



Adjuvant Therapy in High-Risk Localized Renal Cell Carcinoma: are we ready for this indication?

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Disclosures

• Speaker: Roche, Astra Zeneca, Astellas, Janssen

No conflict of interest for this presentation



INTRODUCTION

• 300.000 cases of kidney cancer worldwide

90% of these cancers are renal cell carcinoma

• 65% diagnosed with localized and 16% with loco-regional disease

- Depending on stage and risk factors, up to 40% will recur
 - High-risk patients (approx. 15%) 5y rate of recurrence = 60%

IDENTIFYING PATIENTS AT HIGH RISK FOR TUMOR RECURRENCE

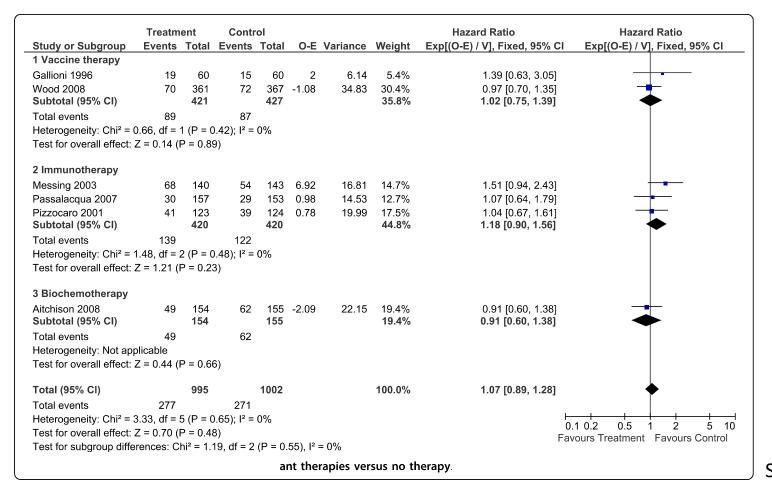
- SSIGN score by Mayo Clinic
 - Designed to predict cancer-specific survival
- The Leibovich score (Mayo Clinic PFS score)
 - Specifically designed to predict progression to metastatic RCC after nephrectomy
- UISS (UCLA integrated staging system) risk score
 - Designed to stratify patients into risk groups and predict survival
- Other risk stratification tools based on molecular features
 - ClearCode34 (34-gene classifier model)
 - 16-gene Recurrence Score

Lam JS, et al. J Urol 2005; Leibovich BC, et al. Cancer 2003 Figlin RA, et al. Annals of Oncol 2018



Adjuvant therapy for locally advanced renal cell cancer: A systematic review with meta-analysis

Adolfo JO Scherr, Joao Paulo SN Lima, Emma C Sasse, Carmen SP Lima and André D Sasse*



