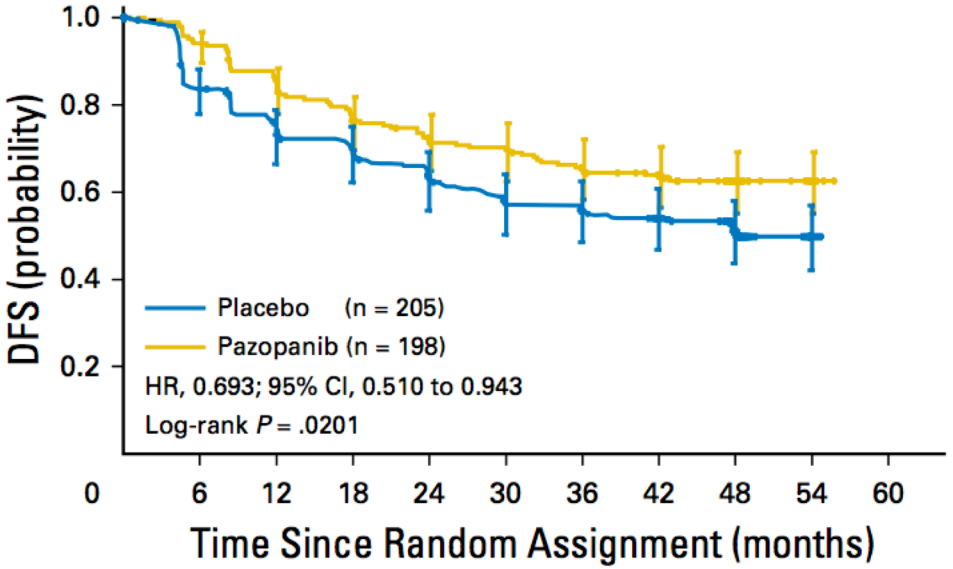
Fig 2. Disease-free survival (DFS) in the intent-to-treat pazopanib 600 mg (ITT_{600mg}) group. HR, hazard ratio.



Protect 800 mg Pazopanib→600 mg, No difference seen in DFS or OS

PROTECT: Signal of Dose Intensity?

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1˚ Outcome
PROTECT	III	1500	Pazopanib	PO	1-Placebo 2- Pazopanib x 1 yr	Predominant clear cell	T2 (G3-4), T3, T4, N1	DFS



No. at risk:

Placebo	205	169	144	134	119	106	97	85	46	3	0
Pazopanib	198	176	156	140	128	123	113	102	48	8	0

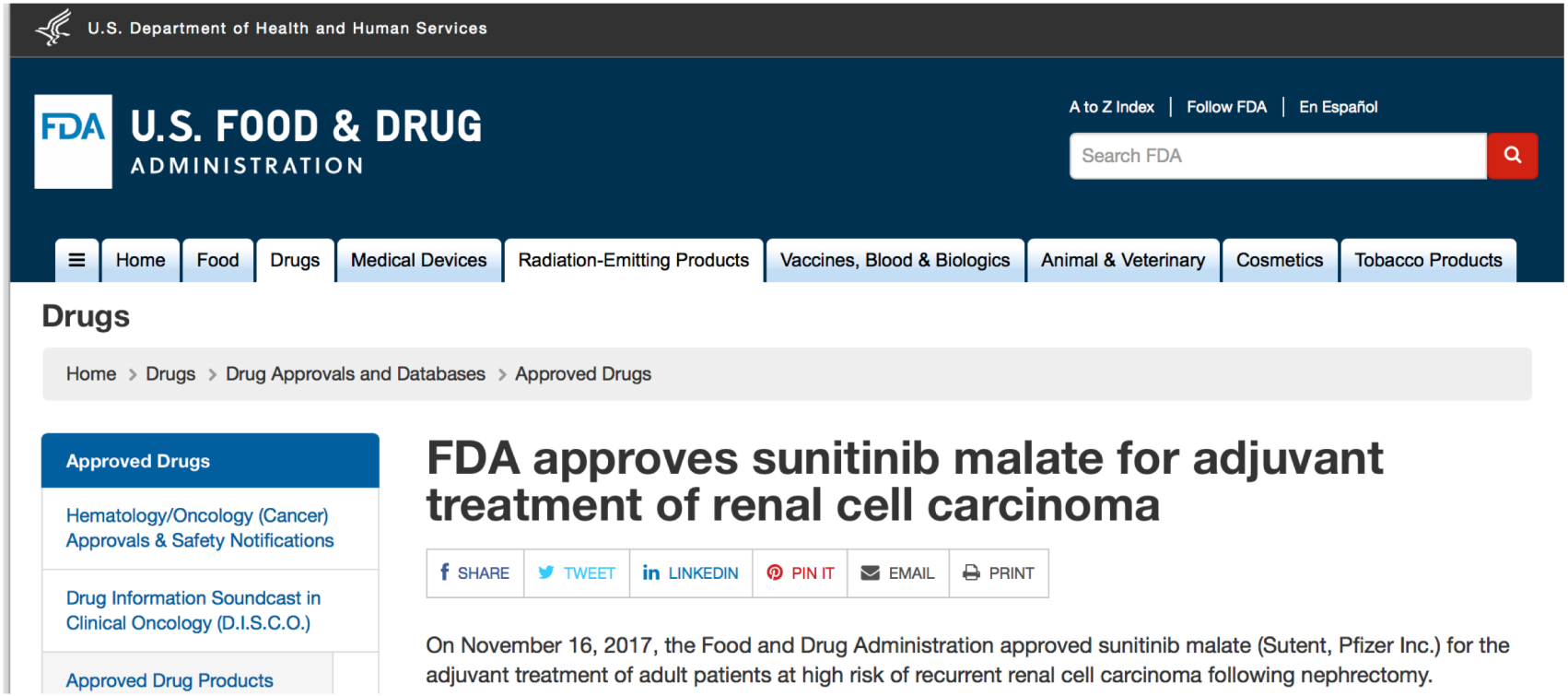
Pazopanib
800 mg dosing (25% of cohort)

