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"Beyond the Abstract," Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: A RECORD-1 subgroup analysis, by Sergio Bracarda, MD

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Drug Tolerability in the Choice of Second-Line Therapy for Metastatic Renal Cell Carcinoma

Sequential treatment with targeted therapies is the current standard of care for patients with metastatic renal cell carcinoma (mRCC).[1, 2, 3, 4] Targeted therapies approved for use in patients with mRCC include the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, the VEGF receptor-tyrosine kinase inhibitors (VEGFr-TKIs) sorafenib, sunitinib, pazopanib, and axitinib, and the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus. VEGF-targeted agents form the first-line standard of care in patients of good or intermediate risk according to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk model. The mTOR inhibitor temsirolimus is recommended in MSKCC poor-risk patients.[5] Systemic treatment options for second-line therapy of VEGFr-TKI-refractory patients include everolimus and axitinib.[4]

Drug tolerability and quality-of-life (QOL) issues are experienced by all patients receiving systemic therapy for mRCC. Adverse event (AE) profiles differ from one targeted agent to another. Hypertension and hand-foot syndrome are more frequently observed in patients receiving VEGFr-TKIs, while pneumonitis and dyslipidemia are more frequently observed in patients receiving mTOR inhibitors.[6] In general, drug-related AEs can be managed throughout therapy, but in some patients, they can lead to drug interruptions or discontinuation, which in some cases translate into reduced efficacy. In a recent meta-analysis of patients treated with sunitinib, those with the highest exposure to drug displayed longer time-to-progression, longer overall survival, a higher probability of response to treatment, and greater reductions in tumor size; this highlights the importance of maintaining patients on recommended dosing and, if possible, avoiding unscheduled dose reductions or interruptions during treatment.[7]

In patients receiving either axitinib or sorafenib following first-line sunitinib in the pivotal AXIS trial supporting the recent approval of axitinib, one or more dose reductions or drug interruptions were reported in 31% and 77% of patients, respectively, in the axitinib arm and 52% and 80% of patients, respectively, in the sorafenib arm.[8] In the pivotal RECORD-1 trial supporting the approval of everolimus, one or more dose reductions or drug interruptions were reported in only 7% and 38%, respectively, of patients receiving everolimus following first-line sunitinib, sorafenib, or both agents.[9,10] Patients receiving either axitinib or sorafenib following first-line sunitinib in the AXIS trial reported higher incidences of AEs than those receiving axitinib or sorafenib after first-line cytokine therapy (***Figures 1 and 2***). These data suggest a possible higher propensity for class-effect toxicity with sequential administration of VEGF-targeted agents. Class-effect AEs reported in the axitinib and sorafenib arms included diarrhea, hypertension, fatigue, palmar-plantar erythrodysesthesia, rash, and alopecia.[8]

Drug tolerability and patient QOL need to be considered carefully by physicians when choosing a second-line agent, especially when a patient has discontinued life-sparing therapy because of unacceptable toxicity. Patients who experience intolerance to VEGFr-TKI

therapy may benefit from switching to an mTOR inhibitor because the AE profile of mTOR inhibitors generally does not overlap with that of VEGFr-TKIs.[10,11,12] In the subgroup analysis of patients in the RECORD-1 trial who were intolerant to a first-line VEGFr-TKI (sunitinib, sorafenib, or both agents), the majority (86.7%) of patients not only tolerated but also benefited from treatment with everolimus. The median progression-free survival (PFS) observed in everolimus-treated patients who were intolerant to previous VEGFr-TKI therapy (5.4 months) was similar to the median PFS of all everolimus-treated patients in RECORD-1 (4.9 months).[10,13] These results provide further evidence that everolimus should be the preferred choice for second-line therapy in mRCC patients intolerant to VEGFr-TKIs.

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Figure 1. Axitinib arm of the AXIS trial.

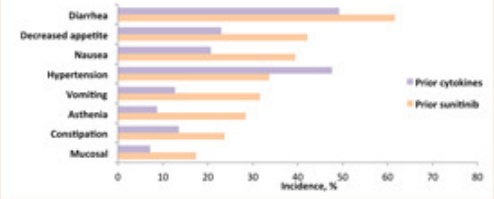
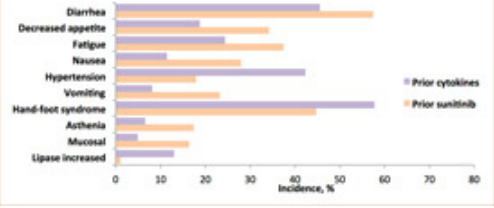


Figure 2. Sorafenib arm of the AXIS trial.



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