Scherr et al. BMC Cancer 2011

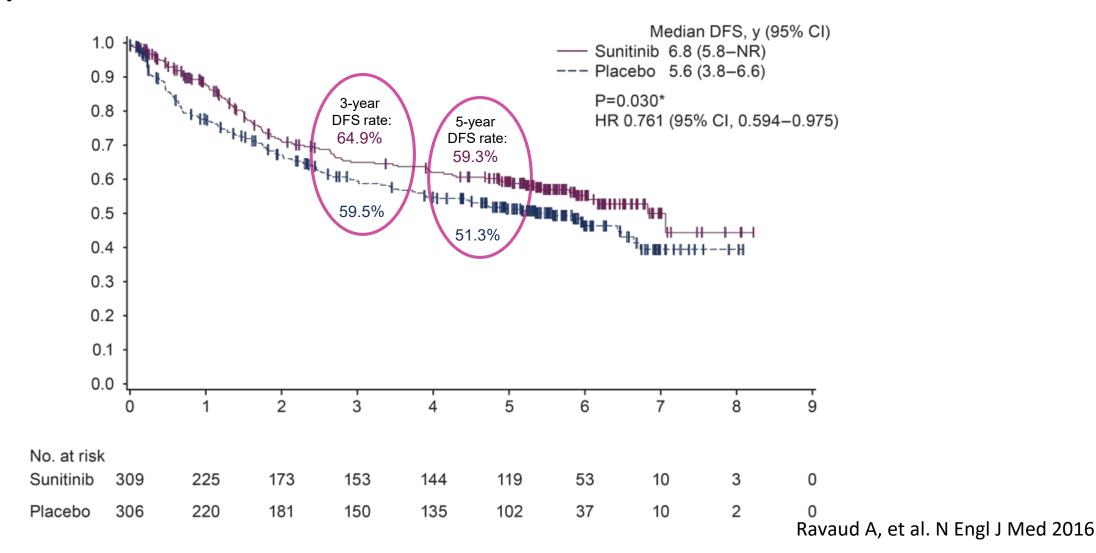


Adjuvant RCC studies of the targeted therapy era

Study	Arms	Duration	N	Primary endpoint
ASSURE	Sunitinib Sorafenib Placebo	1 year	1923	NO DIFFERENCE
S-TRAC	Sunitinib Placebo	1 year	720	Disease-free survival
ATLAS	Axitinib Placebo	3 years	690	STOPPED DUE FUTILITY
SORCE	Sorafenib Sorafenib Placebo	3 years 1 year 3 years	1656	PENDING
PROTECT	Pazopanib Placebo	1 year	1500	NO DIFFERENCE
EVEREST	Everolimus Placebo	54 weeks	1218	PENDING