2˚ analysis of DFS- ITT 800mg (HR, 0.69; 95% CI, 0.51 to 0.94; P = .02)

The DFS for ITT-800mg group found 33.7% decrease in the relative risk of recurrence or death (HR, 0.66; 95% CI, 0.49 to 0.90; P = .008

Dosing Responsible for Trial Differences?

11/2017: FDA Approval



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Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products

FDA approves sunitinib malate for adjuvant treatment of renal cell carcinoma

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On November 16, 2017, the Food and Drug Administration approved sunitinib malate (Sutent, Pfizer Inc.) for the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy.

To be added as an *option* to many clinical guideline panels

Lessons from Adjuvant Trials

- Adjuvant patients are VERY different from metastatic and less willing to tolerate toxicity
- High rate of dose reduction & interruption of therapy→ ~40% in most of these studies
- Adjuvant sunitinib will be an option, but not likely to be used unless OS benefit shown on FU (not likely…)
- IO trials enrolling but some issues
  -many screen failures
  -competition
  -slower for ProsperRCC (biopsy?)

Neoadjuvant TKI Therapy: a New Paradigm?

- Tumor Thrombus-
  - Case reports of shrinking thrombus ("medical" angio-infarction)
- Down-sizing-
  - Allow nephron-sparing surgery
  - Allow laparoscopic surgery
  - Make "unresectable" ammenable to OR
- Biologic evaluation
  - Identify rapidly progressing patients that should not undergo cytoreductive nephrectomy
  - Determine responsiveness for subsequent therapy

Shuch, B et al. *BJU*. 2008

Prospective Neoadjuvant Trials

Study	n	Agent	M0 %	% Clear Cell	% Δ in Median/mean Diameter	RECIST Response (%)
Jonasch 2009	50	Bevacizumab	0	96	n/a	0
Cowey 2010	30	Sorafenib	56	70	-9.6	7
Silberstein 2010	12	Sunitinib	58	100	-21.1	28
Hellenthal 2010	20	Sunitinib	80	100	-11.8	5
Powles 2011	66	Sunitinib	0	100	-13	6
Rini 2011	29	Sunitinib	34	75	-22	37
Powles 2013*	102	Pazopanib	0	100	-14	14
Karam 2014	24	Axitinib	100	100	-28.3	46
Alvarez 2014*	23	Pazopanib	100	100	-26	32

- *Many have been performed but vary by agent and population*
- *Trials have used several weeks of therapy before planned surgery*
- *Median time to response ~80 days with TKI's (sorafenib)*

