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Brief Correspondence

# Updated European Association of Urology Guidelines Regarding Adjuvant Therapy for Renal Cell Carcinoma

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**Abstract**

The European Association of Urology Renal Cell Carcinoma (RCC) guidelines panel updated their recommendation on adjuvant therapy in unfavourable, clinically non-metastatic RCC following the recently reported results of a second randomised controlled phase 3 trial comparing 1-yr sunitinib to placebo for high-risk RCC after nephrectomy (S-TRAC). On the basis of conflicting results from the two available studies, the panel rated the quality of the evidence, the harm-to-benefit ratio, patient preferences, and costs. Finally, the panel, including representatives from a patient advocate group (International Kidney Cancer Coalition) voted and reached a consensus to not recommend adjuvant therapy with sunitinib for patients with high-risk RCC after nephrectomy.

***Patient summary:*** In two studies, sunitinib was given for 1 yr and compared to no active treatment (placebo) in patients who had their kidney tumour removed and who had a high risk of cancer coming back after surgery. Although one study demonstrated that 1 yr of sunitinib therapy resulted in a 1.2-yr longer time before the disease recurred, the other study did not show a benefit and it has not been shown that patients live longer. Despite having been diagnosed with high-risk disease, many patients remain without recurrence, and the side effects of sunitinib are high. Therefore, the panel members, including patient representatives, do not recommend sunitinib after tumour removal in these patients.

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There are currently no adjuvant therapies recommended after nephrectomy for patients with renal cell carcinoma (RCC) [1]. Drugs that target the vascular endothelial growth factor receptor (VEGF-R) such as sunitinib and sorafenib are effective in disease control in the metastatic setting; however, they rarely completely eradicate the disease [2]. A number of trials have investigated whether adjuvant VEGF-targeted therapy can improve outcomes. To date, results have been reported for two studies [3,4]. The first was a randomised phase 3 study (ASSURE) involving 1943 patients with completely resected RCC (pT1b–4 and any N grade; Supplementary Table 1) [4]. Patients were randomised 1:1:1 to sunitinib, sorafenib, or placebo. The disease-free survival (DFS) and overall survival (OS) results for sunitinib were hazard ratio (HR) 1.02 (97.5% confidence interval [CI] 0.85–1.23) and HR 1.17 (97.5% CI 0.90–1.52), respectively.

In the ASSURE study, 62% of patients in the sunitinib arm developed grade 3 or 4 toxicity and 34–44% withdrew (depending on the dosing cohort; Supplementary Table 1). The sunitinib and sorafenib doses were modified during the trial to address toxicity concerns. This did not appear to affect efficacy in an exploratory subset analysis. There was no survival advantage for either drug, with not even a trend towards benefit in the treatment arm.

The S-TRAC trial was the second double-blind, placebo-controlled, randomised phase 3 trial for which results were reported [3]. The results contradict ASSURE for DFS. The S-TRAC study included 615 patients in a 1:1 randomisation. The HR was 0.76 (95% CI 0.59–0.98; $p = 0.03$) for DFS, and OS was immature. Grade 3/4 toxicity in the study was 60.5% for patients receiving sunitinib, which translated into significant differences in quality of life in terms of loss of appetite and diarrhoea. The study was smaller than ASSURE and had shorter follow-up. While the majority of patients overlapped, S-TRAC consisted of a population at slightly higher risk. Furthermore, there was no central radiologic review in ASSURE. This point is important because the DFS HRs, the primary endpoint of the trials, were different (central review for S-TRAC and investigator review for ASSURE, Supplementary Table 1). It is noteworthy that the investigator assessment for DFS in S-TRAC did not reach statistical significance (HR 0.81, 95% CI 0.64–1.02; $p = 0.08$), as was the case with ASSURE.