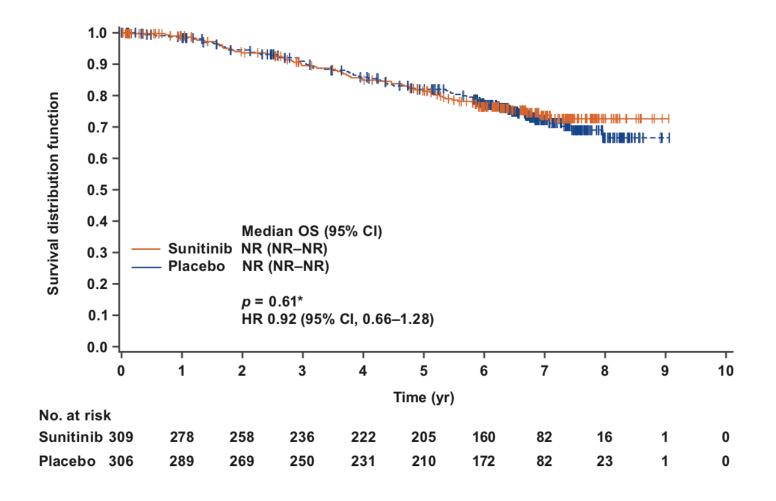


STRACT Trial: Disease-Free Survival By Blinded Independent Central Review





STRACT Trial: Updated Overall Survival

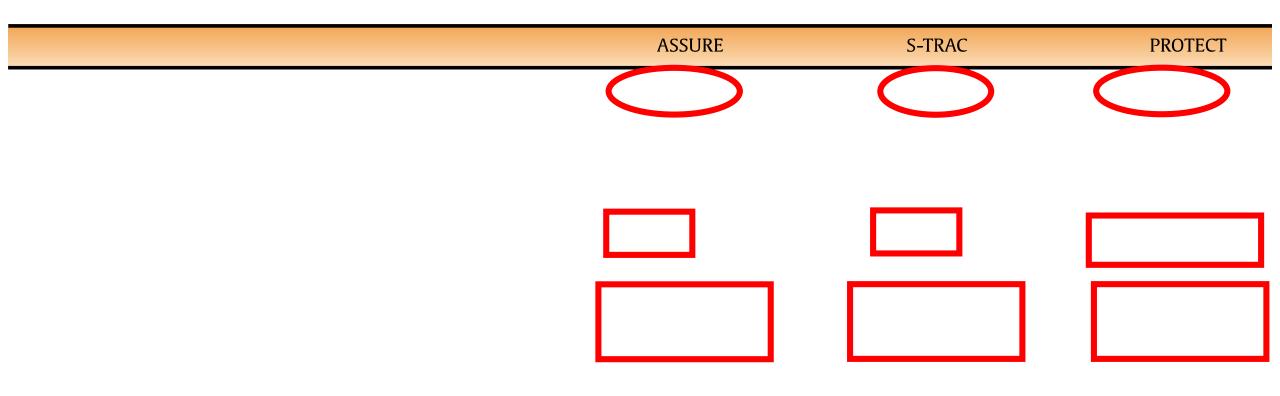




STRACT Trial: Common Adverse Events

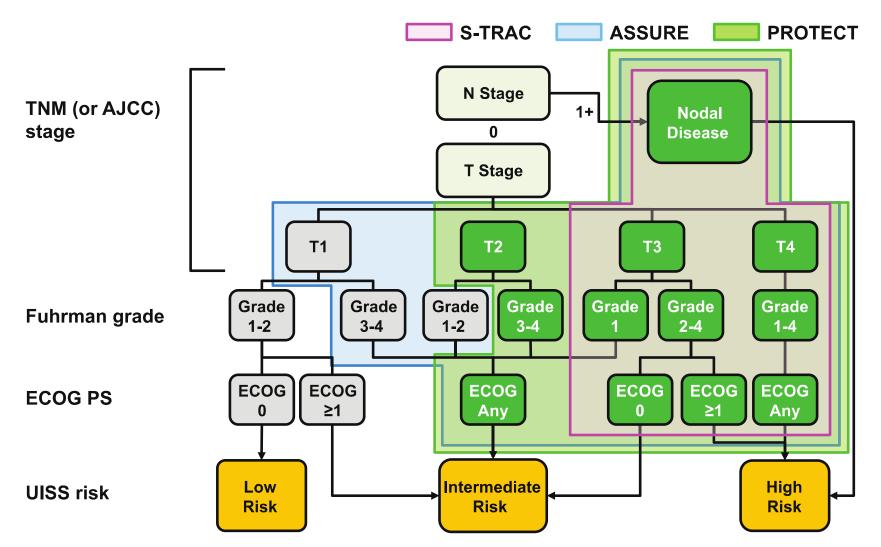
		Sunitinib (n=306)		Placebo (n=304)				
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4		
Adverse Event, %								
Any adverse event	99.7	48.4	12.1	88.5	15.8	3.6		
Diarrhea	56.9	3.9	0	21.4	0.3	0		
PPE	50.3	15.0	1.0	10.2	0.3	0		
Hypertension	36.9	7.8	0	11.8	1.0	0.3		
Fatigue	36.6	4.2	0.7	24.3	1.3	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		

