THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 7

REVIEW ARTICLE

Review of the Targeted Therapy for Advanced/Aggressive Olfactory Neuroblastoma as Adjuncts to Standard Therapy

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OPEN ACCESS

PUBLISHED
31 July 2025

CITATION
Madhwacharya, AB., Karim, J., et al., 2025. Review of the Targeted Therapy for Advanced/Aggressive Olfactory Neuroblastoma as Adjuncts to Standard Therapy. Medical Research Archives, [online] 13(7). https://doi.org/10.18103/mra.v13i7.6629

DOI
https://doi.org/10.18103/mra.v13i7.6629

ISSN
2375-1924

ABSTRACT

Olfactory neuroblastoma is a rare and histologically variable malignancy arising from the olfactory neuroepithelium. While it may present indolently in early stages, aggressive or advanced forms often involve intracranial invasion, high-grade histology, and distant metastasis, leading to poor prognosis and frequent recurrence. The traditional management of olfactory neuroblastoma relies on surgical resection combined with radiotherapy, with chemotherapy applied in recurrent or metastatic settings. However, these modalities frequently fall short in high-risk cases due to resistance, recurrence, or anatomical constraints.

This review focuses on the evolving role of targeted therapy as a precision approach to treating aggressive and advanced olfactory neuroblastoma. The aim is to summarize current evidence from translational research and early-phase clinical trials regarding therapies directed at molecular abnormalities commonly identified in these tumors. Key genetic alterations include mutations in tumour protein p53 (TP53), dicer 1 ribonuclease III (DICER1), fibroblast growth factor receptor 3 (FGFR3), isocitrate dehydrogenase 2 (IDH2), anaplastic lymphoma kinase (ALK), and aberrant activation of the phosphatidylinositol 3-kinase (PI3K)/mechanistic target of rapamycin (mTOR) pathway.

Therapeutic strategies under investigation include tyrosine kinase inhibitors (e.g., erlotinib, sorafenib), ALK inhibitors (e.g., crizotinib), mTOR inhibitors (e.g., everolimus), and immune checkpoint inhibitors (e.g., nivolumab). While early data are promising, robust clinical validation remains limited. This review also addresses the current limitations of targeted therapy in olfactory neuroblastoma, such as tumour heterogeneity, lack of large-scale trials, and challenges in molecular profiling. Continued integration of genomic data into clinical decision-making may enable more effective, individualized treatment strategies for this rare but formidable malignancy.

Keywords: *Olfactory neuroblastoma, targeted therapy, tyrosine kinase inhibitors, molecular profiling, precision oncology, FGFR3, ALK, mTOR pathway, immunotherapy, aggressive sinonasal tumors.*

1. Introduction

Olfactory neuroblastoma is also called as esthesioneuroblastoma. It is a rare malignant tumour from the olfactory neuroepithelium within the nasal cavity. ONB has been clinically significant since its initial description by Berger et al. in 1924[1]. However, the infrequency of the malignancy has accounted for over three to six per cent of all sinonasal tumours[2]. Despite being rare, ONB needs multidisciplinary management because of their aggressive nature that may lead to local invasion and distant metastasis.

EPIDEMIOLOGY OF OLFACTORY NEUROBLASTOMA

Characterized by a distinct pattern in its epidemiology, the disease exhibits a unimodal distribution with peak incidence among adults aged 50 to 60 years[3]. Historically, it has also shown a bimodal distribution, with increased rates among younger adults aged 10 to 20. Recent epidemiological studies may challenge this view. A retrospective Surveillance, Epidemiology, and End Results (SEER) registry analysis of 636 cases from 1977 to 2016 has identified a greater number of male patients that was 59.7% and a high prevalence was observed among Caucasians with a median age at diagnosis of 51.4 years[4]. The study by Fiani et al.[5], has also shown that 78.3% of patients were presented with primary tumors that were confined to the nasal cavity. Also, 10-33% have shown involvement of cervical lymph nodes. The spread of metastasis has been observed in 20 to 48 per cent of cases that have common sites like bones and lungs. Socioeconomic status (SES) also has some influence on the presentation of disease and its prognosis. A separate SEER analysis found that patients in the lowest SES groups were 85% more likely to present with advanced-stage ONB compared to those in the highest SES groups. Also, lower SES was related to 70 per cent worse disease-specific survival (DSS). This highlights the disparities in healthcare access and early diagnosis[6].

