

## FDA Approves an Adjuvant Targeted Therapy for Post-Surgery RCC Patients, but Questions and Clinical Challenges Remain

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### Editorial

After years of attempts to find an adjuvant therapy to reduce the risk of renal cell carcinoma recurrence after nephrectomy, we now have an FDA-approved targeted therapy for this indication. There have been numerous negative studies previously, and some felt that VEGF targeted therapy would never gain regulatory approval in the adjuvant setting, however, results of phase III S-TRAC trial have changed all of that.

The results of the S-TRAC trial, which were presented at ESMO in 2016 and subsequently published in the New England Journal of Medicine, showed that disease-free survival (DFS) was prolonged by 1.2 years in clear cell RCC patients who received adjuvant sunitinib after nephrectomy compared to those who received placebo [1,2].

The trial randomized 615 patients with clear cell RCC to receive adjuvant sunitinib 50 mg daily on the standard 4 weeks on, 2 weeks off schedule (n=309) or placebo (n=306), with patient characteristics being well balanced between both arms. The median age of patients in the treatment arm of the study was 57 years and 71.8% were males, consistent with the epidemiology of this disease. 73.8% of patients had an ECOG performance score of 0.

The study allowed for one dose reduction to 37.5 mg per day. 54.2% of the patients were able to maintain treatment at the 50 mg per day dose level. The median daily dose was 45.9 mg.

90.6% of those in the treatment arm had a stage III tumor, with no lymph node involvement and no distant metastatic disease. 37.2% of subjects were considered low-risk (defined as any Fuhrman grade and ECOG score of 0 or Fuhrman grade 1 and ECOG score of  $\geq 1$ ) and 53.4% were high-risk (Fuhrman grade  $\geq 2$  and ECOG score of  $\geq 1$ ).

After a median follow-up of 5.4 years, of median DFS of 6.8 years was observed in the sunitinib arm compared to 5.6 years with placebo (HR, 0.76; 95% CI, 0.59-0.98; P=0.03). The difference was most pronounced in higher risk patients, where the median DFS was 6.2 years in those in the sunitinib arm versus 4.0 years for those receiving a placebo (HR, 0.74; 95% CI, 0.55-0.99; P=0.04).

These improvements were not without costs as grade 3/4 adverse events (AEs) were experienced by 63.4% of patients receiving sunitinib group versus 21.7% in those receiving the placebo. The most common side effects in the sunitinib arm were diarrhea (56.9%), palmar-plantar erythrodysesthesia (50.3%), hypertension (36.9%), fatigue (36.9%), and nausea (34.3%).

The approval of sunitinib for this adjuvant indication was not without controversy. When reviewing the data in September the FDA's Oncologic Drugs Advisory Committee was not convinced by the data, and the approval vote was tied 6-to-6. The FDA granted approval despite this lack of confidence from the committee.

Despite the approval, the facts remains that an overall survival benefit using sunitinib in the adjuvant setting has not been established and that the DFS benefit in the S-TRAC was relatively modest, in the face of a generally poorly tolerated therapy. It is also unclear which patients would potentially benefit from adjuvant therapy in RCC, as there are many ways to define high risk of recurrence.

Modifying the sunitinib standard schedule to a two week on, one week off schedule for example may help to limit some toxicities of the therapy, but whether most patients will choose to undergo a year of adjuvant therapy to reduce the risk of recurrence has yet to be seen.

It is still advisable to enroll patients on adjuvant trials whenever possible, as the NCCN and other guidelines strongly encourage clinical trial enrollment and we still have much to discover about preventing recurrent RCC after definitive surgery.

### References

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