Differences between ASSURE, S-TRACT & PROTECT





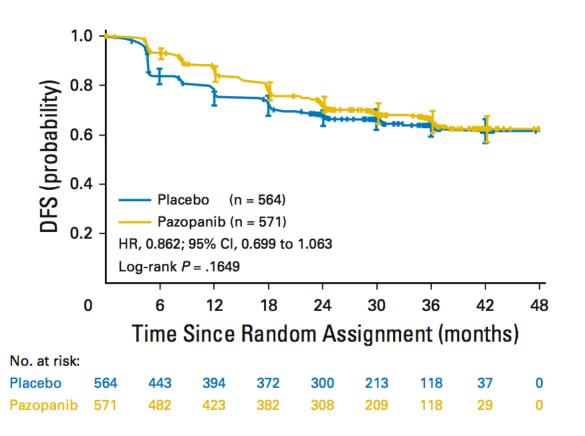
Risk overlap between patient population

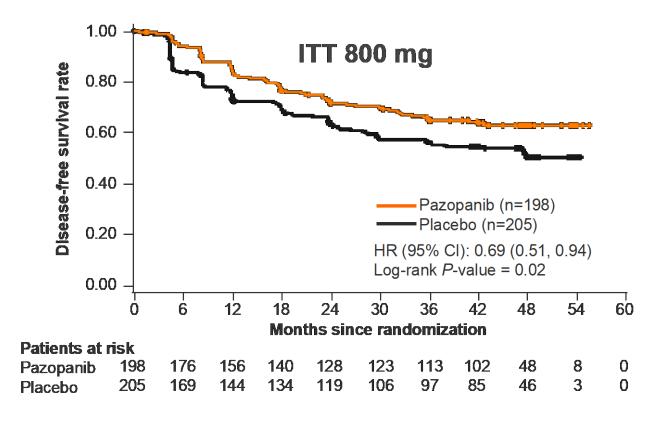


Figlin RA, et al. Annals of Oncol 2018



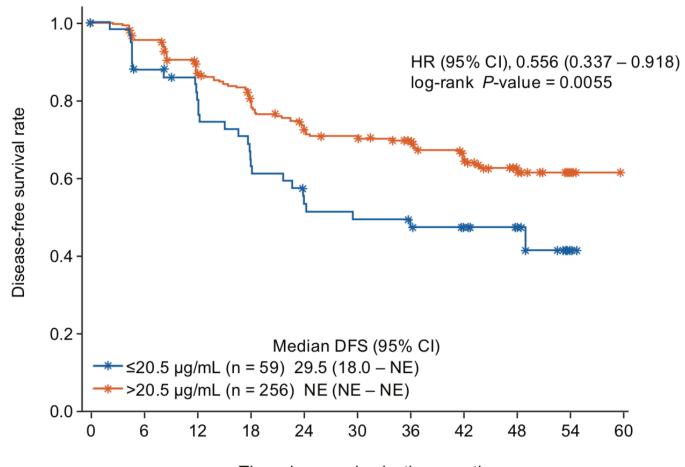
PROTECT Trial: Disease-free survival (DFS) in the intent-to-treat pazopanib 600 / 800 mg







PROTECT Trial: Relationship between pazopanib C $_{\rm trough}$ and DFS plotted by early C $_{\rm trough}$ (week 3 or 5)



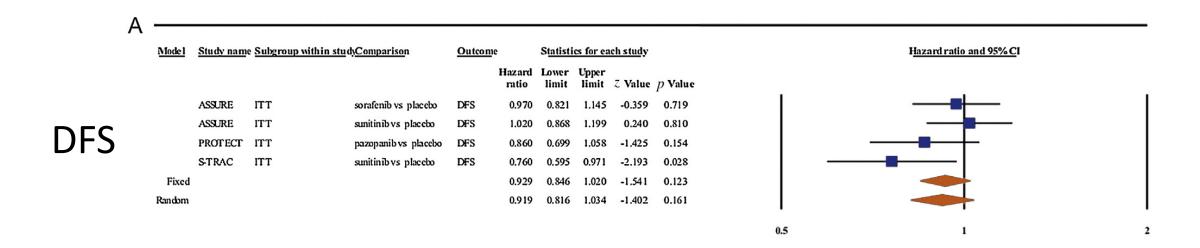
available at www.sciencedirect.com
journal homepage: www.europeanurology.com





Adjuvant Vascular Endothelial Growth Factor—targeted Therapy in Renal Cell Carcinoma: A Systematic Review and Pooled Analysis

Maxine Sun^a, Lorenzo Marconi^b, Tim Eisen^c, Bernard Escudier^d, Rachel H. Gles^{e,f}, Naomi B. Haas^g, Lauren C. Harshman^a, David I. Quinn^h, James Larkinⁱ, Sumanta K. Pal^j, Thomas Powles^k, Christopher W. Ryan^l, Cora N. Sternberg^m, Robert Uzzoⁿ, Toni K. Choueiri ^{a,1}, Axel Bex^{o,1}