CLINICAL PRESENTATION AND STAGING

Olfactory neuroblastoma presents commonly with nonspecific symptoms that lead to delays in the diagnosis. The most common early manifestations were nasal obstruction and epistaxis along with hyposmia or anosmia. Also, sometimes preceding diagnosis by several years[4 7,8]. As the disease progresses the symptoms may differ depending on the local invasion extent. The tumor extends into the orbit and may lead to proptosis, diplopia, or visual disturbances. Meanwhile, the intracranial invasion may lead to headaches or syndrome of inappropriate antidiuretic hormone secretion (SIADH)[9]. Imaging plays a vital role in the diagnosis and staging of ONB. A characteristic dumbbell-shaped mass crossing the cribriform plate is observed often in radiological studies[10]. Computed tomography (CT) was useful for the assessment of the involvement of the bone. Magnetic resonance imaging (MRI) gives a better visualization regarding the soft tissue, orbital, and intracranial extension. ONB normally appears to be hypointense on T1-weighted MRI and iso to hyperintense on T2-weighted images that were enhanced by contrast[11]. Whole-body CT or Positron Emission Tomography (PET) scans are recommended for evaluating systemic disease[12]. Gallium-68 DOTATOC PET has been researched for the detection of somatostatin receptor expression. This proves its utility in diagnosis, staging, and treatment monitoring[13].

Olfactory neuroblastoma was staged with the help of multiple classification systems. The Kadish system that was first proposed in 1976 has categorized tumours as follows[14 15],

- Stage A: The tumor is restricted to the nasal cavity.
- Stage B: The tumor extends into the paranasal sinuses.
- Stage C: The tumor has spread beyond the sinonasal area, affecting structures such as the orbit and intracranial region.
- Stage D: There is involvement of the cervical lymph nodes or the presence of distant metastases.

The modified Kadish system is significant in predicting outcomes, as demonstrated by 10-year overall survival (OS) and disease-specific survival (DSS) rates, which range from 83.4% and 90% in

Stage A to 13.3% and 35.6% in Stage D, respectively[16]. Additionally, staging methods such as the tumor-node-metastasis (TNM) classification and the Dulguerov-modified TNM system offer further stratification by incorporating imaging findings and tumor invasion patterns[17].

Table 1. Olfactory Neuroblastoma Staging System

Staging System	Staging system
Kadish Staging	**Stage A:** Tumor is limited solely to the nasal cavity.
	Stage B: Tumor involves both the nasal cavity and the paranasal sinuses.
	Stage C: Tumor extends beyond the nasal cavity and paranasal sinuses.
Morita Modification	**Stage A:** Tumor remains confined to the nasal cavity.
	Stage B: Tumor affects both the nasal cavity and the paranasal sinuses.
	Stage C: Tumor spreads beyond the nasal cavity and paranasal sinuses.
	Stage D: Tumor shows regional or distant metastasis.
Dulguerov Modified TNM Staging	**Primary Tumor (T)**
	T1: Tumor is confined to the nasal cavity or paranasal sinuses (excluding involvement of the sphenoid or superior ethmoid sinuses).
	T2: Tumor includes the sphenoid sinus and extends to or erodes the cribriform plate.
	T3: Tumor extends into the orbit or anterior cranial fossa without invading the dura.
	T4: Tumor involves the brain.
	Lymph Nodes (N)
	N0: No metastasis is observed in the cervical lymph nodes.
	N1: Metastasis is present in any cervical lymph node.
	Distant Metastasis (M)
	M0: No distant metastasis.
	M1: Distant metastasis is present.

Table 1: Summarizes key classification systems for olfactory neuroblastoma

CHALLENGES IN TREATING ADVANCED/ AGGRESSIVE OLFACTORY NEUROBLASTOMA

Despite having multimodal treatment approaches the advanced ONB was difficult to manage because of its aggressive behavior and high recurrence rates. Surgical resection was considered as the gold standard traditionally with open craniofacial resection as the main approach. However, in recent years, endoscopic endonasal resection has obtained popularity because of its lower rates of complications, shorter hospital stays, and comparable oncological outcomes[10]. Radiotherapy is a critical adjunct used for the treatment of ONB. However, there are not yet universally accepted guidelines available for its application. The role of chemotherapy is controversial and there is ongoing debate regarding its optimal use in induction and concurrent settings. The prognosis of ONB remains variable because of its heterogeneity and high metastatic potential. Hyams grading is a histopathological system that classifies ONB from Grade I (well-differentiated) to Grade IV (poorly differentiated). It has been related to survival outcomes. High-

grade tumours (III/IV) show significantly worse survival rates than low-grade tumours (I/II). That is with 5-year survival rates of 56% vs. 25% and 10-year rates of 67% vs. 36% respectively[18 19].

RATIONALE FOR TARGETED THERAPY AS AN ADJUNCT TO STANDARD TREATMENTS

Considering the limitations of conventional therapies, targeted approaches can be used as an alternative by focusing on the molecular pathways that are implicated in the progression of ONB. ONB shows various genetic alterations, and this makes precision medicine an alternative for therapy. The targeted agents that were directed at angiogenesis, tyrosine kinase receptors, immune checkpoints, and the PI3K/AKT/mTOR signaling pathway have shown some potential to improve patient outcomes[10]. Due to the rarity of the ONB, there is a need for further research and clinical trials. These may help in defining the optimal integration of targeted therapies into current treatment approaches.

