



Role of Molecular Targeted Therapeutic Drugs in Treatment of Oral Squamous Cell Carcinoma: Development and Current Strategies—A Review Article

Himanshu Singh¹ Vedant Patel²

¹Department of Oral and Maxillofacial Pathology and Oral Microbiology, Index Institute of Dental Sciences, Indore, Madhya Pradesh, India

²Department of Prosthodontics and Crown & Bridge, Index Institute of Dental Sciences, Indore, Madhya Pradesh, India

Address for correspondence Himanshu Singh, MDS, Department of Oral and Maxillofacial Pathology and Oral Microbiology, Index Institute of Dental Sciences, Indore 452016, Madhya Pradesh, India (e-mail: himanshustar3g@gmail.com).

Glob Med Genet 2022;9:242–246.

Abstract

Because of active advancement in the field of biomedicine, people have in-depth knowledge of biological nature of malignant tumors and are able to recognize the overexpression of different molecules such as vascular endothelial growth factor receptor, cyclin-dependent kinase, and programmed cell death receptor. Presently, various targeted therapeutic drugs are used in different clinical trials in those patients suffering from oral squamous cell carcinoma. In this review, we converse about the various targeted therapeutic drugs and their advancement in the treatment of oral squamous cell carcinoma. This review scrutinizes the existing documentation in the literature related to the targeted therapies for oral squamous cell carcinoma. English language articles were searched in various databases such as PubMed, Scopus, Science Direct, and Google Scholar. The keywords used for searching are “oral squamous cell carcinoma,” “targeted therapy,” and “therapeutic drugs.”

Keywords

- oral squamous cell carcinoma
- therapeutic drugs
- targeted therapy

Introduction

Oral cancer is cited as tumors particularly arising in the hard palate, anterior two-thirds of the tongue, lips, upper and lower alveolar ridges, posterior deltoid muscles of molars, buccal mucosa, and oral cavity.¹ Approximately 90% of oral cancer have squamous differentiation in the mucosal epithelium; therefore, it is known as oral squamous cell carcinoma (OSCC). It is the sixth most prevalent cancer worldwide. OSCC has a survival rate of 5 years in approximately 50 to 60% of cases in the early stage. In advanced stages of OSCC, it drops to 30 to 40% of cases. Unluckily, 60 to 80% of cases of OSCC are recognized at the advanced stage. With regular development in diagnosis and treatment knowledge, the survival rate has been increased.² In the present scenario, proteomics, genomics, metabolomics, and different biomedical sciences have

been established expeditiously. Subsequently, targeted therapies that target cancer-specific genetic targets, for example, genes responsible for invasion, division, proliferation, and metastasis of carcinogenic cells, have deliberately become the hot topic in the field of research.^{3,4} Targeted therapies choose comparable therapeutic drugs as per the specific carcinogenesis location. It has the advantages of low toxicity, high selectivity, and high therapeutic indexes. In modern day, individual targeted therapeutic drugs have accomplished promising results in cancer treatment.

This review scrutinized the existing documentation in the literature related to the targeted therapies for OSCC. English language articles were searched in various databases such as PubMed, Scopus, Science Direct, and Google Scholar. The keywords used for searching are “oral squamous cell carcinoma,” “targeted therapy,” and “therapeutic drugs.”

DOI <https://doi.org/10.1055/s-0042-1756663>.
ISSN 2699-9404.

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

In this review, characterization of presently most encouraging and well-known molecular targeting strategies, which is directly used in the treatment of advanced head and neck cancer, is discussed.

Drugs Targeting the Programmed Cell Death Receptor 1

Programmed cell death receptor-1 (PD-1) is associated with the CD28 family. PD1 is expressed on natural killer cells, T-cells, B-cells, dendritic cells, and macrophages. When PD1 binds with PD-L1 (programmed cell death ligand 1), it results in apoptosis of effector T-cells, which leads to immune escape of tumor.^{5,6} Also, it increases the synthesis of interleukin-10 cytokines, which suppress inflammatory responses.⁷ In various studies, it is observed that overexpression of PD-L1 is seen in 50 to 90% of OSCC patients. This increased expression is positively correlated with cervical lymph node metastasis. Their coexpression was analogous to the prognosis of different malignant tumors such as melanoma and OSCC.^{8,9} Presently, two drugs are used to target PD-1. They are nivolumab and pembrolizumab. These drugs are permitted for use by the U.S. Food and Drug Administration in the treatment of advanced melanoma. Pembrolizumab is used for head and neck squamous cell carcinoma patients.^{10,11}

