KIDNEY CANCER

SWITCHing inconsequential

The order in which patients with metastatic renal cancer are treated with sorafenib and sunitinib does not affect progression-free survival (PFS), according to results from the SWITCH trial, which have recently been published in *European Urology*.

Both sorafenib and sunitinib are multikinase inhibitors—their targets include vascular endothelial growth factor receptors and platelet-derived growth factor receptors—and are approved for the first-line treatment of patients with advanced renal cell carcinoma (RCC). Often, the disease progresses during treatment with such targeted therapies and, in these cases, sequencing of different agents is common; however, which agents and which order of agents provide optimal cancer control is still unclear.

The SWITCH trial is the first prospective, randomized phase III trial initiated to evaluate whether using sorafenib followed by sunitinib (So–Su) is superior to sunitinib followed by sorafenib (Su–So) in extending PFS in patients with metastatic RCC. Previous retrospective studies had suggested that treating patients with So–Su might yield better outcomes than treatment with Su–So.

In the multicentre trial set in Germany, Austria and the Netherlands, the researchers equally randomized a total of 365 patients to either treatment arm. Patient characteristics were overall well balanced; the median patient age was 65 years, 87% of patients had clear cell histologic appearance and 92% had undergone partial or radical nephrectomy. First-line treatment continued until disease progression or intolerable toxicity; then—after a treatment-free period to ensure additive toxicity was unlikely—patients received the second-line inhibitor. The primary end point of the study was PFS measured as the time from randomization to confirmed disease progression or death while on treatment with the second-line inhibitor. The secondary end points included total time to progression, overall survival, and PFS during first-line inhibitor use and during second-line inhibitor use.

After a mean follow-up period of 10.3 months, 97% of patients had received first-line therapy and 49% had received second-line therapy, with significantly more patients receiving second-line therapy in the So–Su arm than in the Su–So arm (57% versus 42%; $P < 0.01$). In their report, the investigators highlight that this finding is similar to data from other studies, but that the reasons for this discrepancy are not quite clear. The mean duration of second-line therapy was shorter in the Su–So arm than in the So–Su arm (16.0 weeks versus 28.2 weeks, $P < 0.001$).

The median PFS at the cut-off point was 12.5 months in the So–Su arm and 14.9 months in the Su–So arm, demonstrating that So–Su was not superior to Su–So (HR 1.01, 90% CI 0.81–1.27). Total time to progression, overall survival and median first-line PFS were also similar between groups and, although the median second-line PFS was longer in patients receiving So–Su than in those receiving Su–So (5.4 months versus 2.8 months; $P < 0.001$), the authors remark that event numbers were low and the results regarding second-line therapy should be considered with caution.

Subgroup analyses, taking into consideration factors such as patient age, sex and performance status, showed no differences between treatment arms, apart from overall survival results in patients aged ≤ 65 years compared with those aged > 65 years. In an updated overall survival analysis, patients > 65 years of age had an 11.7 months longer overall survival in the So–Su arm in comparison with those in the Su–So arm ($P < 0.04$); however, the study population had not been stratified according to age and the investigators highlight that this finding should be treated as “hypothesis-generating only”.

Adverse event rates in the two treatment groups were overall comparable but the types of adverse events differed. In addition, generally, fewer adverse events occurred during second-line in comparison with first-line therapy, possibly owing to cross-tolerance and adaptation to inhibitor treatment or the fact that patients who proceed to a second-line therapy tend to be more fit than those who discontinue treatment during or after first-line therapy.

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Original article Eichelberg, C. *et al.* SWITCH: a randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the treatment of metastatic renal cell cancer. *Eur. Urol.* doi:10.1016/j.eururo.2015.04.017