

Sequential Therapies in Kidney Cancer

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Extraordinary advances have been made in oncology over the past decade, in conjunction with progress in the fields of molecular biology and biotechnology. Perhaps one of the tumors in which there has been a revolution with regard to understanding tumor biology and remarkable developments in treatment is kidney cancer¹.

Conventional treatment, which has been the standard of care for many years, was based on cytokines, mainly interferon alpha and interleukin-2².

Understanding the pathophysiology of kidney cancer, in which tumor angiogenesis is the main result of mutations in etiopathogenesis. That is why therapeutic strategies are based on drugs that can block the different pro-angiogenic signaling pathways. There are essentially two main treatment strategies: tyrosine kinase inhibitors (TKIs) such as pazopanib, sunitinib, sorafenib and axitinib and mTOR signaling pathway inhibitors, such as everolimus and temsirolimus, with the combination of bevacizumab plus interferon considered as a second choice for first-line treatment as it is associated with higher toxicity³.

The classification of metastatic disease into favorable, intermediate and poor risk categories, initially based on Motzer's criteria and subsequently on Heng's prognostic models, has been helpful for determining which patients will benefit from treatment with a certain drug^{4,5}. In this way treatment options are ranked as first-line, second-line, third-line or palliative care.

It is clear that combination treatment may increase toxicity but does not improve either progression-free survival (PFS) or overall survival as evidenced by the INTORACT trial⁶.

So for now single drug treatment remains the best alternative, mainly with sunitinib, temsirolimus and pazopanib as first-line therapy and sorafenib, axitinib and everolimus as second-line options. The combination regimen of bevacizumab plus interferon for first-line treatment is the exception.

That said, given that a significant percentage of patients will be directed to receive one of the first-line treatment regimens, the question arises as to what treatment is the most effective. Thus, according to various guidelines, after failure of cytokine therapy the first treatment option is sorafenib and after failure of TKIs, everolimus and axitinib are considered to be the preferred options.

A therapeutic alternative that has been explored is sequential therapy, i.e., which type of drug should be given first. To this end the SWITCH trial was conducted and although the results have not yet been published, they were presented at the ASCO Genitourinary Cancers Symposium in February 2014⁷ (Fig. 1).

- Primary objective: Total PFS (from randomization to confirmation of progression or death during second-line therapy or first-line therapy for patients who did not receive second-line treatment).

