A META-ANALISYS OF CLINICAL AVAIABLE TRIALS OF ADJUVANT TARGETED THERAPIES IN RENAL CELL CARCINOMA.

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Aim: The aim of our meta-analysis was to evaluate the effect of the adjuvant targeted treatment in terms of overall survival (OS) and disease free survival (DFS) in localized surgically removed RCC and to evaluate the correlation between adjuvant tyrosine kinase inhibitors (TKIs) and DFS in patients with low and high risk RCC.

Materials and Methods: We carried out a meta-analysis of available phase III randomized clinical trials exploring adjuvant TKIs in RCC. We adopted the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. We identified 2970 potentially relevant studies subsequently restricted to 5 according to the characteristics and the data available on each study. Of these, 4 were able to provide complete data for low/high risk analysis.

OS comparison among studies using a fixed effect model Hazard Ratio Hazard Ratio SE Weight IV Even 955 CI

Results: For the analysis of the effect of adjuvant treatment on OS/DFS we selected 4 randomized phase III trials for a total of 4820 patients with clear cell RCC. In overall population adjuvant TKIs resulted in better DFS benefit with a pooled HR of 0.84 (95% confidence interval of 0.76 – 0.93) without significant OS benefit (pooled HR: 0.89; 95% Cl 0.76-1.04). Both analyses were associated with a very low level of heterogeneity (l² value of 0%).

For the comparison of adjuvant TKI and DFS in low and high risk populations we selected the 3 phase III trials with risk stratification data for a total of 3282 patients. In low risk population adjuvant TKIs did not significantly impact DFS (pooled HR of 0.98, 95% CI of 0.82 – 1.17) while a positive trend in DFS was observed in high risk population (pooled HR 0.85; 95%CI 0.75-0.97). Both analyses were associated with a very low level of heterogeneity (I² value of 0% in low risk analysis and 7% in high risk analysis).

Deficition

Ferv high risk: other pT3-4 or anyT N+

 .5 ruge: 1.5, NU or undetermined, M0, Fuhrman grade ≥2, ECOG PS ≥1
T4 + any T, N+: T4 or any T N+, M0, any Fuhrman grade, any ECOG PS
T3 High + T4 + any T, N+

Highest risk: pT3 with Fuhrman grade ≥3 or pT4 and/or N+, any T, any Fuhrman grade. 1 No. of patients (%)

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Low risk

Intermediate high visk: pT1b grade 3-4, pT2 50% grade 1-4, or pT3a grade 1-2

Lower risk: pT2 or pT3 with Fuhrman grade 41%

3 Low: pT3, N0 or undetermined, M0, any uhman grade, ECOG PS 0; or Fuhrman rade 1, ECOG PS 1

study of Subgroup	log[hazaru katio]	36	weight	IV, FIXEU, 95% CI	IV, FIXeu	, 93/6 CI	
ASSURE sorafenib	-0.223	0.165	22.2%	0.80 [0.58, 1.11]	-		
ASSURE sunitinib	0.058	0.158	24.2%	1.06 [0.78, 1.44]	-	.	
PROTECT	-0.194	0.137	32.2%	0.82 [0.63, 1.08]			
S-TRAC	-0.083	0.168	21.4%	0.92 [0.66, 1.28]	-	-	
Total (95% CI)			100.0%	0.89 [0.76, 1.04]	•		
Heterogeneity: Chi2 = 2	2.00, df = 3 (P = 0.5	57); 1 ² =	0%		0.01 0.1 1	10	100
Test for overall effect:	Z = 1.49 (P = 0.14)					Favours Placebo	100

DFS comparison among studies using a fixed effect model

				Hazard Ratio	Hazard	Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed,	95% CI
ASSURE sorafenib	-0.105	0.12	18.2%	0.90 [0.71, 1.14]	-	
ASSURE sunitinib	-0.061	0.121	17.9%	0.94 [0.74, 1.19]	+	
ATLAS	-0.139	0.14	13.4%	0.87 [0.66, 1.14]	-	
PROTECT	-0.22	0.088	33.8%	0.80 [0.68, 0.95]	-	
S-TRAC	-0.274	0.125	16.8%	0.76 [0.60, 0.97]	+	
Total (95% CI)			100.0%	0.84 [0.76, 0.93]	•	
Heterogeneity: Chi2 =	2.17, df = 4 (P = 0.2	70); I ² =	0%		0.01 0.1 1	10 10
Test for overall effect:	Z = 3.30 (P = 0.001	0)				Favours Placebo

