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Adjuvant Sunitinib for high risk RCC: Not Ready for Prime Time

Alan H. Bryce, M.D.
Chair, Genitourinary Disease Group, Mayo Clinic
Interim Chair, Division of Hematology and Medical Oncology, Mayo Clinic, Arizona

Background

- 15-20% of RCC patients present with high risk locoregional disease (stage III)
- 5 year OS for Stage III is ~50-60%
- Anti VEGF TKIs, including sunitinib, have proven OS benefit in metastatic disease
- Two large randomized phase III studies of adjuvant TKI therapy enrolling a total of 1909 patients have been completed

Dataset

- ASSURE (E-2805)
  - N=1943
  - Patients with high grade RCC, ≥T1b, non metastatic, post nephrectomy, cc or non-cc
    - 100% UISS intermediate high or very high
  - Randomized 1:1:1 to sunitinib, sorafenib, or placebo
- S-TRAC
  - N= 615
  - High risk RCC (stage III) ccRCC, post nephrectomy
  - 1:1 sunitinib versus placebo
- Primary Endpoint of both studies = PFS
  - ASSURE investigator assessed
  - S-TRAC central review

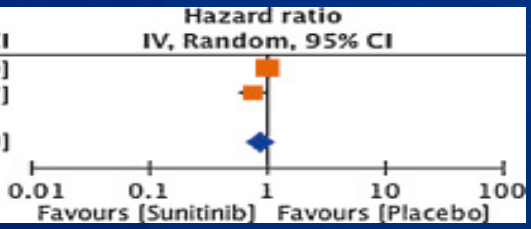
Results

	ASSURE		S-TRAC	
	Sunitinib	Placebo	Sunitinib	Placebo
N (ITT)	647	647	309	306
DFS	5.8 yrs	6.6 yrs	6.8 yrs	5.6 yrs
5yr DFS	54.3%	59.3%	59.3%	51.3%
HR	**1.02 (97.5% CI 0.85-1.23)**		**0.76 (95% CI 0.59-0.98)**	
P value	0.8038		0.03	
5yr OS	77.9%	80.3%	79.3%	79.1%
HR	**1.17 (97.5% CI 0.90-1.52)**		**1.01 (95% CI 0.72-1.44)**	
P value	0.1762		0.94	

Meta Analysis

Study or subgroup	log[hazard ratio]	SE	Sunitinib Total	Placebo Total	Weight	Hazard ratio IV, Random, 95% CI
ASSURE	0.0198	0.0824	647	647	55.4%	1.02 [0.87, 1.20]
S-TRAC	−0.2731	0.1264	309	306	44.6%	0.76 [0.59, 0.97]
Total (95% CI)			956	953	100.0%	0.89 [0.67, 1.19]

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.77$, df = 1 ($p = 0.05$); $I^2 = 73\%$
Test for overall effect: Z = 0.76 ($p = 0.45$)



- Toxicity
  - Grade 3-4 toxicity 60.5-62%
    - 4 Sunitinib related deaths
  - Inferior QoL on sunitinib
- Investigator assessed DFS on S-TRAC
  - HR 0.81 (95% CI 0.64-1.02; p=0.08)
- Only 30% of ASSURE patients would have qualified for S-TRAC

Bex, A. et al. Eur Uro 71(5):2017;719-722

ODAC
Sept 19, 2017

- Question of whether to recommend Sunitinib as adjuvant therapy for high risk RCC (S-TRAC)
- 12 member panel split 6-6
- Updated HR for OS 0.92 (95% CI: 0.66, 1.28)
  - Final analysis due January 2019

Pitfalls
Everyone else is doing it…

- Is DFS an appropriate endpoint in this setting
  - Yes- it is used in other cancers (melanoma, colon ca, breast ca)
    - OS takes too long to achieve
  - No- Lemmings
    - No just disease, but MOA matters
    - No VEGF targeted therapy has ever worked in adjuvant therapy, in any cancer
    - OS data is negative to date w final analysis pending

Pitfalls
It's not how you start the race…

- Is DFS a surrogate for OS?
  - Surrogacy has been proven in other cancers, but not in RCC
  - Cross resistance between VEGF therapies occurs, so we placebo patients may get greater benefit from later therapy
    - And enjoy higher overall QoL
  - If you can get the same outcome but start therapy years later, why wouldn't you?

Pitfalls
When does a met become a met?

- DFS is defined by the appearance of a new lesion meeting size criteria
  - Anti VEGF therapy can decrease tumor size by decreasing vascularization…
    - …without affecting tumor cell content
  - Slowing the maturation of the first met may well increase DFS without improving OS

- DFS may be a radiographic artifact without clinical signficance

Summary

- Sunitinib should not be used as adjuvant therapy in high risk RCC
  - There is no demonstrable clinical value
  - DFS is only a number, not an outcome
  - QoL matters, as does treatment related mortality
  - Adjuvant Sunitinib is chronic therapy, with chronic toxicities
  - Our obligation is to the patient