# Complete response after treatment with first-line targeted anti-vascular endothelial growth factor therapy in metastatic renal cancer: what next?

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In a recent issue of *European Urology*, Buchler *et al*. (1) reported population-based results from a cohort of patients who achieved complete response (CR) after treatment with first-line targeted anti-vascular endothelial growth factor (VEGF) therapy. From the initial cohort of 2,803 patients, 100 individuals achieving CR were identified (3.6%). The median time from treatment initiation to CR was 10.1 months. Median progression-free survival (PFS) from therapy initiation was 3.8 years (95% CI: 2.9–4.6 years) and the 5-year overall survival (OS) was 80% (95% CI: 70%–91%). There was no statistically-significant difference in survival rates between patients continuing or discontinuing treatment after achieving CR.

The authors (1) examined data collected from the RENal Information System (RenIS) registries (2). In order to account for patients who discontinued therapy after the arbitrarily-set 1-month cut-off but without evidence of disease progression, sensitivity analyses were also performed on different time intervals, and virtually the same results were observed. It should be noted that the population included in their study was mostly of young patients (median age 60 years) and it is possible that the results may not be applicable to older patients (3). Moreover, given the retrospective nature of the study, selection bias cannot be completely excluded.

Approximately 63,000 patients will be diagnosed with RCC in 2016 (4) and, although most of the patients will be diagnosed with small-size low-grade lesions, roughly 17% of individuals will have metastatic disease at the time of diagnosis. Therapeutic options for management of these patients greatly improved in the last decade after the introduction of VEGF-targeted treatment modalities. Today, IL-2 based treatments are still a viable option in highly-selected subgroups of individuals (5), but they have been surpassed by the use of anti-angiogenetic drugs, such as sunitinib, pazopanib and bevacizumab (6). Nowadays, current first-line options for patients with metastatic renal cell carcinoma (mRCC) include different agents such as tyrosine-kinase inhibitors (TKI) (7) and VEGF-directed antibodies (8,9). The introduction of angiogenesis inhibitors in clinical practice relies on recent understandings of the biology of this disease (10). The metastatic Renal-Cell Carcinoma Database Consortium demonstrated improved survival rates after the introduction of targeted therapy in daily clinical practice (11). However, only a small proportion of patients obtain initial CR after treatment (12-15). In this regard, a meta-analysis recently performed by Iacovelli *et al*. (16) reported CR after antiangiogenetic therapy of 2%, without significant differences based on the type of anti-angiogenetic drug used.

The idea that continuous VEGF-targeted therapy might not be necessary after CR has been previously formulated even for different treatment modalities. For example, in the era of interleukine-based therapy, it was observed that patients treated with interleukin-2 were able to maintain CR without any need for subsequent treatment (17). Conversely, Albiges *et al*. (18) analysed a cohort of 64 patients who achieved CR after treatment with TKIs and reported lower survival rates after discontinuation of TKIs treatment. However, it is important to note that these

studies involved a relative small numbers of patients. In this regard, the report from Buchler *et al*. (1) contains the largest series of patients who achieved CR after medical treatment for mRCC reported to date (n=100) allowing sub analyses in specific subgroup of individuals.

Interestingly, the majority of patients enrolled by Buchler *et al*. (1) were treated with sunitinib, a generally recognized standard first-line treatment (19). The second most represented treatment group was of individuals treated with sorafenib, which (7,19) is no longer used as first-line therapy. However, it still represents a viable option for second or third-line therapy, given that OS rates resulted not inferior to other treatment regimens (20).

As advanced medical therapies such as anti-VEGF agents are associated with notable side-effects (21), questions remain about the usefulness of continued therapy after CR. From a clinical point of view, discontinuation of first-line anti-VEGF therapy might also be associated with reduced resistance towards antiangiogenetic drugs. Although Buchler *et al*. (1) did not report data about second-line treatments, they reported that patients who discontinued anti-VEGF treatment after CR seemed to have better PFS rates after initiation of second-line therapy. Clearly, the potential advantage of treatment discontinuation after CR for better cancer control at second-line treatment still needs to be properly addressed, since several treatments with proven efficacy in second-line setting exist (6,22,23).

In conclusion, Buchler *et al*. should be commended for calling attention to the group of mRCC patients who achieve CR after medical therapy. They provided useful information with significant implications for future research and ongoing trials. Although, further efforts are needed to better determine the best clinical management for those mRCC patients who experienced CR after treatment.

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