Cytokine-based immunotherapy was the only viable option in metastatic, nonresectable renal cell carcinoma (RCC) for many years. Systemic immunotherapy has become increasingly established as a standard therapy during the last 15 years. In this context, interleukin-2 (IL-2) and interferon-alpha (IFN-alpha) turned out to be the most effective single agents in RCC. Subsequently, the approved subcutaneous application of these compounds was the preferred administration route in Germany. Response rates with cytokine combination therapy were almost similar to those of more aggressive concepts using additional chemotherapeutic agents. Currently, new compounds targeting specific signaling pathways are readily available and have passed clinical testing. Such small molecules like tyrosine kinase inhibitors, monoclonal antibodies, or the mTOR inhibitor CCI-779 may dramatically change the established concepts of systemic RCC treatment. This paper gives an overview of established, current, and evolving concepts of systemic therapy in RCC.