Variability in Assessment of Surgical Feasibility converting Radical→ Partial

Before axitinib treatment	After axitinib treatment					
	Number of independent reviewers agreeing PN was feasible					
	0	1	2	3	4	5
Number of independent reviewers agreeing PN was feasible						
0	4/8	1/8	2/8	1/8	0	0
1	0	1/8	2/8	1/8	0	4/8
2	0	0	0	0	0	0
3	0	0	0	0	0	1/1
4	0	0	0	0	0	2/2
5	0	0	0	0	0	3/3

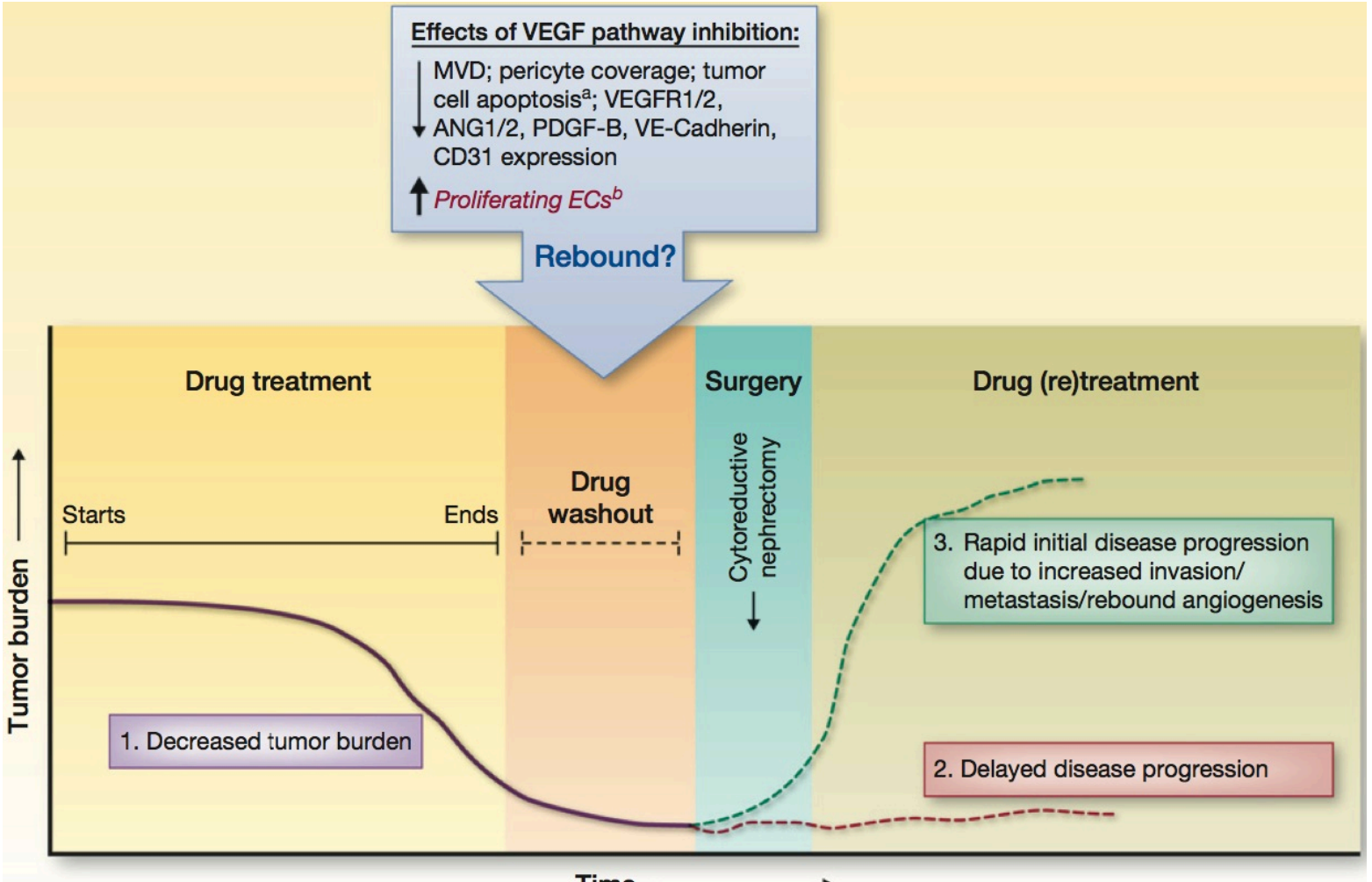
Cohort	N	κ	95% CI
Overall	45	0.611	0.452–0.772
Moderate complexity	13	0.611	0.000–0.734
High complexity	32	0.428	0.180–0.655
Before axitinib treatment		0.550	0.235–0.761
Moderate complexity	5	0.461	0.000–0.697
High complexity	17	0.492	0.037–0.821
After axitinib treatment		0.609	0.378–0.814
Moderate complexity	8	Complete agreement*	
High complexity	15	0.352	0.053–0.682

