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Review Article

Emerging Role of Lenvatinib in Treating Platinum-Refractory Head and Neck Cancer in Resource-Limited Settings

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Abstract

Lenvatinib, an oral multiple tyrosine kinase inhibitor, is currently being explored in the area of head and neck squamous cell carcinoma (HNSCC). Two-thirds of total patients are presented in the advanced stage leading to poor prognosis with conventional treatment. The addition of immunotherapy is the standard approach to it. However, in developing nations and resource-limited setups, affordability is the major concern. To encounter this, lenvatinib has become a novel cost-effective treatment for HNSCC. Lenvatinib targets a varied range of receptors including vascular endothelial growth factor receptor, platelet-derived growth factor receptor α, fibroblast growth factor receptor, KIT (stem cell factor receptor), and rearranged during transfection, all of which are involved in the pathogenesis of HNSCC leading to the establishment of its role in HNSCC. It inhibits angiogenesis in endothelial cells and proliferation in tumor cells. Instances of resistance were observed in monoreceptor targeting agents, which are also overcome by lenvatinib, leading to potent antitumor activity. Clinical studies are being conducted to establish the role of lenvatinib as a third-line therapy in HNSCC. In this review, we discuss the role of lenvatinib in resource-limited, platinum-refractory, and recurrent/metastatic HNSCC.

Keywords
- lenvatinib
- advanced head and neck cancer
- platinum-refractory
- resource-limited settings
- clinical trials

Introduction

Head and neck cancers (HNCs) comprise a heterogeneous group of malignancies that are classified into three different groups: oral cavity (covering tongue and mouth), oropharynx (involving tonsil and oropharynx), and other HNC (encompassing larynx and pyriform fossa).[1] A substantial majority (~90%) of HNC are attributable to head and neck squamous cell carcinoma (HNSCC).[2] HNSCC makes up the seventh most prevalent cancer diagnosis in the world. According to GLOBOCAN estimates, HNSCC accounts for around 4.5% of cancer diagnoses and deaths annually, with 890,000 new cases and 450,000 deaths.[3] Furthermore, the most prevalent malignancies in developing nations such as India, Pakistan, Bangladesh, and Southeast Asia are those of HNC.[4] HNC makes up 30% of all cancer cases in India. GLOBOCAN 2020 predicts that by 2040, there will be 2.1 million new instances of cancer in India, a 57.5% rise from 2020.[5]

The major conventional risk factors for the rise of HNSCC in developing nations are tobacco (betel quid), smoking, and

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alcohol. Due to these social habits, oral cavity squamous cell carcinoma is predominated (nearly 90%) in developing countries.[6] In contrast to this, in developed nations human papillomavirus (HPV) is identified as the leading cause of HNSCC.[7,8] On the other hand, nonoral cavity cancer specifically oropharyngeal and laryngeal cancers are associated with HPV infection.[9] The treatment of oral cavity cancer varies according to stages. The early-stage treatment regimen includes surgery while patients having an increased risk of locoregional recurrence also receive postoperative adjuvant therapy, which includes radiation. The addition of platinum compound with radiation in an adjuvant setup increased the 2-year locoregional control rate by 4.5%.[10] However, about two-thirds of patients with HNSCC present with locally advanced HNC due to various psychosocial factors and resource-limited setup of the health care system.[11,12]

Despite aggressive multimodality treatment, the rate of locoregional failure is approximately 50%.[13] The advanced-stage treatment regimen includes neoadjuvant therapy followed by surgery and adjuvant therapy. Neoadjuvant first-line therapy encompasses the EXTREME regimen, which includes combination of platinum compounds with 5-fluorouracil and cetuximab that increases overall survival (OS) by 10.1 months. However, 50% of the patients with HNSCC undergo recurrent/metastatic (R/M) disease having poor prognosis and median survival ranging from 6 to 12 months, which suggested inclusion of immunotherapy in the regimen.[13–15] Various immunological agents are approved for HNSCC (illustrated in ►**Fig. 1**). The addition of pembrolizumab or nivolumab to the frontline therapy in R/M disease increases the median OS by 13 months in total population as per the KEYNOTE-048 study.[16,17] However, chemotherapy has its drawbacks of grade 3 and 4 toxicities and the adoption of these targeted regimens is only 1 to 3% in low- and middle-income countries due to affordability issues attributing to nearly 70% of all cancer-related fatalities.[18] So, oral metronomic chemotherapy (OMCT) with low-dose immunotherapy becomes a second-line regimen. Low-dose immunotherapy decreases the cost by 5 to 9%; however, it increases OS by just 3 months compared with standard therapy.[19] As a result, more accessible and effective alternative therapy for resource-limited setup such as lenvatinib has gained a lot of attention. Lenvatinib is a small molecule multitargeted kinase inhibitor that targets several receptors leading to both antiangiogenic and antiproliferative activity.[20] It has demonstrated effectiveness in stabilizing various progressive diseases listed in ►**Table 1**. However, questions about the efficacy of lenvatinib monotherapy or in combination regimens for third-line treatment in HNSCC are still uncovered. Here, in an attempt to focus on these unmet topics, we discuss recent data about lenvatinib treatment in resource-limited, platinum-refractory, and R/M HNSCC from clinical trials and clinical practice.

