UCSF

UC San Francisco Previously Published Works

Title

Emerging tyrosine kinase inhibitors for head and neck cancer

Authors

Long, Zhen

Grandis, Jennifer R

Johnson, Daniel E

Emerging tyrosine kinase inhibitors for head and neck cancer

Zhen Long,

Jennifer R. Grandis,

Daniel E. Johnson[*]

Department of Otolaryngology – Head and Neck Surgery, University of California, San Francisco, California, USA

Abstract

Introduction: Conventional regimens for head and neck squamous cell carcinoma (HNSCC) are limited in efficacy and are associated with adverse toxicities. Food and Drug Administration (FDA) approved molecular targeting agents include the HER1 (EGFR)-directed monoclonal antibody cetuximab and the immune checkpoint inhibitors nivolumab and pembrolizumab. However, clinical benefit is only seen in roughly 15–20% of HNSCC patients treated with these agents. New molecular targeting agents are needed that either act with monotherapeutic activity against HNSCC tumors or enhance the activities of current therapies, particularly immunotherapy. Small molecule tyrosine kinase inhibitors (TKIs) represent a viable option towards this goal.

Areas covered: This review provides an update on TKIs currently under investigation in HNSCC. We focus our review on data obtained and trials underway in HNSCC, including salivary gland cancers and nasopharyngeal carcinomas, but excluding thyroid cancer and esophageal cancer.

Expert opinion: While some emerging TKIs have shown clinical benefit, the positive effects have, largely, been modest. The design of clinical trials of TKIs has been hampered by a lack of understanding of biomarkers that can be used to define patient populations most likely to respond. Further preclinical and translational studies to define biomarkers of TKI response will be critically important.

Keywords

head and neck squamous cell carcinoma; tyrosine kinase inhibitor; immunotherapy; receptor tyrosine kinase

[*]**Corresponding author:** Daniel E. Johnson, Tel: 415-502-3470, Daniel.Johnson@ucsf.edu.

1.0 Background

HNSCC is a common cancer that frequently results in lethality. Approximately 50–60 thousand new cases of HNSCC are diagnosed each year in the United States, and worldwide these numbers approach 1 million new cases per year (1). In the United States, the prevalence of HPV-negative HNSCC continues to decline, associated with a decrease in tobacco consumption, but the prevalence of HPV-positive HNSCC is steadily rising, particularly among younger adults and males. Risk factors associated with HPV-negative HNSCC include tobacco use, exposure to environmental pollutants, excessive alcohol consumption, and chewing of areca nut products (eg. betel quid), a culturally ingrained practice in many parts of the world (1). In view of these common risk factors, it is highly likely that development of HPV-negative HNSCC will continue to be a significant worldwide problem for years to come.

Conventional, standard-of-care approaches for the treatment of HNSCC, including surgery, radiation, and/or chemotherapy, frequently result in disfigurement, deficiencies in speech and swallowing, and a myriad of other adverse toxicities. The development and FDA approval of the molecular targeting agents cetuximab (2, 3), nivolumab (4), and pembrolizumab (5–7) has led to significant improvement in outcomes for HNSCC, although only minority of patients currently experience clinical benefit from these approaches. Efforts to develop new agents that will be well-tolerated and effective in the treatment of HNSCC have focused on drugs that will enhance anti-tumor immunity, inhibit tumor angiogenesis, or directly inhibit the proliferation and survival of the tumor cells.

The HNSCC tumor microenvironment is often characterized as highly immunosuppressive, and the balance of anti-tumor versus immunosuppressive immune cells in this microenvironment is associated with patient prognosis (8–11). FDA-approved nivolumab and pembrolizumab recognize and inhibit the immune checkpoint protein PD-1 on the surface of T-cells, stimulating the anti-tumor activity of these cells. This forms the basis for the clinical benefit of these immunotherapy drugs in HNSCC. However, it remains unknown why only a minority of patients respond to these drugs, and how resistance develops. One hypothesis is that overexpression or hyperactivation of receptor tyrosine kinases (RTKs) on tumor cells renders these cells resistant to the action of cytotoxic T-cells (12). Hence, targeted inhibition of these RTKs may prove an effective means for broadening the use and effectiveness of immunotherapies.

HNSCC tumor cells overexpress a broad variety of RTKs. For example, HER1 (EGFR) is overexpressed on 80–90% of HNSCC tumors, and it's overexpression is associated with poor prognosis (13, 14). This observation led to the development of cetuximab for HNSCC treatment (2, 3), although, strikingly, the levels of HER1 expressed on tumor cells do not correlate with response to cetuximab. Other RTKs that may be overexpressed or hyperactivated by HNSCC cells include other members of the HER family (HER2, HER4) and members of the FGFR, VEGFR, and PDGFR families, as well as c-MET. Activation of these RTKs leads to activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and STAT3 signaling pathways. These pathways induce the expression of genes that drive cellular proliferation and survival, migration, invasion, and metastasis. Additionally, activation of

these pathways in tumor cells represents a common mechanism of drug resistance. Thus, efforts to develop inhibitors of these RTKs is a plausible strategy for limiting their oncogenic effects in HNSCC tumors.

HNSCC tumor cells and associated stromal cells also produce abundant levels of growth factors, such as VEGF and FGFs, that induce new blood vessel growth (angiogenesis), supplying the tumor with oxygen and nutrients. The ability to induce angiogenesis is dependent on the activity of specific growth factor receptors on the surface of endothelial cells, including RTKs in the FGFR, VEGFR, and PDGFR. Thus, targeting of these RTKs can reduce tumor angiogenesis, and thereby inhibit tumor growth.

Two general approaches are used to develop inhibitors of RTKs. The first approach involves the development of antibodies, such as cetuximab, that block the binding of growth factors or cytokines to their cognate RTK or otherwise interfere with RTK function. The other approach involves the generation of small organic molecules that inhibit the intrinsic tyrosine kinase activities of RTKs. These small molecules are referred to as tyrosine kinase inhibitors (TKIs) and generally function by disrupting ATP binding to the kinase domain. A broad number of these TKIs have now been developed and new TKIs are emerging frequently. Given the potential of these TKIs to inhibit tumor growth, invasion, metastasis, and angiogenesis, as well as their potential to enhance anti-tumor immunity, they continue to be actively investigated in cancer preclinical models and in the clinic, alone and in combination with other agents. Some of the TKIs under investigation are specific for a single RTKs, while others, called multi-targeted TKIs, inhibit several different RTKs. In this review we summarize recent investigations of TKIs in HNSCC.

2.0   Medical need

HNSCC is now understood to be comprised of two distinct cancers: 1) those associated with prior infection with the human papilloma virus (HPV) known as HPV-positive or; 2) those associated with known risk factors including tobacco and alcohol (HPV-negative)(1). While the prognosis of HPV-positive HNSCC is much better than HPV-negative HNSCC, without widespread vaccination prior to HPV exposure, the incidence of oropharyngeal cancers associated with HPV is rapidly increasing. At present, there are no selective therapies for HPV-positive HNSCC. Given the improved survival of HPV-positive HNSCC, studies to date have compared the efficacy of lower doses of chemotherapy and/or radiation to achieve the same outcomes.

Newly diagnosed HNSCC without distant metastasis is treated with surgery followed by adjuvant radiation or chemoradiation (oral cavity) or chemoradiation (pharynx or larynx) (1). The FDA approval of cetuximab in 2006 highlighted the importance of the HER1 (EGFR). However, this agent tends to be used in combination with radiation in patients who cannot tolerate the known toxicities associated with platinum chemotherapy. While the 2016 FDA-approval of immune checkpoint inhibitors (ICIs) provided immunotherapy options, only a minority of HNSCC patients will respond to cetuximab or ICIs. Given that overexpression and hyperactivation of receptor and non-receptor tyrosine kinases is common

in most HNSCC tumors, investigation of TKIs is a rational strategy to identify new, more effective, and/or less toxic agents.

TKIs are being investigated as part of multimodality therapy for newly diagnosed and/or recurrent or metastatic (R/M) HNSCC. If orally available TKIs with limited toxicity can replace systemic chemotherapy and/or allow dose-reduction of radiation or chemotherapy, that would be a therapeutic advance for both HPV-positive and HPV-negative HNSCC.

3.0 Existing treatment

Surgical resection with curative intent remains the primary therapeutic approach for oral cavity cancers (1). Most cancers that arise in the mouth can be removed with minimal morbidity with the exception of resections that involve the root of the tongue (such as a total glossectomy) and/or vascularized flap reconstruction. Neck dissection to remove the cervical lymph nodes (generally a selective or functional dissection to preserve other anatomic structures) is usually performed in conjunction with resecting the primary tumor to more accurately stage the tumor and remove any metastatic deposits in the neck. Despite extensive investigation of radiographic imaging and sentinel lymph node biopsy to avoid surgery for clinical N0 necks, neck dissections are still commonly performed in conjunction with primary tumor resection (15, 16).

Treatment options for HNSCC have changed little over the past several decades with the exception of the introduction of cetuximab in 2006 and ICIs in 2016 (1). Despite ubiquitous HER1 (EGFR) expression in HNSCC tumors, only a subset of patients will respond to cetuximab-containing regimens. For tumors that arise in the pharynx or larynx, chemoradiation (generally with platinum) remains the primary treatment approach. Cetuximab is generally reserved for patients whose co-morbidities preclude administration of platinum. ICIs are indicated in the setting of PD-L1 expression. However, as with cetuximab, only a subset of HNSCC patients will respond to ICI therapy.

Platinum agents (cisplatin or carboplatin) are the most commonly employed chemotherapy drugs for HNSCC treatment. While they have been shown to be active, primarily by sensitizing tumors to radiation, platinum toxicity limits their utility. The most common side effects of platinum agents include neurotoxicity (including hearing loss) and nephrotoxicity. Studies are underway to test the impact of agents which mitigate platinum toxicity in preclinical models, such as atorvastatin (17).

External beam radiation alone remains the primary modality for early vocal fold HNSCC. Radiation in combination with platinum or cetuximab is generally administered for pharyngeal or laryngeal HNSCC. To reduce the well-known toxicity of radiation to structures in the radiation fields, intensity-modulated radiation therapy (IMRT) has emerged as the gold standard, administered five times a week for 6–7 weeks. More concentrated radiation approaches administered for a shorter duration such as stereotactic body radiotherapy (SBRT) have been studied (18).

To date, TKIs alone or in combination with other agents, have not demonstrated improved outcome compared with standard of care. A number of trials are ongoing to determine the role of agents that target kinases, which are present and activated in HNSCC.

4.0 Current research goals

In this review we summarize recent preclinical and clinical findings (2018-present) for all TKIs currently under clinical investigation in HNSCC. Table 1 includes all 15 TKIs we investigated, along with their molecular targets and their current stage of clinical development in HNSCC, including salivary gland tumors, and nasopharyngeal carcinomas. Figure 1 provides schematic depiction of the site of action of these 15 TKIs in cell signaling pathways that are key to tumor cell proliferation and survival, suppression of anti-tumor immunity, and induction of angiogenesis.

5.0 Scientific rationale

HNSCC tumor cells are characterized by hyperproliferation, enhanced resistance to cell death stimuli, and the capacities to inhibit anti-tumor immunity and promote angiogenesis. Each of these phenotypic characteristics contributes to the transformed nature of HNSCC cells and, ultimately, promotes tumor growth and poor clinical outcomes. Notably, each of these oncogenic phenotypes is strongly driven by signaling via receptor and intracellular tyrosine kinases in the tumor cells, tumor-associated stromal cells, and endothelial cells. Thus, there is strong rationale for inhibiting tyrosine kinases in the tumor microenvironment as a therapeutic approach for treating patients with HNSCC. Indeed, in 2006, cetuximab, a monoclonal antibody against the RTK HER1 (EGFR), was the first molecular targeting agent approved by the FDA for use in HNSCC (2).

In addition to antibodies directed against cell surface RTKs, a large number of small molecule inhibitors, termed TKIs, of RTKs and cellular tyrosine kinases have been developed and are currently undergoing clinical evaluation. A subset of these TKIs have recently, or are currently, undergoing evaluation in HNSCC, alone or in combination with other agents. As results are generated from both preclinical studies and clinical studies of these TKIs it is important to evaluate whether these drugs: i) exhibit activity as monotherapy, ii) enhance the activity of other agents currently used in HNSCC treatment, and iii) are associated with adverse toxicities when used either alone or in combination with other agents. This review provides a summary of recent data in HNSCC with emerging TKIs.