**All five reviewers reported 'Yes' (PN is feasible) for all eight scans.*

Surgical trials determining feasibility with neoadjuvant therapy in radical nephrectomy candidates followed by surgery not practical

Karam, J. A., et al. (2015). *BJU International*.

Stopping Therapy: Rebound Effect and Potential for Harm



Ebos, J. M. L., & Pili, R. (2012). Mind the gap: potential for rebounds during antiangiogenic treatment breaks. *Clinical Cancer Research*, *18*(14), 3719–3721.

Lessons from Neoadjuvant TKI Trials

- Similar toxicity profile
- Some concerns over wound healing
- Must proceed to surgery and get back on therapy quickly to prevent potential rebound
- Downsizing frequent, but not frequent enough to alter surgical approach

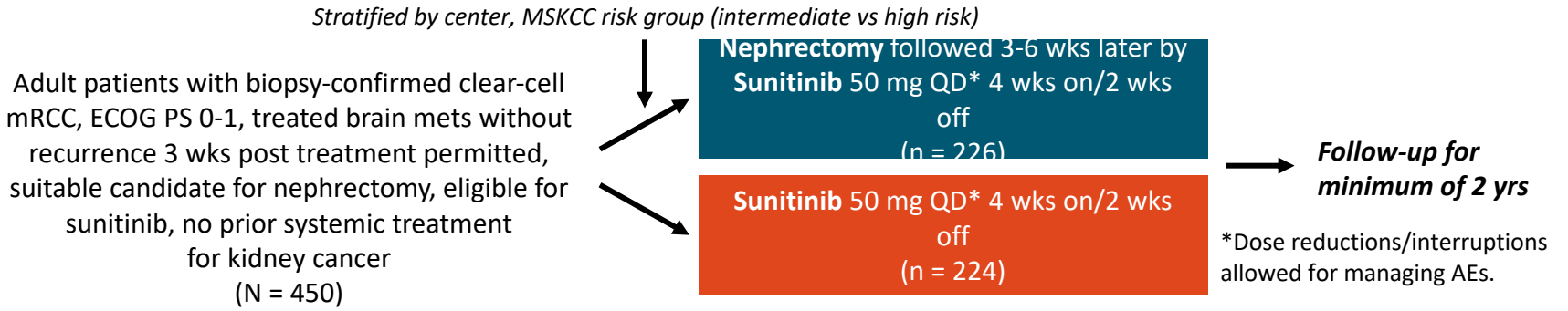
Likely Small Niche

Neoadjuvant IO Therapy?

- Recognition of antigens to activate immune system
- Removing available antigen from primary tumor may be limiting effect of adjuvant therapy
- Preclinical data supported “sandwich” immunotherapy
- Appears safe in perioperative setting from melanoma and early RCC experience (though only published in abstract form)

CARMENA: Study Design

- Final analysis of multicenter, randomized, open-label noninferiority phase III trial
  - Steering committee closed trial after second interim analysis (prespecified at 326 events) due to slow recruitment; second interim analysis deemed sufficient to meet trial objectives



- Primary endpoint: OS
  - Trial designed to have 80% power with 1-sided $\alpha = 0.05$ to show noninferiority with 576 patients enrolled (observed deaths, n = 456)
- Secondary endpoints: PFS, ORR (RECIST v1.1), clinical benefit, treatment adherence, nephrectomy in sunitinib-only arm, postoperative morbidity and mortality, safety

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

CARMENA: Baseline Characteristics

- Median follow-up of 50.9 mos at data cutoff (December 12, 2017)