Molecular Mechanism of Lenvatinib

Lenvatinib is an oral multitargeted tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptor (VEGFR 1–3), platelet-derived growth factor receptor α

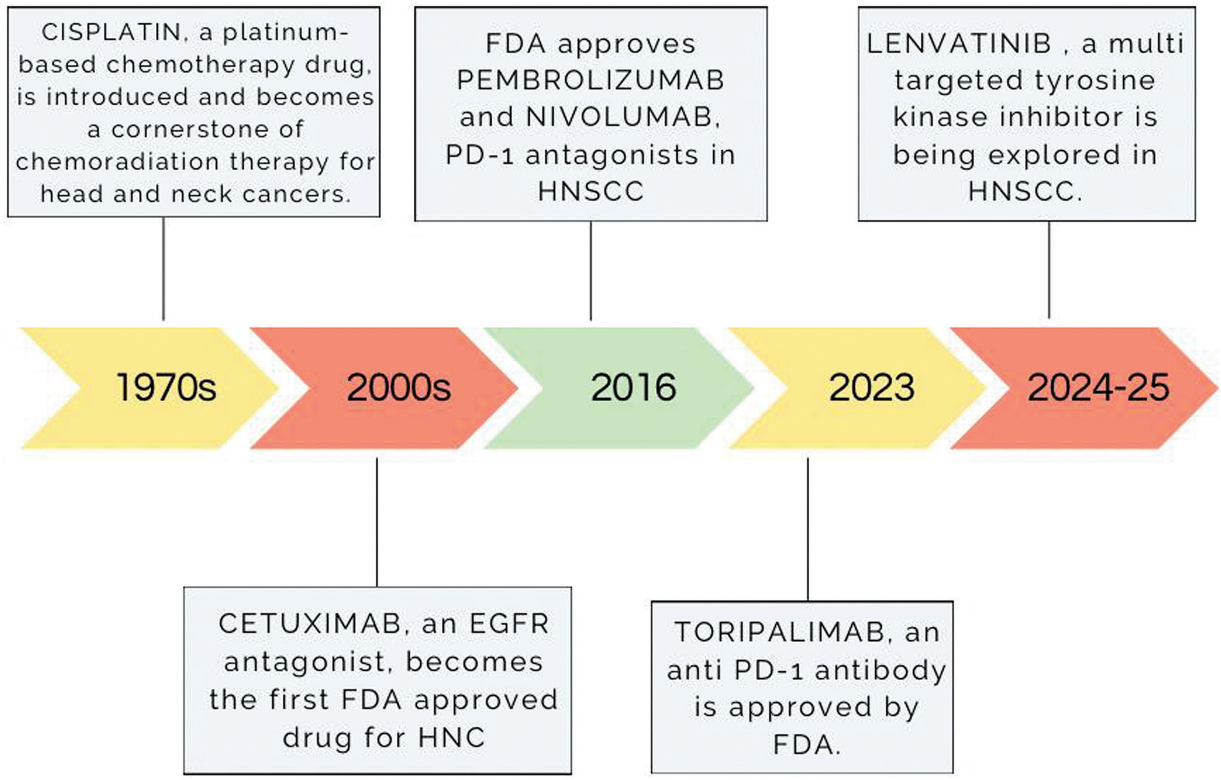

Fig. 1 Timeline of approved agents for head and neck cancer treatment. This figure illustrates the evolution of approved therapeutic agents for head and neck cancer (HNC) over the years. The timeline provides a clear view of the advancement of therapy for HNC.