2. Standard Therapy for Advanced/ Aggressive Olfactory Neuroblastoma Surgery

Surgical resection is one of the common treatment methods for localized and locally advanced ONB. It is with the extent of resection as a critical factor in overall survival and event-free survival[20]. Open craniofacial resection (CFR) has been the standard for treating advanced ONB historically. However, in recent years endoscopic endonasal approaches have obtained prominence because of their lower rates of complications and shorter hospital stays[21]. The International Consensus Statement on Endoscopic Skull Base Surgery recommends endoscopic resection for Kadish A and B tumours. Meanwhile, Kadish C tumours can be treated endoscopically only if negative margins can be obtained. Tumours that have orbital involvement or those extending laterally to the orbital axis, midface, or hard/soft palate must be managed with the help of surgery[22]. Challenges in surgery occur in cases of orbital, dural, or brain invasion. As it is very difficult to obtain a negative margin in these cases. In the situation where complete resection is not feasible, combined intracranial and extracranial methods may be needed. This can be done by incorporating endoscopic and transcranial neurosurgical techniques[5]. However, the advancements in endoscopic techniques provide visualizations that are comparable to bilateral subfrontal approaches. But these combined approaches are becoming less common. Because of the rarity of the ONB, the comparative studies between endoscopic and open surgical techniques remain challenging. However, the reviews and meta-analyses suggest at least equivalent survival rates between these approaches[22]. No significant rates have been observed in the pooled analysis of 226 patients regarding survival outcomes between endoscopic and open surgery for T1 and T2 sinonasal malignancies[22]. A meta-analysis by Schwart et al.[23] has shown that endoscopic surgery (ES) had total resection rates of 98.1% vs. 85.2% and an improvement in progression-free survival of 8% vs. 22.1% when compared to transcranial surgery (TS). Even with these benefits complications like cerebrospinal fluid (CSF) leaks, meningitis, and infections still occur. The CSF leak happens in 7.2% of ES cases and 18% in combined craniofacial approaches. The usage of pedicled nasoseptal flaps for repair has reduced the postoperative CSF leak rates by 5.3% significantly[24].

Long-term survival data indicate that ES is the preferred treatment for early-stage disease that can be accessed endoscopically, whereas TS remains a viable option for more advanced cases requiring the most extensive safe resection. For example, Spielman et al. found that among 339 ONB patients treated with ES, 86.9% achieved negative margins, the overall recurrence rate was 10.3%, and the 5-year survival rate reached 91.1%[25]. In contrast, Patel et al. reported on 151 patients who underwent TS 77% of whom had Kadish stage C tumors with an overall 5-year survival of 78% and a recurrence-free survival of 64%[26]. The surgical management of cervical lymph nodes in ONB remains debated, as cervical metastases are present in 5–8% of patients at

diagnosis and can increase to 20–25% later; neck dissection is typically performed when radiological or clinical evidence of nodal disease is present[27].

RADIOTHERAPY

Radiotherapy (RT) plays a significant role in the management of ONB. This can be particularly seen in cases of incomplete resection or locally advanced disease. However, the standardized recommendations for its application remain lacking. RT is often used postoperatively (PORT) for the improvement of local control and the evidence suggests better survival outcomes in Kadish stage C and D patients receiving PORT compared to those without RT[28]. A SEER database analysis has reported five and ten-year overall survival rates of 70.7% and 53.4% with PORT versus 42.6% and 29.5% without PORT respectively[28]. For early-stage diseases like Kadish A and B, some studies have observed no survival difference between primary RT and combined surgery plus RT[14,29]. However, combined therapy generally helps in improving the control of tumours. Some of the recommended doses for RT include 45 Gy preoperatively, 50-60 Gy postoperatively, and 60-70 Gy for definitive RT[30]. Intensity-modulated radiotherapy (IMRT) has been observed to reduce the toxicity and also preserve the adjacent critical structures. This was reported in retrospective studies as low rates of high-grade toxicity[31]. New techniques like proton beam radiation therapy (PBRT) and carbon-ion therapy have their advantages because of their dose-focusing Bragg peak which reduces the exposure to the surrounding tissues and increases the control for tumour[32,33]. Preliminary data has suggested that PBRT is tolerated well and provides acceptable survival outcomes without any significant acute or late toxicities[34].