These data prompt a number of questions that need to be addressed before we can consider changing the standard of care. First, is DFS a good surrogate endpoint in this setting? OS takes longer to achieve, and DFS has at times translated into an OS advantage in the adjuvant setting in other diseases [5–7]. In breast cancer trials, DFS HRs >0.76 without OS benefit have resulted in regulatory approval and adoption as a standard of care [6]. Therefore, DFS is a reasonable endpoint and a precedent exists, but DFS needs to translate into OS in the long run [7]. The assumption that this OS signal is inevitable with S-TRAC is questionable owing to the preliminary OS results in ASSURE and S-TRAC (HR 1.01, 95% CI 0.72–1.44; $p = 0.94$ for S-TRAC; HR 1.17, 97.5% CI 0.90–1.52; $p = 0.1762$ for ASSURE, Supplementary Table 1). There are also uncertainties for the current treatment algorithm for metastatic RCC. Treatment for first-line metastatic renal cancer is VEGF-targeted therapy, as is being tested in the adjuvant setting. Cross-resistance between VEGF-targeted therapies occurs, and it is possible that patients who relapse early on sunitinib will do less well with subsequent VEGF-targeted therapy [8]. This has been described as "the law of diminishing returns" in VEGF-resistant metastatic RCC [9]. Currently there is no indication of even a trend towards a survival advantage in either study, although the data are immature. To achieve positive results after initially overwhelming negative OS results to date, much later analysis after longer follow-up will be required. The results would need to show the Kaplan-Meier OS curves parting significantly after a number of years of follow-up in a nonproportional HR manner. It seems uncertain that this will occur from the data available to us.

In reality, the definition of early metastatic disease is a grey area. The presence of metastasis is determined via cross-sectional imaging, which is only able to identify sizeable cancer deposits from a molecular perspective. Therefore, large numbers of patients with high-risk disease probably have early, as yet undetected, metastatic disease. Intervention with sunitinib in these patients will essentially be treating early metastatic disease. Stabilisation with sunitinib, especially at the beginning of the intervention period, would therefore be expected. Perhaps a more pertinent question is why this was not seen in ASSURE. Nevertheless, the data available to us do not currently support the hypothesis that VEGF-targeted therapy can prevent relapse and extend survival.

What we can confidently say is that there is an issue around tolerability, which was consistent in both studies. A year of therapy clearly comes with significant toxicity that can affect quality of life.

Where multiple studies exist, meta-analysis is a powerful tool. Again, for breast cancer and other tumour types, meta-analysis is the driver that influences guidelines, rather than a single study [5,7,10]. Results from a meta-analysis of ASSURE and STRAC trials show statistically nonsignificant results for DFS owing to the sheer size of ASSURE (Fig. 1; combined HR 0.89, 95% CI 0.67–1.19). OS is immature, but

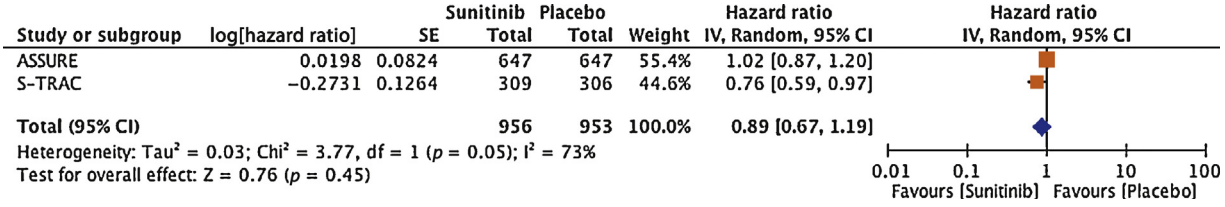


**Fig. 1 – Meta-analysis of disease-free survival (DFS) for S-TRAC and ASSURE. CI = confidence interval; SE = standard error; df = degrees of freedom.**

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negative at this stage. This meta-analysis has shortcomings such as subtle differences in patient populations and methods of assessment, but it is an important piece of the jigsaw.

In conclusion, it is preferable to look at the adjuvant studies together rather than in isolation. The outcomes of the placebo arms of the two trials are similar, which is reassuring from a trial conduct perspective. The results for DFS are contradictory and the reason is not clear. Despite imbalances in risk assessment, inclusion of non–clear cell RCC, and starting dosages, these studies have much more in common with one another than differences (Supplementary Table 1). The DFS at 5 yr in the placebo arm of both studies is almost identical. The pathological T3–4 subgroup in ASSURE matching the patients included in S-TRAC is even numerically stronger and did not reveal a benefit for DFS (HR 1.04, 95% CI 0.83–1.31) or OS in exploratory subgroup analysis [4]. Without a consistent trend towards a DFS signal, it is not possible to confidently say that there is likely to be a survival benefit. The one area for which there is clarity is toxicity, which is an important consideration. Considerations for the future include the outcomes of other trials in the area and long-term OS data.