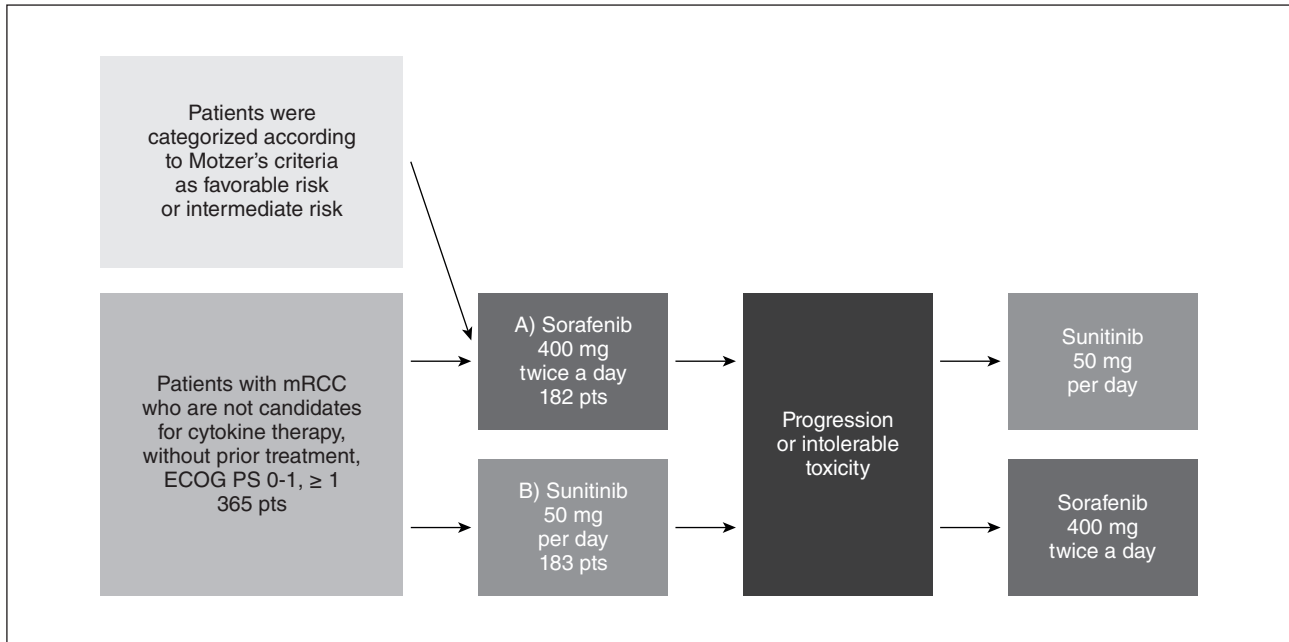


Figure 1. Phase III SWITCH Trial: Sorafenib → Sunitinib vs. Sunitinib → Sorafenib for RCC.

- Patients from Germany, Austria and the Netherlands were recruited.
- Patients were evaluated every 12 weeks and at the end of treatment.

This was the first prospective study to compare sequential administration of sorafenib followed by sunitinib or vice-versa as there is no compelling evidence regarding the optimal sequence of administration.

It was conducted in patients with metastatic renal cell carcinoma who had not received prior treatment, who had good performance status and were classified as low-risk or intermediate-risk according to Memorial Sloan Kettering Cancer Center (MSKCC) prognostic criteria. The patients were openly randomized to treatment with conventional doses of sorafenib/sunitinib (arm A) or sunitinib/sorafenib (arm B). The primary endpoint was PFS during the second-line treatment.

A total of 365 patients were enrolled (182 in arm A and 183 in arm B) (Fig. 2).

There was no difference in PFS between the two arms. The two curves are superimposed, with a hazard ratio (HR) of 1.01. There was a slight numerical advantage for starting with sunitinib followed by sorafenib rather than the other way around: median PFS was 14.9 months for patients who started with sunitinib and 12.5 months when treatment was initiated with sorafenib.

It is very important to consider that many patients were unable to cross over to receive the second-line therapy: only 57 patients who started with sorafenib crossed over to receive the second-line treatment and only 42% of patients who started with sunitinib crossed over to sorafenib. One explanation for this may be that many of the patients who dropped out of the study may have received some other treatment and were not counted at the time of first progression. Many investigators may have thought that a longer PFS would be achieved but this circumstance was also seen in the phase II RECORD-3 study⁸ (Fig. 3).

Just as for progression-free survival, there was no significant difference with regard to median overall