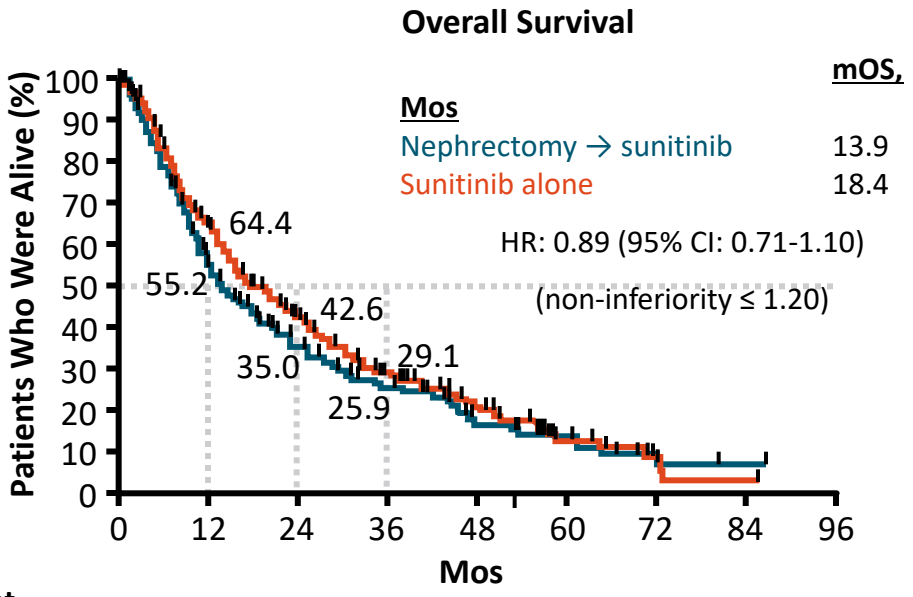
Characteristic, n (%)	Nephrectomy → Sunitinib (n = 226)	Sunitinib (n = 224)
Median age, yrs (range)	63 (33-84)	62 (30-87)
Male	169 (74.8)	167 (74.6)
MSKCC risk category	n = 225	n = 224
▪ Intermediate	125 (55.6)	131 (58.5)
▪ Poor	100 (44.4)	93 (41.5)
ECOG PS		
▪ 0	130 (57.5)	122 (54.5)
▪ 1	96 (42.5)	102 (45.5)
Fuhrman grade of RCC	n = 150	n = 156
▪ 1 or 2	77 (51.3)	82 (52.6)
▪ 3 or 4	73 (48.7)	74 (47.4)
Tumor stage	n = 67	n = 49
▪ T1	5 (7.5)	7 (14.3)
▪ T2	13 (19.4)	13 (26.5)
▪ T3 or T4	47 (70.1)	25 (51.0)
▪ Tx	2 (3.0)	4 (8.2)

Characteristic, n (%)	Nephrectomy → Sunitinib (n = 226)	Sunitinib (n = 224)
Node stage	n = 66	n = 49
▪ N0	23 (34.8)	18 (36.7)
▪ N1	13 (19.7)	6 (12.2)
▪ N2	7 (10.6)	13 (26.5)
▪ Nx	23 (34.8)	12 (24.5)
Median primary tumor size, mm (range)	88 (6-200)	86 (12-190)
Median no. mets (range)	2 (1-5)	2 (1-5)
Median tumor burden, mm (range)	140 (23-399)	144 (39-313)
Location of mets	n = 217	n = 221
▪ Lung	172 (79.3)	161 (72.9)
▪ Bone	78 (35.9)	82 (37.1)
▪ LN	76 (35.0)	86 (38.9)
▪ Other	78 (35.9)	90 (40.7)