6.0 Competitive environment

6.1 Afatinib

Afatinib (Gilotrif) is a pan-EGFR irreversible TKI that targets HER1 (EGFR/ERBB1), HER2 (ERBB2), and HER4 (ERBB4). Approved for use in HER1 mutant NSCLC, afatinib has been extensively tested in HNSCC preclinical models and clinical trials. Many studies have reported the anti-tumor impact of afatinib in HNSCC preclinical models, including models of drug-resistance (19, 20). However, given the extensive clinical data, we will focus the discussion on the more recently published clinical trials.

In a pre-operative window-of-opportunity trial, afatinib was well tolerated and most patients demonstrated a metabolic response as assessed by FDG-PET scanning (NCT01538381)(21). Several groups have studied the role of afatinib in the adjuvant setting following surgical resection with curative intent. In a Phase I trial, afatinib was added to post-operative radiation therapy, with or without docetaxel (22). The regimen was difficult to tolerate and unlikely to be advanced. In the Phase III randomized, double-blind, placebo-controlled LUX-Head & Neck 2 trial, afatinib did not improve survival and was associated with adverse events. Therefore, the benefit of afatinib in the adjuvant setting is likely limited.

Fanconi anemia (FA) is a rare genetic disease characterized by a high incidence of HNSCC. Due to their germline DNA repair defects, patients with FA cannot tolerate standard chemotherapy. Afatinib showed activity in a FANCA-deficient cancer tumor cell line and a trial is underway to test the toxicity and efficacy of this agent in FA-HNSCC patients in Europe (23).

Several studies have investigated afatinib in R/M HNSCC. In the Phase III LUX-Head and Neck 1 trial (LH&N1; NCT01345682), second-line afatinib improved progression-free survival (PFS) versus methotrexate in patients with R/M HNSCC (24). Similar findings were observed in Asian HNSCC patients in a separate trial (NCT01856478)(25). In the ALPHA study (NCT03695510), patients received afatinib in combination with pembrolizumab in cisplatin-refractory HNSCC, with some evidence of activity to warrant further testing (26).

Afatinib has been incorporated into induction chemotherapy regimens. One group looked at afatinib in combination with ribavirin, paclitaxel and carboplatin in HPV-positive HNSCC and reported the combination to be safe and well-tolerated (27).

Overall, afatinib has been extensively studied in HNSCC with many trials still ongoing (Table 1). To date, it has shown promise as second-line therapy for R/M HNSCC and may be safe and effective in FA-associated HNSCC.

6.2 Anlotinib

Anlotinib is an orally bioavailable multi-targeted TKI that inhibits VEGFR1–3, FGFR1–4, c-KIT, and PDGFRs (28–30). Preclinical studies have shown that anlotinib inhibits the proliferation of tumors cells and HUVECs and is anti-angiogenic (28, 29). Anlotinib has been evaluated in clinical studies of NSCLC, renal cell carcinoma, thyroid cancer, gastric cancer, hepatocellular carcinoma, soft tissue sarcoma, esophageal squamous cell carcinoma, and small cell lung cancer (30). In 2018, the Chinese Food and Drug Administration approved anlotinib as a third-line therapy for advanced refractory NSCLC. Preclinical studies of anlotinib in HNSCC cell lines have demonstrated inhibition of cell growth associated with induction of apoptosis and inhibition of the PI3K/AKT signaling pathway (31–33). Treatment of three HNSCC PDX models with anlotinib reduced tumor cell growth *in vivo* (31). The combination of anlotinib and pembrolizumab is being investigated in a Phase II trial of R/M HNSCC (NCT04999800), and as monotherapy in head and neck adenocarcinomas (NCT04910854)(Table 1). Additionally, it is being investigated in Phase II trials in nasopharyngeal carcinoma as monotherapy (NCT03906058), and in combination with chemotherapy (NCT05232552) or toripalimab (NCT04996748).

6.3 Axitinib

Axitinib (Inlyta) is an oral TKI that exhibits potent activity against VEGFR1–3, and reduced activity against PDGFR and c-KIT (34–36). Preclinical studies of axitinib have demonstrated anti-tumor and anti-angiogenic activity in multiple cancer models. Axitinib has been approved by the FDA for advanced renal cell carcinoma. Additionally, the combination of axitinib and pembrolizumab has been approved as first-line therapy for patients with advanced renal cell carcinoma, and the combination of axitinib and avelumab has also been approved for use in advanced renal cell carcinoma. A Phase II trial of axinitib in patients with nasopharyngeal carcinoma who had progressed on platinum-based therapy demonstrated a favorable safety profile, with only limited occurrence of grade 3/4 toxicities. Of 37 evaluable patients, the clinical benefit rate (defined as complete response, partial response, or stable disease for more than 3 months according to RECIST criteria) was 78.4% after 3 months and 43.2% after 6 months (37). A Phase II trial of axitinib in 26 patients with R/M salivary gland carcinomas reported 2 partial responses, 13 with stable disease, and 11 with progressive disease, and failed to meet the primary endpoint (38). Swiecicki *et al.* (39, 40) have reported results of a Phase II trial of axitinib in heavily-pretreated, R/M HNSCC. Of 28 evaluable participants, the median overall survival was 9.8 months, with 70% surviving at 6 months, demonstrating clinical efficacy. Although the mechanism remains incompletely understood, greater responses were observed in patients with alterations in components of the PI3K signaling pathway (75% versus 17%). Axitinib is currently being investigated in Phase II trials of HNSCC (NCT02762513) and salivary gland cancers (NCT02857712)(Table 1).

6.4 Cabozantinib

Cabozantinib (Cabometyx) is an orally bioavailable multi-targeted TKI, which targets VEGFR2, c-MET, and RET (41–43). In preclinical models representing multiple types of cancer, cabozantinib has been shown to inhibit migration, tumor growth and angiogenesis, and metastasis (41, 43). The FDA has approved the use of cabozantinib for previously untreated advanced renal cell carcinoma, previously treated hepatocellular carcinoma, and previously treated radioiodine-refractory differentiated thyroid cancer. Additionally, in 2021 FDA approved the combination of cabozanitinib plus nivolumab as first-line therapy for advanced renal cell carcinoma. A Phase II single-center study of cabozanitinib in R/M salivary gland cancer (NCT03729297) was closed prematurely due to cabozanitinib-associated wound complications particularly in areas of prior irradiation (44). Phase II trials in advanced HNSCC of cabozanitinib in combination with nivolumab (NCT05136196) or cabozanitinib in combination with pembrolizumab (NCT03468218) are ongoing (Table 1). In addition, there are several Phase I trials in HNSCC that incorporate cabozanitinib (NCT03170960, NCT03667482, NCT04514484).

6.5 Dacomitinib

Dacomitinib (Vizimpro) is a pan-HER (ERRB) inhibitor, whose targets include HER1 (EGFR/ERBB1), HER2 (ERBB2) and HER4 (ERBB4). It is especially active in the setting of HER1 (EGFR) tyrosine kinase mutations and is FDA approved for use in NSCLC.

There are a few reports of the anti-tumor effects of dacomitinib in HNSCC preclinical models, alone and in combination with other agents and modalities including radiation (45, 46). A Phase I trial of dacomitinib in combination with cisplatin and radiation showed that the regimen was feasible but the value of adding dacomitinib to standard of care was unclear (47). Two trials that include dacomitinib are ongoing in HNSCC (NCT04946968, NCT00768664)(Table 1). In the meantime, the role of this agent in HNSCC therapy remains undetermined.

6.6 Dasatinib

Dasatinib (Sprycel) is a multi-target tyrosine kinase inhibitor, whose targets include BCR-ABL and SRC family kinases (SFKs), among various cancer kinases. Overexpression/ hyperactivation of SFKs and the crosstalk between EGFR and SFKs in HNSCC has provided the most compelling rationale to study these agents in this malignancy (48–50). Many groups have described the anti-tumor impact of dasatinib, alone or in combination with other agents in HNSCC preclinical models (51–53). Dasatinib alone demonstrated no activity in a window-of-opportunity trial (48) or in recurrent or metastatic HNSCC (54).

Based on compelling results in our HNSCC preclinical models, we undertook a Phase II clinical trial of dasatinib plus cetuximab in cetuximab-resistant HNSCC (55). We found that serum IL6 levels served as predictive biomarkers to this regimen and the trial was modified to include serum high IL6 as an additional inclusion criteria.

Without predictive biomarkers, the role of dasatinib for HNSCC therapy remains unknown.

6.7 Dovitinib

Dovitinib is an oral multi-targeted TKI with low nanomolar activity against FLT3, c-KIT, FGFR1, FGFR3, and VEGFR1–4 (56). A large number of clinical trials incorporating dovitinib are underway in a variety of hematologic and solid tumor malignancies, and a new drug application has been submitted for dovitinib as a third-line therapy for renal cell carcinoma. Preclinical studies in HNSCC have demonstrated dovitinib inhibition of cell line proliferation, and inhibition of tumor growth concomitant with reduced metastasis to regional lymph nodes (57–61). Dovitinib is not currently being evaluated in HNSCC.

6.8 Erlotinib

Erlotinib (Tarceva), like gefitinib (Iressa), is a reversible TKI that primarily targets HER1 (EGFR). It has been studied extensively in HNSCC preclinical models and clinical trials. Both agents block HER1 tyrosine phosphorylation and oncogenic properties such as proliferation, migration and invasion *in vitro* (62). Many studies have explored candidate predictive biomarkers to erlotinib since HER1 is rarely mutated in HNSCC and expression levels have not proven to serve as reliable indicators of erlotinib response (63, 64).

Most clinical trials have focused on combination therapy including erlotinib, given the very modest clinical activity of this agent in unselected HNSCC populations. In a single, Phase II study adding erlotinib to cisplatin and docetaxel in recurrent or metastatic HNSCC, improved response rates compared with historical controls were observed, supporting further

testing (65). Another group tested the impact of dual HER1 blockade with cetuximab and erlotinib in combination with the angiogenesis inhibitor bevacizumab in a Phase I trial which included 10 HNSCC patients and reported that the regimen was well tolerated and conferred clinical benefit (66). A Phase I study tested the impact of adding erlotinib to an induction chemotherapy regimen of cisplatin, docetaxel, and 5-FU followed by cisplatin, bevacizumab and erlotinib with concurrent radiotherapy for advanced HNSCC and reported that while the regimen was active, excessive toxicity prevented further clinical testing (67). Another study found no impact of erlotinib on clinical outcomes in a trial comparing neoadjuvant erlotinib with platinum-docetaxel vs. placebo with platinum-docetaxel in stage III-IVB OSCC patients (68). Several studies conducted in India have incorporated erlotinib into combination oral metranomic chemotherapy regimens with evidence of tolerability and clinical activity in both the palliative (69) and induction settings (70).

We previously reported an exceptional HNSCC responder to single agent erlotinib linked to a relatively rare somatic MAPK1 mutation (71). While erlotinib continues to be investigated in HNSCC and nasopharyngeal carcinoma (Table 1), a clear role for the use of this agent in the absence of more prevalent predictive biomarkers, remains undetermined.

6.9 Gefitinib

HER1 (EGFR) is amplified and/or overexpressed in the majority of HNSCC tumors. Gefitinib is one of the first HER1 TKIs to be studied and FDA-approved in HER1-mutant NSCLC, it has also been extensively studied in HNSCC. In general, gefitinib has been shown to inhibit HER1 tyrosine phosphorylation and reduce HNSCC proliferation *in vitro*, an effect that is enhanced by the addition of chemotherapy (72). The development of drug resistance has limited the impact of gefitinib in HNSCC and many studies have explored ways to improve the therapeutic benefits of gefitinib by combining the drug with other agents, including HDAC inhibitors and Aurora kinase inhibitors (73, 74). However, no synergistic combinations have advanced to clinical testing.

Despite activity in preclinical models, gefitinib has not demonstrated robust activity in HNSCC patients, especially as single agent therapy (75). When comparing to methotrexate, an FDA-approved agent in HNSCC, gefitinib was only marginally better in terms of overall response and safety (76). Without positive Phase III clinical trial results, it is unlikely that gefitinib will prove useful for HNSCC patients.

6.10 Lapatinib

Although HER1 (EGFR/ERBB1) is the most highly overexpressed HER family member in HNSCC, other HER receptors, including HER2 (ERBB2) are also detected to some degree in a subset of HNSCCs. Lapatinib (Tykerb) is a reversible TKI that targets both HER1 and HER2. Lapatinib has been studied in HNSCC preclinical models as well as in clinical trials. Like other EGFR TKIs, lapatinib has been shown to inhibit EGFR signaling and demonstrate anti-cancer properties in HNSCC preclinical studies. Drug resistance has limited clinical development of this agent and several studies have explored mechanisms to determine more effective combination strategies (77).