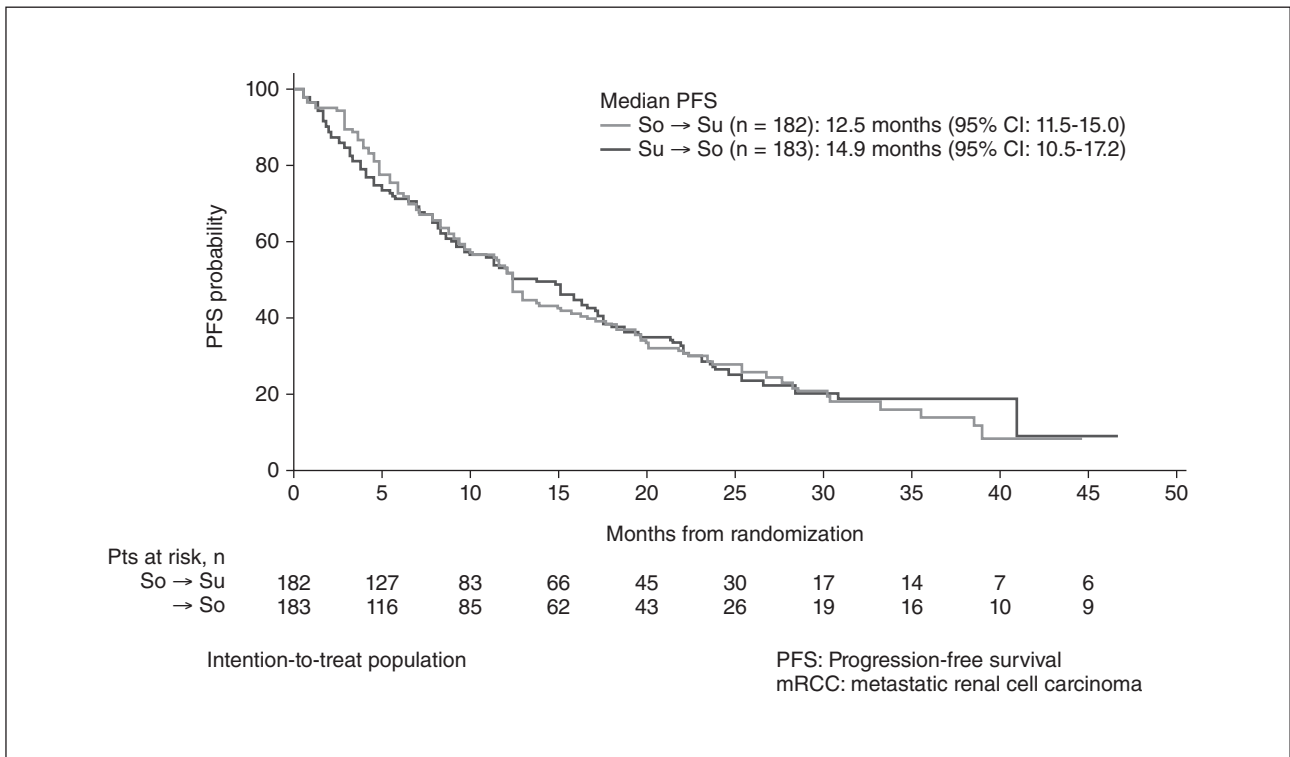


Figure 2. SWITCH Trial: Sorafenib → Sunitinib vs. Sunitinib → Sorafenib for mRCC: PFS (adapted from Michel MS, et al.⁷).