CHEMOTHERAPY

Chemotherapy is mainly used for unresectable or metastatic ONB. even though the response rates may differ. Common regimens include cisplatin (DDP)-based combinations with etoposide (VP-16), cyclophosphamide, or vincristine. However, it is rare for chemotherapy alone to achieve long-term control of the disease. So, it is mostly combined with multimodal treatment strategies. Induction chemotherapy (IC) mainly aims to decrease the burden of tumours and helps in facilitating the preservation of organs in structures like orbit and brain[35]. Also, IC may help in predicting the treatment response and clinical outcomes[36]. However, the evidence that supports IC is limited to small retrospective series. Studies on Kadish C patients treated with IC followed by surgery and RT report response rates ranging from 25% to 100% and with five-year overall survival rates of approximately 72%[33,34]. A review of neoadjuvant chemotherapy identified 66.7% of response rates for the DDP+VP-16 regimen[35]. Also, 60 per cent has been observed for the same regimen in another study[37] and varying outcomes can be observed in smaller cohorts[38]. IC may improve the resectability of tumours and decrease the distant metastasis risk and its role in the standard treatment for ONB remains unproven because of the lack of prospective trials.

LIMITATIONS OF STANDARD TREATMENT APPROACHES

Despite advances in surgical, radiotherapeutic, and chemotherapeutic techniques, standard ONB treatments face significant limitations:

- High recurrence rates (30–60% in advanced cases) remain a major challenge.
- Standard treatments are largely ineffective for metastatic disease.
- Toxicities associated with RT (e.g., mucositis, xerostomia, radiation-induced necrosis) and chemotherapy limit their long-term utility.
- Resistance to conventional therapies necessitates the exploration of alternative approaches, including targeted and immunotherapies.

Surgery, RT and chemotherapy remain as the pillars of management of ONB. Their limitations highlight the need for novel therapeutic strategies to improve outcomes in advanced cases. The integration of targeted therapy and immunotherapy into ONB treatment paradigms helps in further investigation

to improve the efficacy and reduce toxicities associated with standard therapies.

3. Molecular Pathogenesis and Therapeutic Targets

GENETIC AND MOLECULAR ALTERATIONS IN OLFACTORY NEUROBLASTOMA

The molecular basis of ONB has revealed crucial genetic and molecular changes that may drive tumor progression. In 1995, Carney and colleagues conducted the first genetic analysis of ONB, showing that these tumors express hASH1 the human counterpart of the Drosophila achaete-scute gene while lacking OMP mRNA[39]. Since hASH1 is essential for the maturation of olfactory neurons and neuroendocrine differentiation, this finding supports the idea that ONB may arise from immature neural crest cells in the olfactory epithelium[40]. Taggart et al. later confirmed that hASH1 is not only present in ONB but also in other sinonasal neuroendocrine tumors, with higher levels correlating with more advanced tumor grades[41]. Additionally, hASH1 has proven valuable in distinguishing ONB from other sinonasal cancers, such as undifferentiated nasopharyngeal carcinoma, diffuse large B-cell lymphoma, and malignant melanoma[42]. Inhibition of hASH1 via RNA interference leads to cell cycle arrest, suggesting that its overexpression might trigger ONB tumorigenesis[43]. Although notch-dependent pathways help reduce hASH1 expression, further research is needed to fully understand ONB's pathogenesis[44].

ANGIOGENESIS AND OLFACTORY NEUROBLASTOMA PROGRESSION

Tumor angiogenesis plays an important role in the progression of ONB. This was driven by the imbalance between pro-angiogenic and anti-angiogenic factors. The angiogenic switch concept in which the tumour acquires the ability to stimulate new formation of blood vessels is well documented in ONB[45]. Activation of STAT3(Signal Transducer and Activator of Transcription 3) in ONB cells leads to increased transcription of hypoxia-inducible factor 1-alpha (HIF-1α). This, in turn, induces the expression of erythropoietin (Epo) and its receptor (EpoR) that helps in promoting autocrine signaling and neoangiogenesis[46]. Bcl-2 is also known for its anti-apoptotic properties, this also helps in the angiogenic pathway through interactions with the HIF-1α/Epo/EpoR system[47]. Bcl-2 transcription was activated by hASH1, blocking hASH1 could potentially inhibit Bcl-2 activity. This makes Bcl-2 inhibitors a promising candidate for treating high-grade ONB[48]. Bcl-2 expression has been associated with better responses to neoadjuvant chemotherapy however it is also related to poorer prognosis[49]. Also, proteasome inhibitor bortezomib has been reported to sensitize ONB cells to Tumour Necrosis Factor- Related Apoptosis-Inducing Ligand(TRAIL)-induced apoptosis. This suggests its potential as a therapeutic strategy for Bcl–2–positive ONB tumors[50]. Vascular endothelial growth factor (VEGF) is another key angiogenic regulator of upregulation through Bcl-2 in ONB cells[51]. The anti-angiogenic agent bevacizumab has shown clinical efficacy by stabilizing metastatic ONB for 28 months in a case study. This indicates its potential role in ONB management[52].