A series of clinical trials have explored the impact of lapatinib delivered in the neoadjuvant setting, prior to surgery. In one Phase II trial, HNSCC patients were treated with weekly carboplatin, paclitaxel, and daily lapatinib for 6 weeks followed by surgical resection. The regimen was well tolerated with a high response rate (78). A second trial from the same group of investigators studied a combination of carboplatin, paclitaxel and daily lapatinib followed by transoral surgery and neck dissection. The regimen was feasible with excellent survival outcomes (79).

Like the other EGFR TKIs, lapatinib appears to be safe and active in HNSCC although the precise role of this agent in HNSCC therapy remains unknown. There are three ongoing Phase II trials in HNSCC that incorporate lapatinib (NCT0171658, NCT01044433, NCT01612351)(Table 1).

6.11 Lenvatinib

Lenvatinib (Lenvima) is a multi-targeted TKI that inhibits VEGFR1–3, as well as other RTKs, including FGFR1–4, c-KIT, PDGFR, and RET (80, 81). The SELECT trial was a randomized, double-blind Phase III investigation of lenvatinib versus placebo in 392 patients with radioiodine-refractory differentiated thyroid cancer (82, 83). This study demonstrated that lenvatinib treatment was associated with a substantial increase in PFS relative to treatment with placebo (p<0.001; median PFS with lenvatinib was 18.3 months versus 3.6 months with placebo). Subsequently the FDA approved lenvatinib for differentiated thyroid cancer, as well as advanced renal cell carcinoma, and unresectable hepatocellular cancer. Preclinical studies in mouse models of brain, breast, and pancreatic cancer demonstrating upregulation of PD-L1 in response to VEGFR inhibition and enhancement of responses with the combination of VEGFR inhibitors and anti-PD-L1 (84) provided the rationale for combining lenvatinib with immune checkpoint inhibitors. This led to FDA approval of lenvatinib in combination with pembrolizumab in endometrial cancer, and as a first-line treatment for advanced renal cell cancer. The impact of this combination of HNSCC has recently been reported from the Phase II expansion cohort of a Phase IB/II trial of lenvatinib (20 mg/day)/pembrolizumab (200 mg IV every 3 weeks) in patients with selected advanced solid tumors (NCT02501096), including HNSCC (85). The overall response rate for HNSCC at 24 weeks was 36% (8/22), which compares favorably with the overall response rate for either agent alone. A different trial of 14 HNSCC patients in Taiwan observed an objective response rate to the lenvatinib/pembrolizumab combination of 28.6% (86). A Phase II trial has evaluated lenvatinib in R/M adenoid cystic carcinoma (87). Of 32 evaluable patients, 5 exhibited a partial response and 24 had stable disease. Eighteen patients discontinued treatment due to lenvatinib-related effects, with the most common being hypertension and oral pain. Toxicities were considered similar to those previously observed and required monitoring and management of patients. There are four ongoing clinical studies in HNSCC that incorporate lenvatinib (Table 1).

6.12 Pazopanib

Pazopanib (Votrient) is an oral multi-targeted TKI that primarily targets VEGFR1–3, PDGFRα, PDGFβ, and c-KIT (88, 89). The anti-tumor effects of pazopanib occur via inhibition of angiogenesis and inhibition of tumor cell growth (89). The FDA has approved

pazopanib for use in advanced renal cell carcinoma and advanced soft tissue sarcoma. Altered liver function and hypertension are relatively common adverse effects and may result in discontinuation of pazopanib treatment (89). A Phase I trial of pazopanib in combination with weekly cetuximab in recurrent or metastatic HNSCC did not reach a maximum tolerated dose and administration of 800 mg/day pazopanib with weekly cetuximab was determined to be feasible (90). Two of 31 evaluable patients achieved a complete response and 9 had a partial response. Moreover, 5/18 patients with platinum-resistant disease and 3/12 with cetuximab-resistant disease exhibited measurable tumor responses. Pazopanib is currently being evaluated in a Phase I trial in HNSCC in combination with cetuximab (NCT01716416) and in a Phase II as monotherapy in salivary gland carcinomas (NCT02393820)(Table 1).

6.11   Poziotinib

Poziotinib is an irreversible, orally bioavailable TKI that targets HER1 (EGFR), HER2, and HER4. Poziotinib is structurally similar to afatinib and dacomitinib, but unlike these inhibitors poziotinib demonstrates activity against mutant HER2 proteins resulting from exon 20 mutations (91–95). Because mutations in exon 20 of the *HER2* gene are relatively common in lung cancer (~3%), poziotinib represents a promising therapeutic option for this patient population. Elamin *et al.* (96) have reported results from a Phase II trial of poziotinib in 30 patients with *HER2* exon 20-mutant NSCLC, 90% of whom had received prior platinum-based therapy (NCT03066206). A promising 27% response rate (via RECIST version 1.1) was observed, along with a 5.5 months median PFS and 15 months median overall survival. Similarly, the ZENITH20–2 multicenter Phase II trial examined poziotinib in 90 pre-treated patients with NSCLC harboring *HER2* exon 20 alterations (NCT03318939). In 90 patients, with a median follow-up of 9 months, the objective response rate was 27.8% and median PFS was 5.5 months (97). Tumor reduction was observed in 74% of patients. A new drug application has been submitted to the FDA for poziotinib in *HER2* exon 20-mutant NSCLC. A Phase II study of poziotinib in 49 patients with heavily pretreated, R/M HNSCC has reported an overall response rate of 22.4%, a median PFS of 4.0 months, and a median overall survival of 7.6 months (NCT02216916) (98).

6.12   Sorafenib

Sorafenib (Nexavar) is an orally bioavailable inhibitor of the VEGFR, PDGFR, and c-KIT tyrosine kinases (99, 100). In addition, sorafenib has the notable distinction of acting to inhibit the serine/threonine kinases C-RAF and B-RAF, including the V600E B-RAF activated mutant commonly found in melanoma. Sorafenib has been approved by the FDA for use in advanced renal cell carcinoma, unresectable hepatocellular cancer, and metastatic differentiated thyroid cancer. Studies of sorafenib in HNSCC preclinical models have shown that the agent acts to sensitize cells to radiation or cisplatin (101–103). A study by the Southwest Oncology Group evaluated sorafenib monotherapy in a Phase II setting of chemotherapy naïve patients with recurrent or metastatic HNSCC (104). This trial found that response rates were low, with one confirmed and two unconfirmed partial responses among 41 evaluable patients. A different trial of sorafenib in recurrent and/or metastatic HNSCC observed one patient with a partial response and 12 with stable disease among 23

evaluable participants (105). Another Phase II trial in R/M HNSCC found that addition of sorafenib to cetuximab did not improve clinical benefit (106). An additional study of the sorafenib/cetuximab combination (NCT00815295) has been completed, and one completed (NCT02035527) and one ongoing (NCT00494182) trial of sorafenib in combination with conventional chemotherapy are awaiting publication of results.

6.13 Vandetanib

Vandetanib (Caprelsa) is an oral multi-targeted TKI that inhibits VEGFR-2, HER1 (EGFR), and RET (107–109). Vandetanib has been approved by the FDA for use in advanced medullary thyroid cancer. In HNSCC preclinical models vandetanib has been shown to enhance anti-cancer effects *in vitro* and *in vivo* when used in combination with cisplatin, radiation, or photodynamic therapy (110–112). Although a Phase I study of vandetanib plus radiation in patients with locally advanced HNSCC demonstrated tolerability of the treatment regimen (113), a study of vandetanib in combination with cisplatin/radiation (NCT00720083) was terminated early (withdrawal of drug), while a Phase II study of vandetanib plus docetaxel (NCT00459043) yielded unremarkable improvement in PFS (114). A placebo-controlled trial of vandetanib as a chemopreventive agent in patients with premalignant lesions has recently been completed and awaits publication (NCT01414426).

7.0 Conclusion

To date, clinical investigations of TKIs in HNSCC have not yielded substantial improvements in patient outcomes. This has been particularly true when TKIs have been evaluated as monotherapy. However, a few encouraging results have been reported, particularly when TKIs are combined with other agents. For example, positive outcomes have been observed with: i) afatinib as second-line therapy for R/M HNSCC, ii) afatinib in combination with pembrolizumab in cisplatin-refractory HNSCC, iii) axitinib in R/M HNSCC, iv) erlotinib in combination with cisplatin and docetaxel in R/M HNSCC, v) dasatinib plus cetuximab in cetuximab-resistant HNSCC, vi) erlotinib in combination with cetuximab and bevacizumab, and vii) lapatinib in combination with carboplatin and paclitaxel in the neoadjuvant setting. In several trials, addition of TKIs to a standard regimen led to increased adverse toxicities, highlighting the need for careful monitoring in combination studies. Overall, the promise of TKIs for HNSCC therapy remains unclear as most trials have enrolled unselected patient populations with advanced disease. The identification of biomarkers associated with response to TKIs is lagging, but will allow selection of patients most likely to benefit from the use of these convenient, and generally well-tolerated, molecular targeting agents.

8.0 Expert opinion

Despite the strong rationale for inhibition of tyrosine kinases in cancer therapy, and considerable preclinical data demonstrating TKI inhibition of HNSCC tumor growth, results from clinical studies have, largely, been disappointing. No TKIs, including both single-target TKIs and multi-targeted TKIs, have been approved by the FDA for treatment of HNSCC. It is important to acknowledge limitations to current preclinical models. Findings using cell line models are seldom good predictors of response in clinical trials and cell-line

derived xenograft tumors have the same potential for having diverged substantially from the genetics/phenotype of the original primary tumor. The use of patient-derived xenograft (PDX) models, where tumor specimens from the patient are directly implanted into mice, are better avatars of the primary tumor and more preclinical studies should be focused on these models. However, PDX models are grown in immunodeficient mice, thereby lacking an important determinant of tumor growth and response to anti-cancer agents. Organoid models that incorporate immune components may provide an advantage in this regard. The availability of genetically engineered mouse models of HNSCC is very limited, and these models, unlike human HNSCC, are genetically homogenous and live in carefully controlled environments. Models of spontaneously arising HNSCC may prove more representative of human HNSCC, but such models are rare. However, one such model is found in household cats, where oral squamous cell carcinoma (ie. HNSCC) occurs frequently and closely mimics the genetics and histology of human HNSCC (115–127). Feline HNSCC is highly lethal, with no effective therapy. We recommend that clinical trials involving pet cats with HNSCC be done in collaboration with academic centers with veterinary oncology and clinical trials expertise with companion animals.

Another major deficiency in the clinical evaluation of TKIs in HNSCC is that trials are, largely, conducted with unselected patient populations. Preclinical and clinical/translational studies are desperately needed to identify biomarkers that will point to patient populations most likely to respond to TKIs. It is noteworthy that Swiecicki *et al.* (40) observed a markedly higher response to axitinib in patients with alterations in PI3K signaling pathway components, and Stabile *et al.* (55) found that the response to dasatinib plus cetuximab is associated with serum levels of IL6. We strongly recommend that clinical trials of TKIs incorporate rigorous correlative studies that analyze specimens taken before and after treatment, as a means of investigating candidate biomarkers. Since RTKs signal via the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and STAT3 signaling pathways we recommend that activation of these pathways be examined at both the protein and genetic levels. Particular care should be taken to analyze specimens from exceptionally responding patients, as was the case in identifying a mutant MAPK1 protein in an exceptional responder to single-agent erlotinib.

Finally, it is notable that afatinib, and potentially other TKIs, may exhibit activity in FA-associated HNSCC (23). Individuals with FA are at a greater than 500-fold elevated risk of developing HNSCC relative to the general population, and cannot tolerate DNA damaging agents (128). The development of HNSCC in FA patients is uniformly fatal. It is unclear whether FA-HNSCC is markedly distinct from the sporadic HNSCC that occurs in non-FA patients, but the potential utility of TKIs in this patient population would provide a dramatic positive step in the treatment of these individuals.

Funding

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92. doi: 10.1038/s41572-020-00224-3. PubMed PMID: 33243986. [PubMed: 33243986] * This review provides a comprehensive summary of the epidemiology, risk factors, molecular mechanisms of carcinogenesis, and treatment strategies for head and neck squamous cell carcinoma.

2. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567–78. PubMed PMID: 16467544. [PubMed: 16467544] * Results from this trial led to the approval of cetuximab treatment for head and neck squamous cell carcinoma.

3. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, Raben D, Baselga J, Spencer SA, Zhu J, Youssoufian H, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010;11(1):21–8. doi: 10.1016/S1470-2045(09)70311-0. PubMed PMID: 19897418. [PubMed: 19897418]

4. Ferris RL, Blumenschein G Jr., Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW, Gillison ML. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016;375(19):1856–67. doi: 10.1056/NEJMoa1602252. PubMed PMID: 27718784. [PubMed: 27718784]

5. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, Heath K, McClanahan T, Lunceford J, Gause C, Cheng JD, Chow LQ. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016;17(7):956–65. doi: 10.1016/S1470-2045(16)30066-3. PubMed PMID: 27247226. [PubMed: 27247226]

6. Mehra R, Seiwert TY, Gupta S, Weiss J, Gluck I, Eder JP, Burtness B, Tahara M, Keam B, Kang H, Muro K, Geva R, Chung HC, Lin CC, Aurora-Garg D, Ray A, Pathiraja K, Cheng J, Chow LQM, Haddad R. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer. 2018;119(2):153–9. doi: 10.1038/s41416-018-0131-9. PubMed PMID: 29955135; PMCID: PMC6048158. [PubMed: 29955135]

7. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G Jr., Psyrri A, Baste N, Neupane P, Bratland A, Fuereder T, Hughes BGM, Mesia R, Ngamphaiboon N, Rordorf T, Wan Ishak WZ, Hong RL, Gonzalez Mendoza R, Roy A, Zhang Y, Gumuscu B, Cheng JD, Jin F, Rischin D, Investigators K-. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394(10212):1915–28. doi: 10.1016/S0140-6736(19)32591-7. PubMed PMID: 31679945. [PubMed: 31679945]

8. Whiteside TL. Immunobiology of head and neck cancer. Cancer Metastasis Rev. 2005;24(1):95–105. doi: 10.1007/s10555-005-5050-6. PubMed PMID: 15785875. [PubMed: 15785875]

9. Mandal R, Senbabaoglu Y, Desrichard A, Havel JJ, Dalin MG, Riaz N, Lee KW, Ganly I, Hakimi AA, Chan TA, Morris LG. The head and neck cancer immune landscape and its immunotherapeutic implications. JCI Insight. 2016;1(17):e89829. doi: 10.1172/jci.insight.89829. PubMed PMID: 27777979; PMCID: PMC5070962.

10. Nguyen N, Bellile E, Thomas D, McHugh J, Rozek L, Virani S, Peterson L, Carey TE, Walline H, Moyer J, Spector M, Perim D, Prince M, McLean S, Bradford CR, Taylor JM, Wolf GT, Head, Neck SPI. Tumor infiltrating lymphocytes and survival in patients with head and neck

squamous cell carcinoma. Head Neck. 2016;38(7):1074–84. doi: 10.1002/hed.24406. PubMed PMID: 26879675; PMCID: PMC4900934. [PubMed: 26879675]

11. Fang J, Li X, Ma D, Liu X, Chen Y, Wang Y, Lui VWY, Xia J, Cheng B, Wang Z. Prognostic significance of tumor infiltrating immune cells in oral squamous cell carcinoma. BMC Cancer. 2017;17(1):375. doi: 10.1186/s12885-017-3317-2. PubMed PMID: 28549420; PMCID: PMC5446725. [PubMed: 28549420]

12. Engelsen AST, Lotsberg ML, Abou Khouzam R, Thiery JP, Lorens JB, Chouaib S, Terry S. Dissecting the Role of AXL in Cancer Immune Escape and Resistance to Immune Checkpoint Inhibition. Front Immunol. 2022;13:869676. doi: 10.3389/fimmu.2022.869676. PubMed PMID: 35572601; PMCID: PMC9092944.

13. Rubin Grandis J, Melhem MF, Gooding WE, Day R, Holst VA, Wagener MM, Drenning SD, Tweardy DJ. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Natl Cancer Inst. 1998;90(11):824–32. PubMed PMID: 9625170. [PubMed: 9625170] * This preclinical investigation provided foundational evidence that EGFR is overexpressed and correlated with patient survival in head and neck squamous cell carcinoma.

14. Zhu X, Zhang F, Zhang W, He J, Zhao Y, Chen X. Prognostic role of epidermal growth factor receptor in head and neck cancer: a meta-analysis. J Surg Oncol. 2013;108(6):387–97. doi: 10.1002/jso.23406. PubMed PMID: 24038070. [PubMed: 24038070]

15. Earnest-Noble LB, Lipsky RS, Kuhel WI, Kutler DI. Identification of occult metastatic disease via lymphoscintigraphy-guided neck dissection in N0 oral squamous cell carcinoma. Head Neck. 2022;44(7):1596–603. doi: 10.1002/hed.27059. PubMed PMID: 35429187. [PubMed: 35429187]

16. Snyder V, Goyal LK, Bowers EMR, Kubik M, Kim S, Ferris RL, Johnson JT, Duvvuri U, Gooding WE, Branstetter BF, Rath TJ, Sridharan SS. PET/CT Poorly Predicts AJCC 8th Edition Pathologic Staging in HPV-Related Oropharyngeal Cancer. Laryngoscope. 2021;131(7):1535–41. doi: 10.1002/lary.29366. PubMed PMID: 33428218. [PubMed: 33428218]

17. Fernandez KA, Allen P, Campbell M, Page B, Townes T, Li CM, Cheng H, Garrett J, Mulquin M, Clements A, Mulford D, Ortiz C, Brewer C, Dubno JR, Newlands S, Schmitt NC, Cunningham LL. Atorvastatin is associated with reduced cisplatin-induced hearing loss. J Clin Invest. 2021;131(1). doi: 10.1172/JCI142616. PubMed PMID: 33393488; PMCID: PMC7773379.

18. Vargo JA, Ward MC, Caudell JJ, Riaz N, Dunlap NE, Isrow D, Zakem SJ, Dault J, Awan MJ, Higgins KA, Hassanadeh C, Beitler JJ, Reddy CA, Marcrom S, Boggs DH, Bonner JA, Yao M, Machtay M, Siddiqui F, Trotti AM, Lee NY, Koyfman SA, Ferris RL, Heron DE. A Multi-institutional Comparison of SBRT and IMRT for Definitive Reirradiation of Recurrent or Second Primary Head and Neck Cancer. Int J Radiat Oncol Biol Phys. 2018;100(3):595–605. doi: 10.1016/j.ijrobp.2017.04.017. PubMed PMID: 28899556; PMCID: PMC7418052. [PubMed: 28899556]

19. Liu X, Suo H, Zhou S, Hou Z, Bu M, Liu X, Xu W. Afatinib induces pro-survival autophagy and increases sensitivity to apoptosis in stem-like HNSCC cells. Cell Death Dis. 2021;12(8):728. doi: 10.1038/s41419-021-04011-0. PubMed PMID: 34294686; PMCID: PMC8298552. [PubMed: 34294686]

20. De Pauw I, Lardon F, Van den Bossche J, Baysal H, Fransen E, Deschoolmeester V, Pauwels P, Peeters M, Vermorken JB, Wouters A. Simultaneous targeting of EGFR, HER2, and HER4 by afatinib overcomes intrinsic and acquired cetuximab resistance in head and neck squamous cell carcinoma cell lines. Mol Oncol. 2018;12(6):830–54. doi: 10.1002/1878-0261.12197. PubMed PMID: 29603584; PMCID: PMC5983215. [PubMed: 29603584]

21. Machiels JP, Bossi P, Menis J, Lia M, Fortpied C, Liu Y, Lhommel R, Lemort M, Schmitz S, Canevari S, De Cecco L, Guzzo M, Bianchi R, Quattrone P, Crippa F, Duprez T, Lalami Y, Quiriny M, de Saint Aubain N, Clement PM, Coropciuc R, Hauben E, Licitra LF. Activity and safety of afatinib in a window preoperative EORTC study in patients with squamous cell carcinoma of the head and neck (SCCHN). Ann Oncol. 2018;29(4):985–91. doi: 10.1093/annonc/mdy013. PubMed PMID: 29346507. [PubMed: 29346507]

22. Margalit DN, Haddad RI, Tishler RB, Chau NG, Schoenfeld JD, Bakst RL, Misiukiewicz KJ, Gupta V, Posner M, Hanna GJ, Mahmood U, Rawal B, Catalano PJ, Rath L, Bacay A, McHugh P, Rabinowits G. A Phase 1 Study of Afatinib in Combination with Postoperative Radiation Therapy with and Without Weekly Docetaxel in Intermediate- and High-Risk Patients with Resected

Squamous Cell Carcinoma of the Head and Neck. Int J Radiat Oncol Biol Phys. 2019;105(1):132–9. doi: 10.1016/j.ijrobp.2019.04.034. PubMed PMID: 31082494. [PubMed: 31082494]

23. Montanuy H, Martinez-Barriocanal A, Antonio Casado J, Rovirosa L, Ramirez MJ, Nieto R, Carrascoso-Rubio C, Riera P, Gonzalez A, Lerma E, Lasa A, Carreras-Puigvert J, Helleday T, Bueren JA, Arango D, Minguillon J, Surralles J. Gefitinib and Afatinib Show Potential Efficacy for Fanconi Anemia-Related Head and Neck Cancer. Clin Cancer Res. 2020;26(12):3044–57. doi: 10.1158/1078-0432.CCR-19-1625. PubMed PMID: 32005748. [PubMed: 32005748] * These studies led to approval of gefitinib and afatinib by the European Medicines Agency.

24. Haddad R, Guigay J, Keilholz U, Clement PM, Fayette J, de Souza Viana L, Rolland F, Cupissol D, Geoffrois L, Kornek G, Licitra L, Melichar B, Ribaldo Nicolau U, Rauch D, Zanetta-Devauges S, Cohen EEW, Machiels JP, Tahara M, Vermorken J, Geng Y, Zografos E, Gauler T. Afatinib as second-line treatment in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: Subgroup analyses of treatment adherence, safety and mode of afatinib administration in the LUX-Head and Neck 1 trial. Oral Oncol. 2019;97:82–91. doi: 10.1016/j.oraloncology.2019.08.004. PubMed PMID: 31450171. [PubMed: 31450171]

25. Guo Y, Ahn MJ, Chan A, Wang CH, Kang JH, Kim SB, Bello M, Arora RS, Zhang Q, He X, Li P, Dechaphunkul A, Kumar V, Kamble K, Li W, Kandil A, Cohen EEW, Geng Y, Zografos E, Tang PZ. Afatinib versus methotrexate as second-line treatment in Asian patients with recurrent or metastatic squamous cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 3): an open-label, randomised phase III trial. Ann Oncol. 2019;30(11):1831–9. doi: 10.1093/annonc/mdz388. PubMed PMID: 31501887; PMCID: PMC6927323. [PubMed: 31501887]

26. Kao HF, Liao BC, Huang YL, Huang HC, Chen CN, Chen TC, Hong YJ, Chan CY, Chia JS, Hong RL. Afatinib and Pembrolizumab for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (ALPHA Study): A Phase II Study with Biomarker Analysis. Clin Cancer Res. 2022;28(8):1560–71. doi: 10.1158/1078-0432.CCR-21-3025. PubMed PMID: 35046059. [PubMed: 35046059]

27. Dunn LA, Fury MG, Sherman EJ, Ho AA, Katabi N, Haque SS, Pfister DG. Phase I study of induction chemotherapy with afatinib, ribavirin, and weekly carboplatin and paclitaxel for stage IVA/IVB human papillomavirus-associated oropharyngeal squamous cell cancer. Head Neck. 2018;40(2):233–41. doi: 10.1002/hed.24938. PubMed PMID: 28963790; PMCID: PMC6760238. [PubMed: 28963790]

28. Xie C, Wan X, Quan H, Zheng M, Fu L, Li Y, Lou L. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. Cancer Sci. 2018;109(4):1207–19. doi: 10.1111/cas.13536. PubMed PMID: 29446853; PMCID: PMC5891194. [PubMed: 29446853]

29. Lin B, Song X, Yang D, Bai D, Yao Y, Lu N. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRbeta and FGFR1. Gene. 2018;654:77–86. doi: 10.1016/j.gene.2018.02.026. PubMed PMID: 29454091. [PubMed: 29454091]

30. Shen G, Zheng F, Ren D, Du F, Dong Q, Wang Z, Zhao F, Ahmad R, Zhao J. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. J Hematol Oncol. 2018;11(1):120. doi: 10.1186/s13045-018-0664-7. PubMed PMID: 30231931; PMCID: PMC6146601. [PubMed: 30231931]

31. Hu F, Guo L, Yu J, Dai D, Xiong Y, He Y, Zhou W. Using Patient-Derived Xenografts to Explore the Efficacy of Treating Head-and-Neck Squamous Cell Carcinoma With Anlotinib. Pathol Oncol Res. 2021;27:1610008. doi: 10.3389/pore.2021.1610008. PubMed PMID: 34955687; PMCID: PMC8696349.