(PDGFRα), fibroblast growth factor receptor (FGFR 1–4), stem cell factor receptor (KIT), and rearranged during transfection (RET). Approximately 90% of HNSCC substantially expresses angiogenesis factors and are linked to patient prognosis.[21] VEGF and FGF signaling pathways are important mediators of angiogenesis in endothelial cells (illustrated in ►**Fig. 2**) and PDGFRα, RET, and KIT pathways are involved in the proliferation of cancerous cells (illustrated in ►**Fig. 3**).[22]

The five members of the VEGF kinase family in mammals—the placental growth factor, VEGF-A, VEGF-B, VEGF-C, and VEGF-D—have varying binding affinities for three different VEGF tyrosine kinase receptors, namely, VEGFR 1, 2, and 3.[23] VEGF-A has binding affinity toward VEGFR 1 and 2, while VEGF-B binds to VEGFR 1. VEGF-C/D activates VEGFR 3 by binding to it.[24] The ligand-receptor binding results in the dimerization of the receptor followed by autophosphorylation leading to the triggering of intracellular signaling pathways.[25] Overexpression of VEGFR 1, 2, and 3 triggers the signaling of phospholipase C-γ (PLCγ), phosphatidylinositol 3-kinase (PI3K), and Akt pathways.[24,26] Additionally, the overexpression of VEGFR 1 activates Src homology phosphatase-2 (SHP2) and growth factor receptor-bound protein 2 (Grb2),[27] VEGFR 2 activates MAP kinase (MAPK) and VEGFR 3 activates Grb2 and Sbc pathways, which in turn leads to angiogenesis, vasculogenesis, and lymphangiogenesis, respectively.[28–31]

FGFR encompasses a subset of five members, namely, FGFR 1 to 5, whose signaling involves binding of FGF to the receptors resulting in receptor dimerization and subsequent autophosphorylation.[32,33] The FGF family consists of a subset of 22 FGF ligands.[34] The major signaling pathways activated by FGF/FGFR include the PI3K/Akt, Ras/Raf-MEK-MAPK, PLCγ, and transcription factors such as signal transducers and activators of transcription (STATs).[35,36] Also, FRS2, a unique protein, binds to FGFR and stimulates downstream signaling molecules, namely, Grb2 and Shp2.[34,37] The activation of these signaling pathways results in the promotion of angiogenesis.[38] Besides its antiangiogenic effects, lenvatinib's suppression of VEGF and FGF signaling transforms the intrinsically immunosuppressive tumor microenvironment into an immune-stimulatory state.[39–41]

PDGF family comprises four polypeptide chains, PDGF A, PDGF B, PDGF C, and PDGF D.[42] This polypeptide chain undergoes dimerization through disulfide bonds to form five dimeric ligands—PDGF-AA, PDGF-BB, PDGF-CC, PDGF-DD, and PDGF-AB. PDGF receptors are of two types, PDGFR-α located in cancer cells and PDGFR-β located in stromal cells.[43] Ligand binding majorly to PDFR-AA and PDGFR-BB to PDGF-α receptor leads to subsequent dimerization and autophosphorylation of the receptors, which is a crucial step for activation of kinase activity through a conformational change in receptor, and second, it provides free docking sites for SH-2 domain-containing signaling molecules, consequently stimulating various signaling pathways such as PI3K, AKT/PKB, MAPK, ERK, JAK/STAT, and NOTCH pathways.[42,44–47] Activation of the signaling pathways leads to the promotion of cellular growth and proliferation, migration, invasion, and metastasis of tumor cells.[42]

RET is a transmembrane glycoprotein RTK encoded by RET proto-oncogene located on chromosome 10 and it is linked to cancer development.[48] It interacts with glial cell line-derived neurotrophic factor (GDNF) family ligands with the help of cofactor receptors from the growth factor receptor (GFRα) family (GFRα1–4).[49] This interaction activates RET kinase, which triggers the activation of signaling pathways such as RAS-MAPK, JAK-STAT, PI3K-AKT, and PKC.[50] cKIT is a transmembrane type III RTK that is encoded by kit proto-oncogene found in chromosome 4 of humans.[51] The physiological ligand of cKIT is stem cell factor (SCF) also called cKIT ligand.[52] Activation of cKIT takes place through the binding of SCF, which results in a series of events leading to stimulation of multiple downstream signaling pathways.[53,54] The signaling pathways involved in RET and cKIT are PI3K/AKT, PLCγ, MAPK, JAK/STAT, and RAS/RAF, which in turn promote cell proliferation, growth, and survival.[55–57]