The European Association of Urology Renal Cell Cancer Guidelines Panel, which includes patient representatives and clinicians, considered a number of different scenarios to determine what would be required from S-TRAC to change practice. The decision on whether to change practice was taken in the context of the data available from ASSURE, and the assumption that the level of toxicity with sunitinib would be in line with those seen previously. Results showed that only 1/15 (6%) of the panel would change their standard of care when considering the DFS and OS closest to S-TRAC (DFS: HR 0.75, $p < 0.05$; OS: HR 1.0, $p > 0.05$). Standard practice would only be significantly influenced by a significant survival benefit (Fig. 2). In addition, kidney cancer patients from the International Kidney Cancer Coalition (IKCC) participated in a questionnaire about the implications for STRAC. The results lacked clarity (Supplementary Fig. 1, Fig. 3). Twenty-two patient representatives from the IKCC network were asked what degree of PFS advantage would be needed to justify taking sunitinib for 1 yr. Approximately one-third of patients favoured not taking sunitinib when faced with the S-TRAC results (Fig. 3).

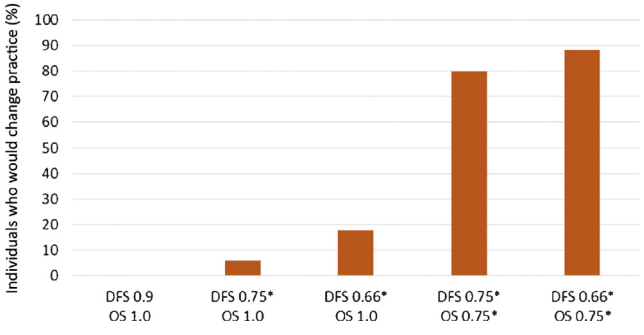


**Fig. 2 – Members were asked which results from S-TRAC would change their standard practice in the context of the data available in ASSURE and toxicity profiles consistent with those seen for sunitinib. * Statistically significant. DFS = disease-free survival; OS = overall survival.**

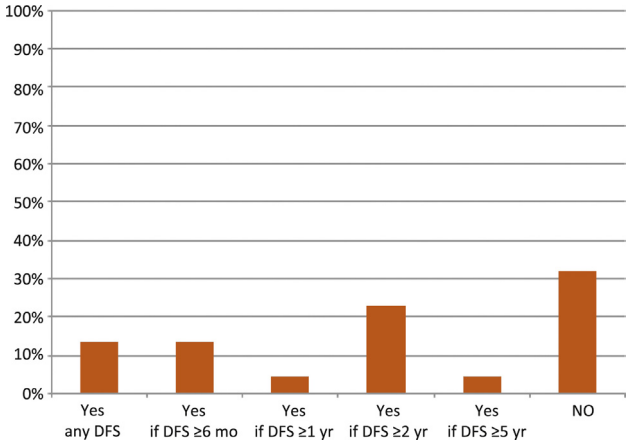


**Fig. 3 – Patient representatives from the IKCC network ($n = 22$) were asked: "After surgery for kidney cancer, if your doctor told that you are at high risk of recurrence (spread), would you consider taking sunitinib (Sutent) for one year in the hope you could delay the onset of recurrence even if your overall survival was not improved?" Patient representatives were patients with nonmetastatic disease who had previously undergone surgery).**

**Table 1 – Recommendation of the European Association of Urology Renal Cell Cancer Guidelines Panel**

| Recommendation | Strength | |
|---|---|---|
| Adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma is not recommended | Weak | ↓ |

Finally, the panel summarised the current evidence (Supplementary Table 2) and judged the strength of the recommendation (Supplementary Table 3). This resulted in the following recommendation, to which 80% of the 15 panel members entitled to vote strongly agreed via anonymous voting (Supplementary Fig. 2). The final recommendation against adjuvant sunitinib reflects the poor benefit-to-harm ratio and the current absence of evidence of an OS benefit (Table 1).

The strength of the recommendation in Table 1 is weak because the panel took into account that some patients would favour having this option despite the toxicity, the unproven OS benefit, and the overall weak quality of the evidence.

***Author contributions:*** Axel Bex had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Bex, Powles.
*Acquisition of data:* Bex, Powles.
*Analysis and interpretation of data:* Bex, Albiges, Ljungberg, Bensalah, Dabestani, Giles, Hofmann, Hora, Kuczyk, Lam, Marconi, Merseburger, Staehler, Volpe, Powles.
*Drafting of the manuscript:* Bex.
*Critical revision of the manuscript for important intellectual content:* Bex, Albiges, Ljungberg, Bensalah, Dabestani, Giles, Hofmann, Hora, Kuczyk, Lam, Marconi, Merseburger, Staehler, Volpe, Powles.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.11.034.

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