32. Deng Z, Liao W, Wei W, Zhong G, He C, Zhang H, Liu Q, Xu X, Liang J, Liu Z. Anlotinib as a promising inhibitor on tumor growth of oral squamous cell carcinoma through cell apoptosis and mitotic catastrophe. Cancer Cell Int. 2021;21(1):37. doi: 10.1186/s12935-020-01721-x. PubMed PMID: 33422069; PMCID: PMC7796634. [PubMed: 33422069]

33. Lu Y, Lin J, Duan M, Rui Y, Zheng H, Zhu L, Zhu X, Wei J. Anlotinib Suppresses Oral Squamous Cell Carcinoma Growth and Metastasis by Targeting the RAS Protein to Inhibit the PI3K/Akt Signalling Pathway. Anal Cell Pathol (Amst). 2021;2021:5228713. doi: 10.1155/2021/5228713. PubMed PMID: 34926131; PMCID: PMC8674064.

34. Hu-Lowe DD, Zou HY, Grazzini ML, Hallin ME, Wickman GR, Amundson K, Chen JH, Rewolinski DA, Yamazaki S, Wu EY, McTigue MA, Murray BW, Kania RS, O'Connor P, Shalinsky DR, Bender SL. Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res. 2008;14(22):7272–83. doi: 10.1158/1078-0432.CCR-08-0652. PubMed PMID: 19010843. [PubMed: 19010843]

35. Patson B RBC, Olszanski AJ. Pharmacokinetic evaluation of axitinib. Expert Opin Drug Metab Toxicol. 2012;8(2):259–70. doi: 10.1517/17425255.2012.652947. PubMed PMID: 22248343. [PubMed: 22248343]

36. Kessler ER, Bowles DW, Flaig TW, Lam ET, Jimeno A. Axitinib, a new therapeutic option in renal cell carcinoma. Drugs Today (Barc). 2012;48(10):633–44. doi: 10.1358/dot.2012.48.10.1860768. PubMed PMID: 23110259. [PubMed: 23110259]

37. Hui EP, Ma BBY, Loong HHF, Mo F, Li L, King AD, Wang K, Ahuja AT, Chan CML, Hui CWC, Wong CH, Chan ATC. Efficacy, Safety, and Pharmacokinetics of Axitinib in Nasopharyngeal Carcinoma: A Preclinical and Phase II Correlative Study. Clin Cancer Res. 2018;24(5):1030–7. doi: 10.1158/1078-0432.CCR-17-1667. PubMed PMID: 29301831. [PubMed: 29301831]

38. Locati LD, Cavalieri S, Bergamini C, Resteghini C, Alfieri S, Calareso G, Bossi P, Perrone F, Tamborini E, Quattrone P, Granata R, Galbiati D, Platini F, Orlandi E, Mariani L, Licitra L. Phase II trial with axitinib in recurrent and/or metastatic salivary gland cancers of the upper aerodigestive tract. Head Neck. 2019;41(10):3670–6. doi: 10.1002/hed.25891. PubMed PMID: 31355973. [PubMed: 31355973]

39. Swiecicki PL, Zhao L, Belile E, Sacco AG, Chepeha DB, Dobrosotskaya I, Spector M, Shuman A, Malloy K, Moyer J, McKean E, McLean S, Wolf GT, Eisbruch A, Prince M, Bradford C, Carey T, Worden FP. A phase II study evaluating axitinib in patients with unresectable, recurrent or metastatic head and neck cancer. Invest New Drugs. 2015;33(6):1248–56. doi: 10.1007/s10637-015-0293-8. PubMed PMID: 26453566. [PubMed: 26453566]

40. Swiecicki PL, Bellile EL, Brummel CV, Brenner JC, Worden FP. Efficacy of axitinib in metastatic head and neck cancer with novel radiographic response criteria. Cancer. 2021;127(2):219–28. doi: 10.1002/cncr.33226. PubMed PMID: 33079405. [PubMed: 33079405]

41. Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou YC, Joly AH. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011;10(12):2298–308. doi: 10.1158/1535-7163.MCT-11-0264. PubMed PMID: 21926191. [PubMed: 21926191]

42. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, Cohen EE, Janisch L, Nauling F, Hong DS, Ng CS, Ye L, Gagel RF, Frye J, Muller T, Ratain MJ, Salgia R. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol. 2011;29(19):2660–6. doi: 10.1200/JCO.2010.32.4145. PubMed PMID: 21606412; PMCID: PMC3646303. [PubMed: 21606412]

43. Bentzien F, Zuzow M, Heald N, Gibson A, Shi Y, Goon L, Yu P, Engst S, Zhang W, Huang D, Zhao L, Vysotskaia V, Chu F, Bautista R, Cancilla B, Lamb P, Joly AH, Yakes FM. In vitro and in vivo activity of cabozantinib (XL184), an inhibitor of RET, MET, and VEGFR2, in a model of medullary thyroid cancer. Thyroid. 2013;23(12):1569–77. doi: 10.1089/thy.2013.0137. PubMed PMID: 23705946; PMCID: PMC3868259. [PubMed: 23705946]

44. van Boxtel W, Uijen MJM, Krens SD, Dijkema T, Willems SM, Jonker MA, Pegge SAH, van Engen-van Grunsven ACH, van Herpen CML. Excessive toxicity of cabozantinib in a phase II study in patients with recurrent and/or metastatic salivary gland cancer. Eur J Cancer. 2022;161:128–37. doi: 10.1016/j.ejca.2021.10.033. PubMed PMID: 34920917. [PubMed: 34920917]

45. Williams JP, Kim I, Ito E, Shi W, Yue S, Siu LL, Waldron J, O'Sullivan B, Yip KW, Liu FF. Pre-clinical characterization of Dacomitinib (PF-00299804), an irreversible pan-ErbB inhibitor, combined with ionizing radiation for head and neck squamous cell carcinoma. PLoS One. 2014;9(5):e98557. doi: 10.1371/journal.pone.0098557. PubMed PMID: 24853121; PMCID: PMC4031184.

46. Wilson GD, Wilson TG, Hanna A, Dabjan M, Buelow K, Torma J, Marples B, Galoforo S. Dacomitinib and gedatolisib in combination with fractionated radiation in head and neck cancer. Clin Transl Radiat Oncol. 2021;26:15–23. doi: 10.1016/j.ctro.2020.11.003. PubMed PMID: 33251343; PMCID: PMC7677653. [PubMed: 33251343]

47. Prawira A, Brana-Garcia I, Spreafico A, Hope A, Waldron J, Razak AR, Chen EX, Jang R, O'Sullivan B, Giuliani M, Bayley A, Cho J, Wang L, Perez-Ordonez B, Weinreb I, Siu LL, Hansen AR. Phase I trial of dacomitinib, a pan-human epidermal growth factor receptor (HER) inhibitor, with concurrent radiotherapy and cisplatin in patients with locoregionally advanced squamous cell carcinoma of the head and neck (XDC-001). Invest New Drugs. 2016;34(5):575–83. doi: 10.1007/s10637-016-0367-2. PubMed PMID: 27289242. [PubMed: 27289242]

48. Bauman JE, Duvvuri U, Gooding WE, Rath TJ, Gross ND, Song J, Jimeno A, Yarbrough WG, Johnson FM, Wang L, Chiosea S, Sen M, Kass J, Johnson JT, Ferris RL, Kim S, Hirsch FR, Ellison K, Flaherty JT, Mills GB, Grandis JR. Randomized, placebo-controlled window trial of EGFR, Src, or combined blockade in head and neck cancer. JCI Insight. 2017;2(6):e90449. doi: 10.1172/jci.insight.90449. PubMed PMID: 28352657; PMCID: PMC5358497 exists.

49. Stabile LP, He G, Lui VW, Thomas S, Henry C, Gubish CT, Joyce S, Quesnelle KM, Siegfried JM, Grandis JR. c-Src activation mediates erlotinib resistance in head and neck cancer by stimulating c-Met. Clin Cancer Res. 2013;19(2):380–92. doi: 10.1158/1078-0432.CCR-12-1555. PubMed PMID: 23213056; PMCID: PMC3549019. [PubMed: 23213056]

50. Egloff AM, Grandis JR. Improving Response Rates to EGFR-Targeted Therapies for Head and Neck Squamous Cell Carcinoma: Candidate Predictive Biomarkers and Combination Treatment with Src Inhibitors. J Oncol. 2009;2009:896407. doi: 10.1155/2009/896407. PubMed PMID: 19636423; PMCID: PMC2712676.

51. Lehman CE, Spencer A, Hall S, Shaw JJP, Wulfkuhle J, Petricoin EF, Bekiranov S, Jameson MJ, Gioeli D. IGF1R and Src inhibition induce synergistic cytotoxicity in HNSCC through inhibition of FAK. Sci Rep. 2021;11(1):10826. doi: 10.1038/s41598-021-90289-1. PubMed PMID: 34031486; PMCID: PMC8144381. [PubMed: 34031486]

52. Park NS, Park YK, Yadav AK, Shin YM, Bishop-Bailey D, Choi JS, Park JW, Jang BC. Anti-growth and pro-apoptotic effects of dasatinib on human oral cancer cells through multi-targeted mechanisms. J Cell Mol Med. 2021;25(17):8300–11. doi: 10.1111/jcmm.16782. PubMed PMID: 34318593; PMCID: PMC8419177. [PubMed: 34318593]

53. Yang Z, Liao J, Cullen KJ, Dan H. Inhibition of IKKbeta/NF-kappaB signaling pathway to improve Dasatinib efficacy in suppression of cisplatin-resistant head and neck squamous cell carcinoma. Cell Death Discov. 2020;6:36. doi: 10.1038/s41420-020-0270-7. PubMed PMID: 32435511; PMCID: PMC7229171. [PubMed: 32435511]

54. Brooks HD, Glisson BS, Bekele BN, Johnson FM, Ginsberg LE, El-Naggar A, Culotta KS, Takebe N, Wright J, Tran HT, Papadimitrakopoulou VA. Phase 2 study of dasatinib in the treatment of head and neck squamous cell carcinoma. Cancer. 2011;117(10):2112–9. doi: 10.1002/cncr.25769. PubMed PMID: 21523723; PMCID: PMC3117018. [PubMed: 21523723]

55. Stabile LP, Egloff AM, Gibson MK, Gooding WE, Ohr J, Zhou P, Rothenberger NJ, Wang L, Geiger JL, Flaherty JT, Grandis JR, Bauman JE. IL6 is associated with response to dasatinib and cetuximab: Phase II clinical trial with mechanistic correlatives in cetuximab-resistant head and neck cancer. Oral Oncol. 2017;69:38–45. doi: 10.1016/j.oraloncology.2017.03.011. PubMed PMID: 28559019; PMCID: PMC5944328. [PubMed: 28559019] * This biomarker-driven trial identified IL-6 as a circulating factor associated with response to dasatinib and cetuximab.

56. Trudel S, Li ZH, Wei E, Wiesmann M, Chang H, Chen C, Reece D, Heise C, Stewart AK. CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t(4;14) multiple myeloma. Blood. 2005;105(7):2941–8. doi: 10.1182/blood-2004-10-3913. PubMed PMID: 15598814. [PubMed: 15598814]

57. Sweeny L, Zimmermann TM, Liu Z, Rosenthal EL. Evaluation of tyrosine receptor kinases in the interactions of head and neck squamous cell carcinoma cells and fibroblasts. Oral Oncol. 2012;48(12):1242–9. doi: 10.1016/j.oraloncology.2012.06.011. PubMed PMID: 22795534; PMCID: PMC3496822. [PubMed: 22795534]

58. Brands RC, Knierim LM, De Donno F, Steinacker V, Hartmann S, Seher A, Kubler AC, Muller-Richter UDA. Targeting VEGFR and FGFR in head and neck squamous cell carcinoma in

vitro. Oncol Rep. 2017;38(3):1877–85. doi: 10.3892/or.2017.5801. PubMed PMID: 28714017. [PubMed: 28714017]

59. Brands RC, De Donno F, Knierim ML, Steinacker V, Hartmann S, Seher A, Kubler AC, Muller-Richter UDA. Multi-kinase inhibitors and cisplatin for head and neck cancer treatment in vitro. Oncol Lett. 2019;18(3):2220–31. doi: 10.3892/ol.2019.10541. PubMed PMID: 31452723; PMCID: PMC6676536. [PubMed: 31452723]

60. Carneiro A, De Vito FB, Moraes-Souza H, Crema VO. RhoA/ROCKs signaling is increased by treatment with TKI-258 and leads to increased apoptosis in SCC-4 oral squamous cell carcinoma cell line. J Oral Pathol Med. 2021;50(4):394–402. doi: 10.1111/jop.13143. PubMed PMID: 33222274. [PubMed: 33222274]

61. Schoffski P, Gebreyohannes Y, Van Looy T, Manley P, Growney JD, Squires M, Wozniak A. In Vivo Evaluation of Fibroblast Growth Factor Receptor Inhibition in Mouse Xenograft Models of Gastrointestinal Stromal Tumor. Biomedicines. 2022;10(5). doi: 10.3390/biomedicines10051135. PubMed PMID: 35625872.