Various growth factors are abundantly produced by HNSCC tumor cells. Eighty-seven percent of HNSCC patients exhibit VEGFR expression, and 97% have PDGFR expression.[58] Overexpression of FGFR in HPV-positive HNSCC and HPV-negative HNSCC was found to be 82 and 75%, respectively.[59] Therefore, blocking these RTKs with the help of a single molecule named lenvatinib can prevent tumor growth by reducing tumor angiogenesis and prevent growth acceleration by inhibiting cell proliferation.[60] Additionally, dual inhibition of VEGFR1–3 and FGFR1–4 signaling activity by lenvatinib results in the reversal of FGF-mediated acquired resistance to VEGF blockade.[22]

Clinical Trials-Based Evidence on Lenvatinib

A phase I/Ib trial intended toward checking the potential of lenvatinib in combination with cetuximab among patients having R/M HNSCC was conducted by enrolling 12 patients regardless of any prior cetuximab therapy for the dose deescalation study (NCT03524326). The primary endpoint was to determine the maximum tolerated dose (MTD) of lenvatinib in combination with cetuximab. Exploratory endpoints encompass overall response rate (ORR) and progression-free survival (PFS) in HNSCC patients receiving treatment at the MTD. A daily 20-mg dose of lenvatinib was given to nine evaluable patients. Six of nine patients had a partial response with ORR of 67%, and for eight of nine patients who had completed the treatment, the median PFS was 3.6 months (range 1.6–10.4). At 24 mg dose, high-grade toxicities such as thrombotic events were reported. The most common grade 3 treatment-related adverse events were hypertension, oral mucositis, and oral cavity fistula. This draws a conclusion that immersion of lenvatinib to cetuximab leads to good responses in the patients. However, there is a need for more research and large-scale randomized trials are needed for patient's refractory to previous lines of treatment or anything similar.[61]

Another trial for defining the role of lenvatinib with pembrolizumab as first-line therapy in R/M HNSCC was conducted by choosing placebo combined with pembrolizumab as a comparator (NCT04199104). A total of 511 patients were

Table 1 Lenvatinib's approval in various cancers

Sr. no.	Types	Trial name	Stage of cancer	Combination	Phase	Treatment arm 1	Treatment arm 2	Outcomes	NCT number
1.	DTC	SELECT	Locally recurrent or metastatic	–	Phase 3	Lenvatinib	Placebo	Median PFS Arm 1 = 18.3months Arm 2 = 3.6 months	NCT01321554
2.	RCC	Study 205 (LEN + EVE)	Advanced RCC	Combination with everolimus	Phase 2	Lenvatinib + everolimus	Lenvatinib	PFS Arm 1 = 5.5 months Arm 2 = 14.6 months	NCT01136733
		CLEAR	Advanced RCC	Combination with pembrolizumab	Phase 3	Lenvatinib + pembrolizumab	Sunitinib	PFS Arm1 = 23.9 months Arm2 = 9.2 months	NCT02811861
3.	HCC	REFLECT	Unresectable HCC	–	Phase 3	Lenvatinib	Sorafenib	Median PFS Arm 1 = 7.3 months Arm 2 = 3.6 months	NCT01761266
4.	Endometrial carcinoma	KEYNOTE 775	Advanced	Combination with pembrolizumab	Phase 3	Lenvatinib + pembrolizumab	Paclitaxel + doxorubicin	Median PFS Arm 1 = 6.7 months Arm 2 = 3.8 months	NCT03517449

Abbreviations: DTC, differentiated thyroid cancer; HCC, hepatocellular carcinoma; NCT, National Clinical Trial; PFS, progression-free survival; RCC, renal cell carcinoma.