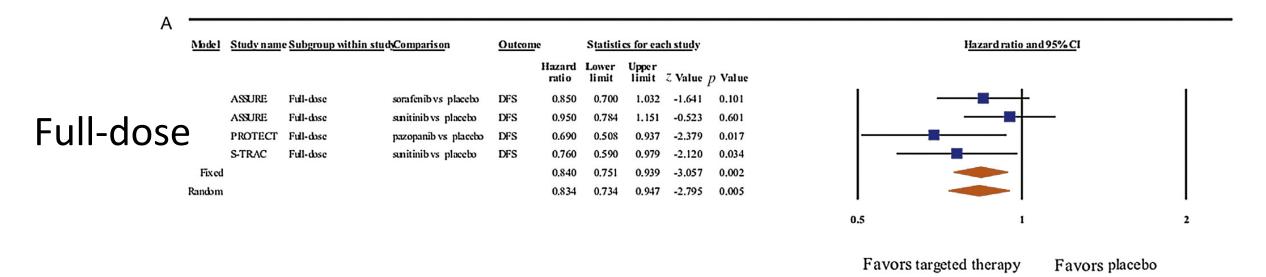


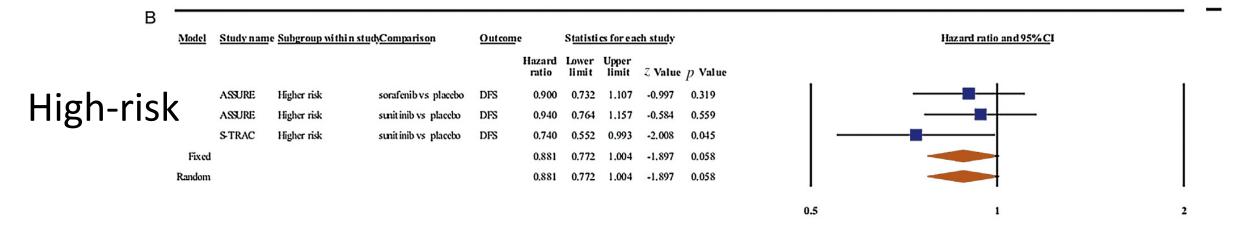
	В	Model	Study nam	e Subgroup within str	ıd <u>,Compariso</u> n	Outcom	e	Statistic	cs for eac	h study			Hazard ratio and 95% CI	_
\bigcirc C							Hazard ratio	Lower limit		Z Value	p Value			
U 3			ASSURE	ITT	sorafenib vs placebo	os	0.980	0.776	1.238	-0.169	0.865			
			ASSURE	ITT	sunitinib vs placebo	OS	1.170	0.930	1.471	1.343	0.179		 •	
			PROTECT	ITT	pazopanib vs placebo	OS	0.790	0.571	1.092	-1.425	0.154			
			S-TRAC	ITT	sunitinib vs placebo	OS	0.920	0.661	1.281	-0.493	0.622			
		Fixed					0.993	0.869	1.135	-0.100	0.920			
		Random					0.983	0.839	1.153	-0.208	0.835			
												0.5	1	2

Favors targeted therapy Favors placebo

Favors targeted therapy

Favors placebo





Favors targeted therapy Favors placebo



On-going adjuvant trials with IOs in RCC

Sponsor	Randomization	Treatment Details	N	Status	Inclusion Stage/Grade	Histology
PROSPER (ECOG- EA8143)	Nivolumab vs surgical SOC	IV Q 2 Wks x 3 mos. then monthly for 6 mos.	766	Ongoing	T2 or higher N+ non-mRCC	Any
IMMotion (Genentech)	Atezolizumab vs Placebo	1200 mg IV q 3 wks for 1 yr.	664	Ongoing	Resected high risk T2 or T3 or resected M0	Clear cell including sarcomatoid features
KEYNOTE - 564 (Merck)	Pembrolizumab vs Placebo	200 mg IV q 3 wk for 1 yr	950	Ongoing	Post- nephrectomy; intermediate- high risk, high risk, and M1 NED RCC	Clear cell including sarcomatoid features
Checkmate - 914 (BMS)	Nivolumab + Ipilimumab vs Placebo	Nivo 3mg/kg and Ipi 1 mg/kg x 4 doses then Nivo for 24 wks	800	Starting 2018	T2a, G3 or G4, N0M0 pathological T2b,T3,T4 G any, pT any, N1	Clear cell RCC including sarcomatoid features



Open Questions / Future Directions

- DFS is the appropriate definitive endpoint ?
- Will a longer follow-up result in an effect on OS with adjuvant targeted therapy? Remote possibility
- What is the the role of mTOR pathway inhibition and immune checkpoint inhibition in the adjuvant setting?
- Can we better select patients at higher risk for recurrence with tools based on molecular features?



Conclusions

- Efficacy of VEGFR-TKIs in the adjuvant RCC setting has been shown in principle
- The balance between potential therapeutic benefit and associated toxicity and effects on quality of life is complex
- Current data strongly suggest that patient selection is crucial
- Patients with high-risk clear cell tumours, who can tolerate the full effective dose, are more likely to benefit
- Collectively, existing data do NOT justify the use of routine adjuvant VEGFR-targeted therapy in resected RCC
- Pending the results of ongoing trials.



Thanks!

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