NEUROTROPHIN RECEPTORS AND OLFACTORY NEUROBLASTOMA PATHOGENESIS

Neurotrophin receptors including high-affinity receptors tropomyosin receptor kinase (TrkA and TrkB) and the low-affinity receptor (p75NR) are critical for ONB progression. Nearly every ONB case expresses TrkA and TrkB, while p75NR is found in 60–100% of tumors. Neurotrophins support neuronal cell growth, differentiation, and survival. Overexpression of TrkB fosters tumorigenesis by activating the ERK (Extracellular signal-Regulated Kinase) and AKT (Protein Kinase B) pathways, which aids in sustaining brain tumor-initiating cells (BTICs) and facilitates metastasis in lung adenocarcinoma[54,55]. Meanwhile, p75NR enhances BTIC survival and proliferation, contingent on proper cleavage by α- and γ-secretases[56]. In contrast, TrkA acts as a pro-apoptotic and anti-angiogenic factor, with its expression linked to better outcomes in pediatric neuroblastoma[57]. However, elevated TrkB levels in pediatric neuroblastoma are associated with poorer

prognosis and resistance to chemotherapy. Notably, clinical trials using the TRK inhibitor lestaurtinib have stabilized disease in cases of recurrent or refractory neuroblastoma[58], and combining chemotherapy with Trk inhibitors like entrectinib and GNF-4256 has significantly suppressed tumor growth in preclinical neuroblastoma models, suggesting that further exploration of Trk inhibitors for ONB treatment is warranted[59].

TP53 MUTATIONS IN OLFACTORY NEUROBLASTOMA

Mutations of TP53 are a hallmark of various malignancies that include high-grade ovarian and colorectal carcinoma. In head and neck cancers, TP53 mutations occur in approximately 40.6% of cases[60]. However, initial studies did not detect TP53 mutations in ONB even if approximately half of ONB cases exhibited p53 overexpression. Another study reported aberrant p53 expression in 62% (16/26) of ONB cases. This suggests a potential role in the progression of tumours[61]. More recent investigations have identified TP53 point mutations in two cases of metastatic ONB. This indicates that p53 aberrations may contribute to disease progression at later stages rather than playing a role in initial tumorigenesis[62].

FIBROBLAST GROWTH FACTOR RECEPTOR DYSREGULATION

Alterations in the fibroblast growth factor receptor (*FGFR*) pathway promote cell survival, proliferation, and differentiation. Studies have indicated that FGFR inhibitors may be effective against ONB and with ongoing clinical trials assessing their therapeutic potential[63].

NOTCH PATHWAY

Aberrant *NOTCH* signaling has been used in oncogenesis across multiple cancers that includes ONB. This pathway plays a role in cellular differentiation and tumour progression, making it a viable target for novel therapeutic interventions[64].

COMMON ONCOGENIC PATHWAYS IN OLFACTORY NEUROBLASTOMA

Several oncogenic pathways drive the progression of ONB by influencing tumour growth, angiogenesis, immune evasion, and therapy resistance. Epidermal growth factor receptor (EGFR) overexpression is related to improved proliferation and invasion of tumour cells. EGFR inhibitors like cetuximab and erlotinib, have shown to be effective in preclinical studies[64]. The VEGF pathway drives angiogenesis, a process essential for tumor growth and survival, and agents such as bevacizumab have been explored to restrict tumor blood vessel formation and progression[64,65]. Similarly, PD-L1 contributes to immune evasion by suppressing T-cell activity, and immune checkpoint inhibitors like pembrolizumab and nivolumab have proven effective in enhancing anti-tumor immune responses[64,66]. Furthermore, the PI3K/AKT/mTOR pathway is often abnormally activated in ONB, leading to increased tumor cell proliferation and survival; therefore, targeting this pathway with inhibitors such as everolimus and temsirolimus can offer significant therapeutic advantages[64].

ROLE OF BIOMARKERS IN THERAPY SELECTION

Biomarker-driven therapy selection is fundamental to personalized oncology. This allows for the identification of patients who may benefit from specific targeted treatments. Molecular profiling of ONB tumours for EGFR, VEGF, and PD-L1 expression can guide therapeutic decisions. Patients with high EGFR expression may respond to EGFR inhibitors and those with VEGF overexpression could benefit from anti-angiogenic therapy[67]. Advances in genetic profiling help in personalized treatment strategies for actionable mutation identification and pathway alterations. This approach improves treatment efficacy by matching therapies to the molecular characteristics of individual tumours[67].

4. Current Targeted Therapies for Olfactory Neuroblastoma

Targeted therapies for ONB can interfere with specific molecular pathways. This involves the growth and progression of tumours. These therapies include angiogenesis inhibitors, tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors, and PI3K/AKT/mTOR pathway inhibitors.

ANGIOGENESIS INHIBITORS

Angiogenesis is the new blood vessel formation. This plays an important role in the ONB progression by supplying tumors with oxygen and nutrients. Targeting angiogenesis can disrupt growth of the tumor and also helps in improving the patient outcomes.