enrolled for the study and the primary endpoints were PFS, OS, and ORR. Secondary endpoints selected were duration of response (DOR), safety, and tolerability. The ORR of the combination to placebo was 46.1% versus 25.4% and the median PFS was also more than doubled with the combination compared with placebo (6.2 vs. 2.8 months, hazard ratio = 0.64). The OS of pembrolizumab with placebo was observed as 15 months whereas the combination of pembrolizumab and lenvatinib had an OS of 17.9 months. Due to no major difference observed in OS, the trial was discontinued.[62]

A study for the establishment of lenvatinib and pembrolizumab combination as a potential therapy for heavily pretreated R/M HNSCC was conducted.[63] A total of 14 participants who had undergone at least two lines of systemic standard treatment were selected. Also, 71% of these participants had experienced anti-PD-1 treatment failure. The primary endpoint was ORR and the secondary endpoints selected were PFS, OS, disease control rate, and DOR. The ORR was 28.6%. The OS and PFS were 6.2 and 4.6 months, respectively, while the disease control rate was 42.9%. On the contrary, the Keynote-055 trial defining the role of pembrolizumab as third-line therapy in R/M HNSCC showed PFS of 2.1 months.[64] This improvement of 2.5 months in PFS indicates an important contribution of lenvatinib to the regimen. However, there is a need for more large-scale randomized trials for lenvatinib monotherapy trials in order to determine its independent role in R/M HNSCC.

Ongoing Clinical Trials

An ongoing trial LEAP-009 (NCT04428151) aims to assess the safety and effectiveness of lenvatinib monotherapy or lenvatinib plus pembrolizumab in comparison to chemotherapy in patients with R/M HNSCC who have progressed following treatment using platinum-based treatment and a PD-1/L1 inhibitor. Estimated recruitment till now is nearly 400, which is currently underway. The primary endpoint selected is ORR and the secondary endpoints include DOR, PFS, OS, and safety.

Safety Profile of Lenvatinib

Approximately more than 30% of all the patients treated with lenvatinib experience adverse reactions. Across the lenvatinib clinical trials for various malignancies, the most common adverse events leading to dose modification include hypertension, diarrhea, fatigue, acneiform rash, arthralgia, decreased body weight, reduced appetite, headache, stomatitis, nausea, vomiting, proteinuria, oral mucositis, abdominal pain, dysphonia, hand-foot syndrome, and oral cavity fistula. For successfully managing these events, there is the requirement of proper and effective coordination with the patient and clinical team in order to optimize the supportive measures.[22,65]

Resistance Mechanisms of Lenvatinib

The most common problem with all therapeutic medications is the development of drug resistance. As the

