The efficacy of current treatment modalities for stage IV melanoma patients is weak. Therefore, new treatment modalities are urgently needed. The molecular identification of therapeutic targets, which are involved in tumor progression led to the development of new agents. Among the possible targets are molecules of the signal transduction pathway such as Ras, Raf and MEK, the proteasome, histone deacetylases, methyltransferases, and melanoma-induced angiogenesis. Currently, there are numerous phase I-III trials with interesting agents and translational research programs. The most promising results were seen with Sorafenib, a multi-kinase inhibitor, in combination with Carboplatin and Paclitaxel. The US trial in 54 mainly pretreated advanced melanomas demonstrated 37% partial responses and 48% stabilized diseases. Currently, an international and a US/Canadian trial are evaluating this approach in metastatic melanoma patients. Regarding other molecules, it is unclear yet, whether they have a potential as a monotherapy or more likely as combinations with other molecules that interfere with the same pathways or alternative anti-tumor mechanisms. Among these are histone deacetylase inhibitors like MS-275 and integrin receptor inhibitors like Vitaxin (Medi-522) or CNTO-95. Another interesting approach is the augmentation of T-cell responses by the use of CTLA-4 antibodies, which inhibit regulatory T-lymphocytes. Early trials demonstrated efficacy particularly in patients, who developed autoimmune phenomena during treatment. Phase III trials using CTLA-4 antibodies alone, combined with vaccination or Dacarbazine are underway.In conclusion, several different treatment approaches are currently under evaluation, which have in principal the capability to define better standards of care.