Drugs Targeting the Cyclin-Dependent Kinase (CDK) Inhibitors

The altered expression of cyclin-dependent kinases (CDK) is associated with the disproportionate proliferation of malignant cells. The cell cycle is normally regulated by cyclin and its regulatory partner, that is, CDKs. These CDKs are divided into two subgroups: cell cycle CDKs and transcriptional CDKs. The altered expression of CDKs is associated with the disproportionate proliferation of malignant cells. The cell cycle is normally regulated by cyclin and its regulatory partner, that is, CDKs. These CDKs are divided into two subgroups: cell cycle CDKs and transcriptional CDK.^{12,13} The CDKs are the principal components of cell-cycle initiation and progression. In various malignancies, increased expression of cyclin and CDKs is seen. Also, decreased expression of endogenous CDK inhibitors and regulators such as CIP/KIP and INK4 is recognized in various malignancies. According to Chang et al, the CDK1 gene expression in OSCC was 17.2 times that of normal tissue. This overexpression is linked with malignant behaviors. Chen et al observed that in patients having recurrent OSCC or lymph node metastasis, CDK1 protein is overexpressed. The expression of CDK1 is considered a prognostic indicator of OSCC survival.^{14,15}

CDKs turn into natural targets for anticancer therapy as CDKs play a considerable role in cellular transcription and cell-cycle regulation. Various studies enlighten that CDKs inhibitors have therapeutic potential for various diseases like kidney diseases, cancer, infectious diseases, and diabetes.¹⁶

Flavopiridol is the first CDK inhibitor that is used in human clinical trials. Flavopiridol is a semisynthetic flavo-

noid-based CDKs inhibitor. It is observed that flavopiridol inhibits cell proliferation by blocking G2/M and G1/S phases. Also, flavopiridol inhibits the growth of OSCC cells in a dose-dependent and time-dependent manner. Mihara et al observed that after exposure to flavopiridol, decreased expression of cyclin A, cyclin B, CDK4, CDK1, and cyclin D was seen.^{17,18}

Drugs Targeting the Vascular Endothelial Growth Factor and Its Receptor Inhibitors

Tumor angiogenesis plays a pivotal role in the growth and metastasis of tumors. Hence, suppressing angiogenesis is advised to be efficient in the treatment of OSCC. The vascular endothelial growth factor (VEGF) is known as a diffusible endothelial cell-specific mitogen as well as an angiogenic factor. It is directly associated with increased vascular permeability.¹⁹ The VEGF is an important molecule in tumor angiogenesis and is highly expressed in OSCC. Various agents that are counter to VEGF and its receptors consist of multi-kinase inhibitors like vandetanib and sorafenib, or monoclonal antibodies like bevacizumab.^{20,21}

Bevacizumab, a humanized monoclonal antibody, targets VEGF-A. It inhibits angiogenesis and increases the distribution of chemotherapeutic agents to tumor cells by reducing pressure within the tumor and by reducing microvascular permeability.

Bevacizumab inhibits biological activity that is mediated by VEGF by binding to VEGF receptors, which in turn reduces tumor angiogenesis and thereupon suppresses tumor growth. In a phase II study, it was observed that a combination of bevacizumab, cetuximab plus cisplatin was well acceptable in phase III/IVB head and neck squamous cell carcinoma, including OSCC.²²

Sorafenib, a multitargeted and multikinase inhibitor, inhibits different targets like Raf serine/threonine kinase, c-Kit, platelet-derived growth factor receptor β (PDGFR- β), and VEGFR (vascular endothelial growth factor receptor) 1–3, by inhibiting the growth and proliferation of tumor cells and also suppressing tumor angiogenesis.²³ By downregulating Mcl-1, it induces tumor cell apoptosis. Combination of sorafenib along with radiation results in synergistic effects on OSCC cells by suppressing the nuclear factor kappa B activity.^{24,25}

The results of preclinical trials suggested that sorafenib in consolidation with chemotherapy increases the antitumor effect by prohibiting cell growth, cell migration, and cell invasion.^{26,27} Sorafenib breaks the radio-resistance of head and neck squamous cell carcinoma by prohibiting the repair of double-stranded DNA breakages.^{28,29}