DFS comparison among patients with low risk tumors

				Hazard Ratio		Hazard Rat		
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI		IV, Fixed, 959	6 CI	
ASSURE sorafenib intermediate high risk	-0.01	0.154	34.6%	0.99 [0.73, 1.34]		+		
ASSURE sunitinib intermediate high risk	0.048	0.151	36.0%	1.05 [0.78, 1.41]		+		
ATLAS lower risk	0.015	0.252	12.9%	1.02 [0.62, 1.66]		+		
S-TRAC T3 Low	-0.198	0.224	16.4%	0.82 [0.53, 1.27]				
Total (95% CI)			100.0%	0.98 [0.82, 1.17]		•		
Heterogeneity: Chi ² = 0.86, df = 3 (P = 0.3					0.01 0.	1 1	10	100
Test for overall effect: Z = 0.18 (P = 0.85)					0.01 0.	Favors TKI Favo		100

DFS comparison among patients with high risk tumors

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI		Hazard Ratio IV. Random, 95% CI	
ASSURE sorafenib very high risk		0.124	25.4%	0.96 [0.75, 1.23]		+	
ASSURE sunitinib very high risk		0.126	24.6%	1.00 [0.78, 1.28]		+	
ATLAS highest risk	-0.307	0.171	14.0%	0.74 [0.53, 1.03]		-	
S-TRAC T3 high	-0.261	0.169	14.3%	0.77 [0.55, 1.07]		-	
S-TRAC T3 High+T4+any T, N+	-0.301	0.149	18.1%	0.74 [0.55, 0.99]			
S-TRAC T4+any T, N+	-0.478	0.351	3.5%	0.62 [0.31, 1.23]			
Total (95% CI)			100.0%	0.85 [0.75, 0.97]		•	
Heterogeneity: Tau ² = 0.00; Chi ² : Test for overall effect: Z = 2.45 (P		.37); I ²	= 7%		0.01	0.1 1 10 Favours TKI Favours Placebo	100

DFS comparison among patients with greater tumor size. ASSURE (T3 and T4 tumors with any Fuhrman grades), S-TRAC (T3 and T4 tumors with any Fuhrman grades and N+ tumors), and ATLAS (T3 with higher Fuhrman grades, T4 and N+ tumors)

					Hazard Ratio	Hazard Ratio
_	Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	ASSURE sorafenib	-0.116	0.057	21.6%	0.89 [0.80, 1.00]	
	ASSURE sunitinib	0.039	0.057	21.6%	1.04 [0.93, 1.16]	+
	ATLAS highest risk	-0.446	0.084	19.5%	0.64 [0.54, 0.75]	•
	S-TRAC T3 High+T4+any T, N+	-0.301	0.0756	20.2%	0.74 [0.64, 0.86]	•
	S-TRAC T3 Low	-0.198	0.111	17.1%	0.82 [0.66, 1.02]	-
	Total (95% CI)			100.0%	0.82 [0.69, 0.97]	•
	Heterogeneity: Tau ² = 0.03; Chi ²	= 27.93, df = 4 (P <	0.0001);	$1^2 = 86\%$		0.01 0.1 1 10 100
	Test for overall effect: Z = 2.30 (P	= 0.02)				Favors [experimental] Favors [control]

Discussion: The results of our analysis showed a positive trend in DFS without significant improvement in OS for patients treated with adjuvant TKIs. The positive trend in DFS has been confirmed in high risk population but not in low risk population. High risk patients were characterized by with one or more of the following features: positive nodes (N+), T4 tumours and T3 tumours with higher Fuhrman grades (3-4). The benefit obtained especially in the high risk population highlights the need to adopt a shared and reliable risk staging system in order to avoid confounding factors coming from the adoption of different staging system in clinical trial and to allow the inclusion of patients more likely to benefit from an adjuvant approach.

Conclusion: Adjuvant TKIs do not translate in statistically significant OS and DFS benefit. However, a positive trend in DFS has been observed in both overall and high risk population suggesting that a better selection of patients is a key issue for the evaluation of new compounds in adjuvant setting.

References:

- [1] Massari F, Bria E, Maines F et al. Clinical Genitourinary Cancer 2013;11(4):471-476.
- [2] Sun M, Marconi L, Eisen T et al. Eur Urol 2018;74(5):611-620.
- [3] Massari F, Di Nunno V, Ciccarese C et al. Cancer Treat Rev 2017;60:152-157.