62. Thwe AM, Mossey P, Ellis IR. Effect of tyrosine kinase inhibitors on cell migration and epithelial-to-mesenchymal transition in Asian head and neck cancer cell lines. J Oral Pathol Med. 2021;50(10):1031–9. doi: 10.1111/jop.13230. PubMed PMID: 34358366. [PubMed: 34358366]

63. Ngan HL, Poon PHY, Su YX, Chan JYK, Lo KW, Yeung CK, Liu Y, Wong E, Li H, Lau CW, Piao W, Lui VWY. Erlotinib sensitivity of MAPK1p.D321N mutation in head and neck squamous cell carcinoma. NPJ Genom Med. 2020;5(1):17. doi: 10.1038/s41525-020-0124-5. PubMed PMID: 32351709; PMCID: PMC7171136. [PubMed: 32351709]

64. Liu S, Wang Y, Han Y, Xia W, Zhang L, Xu S, Ju H, Zhang X, Ren G, Liu L, Ye W, Zhang Z, Hu J. EREG-driven oncogenesis of Head and Neck Squamous Cell Carcinoma exhibits higher sensitivity to Erlotinib therapy. Theranostics. 2020;10(23):10589–605. doi: 10.7150/thno.47176. PubMed PMID: 32929368; PMCID: PMC7482801. [PubMed: 32929368]

65. William WN Jr., Tsao AS, Feng L, Ginsberg LE, Lee JJ, Kies MS, Glisson BS, Kim ES. Single Arm, Phase II Study of Cisplatin, Docetaxel, and Erlotinib in Patients with Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinomas. Oncologist. 2018;23(5):526–e49. doi: 10.1634/theoncologist.2017-0661. PubMed PMID: 29371473; PMCID: PMC5947451 article. [PubMed: 29371473]

66. Subbiah V, Dumbrava EI, Jiang Y, Thein KZ, Naing A, Hong DS, Fu S, Piha-Paul SA, Tsimberidou AM, Janku F, Meric-Bernstam F, Kurzrock R, Falchook G. Dual EGFR blockade with cetuximab and erlotinib combined with anti-VEGF antibody bevacizumab in advanced solid tumors: a phase 1 dose escalation triplet combination trial. Exp Hematol Oncol. 2020;9:7. doi: 10.1186/s40164-020-00159-1. PubMed PMID: 32337094; PMCID: PMC7171918. [PubMed: 32337094]

67. Ahn PH, Machtay M, Anne PR, Cognetti D, Keane WM, Wuthrick E, Dicker AP, Axelrod RS. Phase I Trial Using Induction Ciplatin, Docetaxel, 5-FU and Erlotinib Followed by Cisplatin, Bevacizumab and Erlotinib With Concurrent Radiotherapy for Advanced Head and Neck Cancer. Am J Clin Oncol. 2018;41(5):441–6. doi: 10.1097/COC.0000000000000317. PubMed PMID: 27391356.

68. Le X, Gleber-Netto FO, Rubin ML, Qing Y, Du R, Kies M, Blumenschein G Jr., Lu C, Johnson FM, Bell D, Lewis J, Zhang J, Feng L, Wilson K, Marcelo-Lewis K, Wang J, Ginsberg L, Gillison M, Lee JJ, Meric-Bernstam F, Mills GB, William WN, Myers JN, Pickering CR. Induction chemotherapy with or without erlotinib in patients with head and neck squamous cell carcinoma amenable for surgical resection. Clin Cancer Res. 2022. doi: 10.1158/1078-0432.CCR-21-3239. PubMed PMID: 35443062.

69. Patil VM, Noronha V, Joshi A, Dhumal S, Mahimkar M, Bhattacharjee A, Gota V, Pandey M, Menon N, Mahajan A, Sable N, Kumar S, Nawale K, Mukadam S, Solanki B, Das S, Simha V, Abraham G, Chandrasekharan A, Talreja V, H DS, Srinivas S, Kashyap L, Banavali S, Prabhash K. Phase I/II Study of Palliative Triple Metronomic Chemotherapy in Platinum-Refractory/Early-Failure Oral Cancer. J Clin Oncol. 2019;37(32):3032–41. doi: 10.1200/JCO.19.01076. PubMed PMID: 31539316. [PubMed: 31539316]

70. Kashyap L, Patil V, Noronha V, Joshi A, Menon N, Jobanputra K, Saha S, Chaturvedi P, Banavali SD, Prabhash K. Efficacy and safety of neoadjuvant chemotherapy (NACT) with paclitaxel plus

carboplatin and oral metronomic chemotherapy (OMCT) in patients with technically unresectable oral squamous cell carcinoma (OSCC). Ecancermedicalscience. 2021;15:1325. doi: 10.3332/ecancer.2021.1325. PubMed PMID: 35211194; PMCID: PMC8816505. [PubMed: 35211194]

71. Van Allen EM, Lui VW, Egloff AM, Goetz EM, Li H, Johnson JT, Duvvuri U, Bauman JE, Stransky N, Zeng Y, Gilbert BR, Pendleton KP, Wang L, Chiosea S, Sougnez C, Wagle N, Zhang F, Du Y, Close D, Johnston PA, McKenna A, Carter SL, Golub TR, Getz G, Mills GB, Garraway LA, Grandis JR. Genomic Correlate of Exceptional Erlotinib Response in Head and Neck Squamous Cell Carcinoma. JAMA Oncol. 2015;1(2):238–44. doi: 10.1001/jamaoncol.2015.34. PubMed PMID: 26181029; PMCID: PMC4557203. [PubMed: 26181029]

72. Khalil A, Jameson MJ. The EGFR Inhibitor Gefitinib Enhanced the Response of Human Oral Squamous Cell Carcinoma to Cisplatin In Vitro. Drugs R D. 2017;17(4):545–55. doi: 10.1007/s40268-017-0204-x. PubMed PMID: 28828595; PMCID: PMC5694417. [PubMed: 28828595]

73. Citro S, Bellini A, Miccolo C, Ghiani L, Carey TE, Chiocca S. Synergistic antitumour activity of HDAC inhibitor SAHA and EGFR inhibitor gefitinib in head and neck cancer: a key role for DeltaNp63alpha. Br J Cancer. 2019;120(6):658–67. doi: 10.1038/s41416-019-0394-9. PubMed PMID: 30765872; PMCID: PMC6461861. [PubMed: 30765872]

74. Low JL, Lau DP, Zhang X, Kwang XL, Rohatgi N, Chan JV, Chong FT, Wong SQR, Leong HS, Thangavelu MT, Rikka S, Skanderup AMJ, Tan DSW, Periyasamy G, Koh JLY, Iyer NG, DasGupta R. A chemical genetic screen identifies Aurora kinases as a therapeutic target in EGFR T790M negative, gefitinib-resistant head and neck squamous cell carcinoma (HNSCC). EBioMedicine. 2021;64:103220. doi: 10.1016/j.ebiom.2021.103220. PubMed PMID: 33529999; PMCID: PMC7851772.

75. Tang X, He J, Li B, Zheng Y, Li K, Zou S, Chen L. Efficacy and Safety of Gefitinib in Patients with Advanced Head and Neck Squamous Cell Carcinoma: A Meta-Analysis of Randomized Controlled Trials. J Oncol. 2019;2019:6273438. doi: 10.1155/2019/6273438. PubMed PMID: 31239839; PMCID: PMC6556337.

76. Irshad R, Haider G, Hashmi M, Hassan A. Efficacy of Gefitinib and Methorexate in Patients With Advanced Stage and Recurrent Head and Neck Cancer. Cureus. 2021;13(6):e15451. doi: 10.7759/cureus.15451. PubMed PMID: 34262802; PMCID: PMC8260212. [PubMed: 34262802]

77. Lehman CE, Mendez RE, Dougherty MI, Allak A, Adejumo OL, Taniguchi LE, Khalil A, Gioeli DG, Jameson MJ. Survivin in Insulin-Like Growth Factor-Induced Resistance to Lapatinib in Head and Neck Squamous Carcinoma Cells. Front Oncol. 2019;9:13. doi: 10.3389/fonc.2019.00013. PubMed PMID: 30729097; PMCID: PMC6351440. [PubMed: 30729097]

78. Weiss JM, Grilley-Olson JE, Deal AM, Zevallos JP, Chera BS, Paul J, Knowles MF, Usenko D, Weissler MC, Patel S, Hayes DN, Hackman T. Phase 2 trial of neoadjuvant chemotherapy and transoral endoscopic surgery with risk-adapted adjuvant therapy for squamous cell carcinoma of the head and neck. Cancer. 2018;124(14):2986–92. doi: 10.1002/cncr.31526. PubMed PMID: 29741773. [PubMed: 29741773]

79. Hackman TG, Patel SN, Deal AM, Neil Hayes D, Chera BS, Paul J, Knowles M, Usenko D, Grilley-Olson JE, Weissler MC, Weiss J. Novel induction therapy transoral surgery treatment paradigm with risk-adapted adjuvant therapy for squamous cell carcinoma of the head and neck - Mature clinical and functional outcomes. Oral Oncol. 2020;110:104957. doi: 10.1016/j.oraloncology.2020.104957. PubMed PMID: 32823258. [PubMed: 32823258]

80. Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A, Asada M. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin Cancer Res. 2008;14(17):5459–65. doi: 10.1158/1078-0432.CCR-07-5270. PubMed PMID: 18765537. [PubMed: 18765537]

81. Hao Z, Wang P. Lenvatinib in Management of Solid Tumors. Oncologist. 2020;25(2):e302–e10. doi: 10.1634/theoncologist.2019-0407. PubMed PMID: 32043789; PMCID: PMC7011622. [PubMed: 32043789]

82. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory

thyroid cancer. N Engl J Med. 2015;372(7):621–30. doi: 10.1056/NEJMoa1406470. PubMed PMID: 25671254. [PubMed: 25671254]

83. Killock D. Neuroendocrine cancer: SELECT-lenvatinib in thyroid cancer. Nat Rev Clin Oncol. 2015;12(4):189. doi: 10.1038/nrclinonc.2015.30. PubMed PMID: 25707627.

84. Schmittnaegel M, Rigamonti N, Kadioglu E, Cassara A, Wyser Rmili C, Kiialainen A, Kienast Y, Mueller HJ, Ooi CH, Laoui D, De Palma M. Dual angiopoietin-2 and VEGFA inhibition elicits antitumor immunity that is enhanced by PD-1 checkpoint blockade. Sci Transl Med. 2017;9(385). doi: 10.1126/scitranslmed.aak9670. PubMed PMID: 28404865.