Vandetanib, a tyrosine kinase receptor, adequately inhibits the VEGFR-2 and EGFR tyrosine kinase activities. The result of preclinical studies indicates that vandetanib inhibits the proliferation of xenograft tumor cells that includes OSCC. Vandetanib along with cisplatin and radiotherapy has the potential to conquer resistance to EGFR inhibitors during pre-clinical trials.³⁰

Sunitinib, a kinase inhibitor, targets the PDGFR, VEGFR, and c-Kit tyrosine kinase. It is used for the treatment of

imatinib-resistant gastrointestinal stromal tumors and renal cancer. Monotherapy with sunitinib confirms unsatisfactory activity in the palliative treatment of head and neck squamous cell carcinoma.^{31,32} The combination of sunitinib with cetuximab results in reduced tumor cell proliferation and increases in their differentiation.³³

Drugs Targeting the Mammalian Target of Rapamycin Inhibitors

Mammalian Target of Rapamycin (mTOR) is a serine/threonine-protein kinase. Its function is to control cell survival, the cell cycle, and proliferation. The PI3K/AKT signal pathway shows a significant impact on the regulation of cell growth and cell proliferation.³⁴ As a subsequent molecule of the PI3K/AKT signal pathway, mTOR plays the principal role in the development of tumor, metastasis, invasion, and angiogenesis. In a study done by Liao et al, they observed that 85 patients out of 160 patients suffering from tongue squamous cell carcinoma showed overexpression of phosphorylates mTOR.^{35,36}

There are two types of mTOR inhibitors: first-generation inhibitors and second-generation inhibitors. The first-generation inhibitors were developed from rapamycin. The rapamycin forms a complex with cytoplasmic protein, that is, peptidyl-prolyl cis-trans isomerase tacrolimus binding protein. The rapamycin analogs are temsirolimus and everolimus. The second-generation mTOR inhibitors are PP242, Torin 1, and PP30.³⁷

Temsirolimus is an intravenous drug used for the treatment of kidney cancer. Various research studies or trials show that temsirolimus suppresses the proliferation of head and neck squamous cell carcinoma.³⁸

Everolimus, the derivative of rapamycin, is used as an immunosuppressant for the treatment of kidney cancer. Various studies and trials show that everolimus has anti-angiogenesis and antitumor effects in the treatment of head and neck squamous cell carcinoma.^{39,40}

Drugs Targeting the Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR), a cytoplasmic transmembrane protein, belongs to the human epidermal growth factor receptor tyrosine kinase family. It is generally made up of transmembrane domains, extracellular ligand-binding domains, and intracellular domains having tyrosinase kinase activity.⁴¹ Various endogenous ligands are transforming growth factor- α (TGF- α), , neuregulin, and epiregulin. When these endogenous ligands are attached to the extracellular domain of EGFR, they form heterogeneous or homologous dimers.⁴² These dimers triggered tyrosine kinases, which result in autophosphorylation of tyrosine residue and afterward triggered various downstream signaling pathways like phosphatidylinositol 3-kinase/ protein kinase B(PI3K/Akt) pathway and Ras-Raf-mitogen-activated protein kinase pathway, which give rise to antiapoptosis, proliferation, metastasis, and angiogenesis of tumor cells.⁴³

It is observed that higher expression of EGFR receptor is seen in well-differentiated and moderately differentiated tumors when correlated with high-grade tumors

At present, two types of drugs are used contrary to this target. These drugs are monoclonal antibodies like cetuximab and nimotuzumab, and tyrosine kinase inhibitors (TKIs) like erlotinib, gefitinib, and afatinib.^{44,45}

The monoclonal antibodies act by binding to the extracellular domain of the EGFR that inhibits the link between ligands and results in the inhibition of signal transmission into the cell. Cetuximab is an immunoglobulin G1 (IgG1) monoclonal antibody that is used as first-line treatment, in association with radiotherapy, for advanced head and neck squamous cell carcinoma.⁴⁶

Cetuximab can efficiently prohibit endogenous ligand-activated receptors by binding to the extracellular ligand-binding domain of EGFR, which results in increased cell apoptosis and lessened cell proliferation, metastasis, invasion, and angiogenesis.