Bevacizumab (Anti-VEGF Monoclonal Antibody)

Bevacizumab is a monoclonal antibody against Vascular Endothelial Growth Factor (VEGF). It is used in recurrent ONB cases where it has shown modest benefits in clinical settings. Bevacizumab blocks VEGF-A and prevents the formation of new blood vessels by not providing essential nutrients to the tumours[68]. Various case studies have observed increased progression-free survival in ONB patients who were treated with bevacizumab. This states its potential in disease control[69]. Emerging research suggests that bevacizumab may improve immunotherapy efficacy by increasing immune cell infiltration into the tumour microenvironment. This makes the tumours more susceptible to immune-based treatments[70].

TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors (TKIs) offer a promising approach in the systemic treatment of olfactory neuroblastoma (ONB), especially in cases resistant to surgery, radiotherapy, or chemotherapy. These agents disrupt key signalling pathways that facilitate tumour growth and vascular supply, including VEGFR, PDGFR, c-KIT, and RET. Molecular studies of ONB have demonstrated activation of these receptors, supporting the rationale for TKI use in advanced disease. Sunitinib, a well-established multi-target TKI, has achieved disease stabilization in patients with aggressive ONB, including those with recurrent or metastatic lesions unresponsive to conventional regimens. In one report, sustained radiological stability was observed over several months, with symptomatic improvement and no further disease spread. Pazopanib has similarly shown clinical benefit in a metastatic ONB case, where significant tumour reduction was noted. While large trials are lacking due to the rarity of ONB, recurrent patterns of partial responses across different TKIs reinforce the relevance of angiogenesis and receptor-mediated signalling in ONB progression[71-73].

Despite their potential, TKIs carry a significant toxicity burden. Class-wide adverse effects include hypertension, diarrhoea, fatigue, hand-foot syndrome, and mucosal inflammation, primarily due to endothelial disruption and off-target receptor inhibition. Sunitinib frequently causes hypothyroidism and bone marrow suppression; pazopanib may lead to hepatotoxicity, while sorafenib is associated with skin toxicity and gastrointestinal complaints. A rare but serious complication—posterior reversible encephalopathy syndrome (PRES)—has been reported during lenvatinib therapy, requiring urgent intervention. Monitoring blood pressure, thyroid and liver function, and hematologic indices is essential to safely administer these agents. While currently used off-label, TKIs have demonstrated durable responses in select ONB cases, justifying further investigation through prospective studies. Advances in molecular profiling may soon allow more refined, biomarker-driven application of TKIs in ONB, optimizing benefit while limiting toxicity[74,75].

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

The epidermal growth factor receptor (EGFR) is observed to be most often overexpressed in ONB. This contributes to the proliferation of tumours and resistance to conventional therapies. EGFR tyrosine kinase activity was inhibited by Erlotinib and Gefitinib. This prevents downstream signalling and decreases the proliferation and survival of tumour cells. These inhibitors are observed to be more effective in the cases of EGFR-positive ONB. Here the genetic tests confirm the overexpression of the receptor. It has been observed that the inhibition of EGFR can slow the progression of the disease and improve the response rates[76]. Despite their efficacy, resistance mechanisms like secondary EGFR mutations and alternative signalling pathways activation can limit the long-term benefits of these

drugs[77]. Combination strategies or next-generation TKIs may help in overcoming the resistance.

ANAPLASTIC LYMPHOMA KINASE INHIBITORS

Alterations in anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase, have gained attention as a key driver in various cancers, especially in pediatric neuroblastoma. While ALK mutations are rare in olfactory neuroblastoma (ONB), recent genetic studies have identified sporadic cases where these mutations or overexpression occur, presenting a potential therapeutic target. The advent of ALK inhibitors, such as crizotinib, ceritinib, and lorlatinib, which have demonstrated significant efficacy in ALK-positive non-small cell lung cancers and high-risk neuroblastoma, offers a promising outlook for ONB patients with confirmed ALK pathway activation. Preclinical research has indicated that crizotinib can reduce tumor cell growth in ALK-mutant neuroendocrine models, and early-stage clinical trials in pediatric neuroblastoma support the strategy of ALK inhibition. Although clinical data specific to ONB are still scarce, there have been isolated cases where sinonasal neuroendocrine tumors responded partially to ALK inhibitors, providing further justification for pursuing these treatments. With the shift toward precision medicine, comprehensive molecular profiling, such as next-generation sequencing, plays an essential role in identifying ONB patients who might benefit from such targeted approaches. In the right genomic context, ALK inhibitors could represent a promising, less toxic treatment option for ONB, making it important to explore this avenue further through basket trials or personalized treatment plans[58,59,62].

IMMUNE CHECKPOINT INHIBITORS

The body's immune system is crucial for identifying and destroying cancerous cells. The tumors develop the mechanisms for evading the surveillance of the immune system using immune checkpoint pathways. The immune checkpoint inhibitors can restore the immune activity and improve the ability of the body to fight cancer by inhibiting these pathways.

