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

Veronica Mollica[1] , Francesco Massari[1], Vincenzo Di Nunno[1],
Jeffrey Graham[2], Lidia Gatto[1], Daniel Heng[2]

[1]*Division of Oncology, S. Orsola-Malpighi Hospital, Bologna, Italy*
[2]*Department of Medical Oncology, Tom Baker Cancer Center, Calgary, Alberta, Canada*

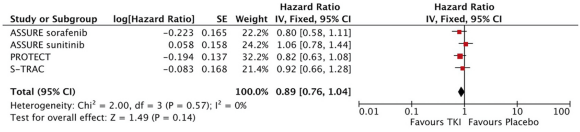
Aim: The aim of our meta-analysis was to evaluate the effect of the adjuvant targeted treatment in terms of overall survival (OS) and disease free survival (DFS) in localized surgically removed RCC and to evaluate the correlation between adjuvant tyrosine kinase inhibitors (TKIs) and DFS in patients 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 DFS and OS analyses and 3 were able to provide complete data for low/high risk analysis.

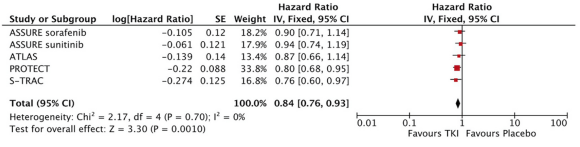
Results: For the analysis of the effect of adjuvant treatment on OS/DFS we selected 4 randomized phase III trials for a total of 4820 patients with clear cell RCC. In overall population adjuvant TKIs resulted in better DFS benefit with a pooled HR of 0.84 (95% confidence interval of 0.76 – 0.93) without significant OS benefit (pooled HR: 0.89; 95% CI 0.76-1.04). Both analyses were associated with a very low level of heterogeneity (I^2 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 (I^2 value of 0% in low risk analysis and 7% in high risk analysis).

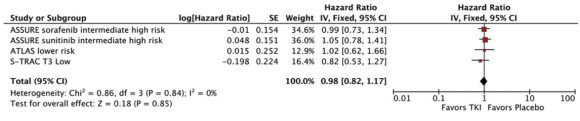
OS comparison among studies using a fixed effect model



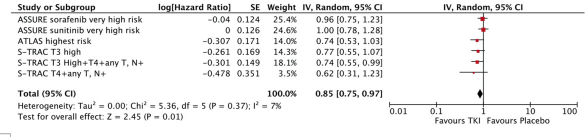
DFS comparison among studies using a fixed effect model



DFS comparison among patients with low risk tumors

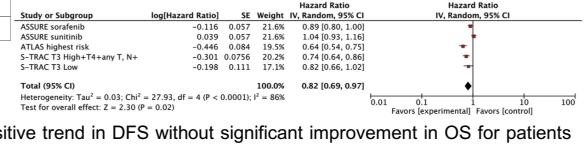


DFS comparison among patients with high risk tumors



	Low risk		High risk	
	Definition	**No. of patients (%)**	**Definition**	**No. of patients (%)**
ASSURE	*Intermediate high risk*: pT1b grade 3–4, pT2 grade 1–4, or pT3a grade 1–2	50%	*Very high risk*: other pT3–4 or any T N+	50%
S-TRAC	*T3 Low*: pT3, N0 or undetermined, M0, any Fuhrman grade, ECOG PS 0; or Fuhrman grade 1, ECOG PS 1	37%	• *T3 High*: T3, N0 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+*	63%
ATLAS	*Lower risk*: pT2 or pT3 with Fuhrman grade ≤2, M0	41%	*Highest risk*: pT3 with Fuhrman grade ≥3 or pT4 and/or N+, any T, any Fuhrman grade, M0	56%

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)



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:

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[3] Massari F, Di Nunno V, Ciccarese C et al. *Cancer Treat Rev* 2017;60:152-157.