Vermorken et al 2008 conducted a randomized phase III clinical trial in different European countries. In their study, they observed that cetuximab when combined with cisplatin extends progression-free survival (PFS) from 3.3 to 5.6 months ($p < 0.001$), the overall survival (OS) from 7.4 to 10.1 months, and increases tumor response rate from 20 to 36% ($p < 0.001$).^{47,48}

Cetuximab monotherapy for platinum-resistant recurrent or metastatic head and neck squamous cell carcinoma shows a PFS of 2.2 to 2.8 months and a response rate of 10 to 13%.⁴⁹

Nimotuzumab, a humanized IgG1 monoclonal antibody, is used in the treatment of head and neck squamous cell carcinoma, nasopharyngeal cancer, and glioblastoma. In comparison with cetuximab, it has a long half-life and moderate affinity, which substantially lowers the side effects such as skin toxicity and immunogenicity. Nimotuzumab has been directly involved in mediating antitumor effects by suppressing the survival, proliferation, and angiogenesis of cancer cells. In a study done by Xu, he observed that docetaxel-cisplatin and fluorouracil were added to nimotuzumab in the treatment of patients with advanced oral cancer, and the efficacy of the combined treatment group was 95%. In the case of the conventional chemotherapy group, the efficacy was 65%. No adverse reactions were seen in both groups.⁵⁰ These results proved that nimotuzumab in consolidation with chemoradiotherapy has extensive high value in the treatment of OSCC.

Panitumumab is a human EGFR monoclonal antibody that is used as a first-line treatment in patients with metastatic colon cancer. In a randomized phase III trial, a combination of panitumumab with chemotherapy did not show any signs of OS of patients with metastatic head and neck squamous cell carcinoma.⁵¹ Gefitinib is the first oral EGFR-TKI. In vitro and in vivo research has concluded that it could prohibit the proliferation of oral squamous cells in a time-dependent and dose-dependent manner, which results in cell accumulation in the G1 phase, cell cycle arrest, and cell decrease in the S phase.^{52,53}

Erlotinib is one of the TKIs that is used in the treatment of oral cavity cancer. In vitro studies prove the effectiveness of

erlotinib, in a dose-dependent manner, in the prohibition of the growth of tongue squamous cell carcinoma.⁵⁴ Erlotinib inhibits the G2/M transition and the intra-S phase of the cell cycle. Erlotinib with cisplatin and radiation shows a synergistic effect in growth inhibition of SCC-15 cells.⁵⁵

Lapatinib, a TKI, shows specificity for EGFR. In various studies, it is seen that lapatinib has an affinity for treating head and neck squamous cell carcinoma. Lapatinib with capecitabine shows effectiveness in the metastatic form of head and neck squamous cell carcinoma.^{56,57}

Other Targeted Therapies

The activin receptor-like kinase 1 (ALK1) belongs to TGF- β and plays an important role in angiogenesis. Dalantercept prohibits ALK1 signaling and is an antiangiogenic agent.⁵⁸ The phase I study shows that dalantercept shows considerable ability as an anticancer therapy in head and neck squamous cell carcinoma.⁵⁹

Bortezomib, a proteasome inhibitor, is used for the treatment of mantle cell lymphoma and multiple myeloma. Primary results show a 50% control rate in patients having metastatic and recurrent head and neck squamous cell carcinoma while taking low-dose bortezomib.⁶⁰

Endostatin, a definitive endogenous angiogenesis inhibitor, inhibits the binding of VEGF to endothelial cells by adhering to integrin, heparin sulfate, and nucleolin receptor on endothelial cells, which results in suppression of tumor cell proliferation and angiogenesis.⁶¹ Endostatin along with chemotherapy was efficient in the treatment of head and neck squamous cell carcinoma.⁶²

Conclusion

Targeted therapy highlights the treatment modalities of cancer at molecular level. These therapies are extremely targeted and specific. As a likely new method, it is universally used in treatment of OSCC. It is proclaimed that in future these targeted therapies succeed the traditional methods and become choice of treatment for tumor cases.

Conflict of Interest

None declared.