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

CARMENA: Overall Survival

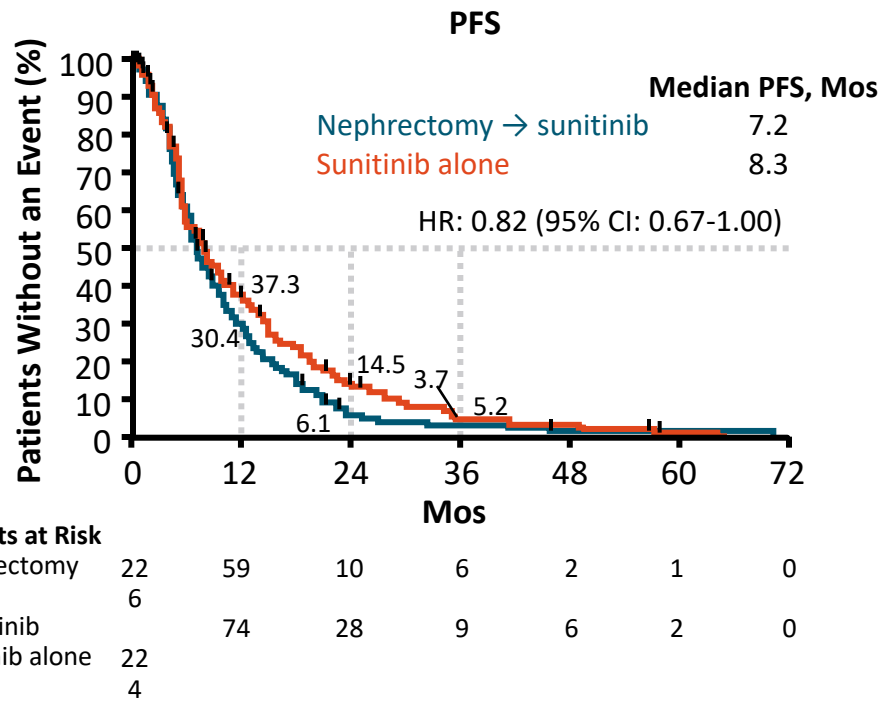
- Sunitinib alone not inferior to nephrectomy → sunitinib (upper boundary of 95% CI ≤ 1.20)
- mOS longer with sunitinib alone vs nephrectomy → sunitinib:
  - MSKCC intermediate-risk: 23.4 vs 19.0 mos (HR: 0.92)
  - MSKCC poor-risk: 13.3 vs 10.2 mos (HR: 0.86)



Patients at Risk									
Nephrectomy → sunitinib	22	11	61	40	19	11	4	1	0
	6	0							
			76	44	26	8	3	1	0
	22	12							
Sunitinib alone	4	8							

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

CARMENA: PFS, Response, and Clinical Benefit



Response	Nephrectomy → Sunitinib (n = 186)	Sunitinib (n = 213)
Best overall response, n (%)	n = 178	n = 208
▪ CR	1 (0.6)	0
▪ PR	50 (28.1)	62 (29.8)
▪ SD	64 (36.0)	97 (46.6)
▪ PD	49 (27.5)	40 (19.2)
▪ NE	14 (7.9)	9 (4.3)
ORR, %	27.4	29.1
DCR,* %	61.8	74.6
Clinical benefit,† n (%)	68 (36.6)‡	102 (47.9)‡

*Disease control defined as CR, PR, or SD. †Defined as disease control beyond 12 wks. ‡*P* = .02

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

CARMENA: Safety, Nephrectomy Outcomes

Severe (Grade 3/4) AEs in Sunitinib-Treated Patients,* n (%)	Nephrectomy → Sunitinib (n = 186)	Sunitinib (n = 213)
Any	61 (32.8)*	91 (42.7)*
Asthenia	16 (8.6)	21 (9.9)
Hand–foot syndrome	8 (4.3)	12 (5.6)
Anemia	5 (2.7)	11 (5.2)
Neutropenia	5 (2.7)	10 (4.7)
Kidney or urinary tract disorder	1 (0)	9 (4)

*P = .04

- In nephrectomy → sunitinib arm, 95% underwent nephrectomy with most (58%) having open surgery
  - Postop mortality within 1 mo of surgery: 2%
  - Postop morbidity: 82 pts (39%)
    - Clavien-Dindo grade 3: 11% of those with postoperative morbidity
    - Clavien-Dindo grade > 3: 5% of those with postoperative morbidity
- In sunitinib-alone arm, 38 patients needed secondary nephrectomy (7 for emergency treatment of primary tumor); 31.3% restarted sunitinib

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

CARMENA: Conclusions

- In final analysis of CARMENA, sunitinib alone not inferior to cytoreductive nephrectomy followed by sunitinib in patients with mRCC
  - HR for death: 0.89 (95% CI: 0.71-1.10; noninferior if upper boundary ≤ 1.20)
  - Median OS longer in sunitinib-alone arm for all patients and in intermediate-risk and poor-risk subgroups
- Clinical benefit rate significantly higher in sunitinib-alone arm (47.9% vs 36.6% with nephrectomy followed by sunitinib; *P* = .02)
- Investigators concluded that nephrectomy should no longer be part of standard of care for patients with mRCC requiring medical treatment

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].