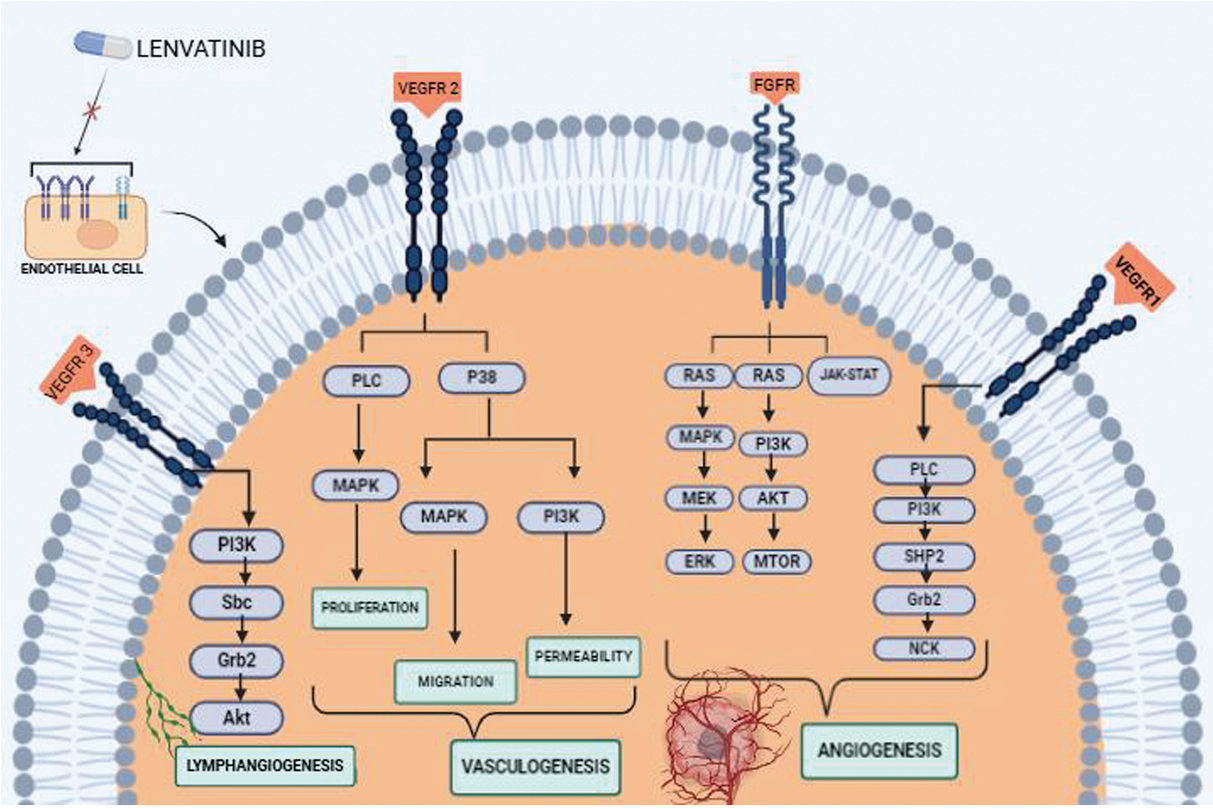

Fig. 2 Molecular mechanisms of vascular endothelial growth factor (VEGFR) and fibroblast growth factor (FGFR) receptors. The figure depicts the role of VEGFR and FGFR occurring in endothelial cells. The signaling pathways of VEGF and FGF promote endothelial cell proliferation, migration, and survival, leading to angiogenesis that results in sustaining tumor growth environment. The figure highlights how lenvatinib blocks VEGFR and FGFR pathway activation. Lenvatinib reduces vascular permeability and endothelial cell proliferation by inhibiting receptor phosphorylation and downstream signaling cascades, thereby limiting their growth and metastasis.

treatment period for the therapy lengthens, the malignant cells may adjust the blocking pathway, which subsequently leads to drug resistance. The major studied mechanism of drug resistance for lenvatinib is blockage of the target receptors such as FGFR, VEGFR, PDGFR, KIT, and RET.[66–68] Additionally, recent developments showed the role of checkpoint modulation, cytokine overproduction, cell apoptosis, cell ferroptosis, and N6-threonylcarbamoyladenosine alteration in the resistance mechanism.[69] However, potential ways to conquer the resistance pattern of lenvatinib in HNSCC such as blocking the resistance targets and increase sensitization of the drug, is still yet to be explored.

Future Modalities of Lenvatinib in HNC

Lenvatinib, a multitargeted drug therapy, is currently being explored in palliative care in advanced and platinum-refractory HNSCC. As it targets a range of receptors, namely, VEGFR, FGFR, PDGFR, RET, and KIT, it can address poor response occurring due to increasing resistance by monoreceptor-targeting agents.[70] Various studies are being designed to establish the role of lenvatinib in this third-line setting. Advancements in the research could possibly integrate lenvatinib into the curative setup, especially for patients with resource-limited settings like developing nations. The lack of established biomarkers underscores the need for additional studies to identify potential predictors of response, optimize patient selection, and enhance treatment outcomes. Currently, ongoing and future studies for enhancing the role of lenvatinib are crucial, as they will reflect the shift in current treatment paradigms by providing more effective strategies for managing the HNSCC.

Conclusion

As conventional therapy fails to respond in advance HNC leading to more recurrences, targeted and immunological agents are rapidly evolving. In resource-limited nations like India affordability becomes the major concern. In HNSCC, first-line immunotherapy is often expensive and thus is not an accessible option in developing nations. However, the financial strain still continues in second-line treatment settings, which consist of low-dose immunotherapy with OMCT, making sustained treatment access challenging. Lenvatinib as a third-line treatment serves as a promising cost-effective and clinically beneficial approach. Lenvatinib targets multiple receptors leading to overcoming the issue of resistance. Currently, ongoing trials are exploring its combination with other targeted agents. However, to fully optimize and harness lenvatinib's potential in clinical use, further research including its efficacy in different