References

- 1 Tshering Vogel DW, Zbaeren P, Thoeny HC. Cancer of the oral cavity and oropharynx. *Cancer Imaging* 2010;10:62–72
- 2 Ghantous Y, Abu Elnaaj I. Global incidence and risk factors of oral cancer. *Harefuah* 2017;156(10):645–649
- 3 Singhvi HR, Malik A, Chaturvedi P. The role of chronic mucosal trauma in oral cancer: a review of literature. *Indian J Med Paediatr Oncol* 2017;38(01):44–50
- 4 Ling D, Nong X. Advances in targeted therapy for oral and maxillofacial head and neck squamous cell carcinoma. *[J] J Oral Maxillofac Surg* 2009;19(02):145–148
- 5 Chen L. Co-inhibitory molecules of the B7-CD28 family in the control of T-cell immunity. *Nat Rev Immunol* 2004;4(05):336–347
- 6 Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002;8(08):793–800
- 7 Grzywnowicz M, Giannopoulos K. The role of receptor programmed death-1 and its ligands in immune system and tumors. *Acta Haematol Pol* 2012;43:132–145
- 8 Mishra A. PD-1/PD-L1 biology and immunotherapy in HPV-positive oral cancers. *Future Oncol* 2017;13(22):1907–1909
- 9 Maruse Y, Kawano S, Jinno T, et al. Significant association of increased PD-L1 and PD-1 expression with nodal metastasis and a poor prognosis in oral squamous cell carcinoma. *Int J Oral Maxillofac Implants* 2018;47(07):836–845
- 10 Mann JE, Hoesli R, Michmerhuizen NL, et al. Surveilling the potential for precision medicine-driven PD-1/PD-L1-targeted therapy in HNSCC. *J Cancer* 2017;8(03):332–344
- 11 Pembrolizumab N. Has antitumor activity in advanced head and neck cancer. *Cancer Discov* 2016;6(07):693
- 12 Roskoski R Jr. Cyclin-dependent protein serine/threonine kinase inhibitors as anticancer drugs. *Pharmacol Res* 2019;139:471–488
- 13 Chohan TA, Qayyum A, Rehman K, Tariq M, Akash MSH. An insight into the emerging role of cyclin-dependent kinase inhibitors as potential therapeutic agents for the treatment of advanced cancers. *Biomed Pharmacother* 2018;107:1326–1341
- 14 Chang JT, Wang HM, Chang KW, et al. Identification of differentially expressed genes in oral squamous cell carcinoma (OSCC): overexpression of NPM, CDK1 and NDRG1 and underexpression of CHES1. *Int J Cancer* 2005;114(06):942–949
- 15 Chen X, Zhang FH, Chen QE, et al. The clinical significance of CDK1 expression in oral squamous cell carcinoma. *Med Oral Patol Oral Cir Bucal* 2015;20(01):e7–e12
- 16 Sánchez-Martínez C, Gelbert LM, Lallena MJ, de Dios A. Cyclin dependent kinase (CDK) inhibitors as anticancer drugs. *Bioorg Med Chem Lett* 2015;25(17):3420–3435
- 17 Mihara M, Shintani S, Nakashiro K, Hamakawa H. Flavopiridol, a cyclin dependent kinase (CDK) inhibitor, induces apoptosis by regulating Bcl-x in oral cancer cells. *Oral Oncol* 2003;39(01):49–55
- 18 Pai A, Jayashree BS. Computational Approach for the design of flavone based CDK2/CyclinA inhibitors: a simulation study employing pharmacophore based 3D QSAR. *Research J Pharm Tech* 2019;12(05):2299–2303
- 19 Okada Y, Ueno H, Katagiri M, et al. Experimental study of anti-angiogenic gene therapy targeting VEGF in oral cancer. *Odontology* 2010;98(01):52–59
- 20 Stîngă AC, Mărgăritescu O, Stîngă AS, et al. VEGFR1 and VEGFR2 immunohistochemical expression in oral squamous cell carcinoma: a morphometric study. *Rom J Morphol Embryol* 2011;52(04):1269–1275
- 21 Ferrara N. The role of vascular endothelial growth factor in pathological angiogenesis. *Breast Cancer Res Treat* 1995;36(02):127–137
- 22 Fury MG, Xiao H, Sherman EJ, et al. Phase II trial of bevacizumab + cetuximab + cisplatin with concurrent intensity-modulated radiation therapy for patients with stage III/IVB head and neck squamous cell carcinoma. *Head Neck* 2016;38(Suppl 1):E566–E570
- 23 Ibrahim N, Yu Y, Walsh WR, Yang JL. Molecular targeted therapies for cancer: sorafenib mono-therapy and its combination with other therapies (review). *Oncol Rep* 2012;27(05):1303–1311
- 24 Hsu FT, Chang B, Chiang IT, Wu TH, Hwang JJ. Synergistic effect of sorafenib with ionizing radiation on human oral cancer cells. *In Vivo* 2014;28(05):925–933
- 25 Fathima MZ, Shanmugarajan TS, Kumar SS, Yadav BVVN. Comparative in silico docking studies of Hinokitiol with sorafenib and nilotinib against proto-oncogene tyrosine-protein kinase (ABL1) and mitogen-activated protein kinase (MAPK) to target hepatocellular carcinoma. *Research J. Pharm. and Tech.* 2017;10(01):257–262