PD-1/PD-L1 Inhibitors

Olfactory neuroblastoma expresses PD-L1, which is an immune checkpoint protein that suppresses the immune response. It can be observed that PD-1/PD-L1 inhibitors like pembrolizumab and nivolumab may be effective treatment options for ONB. These inhibitors block the interaction between PD-1, a receptor found in T cells and PD-L1, which is expressed in tumour cells. This led to improved anti-tumour activity [76]. In early phase clinical trials, it has been observed that pembrolizumab and nivolumab show promise in refractory ONB cases. This can be seen to be particularly effective in patients who have failed to respond to conventional therapies such as surgery, radiation, and chemotherapy. The combination of immune checkpoint inhibitors and angiogenesis inhibitors like bevacizumab may improve the efficacy of the treatment by improving immune cell infiltration into the tumour microenvironment[77].

PI3K/AKT/mTOR Pathway Inhibitors

The **Phosphatidylinositol 3-kinase/Protein Kinase B/Mechanistic Target of Rapamycin** (PI3K/AKT/mTOR) pathway plays a crucial role in cell survival, proliferation, and metabolism. Dysregulation of this pathway is frequently observed in ONB and contributes to tumour progression. As a result, targeting this pathway with inhibitors such as Everolimus is being researched as a potential therapeutic strategy.

Everolimus (mTOR Inhibitor)

Everolimus is a selective inhibitor of the mammalian target of rapamycin (mTOR). It is a key regulator of cellular growth. By blocking mTOR activity, Everolimus disrupts tumour metabolism, proliferation, and angiogenesis. This leads to limiting the progression of tumours[76]. Everolimus binds to FKBP12 and forms a complex that inhibits mTORC1. It suppresses the protein synthesis necessary for tumor growth and inhibits angiogenesis by reducing VEGF production. It also induces cell cycle arrest and prevents uncontrolled cell proliferation [71]. Early research suggests that ONB patients with mutations in the PI3K pathway may

respond favourably to mTOR inhibition. However, long-term efficacy and patient selection criteria require further investigation in clinical trials[77].

OTHER EMERGING TARGETED AGENTS

Several experimental therapies are currently being investigated as potential treatments for olfactory neuroblastoma. These novel agents target different molecular pathways involved in tumour progression, providing new possibilities for improving patient outcomes.

Histone DeAcetylase Inhibitors

Histone DeAcetylase (HDAC) inhibitors can regulate gene expression and influence tumour cell behaviour. These inhibitors work by modifying of the chromatin structure thus promoting tumour cell differentiation and apoptosis. HDAC inhibitors suppress tumour growth by altering histone acetylation, which affects gene transcription and leads to cell cycle arrest and apoptosis. By modifying chromatin structure, these agents can reprogram cancer cells to become less aggressive. Studies indicate that HDAC inhibitors may enhance the effectiveness of chemotherapy and immunotherapy in ONB. In experimental models, combining HDAC inhibitors with immune checkpoint inhibitors has demonstrated improved anti-tumor responses[77]. Given their role in altering tumour cell behaviour, HDAC inhibitors may serve as adjunct therapies alongside existing ONB treatments. However, further clinical trials are needed to determine their safety and efficacy in human patients.

DNA Repair Inhibitors

Defective DNA repair mechanisms are a hallmark of many cancers, including ONB. DNA repair inhibitors target these vulnerabilities, preventing cancer cells from fixing damaged DNA, and leading to tumor cell death. These inhibitors work by blocking essential pathways of DNA repair like poly (ADP-ribose) polymerase (PARP) inhibition, which impairs the ability of cancer cells to repair DNA damage, resulting in instability in gene and apoptosis. Preclinical studies have shown promise, particularly in combination with radiation and chemotherapy, where DNA repair inhibitors increase cancer cell sensitivity to treatment[77]. However, additional studies are necessary for validating their effectiveness and define their role in ONB therapy. While promising, DNA repair inhibitors face challenges such as potential toxicity and resistance mechanisms. Future research should focus on patient selection criteria and combination strategies to optimize therapeutic benefits.

5. Combination Approaches: Integrating Targeted Therapy with Standard Treatments

Combination approaches in cancer therapy, particularly integrating targeted therapies with chemotherapy and radiotherapy, have demonstrated significant potential in improving treatment efficacy, overcoming drug resistance, and enhancing patient survival. This strategy leverages the unique mechanisms of targeted therapies to optimize the effects of standard treatments while potentially minimizing toxicity. The following sections explore the synergistic effects of targeted therapy with chemotherapy, the role of targeted agents in enhancing radiotherapy response, and the strategies for sequential versus concurrent administration.