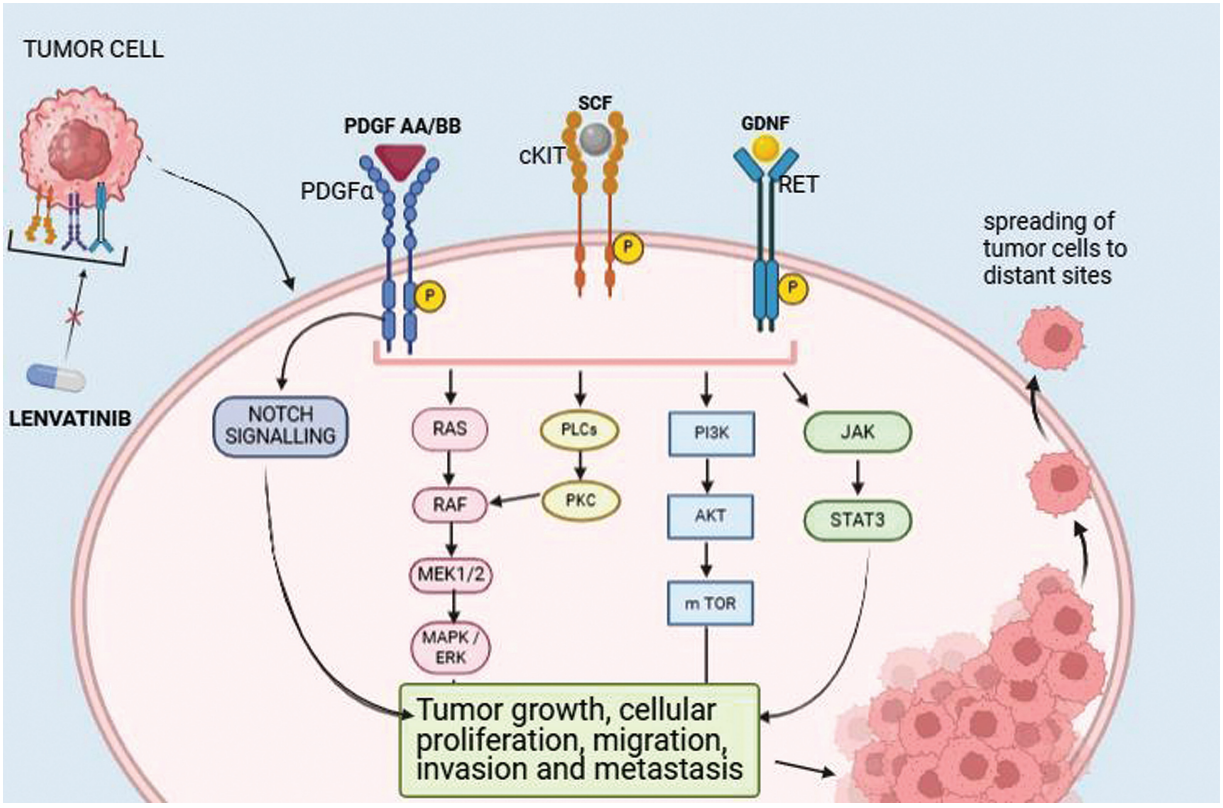

Fig. 3 Molecular mechanisms of platelet-derived growth factor (PDGFR), stem cell factor (cKIT), and rearranged during transfection (RET) receptors. This figure illustrates the molecular signaling pathways of PDGFR, c-KIT, and RET that are involved in the proliferation, differentiation, and metastatic spread of tumor cell. These receptors are often dysregulated in metastatic cancers, which result in uncontrolled tumor growth and increased metastatic potential. Lenvatinib blocks the activity of these receptors by inhibiting their kinase activity, thus preventing the activation of downstream pathways resulting in the suppression of tumor growth, proliferation, migration, and metastasis.

stages along with platinum-refractory HNSCC is required. Emphasizing an in-depth examination will not only unlock the full capabilities of lenvatinib but also promote the advancement strategies for development of other targeted agents.

Data Availability Statement

The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

A.K., R.K., M.M.: Conceptualization. K.R.M., N.H.S., V.G.K.: Writing original draft, data collection, and interpretation. A.K.: Supervision. A.K., R.K., M.M.: Writing review and editing. All authors read and approved the final content.

Patient Consent

Patient consent is not required as no patients were involved in the preparation of this article.

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Conflict of Interest

None declared.

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