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THE MERIT OF TYROSINE KINASE INHIBITORS IN THE ADJUVANT SETTING OF HIGH-RISK RENAL CELL CARCINOMA
A Meta-Analysis

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Background • Loco-regional renal cell carcinoma (RCC) accounts for 15 to 20% of patients with RCC, with a risk of post-surgical relapse of 40% [1,2]. Following the adoption of tyrosine kinase inhibitors (TKIs) as the first-line treatment of metastatic RCC, multiple studies evaluated Sunitinib [3,4] and Pazopanib [5] in the adjuvant setting of high-risk resected RCC. However, these studies have yielded inconclusive results, and there are currently no meta-analyses combining the results of all trials evaluating TKIs in the adjuvant setting of high-risk RCC. The aim was to perform a meta-analysis to evaluate and compare the possible benefit of Sunitinib and Pazopanib on disease-free survival (DFS) in the adjuvant setting of high-risk RCC.

Methods • This meta-analysis included all the phase 3 randomized controlled trials (ASSURE 3, S-TRAC 4 and PROTECT 5) evaluating Sunitinib and Pazopanib in the adjuvant setting of high-risk RCC. A random-effects model was preferentially used to pool the data using the inverse variance method and a subgroup analysis including Sunitinib and Pazopanib subgroups was used in order to account for heterogeneity and allow comparison of the two subgroups. Two variations of the same analysis were undertaken as sensitivity analyses: first with a fixed-effects model, second while excluding the results of the ASSURE study. The primary outcome was the comparison of disease-free survival (DFS) between TKIs and placebo. Hazard ratios were reported along with their 95% confidence intervals (95%CI).

Results • A total of 3447 patients from the three trials were included in the analysis. There was a tendency for a significant overall effect of both TKIs on DFS; however, this tendency only reached the threshold for statistical significance in the fixed-effects model (HR = 0.91; 95%CI = 0.83-0.99; $p = 0.03$) but not in the random-effects model (HR = 0.85; 95%CI = 0.72-1.01; $p = 0.06$, Figure 1). Significant between-study overall heterogeneity was observed ($p = 0.07$; I2 = 58%) and the subgroup analysis showed that this was largely due to the heterogeneity within the Sunitinib subgroup ($p = 0.05$; I2 = 73%, Figure 1). Moreover, a sensitivity analysis excluding the ASSURE study led to results which were markedly more homogeneous ($p = 0.48$; I2 = 0%). While the test for overall effect was found to be significant in the Pazopanib subgroup (HR = 0.80; 95%CI = 0.65-0.98; $p = 0.03$) but not in the Sunitinib subgroup (HR = 0.90; 95%CI = 0.67-1.19; $p = 0.45$), there was no significant difference between the subgroup effects ($p = 0.51$; I2 =0%; Figure 1).

Conclusion • Our analysis showed that Pazopanib and Sunitinib could still have a potential role in the armamentarium of adjuvant treatment in high-risk RCC. However, it failed to demonstrate a significant difference between these agents in this setting.

Keywords: renal cell carcinoma; tyrosine kinase inhibitors; adjuvant treatment

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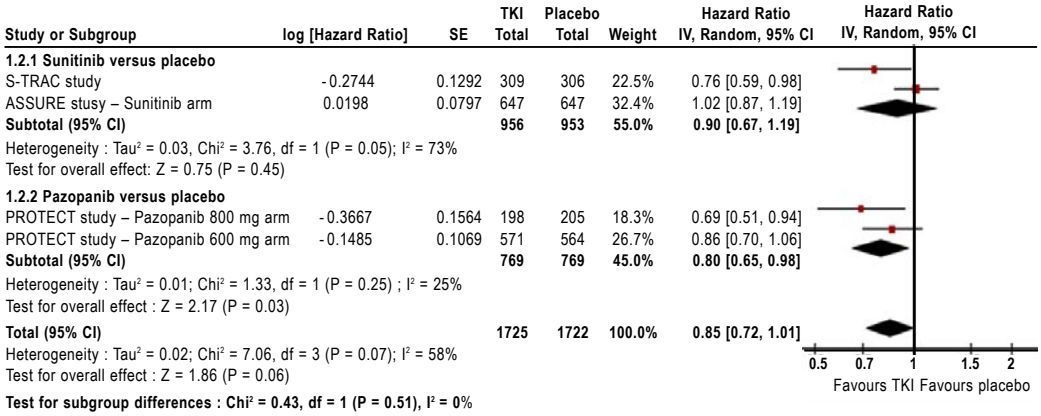

Figure 1. Random effects meta-analysis of the comparison comparison of the effect of Sunitinib and Pazopanib wih placebo on DFS in the adjuvant treatment of resected high-risk renal cell carcinoma

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