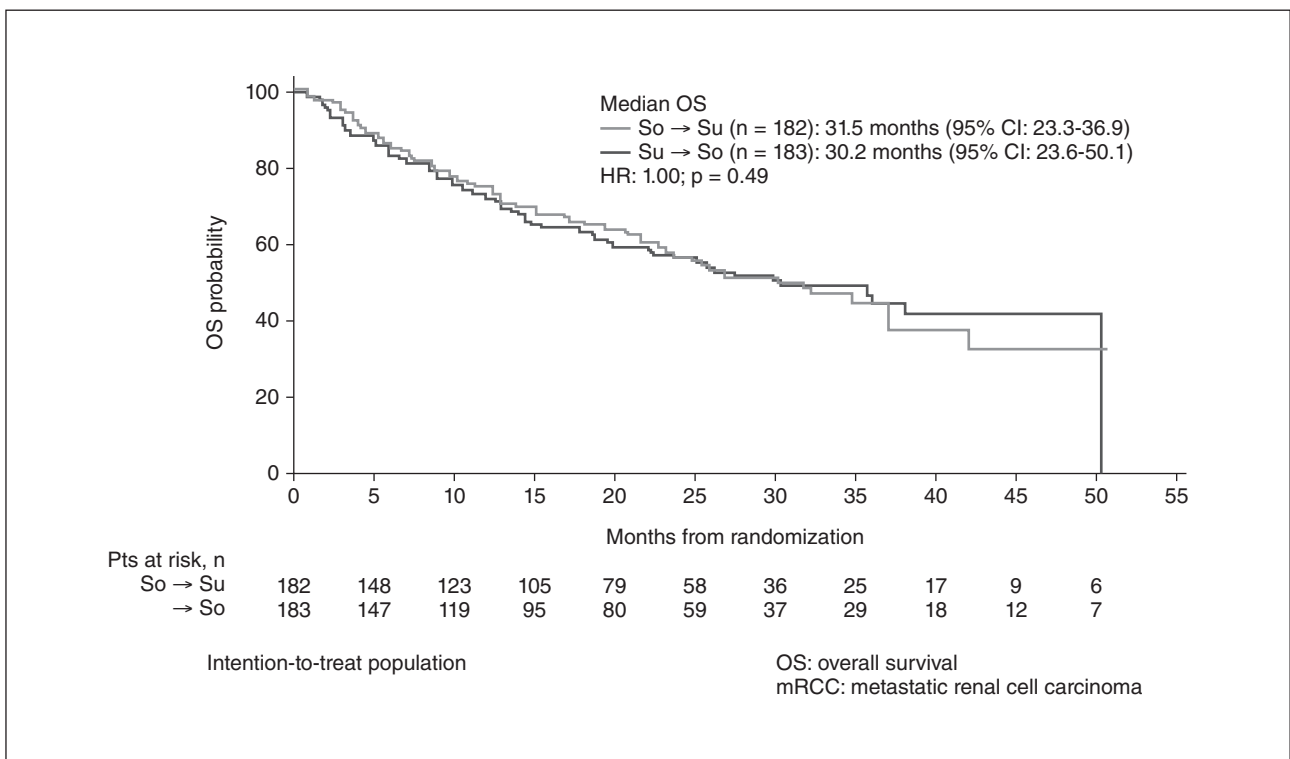


Figure 3. SWITCH Trial: Sorafenib → Sunitinib vs. Sunitinib → Sorafenib for mRCC: OS (adapted from Michel MS, et al.⁷).

survival between the two arms: 31.5 months for sorafenib followed by sunitinib compared to 30.2 months for sunitinib followed by sorafenib (HR: 1.00). It is worth noting that the survival times are similar to those reported in the phase III COMPARZ study that compared the effectiveness of pazopanib and sunitinib as first-line treatment⁹. These studies demonstrate that in the era of TKIs for metastatic renal cancer, patients receiving multiple TKIs may achieve a median survival time of 2.5 years.

These data suggest that sequential therapy may become the standard of treatment for metastatic renal cancer and this study appears to show that it may be regardless of which drug is used as first-line therapy, in this case either sunitinib or sorafenib.

With respect to adverse events, there was a marked difference that led to permanent treatment discontinuation between the two groups (18.6/29.5%). The most common events (> 20%) in first-line treatment of sorafenib vs. sunitinib were alopecia (29/4%), diarrhea (43/29%), dysgeusia (8/21%), fatigue (21/34%), HFSR (37/20%), hypertension (24/24%), nausea (18/24%) and rash (22/3%) whereas adverse events were generally less frequent during second-line therapy.

In conclusion, patients benefited regardless of which drug they received first, whether sunitinib or sorafenib, as median overall survival was the same. It is important to note that this trial was not an equivalence or non-inferiority study: it was designed

as a superiority study, intended to show the benefit of sorafenib as first-line therapy. Therefore, the primary objective was not reached. This does not mean to say that both sequences are equal, but it is worth noting that many of us would have expected better results from initiating treatment with sunitinib so we learned that the sequence may be a good option, besides observing that toxicity during first-line therapy was higher than during second-line treatment.

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