



Editorial on “*Adjuvant treatment for high-risk clear cell renal cancer: updated results of a high-risk subset of the ASSURE randomized trial*”

Matteo Santoni¹, Alessandro Conti², Rodolfo Montironi³, Nicola Battelli¹

¹Oncology Unit, Macerata Hospital, Macerata, Italy; ²Department of Urology, Bressanone/Brixen Hospital, Bressanone, Italy; ³Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Ancona, Italy

Correspondence to: Matteo Santoni, MD. Oncology Unit, Macerata Hospital, via Santa Lucia 2, 62100 Macerata, Italy. Email: mattymo@alice.it.

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We read with great interest the paper entitled “*Adjuvant Treatment for High-Risk Clear Cell Renal Cancer Updated Results of a High-Risk Subset of the ASSURE Randomized Trial*” by Haas *et al.* (1). Last year, the same group published the results of a randomized phase III trial ASSURE comparing 1-year treatment with sorafenib (400 mg twice daily), sunitinib (50 mg/day for 4 weeks of every 6 weeks), or placebo as adjuvant therapies for patients with completely resected renal cell carcinoma (RCC), without reporting significant improvements of the disease-free survival (DFS) in the study arms (2). More recently, Ravaud and his group firstly showed the results of a 750-patient randomized study, S-TRAC (3), (sunitinib 50 mg daily with 4/2 schedule *vs.* placebo in clear cell RCC predominant pT3-4 or node-positive disease). The authors showed an advantage in terms of DFS of 1.2 years (6.8 *vs.* 5.6 years) in this population of patients with high-risk of recurrence treated with sunitinib as adjuvant therapy compared to placebo, without mature results on overall survival (OS) at time of data cut-off (3).

Based on these new evidences, Haas *et al.* performed an updated analysis (1) of data from the Assure trial (2) focusing on the high-risk population. This subgroup was composed by patients with pT3 and higher stage (with tumor growing into a major vein, such as the renal vein or the vena cava, or into tissue around the kidney, but not invading the adrenal gland or overcoming beyond Gerota's fascia, *Figure 1*) or node-positivity. Differently from S-TRAC study (3), they did not find a significant benefit in terms of DFS (5-year rates were 47.7%, 49.9%, and 50.0%

for sunitinib, sorafenib and placebo, respectively) or OS (5-year rates: 75.2%, 80.2% and 76.5%) by treating patients with anti-vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) compared to placebo (1).

So how can we explain the different results obtained by these two studies? Should we treat or not patients with high-risk of recurrent RCC after nephrectomy with sunitinib or do we need more data to better identify the subpopulation of patients who will certainly benefit from this approach? Firstly we can start analysing this questions underling the different population enrolled in these two studies. Indeed, the ASSURE trial included also patients with non-clear cell histology, who represented more than 20% of the whole study accrual (1) and were excluded from the S-TRAC trial (3). Moreover, risk assessment was calculated following AJCC indications (1), while in the S-TRAC study it was used the UISS system (3). In addition, only 67.7% of patients started at full sunitinib dose in the study by Haas *et al.* (1) and it was followed to reduce the dose till a minimum of 25 mg, while Ravaud *et al.* (3) included only patients treated at the beginning with 50 mg of sunitinib, with a maximum reduction allowed till 37.5 mg.

The study by Haas *et al.* also investigated the impact of receiving higher or reduced doses of sunitinib or sorafenib in terms of patients' outcome. They reported that starting dose as well as dose reductions were associated with a DFS that didn't differ from that registered by patients treated with higher doses. These data are consistent with those

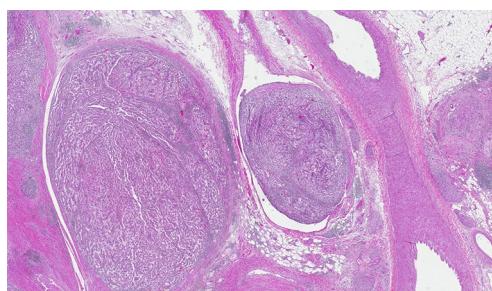


Figure 1 Clear cell RCC with venous invasion in the sinus (pT3a) (4x). RCC, renal cell carcinoma.

published by Iacovelli *et al.* (4), who revealed that toxicity-related dose reductions in 591 patients treated with first-line sunitinib or pazopanib were correlated with longer OS and with a better outcome with second-line treatments (4).

Another very interesting topic is represented by the responsiveness to target agents or immunotherapies of patients with recurrent disease following adjuvant therapy. What we still don't know is the complex series of changes caused in the tumor microenvironment by adjuvant therapy, which is aimed to prolong the time from nephrectomy to tumor recurrence. In this view, it is important to consider the results published by our group in 2014 focused on the biological features of patients with metastatic RCC relapsed >5 years from nephrectomy (5-7). We showed that this group of patients with a long DFS presented a different pattern of metastatic spread, involving unusual site of metastases, such as stomach and glands (5,6), and were particularly responsive to first-line sorafenib, sunitinib or pazopanib without significant differences (5,6). In late-relapsing patients, inflammation resulted highly prognostic, with patients with higher neutrophil to lymphocyte ratio (NLR) associated with shorter PFS and OS compared to patients with lower NLR (7). Taken together, these data underline the particular biological features that characterize patients with prolonged DFS, thus suggesting that patients with increased DFS due to adjuvant therapy should be carefully studied in order to optimize the diagnosis and to select to most potentially effective strategies at tumor recurrence. At this regard, a phase II study (NCT01649180, NEXT, PrE0801) was planned to assess the efficacy of anti-VEGFR TKI axitinib at recurrence after adjuvant therapy in RCC.

Based on the results obtained by Nivolumab in patients with metastatic RCC (8,9), the use of immune checkpoint inhibitors in the adjuvant setting should be carefully

evaluated. A reason to be potentially optimistic is the ability of anti-PD-1 and anti-PD-L1 inhibitors to shape memory phenotype CD8 T cell subsets (10). At present, four different phase III studies are investigating the efficacy and tolerability of Pembrolizumab (NCT03142334, KEYNOTE-564), Atezolizumab (NCT03024996, IMmotion010), Durvalumab alone or with anti-CTLA-4 tremelimumab (NCT03288532) and the combination of Nivolumab and Ipilimumab (NCT03138512, CheckMate 914) as adjuvant therapy in patients with RCC. These studies are actively enrolling at this time and the results are awaited in the next 5 years. An evolution of PD-1/PD-L1 approach is under evaluation in the URroRCC study (NCT02429440), a phase I/II trial that will test the efficacy and safety of intradermal application of adjuvant peptide vaccine (developed by using tumor associated peptides) in combination with either granulocyte macrophage colony stimulating factor (GM-CSF) or Montanide ISA-51 in patients with clear cell and not-clear cell RCC histology.

In conclusion, the results of this sub-analysis of ASSURE trial focused on high-risk RCC patients underline the necessity of more selective criteria in the adjuvant setting, not only based on tumor staging but also on tumor biological and molecular features. This is absolutely required in order to carry the adjuvant approach for RCC patients into the era of personalized and precision medicine.

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Footnote

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