The current standard of care for treating metastatic renal cell carcinoma is sequential therapy with vascular endothelial growth factor–targeted agents (i.e., axitinib, bevacizumab, pazopanib, sorafenib, and sunitinib) and mammalian target of rapamycin inhibitors (i.e., everolimus and temsirolimus). To maximize adherence to and persistence with targeted therapy, which should help improve clinical benefit, a clear understanding of the tolerability profiles of these agents and implementation of early, appropriately aggressive adverse event (AE) prevention and management strategies are key. Active and aggressive AE management should improve the quality of life of patients during the course of their treatment. Nurses are in a unique position to educate patients on the potential AEs they may experience and their prevention and management. This article reviews the safety and tolerability of currently available targeted therapies recommended for use in the second-line treatment setting, as well as their management in the context of maximizing clinical outcomes and patient quality of life.