- 26 Zhang Y, Xue D, Wang X, Lu M, Gao B, Qiao X. Screening of kinase inhibitors targeting BRAF for regulating autophagy based on kinase pathways. *Mol Med Rep* 2014;9(01):83–90
- 27 Yadav A, Kumar B, Teknos TN, Kumar P. Sorafenib enhances the antitumor effects of chemoradiation treatment by downregulating ERCC-1 and XRCC-1 DNA repair proteins. *Mol Cancer Ther* 2011;10(07):1241–1251
- 28 Möckelmann N, Rieckmann T, Busch CJ, et al. Effect of sorafenib on cisplatin-based chemoradiation in head and neck cancer cells. *Oncotarget* 2016;7(17):23542–23551
- 29 Laban S, Steinmeister L, Gleißner L, et al. Sorafenib sensitizes head and neck squamous cell carcinoma cells to ionizing radiation. *Radiother Oncol* 2013;109(02):286–292
- 30 Papadimitrakopoulou VA, Frank SJ, Cohen EW, et al. 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(03):439–447
- 31 Bozec A, Sudaka A, Toussan N, Fischel JL, Etienne-Grimaldi MC, Milano G. Combination of sunitinib, cetuximab and irradiation in an orthotopic head and neck cancer model. *Ann Oncol* 2009;20(10):1703–1707
- 32 Machiels JP, Henry S, Zanetta S, et al. Phase II study of sunitinib in recurrent or metastatic squamous cell carcinoma of the head and neck: GORTEC 2006-01. *J Clin Oncol* 2010;28(01):21–28
- 33 Shakila Banu S, Krishnamoorthy G, Senthamarai R, Mohamed Jaabir MS. Synthesis, spectral characterization and anticancer activity of novel pyrimidine derivatives. *Research J Pharm Tech* 2020;13(12):6243–6247
- 34 Lyu J, Song H, Tian X, Miao Y, Ren G, Guo W. Predictive value of pAKT/PTEN expression in oral squamous cell carcinoma treated with cetuximab-based chemotherapy. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2016;121(01):67–72
- 35 Liao YM, Kim C, Yen Y. Mammalian target of rapamycin and head and neck squamous cell carcinoma. *Head Neck Oncol* 2011;3(01):22–25
- 36 Mohamed MA, Elkhateeb WA, Taha MA, Daba GM. New strategies in optimization of rapamycin production by streptomyces hygroscopicus ATCC 29253. *Research J Pharm Tech* 2019;12(09):4197–4204
- 37 Zaytseva YY, Valentino JD, Gulhati P, Evers BM. mTOR inhibitors in cancer therapy. *Cancer Lett* 2012;319(01):1–7
- 38 Bauman JE, Arias-Pulido H, Lee SJ, et al. A phase II study of temsirolimus and erlotinib in patients with recurrent and/or metastatic, platinum-refractory head and neck squamous cell carcinoma. *Oral Oncol* 2013;49(05):461–467
- 39 Lane HA, Wood JM, McSheehy PM, et al. mTOR inhibitor RAD001 (everolimus) has antiangiogenic/vascular properties distinct from a VEGFR tyrosine kinase inhibitor. *Clin Cancer Res* 2009;15(05):1612–1622
- 40 Naruse T, Yanamoto S, Yamada S, et al. Anti-tumor effect of the mammalian target of rapamycin inhibitor everolimus in oral squamous cell carcinoma. *Pathol Oncol Res* 2015;21(03):765–773
- 41 Mak MP, William WN Jr. Targeting the epidermal growth factor receptor for head and neck cancer chemoprevention. *Oral Oncol* 2014;50(10):918–923
- 42 Normanno N, Bianco C, Strizzi L, et al. The ErbB receptors and their ligands in cancer: an overview. *Curr Drug Targets* 2005;6(03):243–257
- 43 Sari S, Andayani TM, Endarti D, Widayati K. Cost-effectiveness analysis of afatinib versus gefitinib in non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation in Indonesia: observational studies with retrospectives. *Research J Pharmacy Technology* 2022;15(04):1598–2
