About 63,920 new cases of kidney cancer are expected to be diagnosed in 2014 in the United States (American Cancer Society, 2014), with a median age at diagnosis of 64 years and a higher incidence in men (21 per 100,000 men versus 10.6 per 100,000 women) (Surveillance, Epidemiology, and End Results Program, 2014). About 90% of kidney cancers are renal cell carcinoma (RCC) (American Cancer Society, 2014), for which the five-year relative survival rate increased from 50% in 1975–1977 to 71% in 2001–2007 (Siegel, Naishadham, & Jemal, 2012). This likely resulted from the combined effects of earlier diagnosis and improved therapeutic options (Siegel et al., 2012). The evolution of molecularly targeted therapy has contributed to significant improvement in outcomes for the almost two-thirds of patients with RCC who are either diagnosed with metastatic RCC (mRCC) or experience relapse following surgery for localized disease (American Cancer Society, 2014; National Comprehensive Cancer Network [NCCN], 2014; Siegel et al., 2012). Targeted therapies approved for treating advanced RCC include the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab (used in combination with interferon alpha) (Escudier, Pluzanska, et al., 2007); the VEGF receptor tyrosine kinase inhibitors (VEGFR-TKIs) sunitinib, sorafenib, pazopanib, and axitinib (Escudier, Eisen, et al., 2007; Motzer et al., 2007; Rini, Escudier, et al., 2011; Sternberg et al., 2010); and the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus (Hudes et al., 2007; Motzer et al., 2008). Despite the significant benefit provided by first-line therapies, they are noncurative, and patients ultimately develop resistance and show disease progression. Therefore, sequential treatment with targeted therapies is the current standard of care for treating mRCC (NCCN, 2014).

Although sequential treatment is recognized as the best option for maximizing disease control and survival in mRCC, the optimal therapeutic sequence is unknown (Porta et al., 2012). Given that the primary goals of second-line therapy are to control disease progression and maintain patient quality of life (NCCN, 2014), the choice of second-line therapy should be driven by efficacy, safety, and tolerability. This article reviews the safety and tolerability of 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.