SYNERGISTIC EFFECTS OF TARGETED THERAPY WITH CHEMOTHERAPY

Enhanced Efficacy

Targeted therapies, when combined with chemotherapy, can sensitize cancer cells to cytotoxic agents, improving overall treatment response. For example, inhibitors targeting epidermal growth factor receptors (EGFR) have been shown to enhance the effects of platinum-based chemotherapy in **Non-Small Cell Lung Cancer** [78]. This synergistic effect enables better tumour shrinkage and disease control.

Overcoming Drug Resistance

One of the major challenges in chemotherapy is the development of drug resistance. Targeted therapies can mitigate this by inhibiting alternative signalling pathways that cancer cells use to survive

chemotherapy. For instance, combining PI3K inhibitors with chemotherapy has shown promise in overcoming resistance in breast cancer models[63].

CLINICAL EVIDENCE

Various clinical trials have investigated the benefits of combining targeted therapies with chemotherapy. The NCI-ComboMATCH trial is evaluating multiple targeted therapy and chemotherapy combinations, aiming to identify the most effective regimens for various cancers[79]. Early results suggest that these combinations may provide superior outcomes compared to monotherapy alone.

ROLE OF TARGETED AGENTS IN ENHANCING RADIOTHERAPY RESPONSE

Biological Synergy

Radiotherapy relies on DNA damage to kill cancer cells, but its effectiveness can be limited by tumour hypoxia and repair mechanisms. Targeted therapies can enhance radiosensitivity by interfering with DNA repair and altering tumour microenvironments[80].

Mechanisms of Action

- **EGFR Inhibitors**: These agents enhance radiotherapy efficacy by preventing tumor cell proliferation and promoting apoptosis [81].
- **VEGF Inhibitors**: Antiangiogenic therapies, such as bevacizumab, improve oxygenation of tumors, making them more susceptible to radiation[81].
- **DNA Repair Inhibitors**: Agents that target DNA repair enzymes, such as PARP inhibitors, can prevent tumour cells from recovering after radiation-induced damage, leading to increased cell death[80].

Clinical Applications

Studies have demonstrated that combining targeted therapy with radiotherapy leads to improved local tumour control and longer progression-free survival in cancers such as glioblastoma and head and neck squamous cell carcinoma[81]. Ongoing trials aim to refine these approaches by identifying optimal dosing and scheduling strategies.

SEQUENTIAL VS. CONCURRENT ADMINISTRATION STRATEGIES

Concurrent Administration

Simultaneous administration of targeted therapies with chemotherapy or radiotherapy can maximize their synergistic effects. This approach ensures continuous inhibition of cancer-promoting pathways while delivering cytotoxic treatment, potentially leading to better tumour regression[81]. However, concurrent administration may also increase toxicity, requiring careful patient monitoring.

Sequential Administration

An alternative approach is to administer targeted therapies before or after standard treatments. This strategy may help reduce side effects while maintaining efficacy. For example, sequential administration of immunotherapy after radiotherapy has shown promise in stimulating a stronger immune response[80].

Clinical Considerations

The decision between sequential and concurrent administration depends on multiple factors, including cancer type, tumour stage, and patient tolerance. Ongoing research aims to establish personalized treatment protocols that balance efficacy and safety[78].

Conclusion

The review of targeted therapy for advanced and aggressive olfactory neuroblastoma (ONB) underscores the evolving landscape of treatment strategies aimed at improving patient outcomes. ONB, a rare and aggressive malignancy, poses significant clinical challenges due to its high recurrence rates and resistance to conventional therapies. Standard treatment modalities, including surgical resection, radiotherapy, and chemotherapy, remain the foundation of ONB management; however, their effectiveness varies, particularly in advanced cases. The emergence of targeted therapies offers a promising adjunct to these traditional approaches, providing a more precise and potentially less toxic alternative. Agents such as angiogenesis inhibitors (e.g.,

bevacizumab), tyrosine kinase inhibitors (e.g., EGFR inhibitors), and immune checkpoint inhibitors (e.g., pembrolizumab) target molecular pathways critical to tumour progression, metastasis, and immune evasion. The integration of targeted therapies with chemotherapy and radiotherapy has shown synergistic potential, enhancing tumour sensitivity to cytotoxic treatments and improving disease control. Personalized medicine, guided by molecular profiling and biomarker identification, is poised to revolutionize ONB treatment, ensuring that patients receive the most effective therapy tailored to their tumour's genetic makeup. Future research should prioritize well-designed clinical trials to validate these approaches and explore novel molecular targets such as FGFR and NOTCH. Additionally, interdisciplinary collaborations among clinicians, researchers, and pharmaceutical developers are essential to advancing therapeutic innovations. In conclusion, the incorporation of targeted therapy into ONB management marks a critical step toward optimizing patient care, reducing treatment-related toxicity, and improving long-term survival for patients in this challenging clinical milieu.

Conflict of Interest Statement:

None.

Funding Statement:

None.

Acknowledgements:

None.

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