Despite progress in the therapeutic management of patients with squamous cell carcinoma of the head and neck (SCCHN), the mortality rate of patients presenting with advanced disease remains high. One approach to improve treatment efficacy is to add novel molecular targeted agents to the classical treatment regimens. Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) have shown clinical benefits in palliative and curative settings. However, only a minority of patients presenting with recurrent or metastatic (R/M) SCCHN have meaningful tumor regression with these agents and virtually all who do develop acquired tumor resistance after a few months of treatment. For these reasons, other inhibitors of EGFR or molecules that interfere with known molecular pathways activated in squamous cell carcinoma of the head and neck are of considerable interest, either as single agents or in combination with other treatment modalities. Recently, deep sequencing technology has allowed a better characterization of the implicated genes. Somatic mutations in TP53 (47–72%), NOTCH1 (14–19%), CDKN2A (9–22%), PIK3CA (6–21%), FBXW7 (5%), HRAS (4–8%), FAT1 (23%) and CASP8 (8%) have been reported. Beside these mutations, some genes or their related proteins have been found to be altered by other mechanisms (amplification, deletion, epigenetic). Altogether, activating mutations in classical oncogenes seem relatively rare in SCCHN and most of the genetic alterations occur in tumor suppressor genes. These findings are important for the further development of novel therapies for SCCHN although developing new compounds to restore the activity of altered tumor suppressor genes is extremely challenging. In this review, we will discuss the different molecular therapeutic approaches explored in SCCHN. We will also briefly outline new trial designs that could be used to accelerate the investigation of emerging therapeutic agents in this disease.