Melanoma is one of the most aggressive skin cancers and originates from the oncogenic transformation of melanocytes. Its incidence has been continuously increasing in the last decade and it is often inclined to metastasize, leading to about 75% of skin cancer-related deaths. For more than 40 years, few treatment options were available for melanoma and these therapies did not increase the overall survival of patients with advanced melanoma. All clinical trials during that time were unsuccessful. Over the past 10 years, increased biological understanding and access to innovative therapeutic substances have transformed advanced melanoma into a new oncological model for treating other solid cancer types. Treatments that target BRAF mutations using selected BRAF inhibitors combined with MEK inhibitors have significantly improved response and overall survival. Furthermore melanoma has developed into a prototype for testing checkpoint-modulating agents such as anti-CTLA4 or PD1/PDL1-inhibitors, which has increased hope for long-term survival of patients with advanced melanoma.