85. Taylor MH, Lee CH, Makker V, Rasco D, Dutcus CE, Wu J, Stepan DE, Shumaker RC, Motzer RJ. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. J Clin Oncol. 2020;38(11):1154–63. doi: 10.1200/JCO.19.01598. PubMed PMID: 31961766; PMCID: PMC7145588. [PubMed: 31961766]

86. Chen TH, Chang PM, Yang MH. Combination of pembrolizumab and lenvatinib is a potential treatment option for heavily pretreated recurrent and metastatic head and neck cancer. J Chin Med Assoc. 2021;84(4):361–7. doi: 10.1097/JCMA.0000000000000497. PubMed PMID: 33496513. [PubMed: 33496513]

87. Tchekmedyian V, Sherman EJ, Dunn L, Tran C, Baxi S, Katabi N, Antonescu CR, Ostrovnaya I, Haque SS, Pfister DG, Ho AL. Phase II Study of Lenvatinib in Patients With Progressive, Recurrent or Metastatic Adenoid Cystic Carcinoma. J Clin Oncol. 2019;37(18):1529–37. doi: 10.1200/JCO.18.01859. PubMed PMID: 30939095; PMCID: PMC6599407. [PubMed: 30939095]

88. Podar K, Tonon G, Sattler M, Tai YT, Legouill S, Yasui H, Ishitsuka K, Kumar S, Kumar R, Pandite LN, Hideshima T, Chauhan D, Anderson KC. The small-molecule VEGF receptor inhibitor pazopanib (GW786034B) targets both tumor and endothelial cells in multiple myeloma. Proc Natl Acad Sci U S A. 2006;103(51):19478–83. doi: 10.1073/pnas.0609329103. PubMed PMID: 17164332; PMCID: PMC1748251. [PubMed: 17164332]

89. Miyamoto S, Kakutani S, Sato Y, Hanashi A, Kinoshita Y, Ishikawa A. Drug review: Pazopanib. Jpn J Clin Oncol. 2018;48(6):503–13. doi: 10.1093/jjco/hyy053. PubMed PMID: 29684209. [PubMed: 29684209]

90. Adkins D, Mehan P, Ley J, Siegel MJ, Siegel BA, Dehdashti F, Jiang X, Salama NN, Trinkaus K, Oppelt P. Pazopanib plus cetuximab in recurrent or metastatic head and neck squamous cell carcinoma: an open-label, phase 1b and expansion study. Lancet Oncol. 2018;19(8):1082–93. doi: 10.1016/S1470-2045(18)30350-4. PubMed PMID: 30001987; PMCID: PMC6561471. [PubMed: 30001987]

91. Kim HJ, Kim HP, Yoon YK, Kim MS, Lee GS, Han SW, Im SA, Kim TY, Oh DY, Bang YJ. Antitumor activity of HM781–36B, a pan-HER tyrosine kinase inhibitor, in HER2-amplified breast cancer cells. Anticancer Drugs. 2012;23(3):288–97. doi: 10.1097/CAD.0b013e32834e7d9b. PubMed PMID: 23422737. [PubMed: 23422737]

92. Cha MY, Lee KO, Kim M, Song JY, Lee KH, Park J, Chae YJ, Kim YH, Suh KH, Lee GS, Park SB, Kim MS. Antitumor activity of HM781–36B, a highly effective pan-HER inhibitor in erlotinib-resistant NSCLC and other EGFR-dependent cancer models. Int J Cancer. 2012;130(10):2445–54. doi: 10.1002/ijc.26276. PubMed PMID: 21732342. [PubMed: 21732342]

93. Nam HJ, Kim HP, Yoon YK, Hur HS, Song SH, Kim MS, Lee GS, Han SW, Im SA, Kim TY, Oh DY, Bang YJ. Antitumor activity of HM781–36B, an irreversible Pan-HER inhibitor, alone or in combination with cytotoxic chemotherapeutic agents in gastric cancer. Cancer Lett. 2011;302(2):155–65. doi: 10.1016/j.canlet.2011.01.010. PubMed PMID: 21306821. [PubMed: 21306821]

94. Robichaux JP, Elamin YY, Tan Z, Carter BW, Zhang S, Liu S, Li S, Chen T, Poteete A, Estrada-Bernal A, Le AT, Truini A, Nilsson MB, Sun H, Roarty E, Goldberg SB, Brahmer JR, Altan M, Lu C, Papadimitrakopoulou V, Politi K, Doebele RC, Wong KK, Heymach JV. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. Nat Med. 2018;24(5):638–46. doi: 10.1038/s41591-018-0007-9. PubMed PMID: 29686424; PMCID: PMC5964608. [PubMed: 29686424]

95. Robichaux JP, Elamin YY, Vijayan RSK, Nilsson MB, Hu L, He J, Zhang F, Pisegna M, Poteete A, Sun H, Li S, Chen T, Han H, Negrao MV, Ahnert JR, Diao L, Wang J, Le X, Meric-Bernstam

F, Routbort M, Roeck B, Yang Z, Raymond VM, Lanman RB, Frampton GM, Miller VA, Schrock AB, Albacker LA, Wong KK, Cross JB, Heymach JV. Pan-Cancer Landscape and Analysis of ERBB2 Mutations Identifies Poziotinib as a Clinically Active Inhibitor and Enhancer of T-DM1 Activity. Cancer Cell. 2019;36(4):444–57 e7. doi: 10.1016/j.ccell.2019.09.001. PubMed PMID: 31588020; PMCID: PMC6944069. [PubMed: 31588020]

96. Elamin YY, Robichaux JP, Carter BW, Altan M, Gibbons DL, Fossella FV, Lam VK, Patel AB, Negrao MV, Le X, Mott FE, Zhang J, Feng L, Blumenschein G Jr., Tsao AS, Heymach JV. Poziotinib for Patients With HER2 Exon 20 Mutant Non-Small-Cell Lung Cancer: Results From a Phase II Trial. J Clin Oncol. 2022;40(7):702–9. doi: 10.1200/JCO.21.01113. PubMed PMID: 34550757; PMCID: PMC8887948 [PubMed: 34550757]

97. Le X, Cornelissen R, Garassino M, Clarke JM, Tchekmedyian N, Goldman JW, Leu SY, Bhat G, Lebel F, Heymach JV, Socinski MA. Poziotinib in Non-Small-Cell Lung Cancer Harboring HER2 Exon 20 Insertion Mutations After Prior Therapies: ZENITH20–2 Trial. J Clin Oncol. 2022;40(7):710–8. doi: 10.1200/JCO.21.01323. PubMed PMID: 34843401; PMCID: PMC8887939 [PubMed: 34843401]

98. Lee JH, Heo SG, Ahn BC, Hong MH, Cho BC, Lim SM, Kim HR. A phase II study of poziotinib in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Cancer Med. 2021;10(20):7012–20. doi: 10.1002/cam4.4231. PubMed PMID: 34528763; PMCID: PMC8525103. [PubMed: 34528763]

99. Adnane L, Trail PA, Taylor I, Wilhelm SM. Sorafenib (BAY 43–9006, Nexavar), a dual-action inhibitor that targets RAF/MEK/ERK pathway in tumor cells and tyrosine kinases VEGFR/PDGFR in tumor vasculature. Methods Enzymol. 2006;407:597–612. doi: 10.1016/S0076-6879(05)07047–3. PubMed PMID: 16757355. [PubMed: 16757355]

100. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther. 2008;7(10):3129–40. doi: 10.1158/1535-7163.MCT-08-0013. PubMed PMID: 18852116. [PubMed: 18852116]

101. Laban S, Steinmeister L, Gleissner L, Grob TJ, Grenman R, Petersen C, Gal A, Knecht R, Dikomey E, Kriegs M. Sorafenib sensitizes head and neck squamous cell carcinoma cells to ionizing radiation. Radiother Oncol. 2013;109(2):286–92. doi: 10.1016/j.radonc.2013.07.003. PubMed PMID: 23953412. [PubMed: 23953412]

102. Mockelmann N, Rieckmann T, Busch CJ, Becker B, Gleissner L, Hoffer K, Omniczynski M, Steinmeister L, Laban S, Grenman R, Petersen C, Rothkamm K, Dikomey E, Knecht R, Kriegs M. Effect of sorafenib on cisplatin-based chemoradiation in head and neck cancer cells. Oncotarget. 2016;7(17):23542–51. doi: 10.18632/oncotarget.8275. PubMed PMID: 27015558; PMCID: PMC5029646. [PubMed: 27015558]

103. Beizaei K, Gleissner L, Hoffer K, Bussmann L, Vu AT, Steinmeister L, Laban S, Mockelmann N, Munscher A, Petersen C, Rothkamm K, Kriegs M. Receptor tyrosine kinase MET as potential target of multi-kinase inhibitor and radiosensitizer sorafenib in HNSCC. Head Neck. 2019;41(1):208–15. doi: 10.1002/hed.25440. PubMed PMID: 30552828. [PubMed: 30552828]

104. Williamson SK, Moon J, Huang CH, Guaglianone PP, LeBlanc M, Wolf GT, Urba SG. Phase II evaluation of sorafenib in advanced and metastatic squamous cell carcinoma of the head and neck: Southwest Oncology Group Study S0420. J Clin Oncol. 2010;28(20):3330–5. doi: 10.1200/JCO.2009.25.6834. PubMed PMID: 20498388; PMCID: PMC2903329. [PubMed: 20498388]

105. Lalami Y, Garcia C, Flamen P, Ameye L, Paesmans M, Awada A. Phase II trial evaluating the efficacy of sorafenib (BAY 43–9006) and correlating early fluorodeoxyglucose positron emission tomography-CT response to outcome in patients with recurrent and/or metastatic head and neck cancer. Head Neck. 2016;38(3):347–54. doi: 10.1002/hed.23898. PubMed PMID: 25332069. [PubMed: 25332069]

106. Gilbert J, Schell MJ, Zhao X, Murphy B, Tanvetyanon T, Leon ME, Neil Hayes D, Haigentz M Jr., Saba N, Nieva J, Bishop J, Sidransky D, Ravi R, Bedi A, Chung CH. A randomized phase II efficacy and correlative studies of cetuximab with or without sorafenib in recurrent and/or metastatic head and neck squamous cell carcinoma. Oral Oncol. 2015;51(4):376–82. doi: 10.1016/j.oraloncology.2014.12.011. PubMed PMID: 25593015; PMCID: PMC4459134. [PubMed: 25593015]

107. Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth PF, Bigley AL, Hennequin LF. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res. 2002;62(16):4645–55. PubMed PMID: 12183421. [PubMed: 12183421]

108. Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, Ryan AJ, Fontanini G, Fusco A, Santoro M. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. Cancer Res. 2002;62(24):7284–90. PubMed PMID: 12499271. [PubMed: 12499271]

109. Ciardiello F, Caputo R, Damiano V, Caputo R, Troiani T, Vitagliano D, Carlomagno F, Veneziani BM, Fontanini G, Bianco AR, Tortora G. Antitumor effects of ZD6474, a small molecule vascular endothelial growth factor receptor tyrosine kinase inhibitor, with additional activity against epidermal growth factor receptor tyrosine kinase. Clin Cancer Res. 2003;9(4):1546–56. PubMed PMID: 12684431. [PubMed: 12684431]

110. Sano D, Matsumoto F, Valdecanas DR, Zhao M, Molkentine DP, Takahashi Y, Hanna EY, Papadimitrakopoulou V, Heymach J, Milas L, Myers JN. Vandetanib restores head and neck squamous cell carcinoma cells' sensitivity to cisplatin and radiation in vivo and in vitro. Clin Cancer Res. 2011;17(7):1815–27. doi: 10.1158/1078-0432.CCR-10-2120. PubMed PMID: 21350000; PMCID: PMC3074405. [PubMed: 21350000] *These findings indicate that tyrosine kinase inhibitors can be used to enhance response to conventional chemotherapy and radiation in head and neck squamous cell carcinoma.

111. Gustafson DL, Frederick B, Merz AL, Raben D. Dose scheduling of the dual VEGFR and EGFR tyrosine kinase inhibitor vandetanib (ZD6474, Zactima) in combination with radiotherapy in EGFR-positive and EGFR-null human head and neck tumor xenografts. Cancer Chemother Pharmacol. 2008;61(2):179–88. doi: 10.1007/s00280-007-0460-5. PubMed PMID: 17393165. [PubMed: 17393165]

112. Chu PL, Shihabuddeen WA, Low KP, Poon DJJ, Ramaswamy B, Liang ZG, Nei WL, Chua KLM, Thong PSP, Soo KC, Yeo ELL, Chua MLK. Vandetanib sensitizes head and neck squamous cell carcinoma to photodynamic therapy through modulation of EGFR-dependent DNA repair and the tumour microenvironment. Photodiagnosis Photodyn Ther. 2019;27:367–74. doi: 10.1016/j.pdpdt.2019.06.008. PubMed PMID: 31299389. [PubMed: 31299389]

113. Papadimitrakopoulou VA, Frank SJ, Cohen EW, Hirsch FR, Myers JN, Heymach JV, Lin H, Tran HT, Chen CR, Jimeno A, Nedzi L, Vasselli JR, Lowe ES, Raben D. Phase I study of vandetanib with radiation therapy with or without cisplatin in locally advanced head and neck squamous cell carcinoma. Head Neck. 2016;38(3):439–47. doi: 10.1002/hed.23922. PubMed PMID: 25352401; PMCID: PMC4414661. [PubMed: 25352401]

114. Limaye S, Riley S, Zhao S, O'Neill A, Posner M, Adkins D, Jaffa Z, Clark J, Haddad R. A randomized phase II study of docetaxel with or without vandetanib in recurrent or metastatic squamous cell carcinoma of head and neck (SCCHN). Oral Oncol. 2013;49(8):835–41. doi: 10.1016/j.oraloncology.2013.04.010. PubMed PMID: 23727257. [PubMed: 23727257]

115. Tannehill-Gregg S, Kergosien E, Rosol TJ. Feline head and neck squamous cell carcinoma cell line: characterization, production of parathyroid hormone-related protein, and regulation by transforming growth factor-beta. In Vitro Cell Dev Biol Anim. 2001;37(10):676–83. doi: 10.1290/1071-2690(2001)037<0676:FHANSC>2.0.CO;2. PubMed PMID: 11776973. [PubMed: 11776973]