- 44 Goerner M, Seiwert TY, Sudhoff H. Molecular targeted therapies in head and neck cancer—an update of recent developments-. *Head Neck Oncol* 2010;2(01):8–9
- 45 Dhairiyasheel G, Adhikrao Y, Varsha G. Design and development of solid self-microemulsifying drug delivery of gefitinib. *Asian J Pharm Tech* 2018;8(04):193–199
- 46 Aldoss IT, Ganti AK. Targeted therapy for squamous cell carcinoma of the head and neck. *J Egypt Natl Canc Inst* 2009;21(02):157–166
- 47 Burtneß B. The role of cetuximab in the treatment of squamous cell cancer of the head and neck. *Expert Opin Biol Ther* 2005;5(08):1085–1093
- 48 Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359(11):1116–1127
- 49 Naruse T, Yanamoto S, Matsushita Y, et al. Cetuximab for the treatment of locally advanced and recurrent/metastatic oral cancer: an investigation of distant metastasis. *Mol Clin Oncol* 2016;5(02):246–252
- 50 Xu X. Short-term efficacy of nimotuzumab combined with docetaxel-cisplatin- fluorouracil in the treatment of advanced oral cancer. *Electronic J General Stomatology* 2016;3(11):79–80
- 51 Hamakawa H, Nakashiro K, Sumida T, et al. Basic evidence of molecular targeted therapy for oral cancer and salivary gland cancer. *Head Neck* 2008;30(06):800–809
- 52 Shintani S, Li C, Mihara M, Nakashiro K, Hamakawa H. Gefitinib ('Iressa'), an epidermal growth factor receptor tyrosine kinase inhibitor, mediates the inhibition of lymph node metastasis in oral cancer cells. *Cancer Lett* 2003;201(02):149–155
- 53 Kumar VK, Raju NA, Begum S, Rao JS, Satyanarayana T. The estimation of gefitinib in tablet dosage forms by RP-HPLC. *Research J Pharm Tech* 2009;2(02):341–343
- 54 Moral M, Paramio JM. Akt pathway as a target for therapeutic intervention in HNSCC. *Histol Histopathol* 2008;23(10):1269–1278
- 55 Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 2004;22(01):77–85
- 56 Fumagalli I, Dugue D, Bibault JE, et al. Cytotoxic effect of lapatinib is restricted to human papillomavirus-positive head and neck squamous cell carcinoma cell lines. *OncoTargets Ther* 2015;8:335–345
- 57 Weiss JM, Bagley S, Hwang WT, et al. Capecitabine and lapatinib for the first-line treatment of metastatic/recurrent head and neck squamous cell carcinoma. *Cancer* 2016;122(15):2350–2355
- 58 Cunha SI, Pietras K. ALK1 as an emerging target for antiangiogenic therapy of cancer. *Blood* 2011;117(26):6999–7006
- 59 Hawinkels LJ, de Vries AG, Paauwe M, et al. Activin receptor-like kinase 1 ligand trap reduces microvascular density and improves chemotherapy efficiency to various solid tumors. *Clin Cancer Res* 2016;22(01):96–106
- 60 Dudek AZ, Lesniewski-Kmak K, Shehadeh NJ, et al. Phase I study of bortezomib and cetuximab in patients with solid tumours expressing epidermal growth factor receptor. *Br J Cancer* 2009;100(09):1379–1384
- 61 Wang C, Ren M. Progress in endostatin and its application in cancer therapy. *Int J Genet* 2010;33(05):298–302
- 62 Li L, Cao L. Clinical effect analysis of endostatin combined with chemotherapy in the treatment of multiple advanced malignant tumors, electron. *J Clin Med Lit* 2017;4(95):18632–18634