116. Tannehill-Gregg SH, Levine AL, Rosol TJ. Feline head and neck squamous cell carcinoma: a natural model for the human disease and development of a mouse model. Vet Comp Oncol. 2006;4(2):84–97. doi: 10.1111/j.1476-5810.2006.00096.x. PubMed PMID: 19754818. [PubMed: 19754818]

117. Wypij JM, Fan TM, Fredrickson RL, Barger AM, de Lorimier LP, Charney SC. In vivo and in vitro efficacy of zoledronate for treating oral squamous cell carcinoma in cats. J Vet Intern Med. 2008;22(1):158–63. doi: 10.1111/j.1939-1676.2007.0010.x. PubMed PMID: 18289304. [PubMed: 18289304]

118. Wypij JM. A naturally occurring feline model of head and neck squamous cell carcinoma. Patholog Res Int. 2013;2013:502197. doi: 10.1155/2013/502197. PubMed PMID: 23970998; PMCID: PMC3730145. [PubMed: 23970998]

119. Soltero-Rivera MM, Krick EL, Reiter AM, Brown DC, Lewis JR. Prevalence of regional and distant metastasis in cats with advanced oral squamous cell carcinoma: 49 cases (2005–2011). J Feline Med Surg. 2014;16(2):164–9. doi: 10.1177/1098612X13502975. PubMed PMID: 24027053. [PubMed: 24027053]

120. Supsavhad W, Dirksen WP, Martin CK, Rosol TJ. Animal models of head and neck squamous cell carcinoma. Vet J. 2016;210:7–16. doi: 10.1016/j.tvjl.2015.11.006. PubMed PMID: 26965084. [PubMed: 26965084]

121. Supsavhad W, Dirksen WP, Hildreth BE, Rosol TJ. p16, pRb, and p53 in Feline Oral Squamous Cell Carcinoma. Vet Sci. 2016;3(3). doi: 10.3390/vetsci3030018. PubMed PMID: 29056726; PMCID: PMC5606583. [PubMed: 29056713]

122. Bregazzi VS, LaRue SM, Powers BE, Fettman MJ, Ogilvie GK, Withrow SJ. Response of feline oral squamous cell carcinoma to palliative radiation therapy. Vet Radiol Ultrasound. 2001;42(1):77–9. PubMed PMID: 11245242. [PubMed: 11245242]

123. McDonald C, Looper J, Greene S. Response rate and duration associated with a 4Gy 5 fraction palliative radiation protocol. Vet Radiol Ultrasound. 2012;53(3):358–64. doi: 10.1111/j.1740-8261.2011.01907.x. PubMed PMID: 22182209. [PubMed: 22182209]

124. Poirier VJ, Kaser-Hotz B, Vail DM, Straw RC. Efficacy and toxicity of an accelerated hypofractionated radiation therapy protocol in cats with oral squamous cell carcinoma. Vet Radiol Ultrasound. 2013;54(1):81–8. doi: 10.1111/j.1740-8261.2012.01970.x. PubMed PMID: 23078236. [PubMed: 23078236]

125. Looper JS, Malarkey DE, Ruslander D, Proulx D, Thrall DE. Epidermal growth factor receptor expression in feline oral squamous cell carcinomas. Vet Comp Oncol. 2006;4(1):33–40. doi: 10.1111/j.1476-5810.2006.00091.x. PubMed PMID: 19754827. [PubMed: 19754827]

126. Bergkvist GT, Argyle DJ, Morrison L, MacIntyre N, Hayes A, Yool DA. Expression of epidermal growth factor receptor (EGFR) and Ki67 in feline oral squamous cell carcinomas (FOSCC). Vet Comp Oncol. 2011;9(2):106–17. doi: 10.1111/j.1476-5829.2010.00239.x. PubMed PMID: 21569196. [PubMed: 21569196]

127. Yoshikawa H, Ehrhart EJ, Charles JB, Thamm DH, Larue SM. Immunohistochemical characterization of feline oral squamous cell carcinoma. Am J Vet Res. 2012;73(11):1801–6. doi: 10.2460/ajvr.73.11.1801. PubMed PMID: 23106467. [PubMed: 23106467]

128. Lee RH, Kang H, Yom SS, Smogorzewska A, Johnson DE, Grandis JR. Treatment of Fanconi Anemia-Associated Head and Neck Cancer: Opportunities to Improve Outcomes. Clin Cancer Res. 2021. doi: 10.1158/1078-0432.CCR-21-1259. PubMed PMID: 34045293.
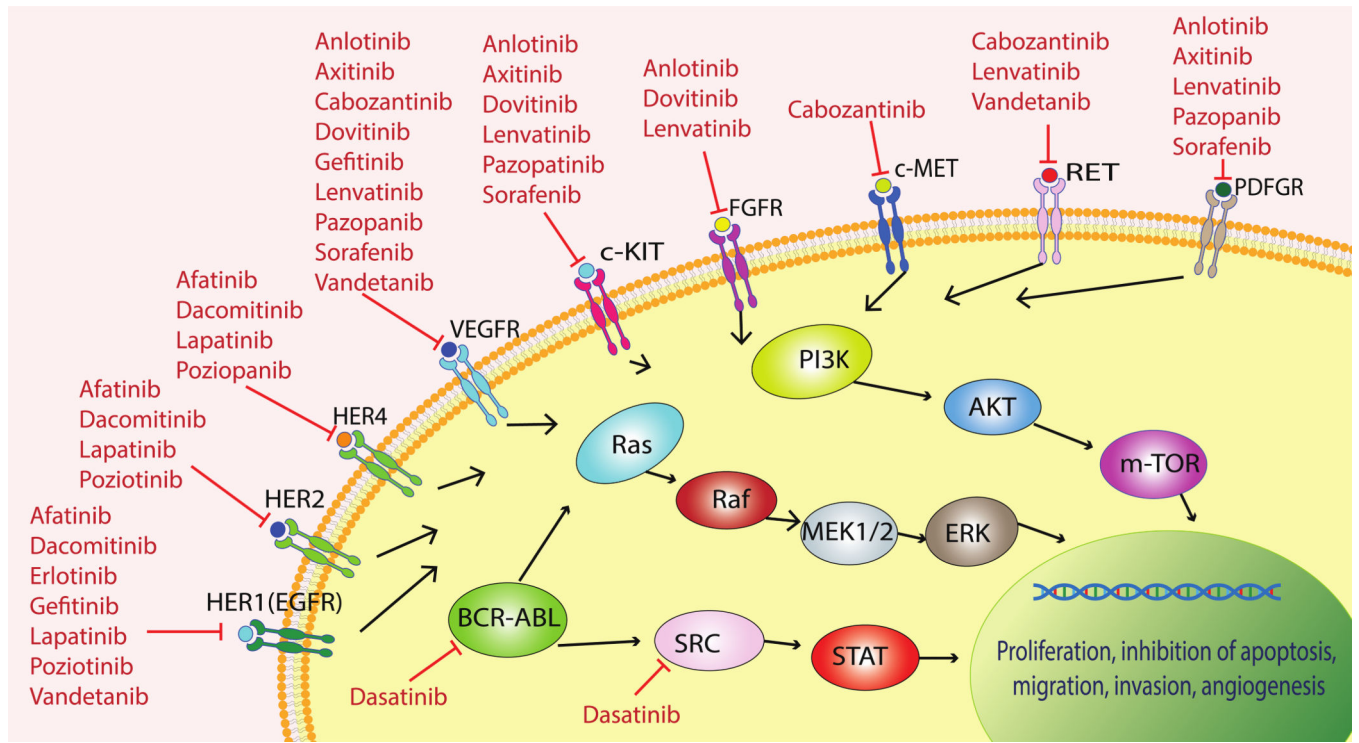
Figure 1.
Sites of molecular targeting for TKIs

Table 1.

TKIs in HNSCC Clinical Trials

Compound	Company	Monotherapy or combination agent	Indication	Stage of development	Clinical trial NCT#	Molecular target(s)
Afatinib	Boehringer Ingelheim	Pembrolizumab	HNSCC	Phase 2	03695510	HER1 (EGFR), HER2, HER4
		Cetuximab	HNSCC	Phase 2	02979977	
		Monotherapy	HNSCC	Phase 3	02131155	
		Monotherapy	HNSCC	Phase 3	01856478	
		Radiation	HNSCC	Phase 1	01783587	
		Monotherapy	HNSCC	Phase 3	01427478	
		Monotherapy	HNSCC	Phase 2	01415674	
		Monotherapy	HNSCC	Phase 2	03088059	
Anlotinib	Jiangsu Chia-Tai Tianqing Pharma	Chemoradiation	HNSCC	Phase 4	04507035	VEGFR1–3, FGFR1–4, PDGFR, c-KIT
		Pembrolizumab	HNSCC	Phase 2	04999800	
		Monotherapy	Head and neck adenocarcinomas	Phase 2	04910854	
		Chemoradiation	Nasophar-yngeal carcinoma	Phase 2	05232552	
		Toripalimab	Nasophar-yngeal carcinoma	Phase 2	04996758	
		Monotherapy	Nasophar-yngeal carcinoma	Phase 2	03906058	
Axitinib	Pfizer	Monotherapy	HNSCC	Phase 2	02762513	VEGFR1–3, PDGFR, c-KIT
		Monotherapy	Salivary gland cancers	Phase 2	02857712	
Cabozantinib	Excelixis	Nivolumab	HNSCC & melanoma	Phase 2	05136196	VEGFR2, RET, c-MET,
		Atezoluzumab	Solid tumors (HNSCC)	Phase 1/2	03170960	
		Pembrolizumab	HNSCC	Phase 2	03468218	
		Cetuximab	HNSCC	Phase 1	03667482	
		Nivolumab	Advanced cancers (HNSCC)	Phase 1	04514484	
Dacomitinib	Pfizer	Monotherapy	HNSCC	Phase 2	00768664	HER1 (EGFR), HER2, HER4
		Monotherapy	Solid tumors (HNSCC)	Phase 2	04946968	
Dasatinib	Bristol-Myers Squibb	Monotherapy	Solid tumors (HNSCC), multiple myeloma, lymphoma	Phase 2	02465060	BCR-ABL, SRC family kinases
Erlotinib	Genentech	Monotherapy	HNSCC	Phase 1	00954226	HER1 (EGFR)
		Monotherapy	HNSCC	Phase 2	00076310	
		+/− chemotherapy	HNSCC	Phase 2	01927744	
		Monotherapy	HNSCC	Phase 1	00079053	
		+/− celecoxib	HNSCC	Phase 2	02748707	
		Chemoradiation	HNSCC	Phase 3	00442455	

Compound	Company	Monotherapy or combination agent	Indication	Stage of development	Clinical trial NCT#	Molecular target(s)
		Monotherapy	HNSCC (oral cancer)	Phase 3	00402779	
		Chemotherapy	HNSCC	Phase 2	01064479	
		Chemotherapy	Nasophar-yngeal carcinoma	Phase 2	00603915	
Gefitinib	Astra Zeneca	Chemoradiation	HNSCC	Phase 2	01185171	HER1 (EGFR)
Lapatinib	GSK	Chemotherapy	HNSCC	Phase 2	01711658	HER1 (EGFR), HER2
		Capecitabine	HNSCC	Phase 2	01044433	
		Chemotherapy	HNSCC	Phase 2	01612351	
Lenvatinib	Easai	GI-101	Solid tumors (HNSCC)	Phase 1/2	04977453	VEGFR1–3, FGFR1–4, c-KIT, PDGFR, RET
		Cetuximab	HNSCC, cutaneous squamous cell carcinoma	Phase 1	03524326	
		Pembrolizumab	HNSCC	Phase 3	04199104	
		+/– pembrolizumab	HNSCC	Phase 2	04428151	
Pazopanib	GSK	Cetuximab	HNSCC	Phase 1	01716416	VEGFR1–3, PDGFR, FGFR,c-KIT
		Monotherapy	Salivary gland carcinoma	Phase 2	02393820	
Poziotinib	Hanmi	Monotherapy	HNSCC, esophageal SCC	Phase 2	03292250	HER1(EGFR), HER2, HER4
Sorafenib	Onyx	Chemotherapy	HNSCC	Phase 2	00494182	VEGFR2, VEGFR4, PDGFR, c-KIT, C-RAF, B-RAF
Vandetanib	Astra-Zeneca	Monotherapy	Precancer-ous H&N lesions	Phase 2	01414426	HER1 (EGFR), VEGFR2, RET