

Durable Major Response With Pazopanib in Recurrent, Heavily Pretreated Metastatic Esthesioneuroblastoma Harboring a Fumarate Hydratase Mutation

Marianne Spengler, MD¹; Megan Wheelden, MD¹; Heath B. Mackley, MD²; and Joseph J. Drabick, MD¹

INTRODUCTION

Esthesioneuroblastoma (also known as olfactory neuroblastoma) is a rare cancer of neural crest origin that arises in the olfactory epithelium of the upper nasal cavity. It accounts for only 3%-5% of sinonasal tumors.¹ Patients commonly present with epistaxis, nasal obstruction, and olfactory and ophthalmic disturbances.^{2,3} Definitive diagnosis requires both radiography and histopathology. Computed tomography and magnetic resonance imaging (MRI) are used to detail bony involvement and tumor extension to adjacent structures for staging.² Histologically, esthesioneuroblastoma appears as characteristic nests of small blue cells separated by fibrovascular septa. Immunohistochemistry aids in distinguishing esthesioneuroblastoma from other small, round, blue cell neoplasms occurring in the sinonasal tract, such as lymphoma, Ewing's tumor, and rhabdomyosarcoma.¹

Owing to its rarity and resultant lack of prospective randomized studies to guide therapy, there is currently no defined standard first-line treatment for esthesioneuroblastoma. The generally accepted standard of care is extrapolated from treatment of other head and neck cancers and usually consists of surgery followed by radiation and sometimes chemotherapy,^{2,4} although neoadjuvant concurrent chemoradiation for locally advanced esthesioneuroblastoma has also been described.⁵

The clinical course of treated esthesioneuroblastoma is variable, with published 5-year survival rates ranging from 45% to 90%.^{2,6,7} Recurrences occur within the first 2-3 years in up to 50% of cases, but recurrences are common as far as 5-10 years after initial diagnosis.^{1,4} Cervical nodal metastasis and distant metastasis occur in 25% and 10% of cases, respectively.^{1,8} For recurrent or progressive disease after initial therapy, systemic chemotherapy has been disappointing.^{3,9} The introduction of biologically targeted agents, including small molecules and monoclonal antibodies, has provided additional treatment options for many cancers, including esthesioneuroblastoma. Several case reports have shown success

with these agents,¹⁰ and we add to the growing evidence base by presenting a case of recurrent metastatic esthesioneuroblastoma in which a prolonged partial response was achieved with pazopanib for over 4 years and ongoing as of this report.

Pazopanib is an oral multi-tyrosine kinase inhibitor (TKI) that targets angiogenesis by inhibiting vascular endothelial growth factor receptors (vascular endothelial growth factor receptor [VEGFR]-1, -2, and -3), platelet-derived growth factor receptors (platelet-derived growth factor receptor- α and - β), stem cell factor receptor (c-KIT), and fibroblast growth factor receptor-1 and -3.¹¹ It is approved by the US Food and Drug Administration for treatment of renal cell carcinoma and certain types of soft tissue sarcoma.^{12,13}


CASE REPORT

This 69-year-old woman developed anosmia and persistent rhinorrhea in 1994. She was referred to an otolaryngologist who removed a tumor from the upper nasal cavity, and pathology demonstrated esthesioneuroblastoma. She underwent complete resection of the tumor and completed a 4-week course of adjuvant radiation therapy (40 Gy in 20 fractions). She had regular follow-up until she developed a nodule in her left temple in 2004, which was excised and demonstrated recurrent disease. She subsequently experienced multiple recurrences and was referred to medical oncology. She received four cycles of chemotherapy with cisplatin 60 mg/m² and etoposide 120 mg/m² to prevent further relapse. A positron emission tomography-computed tomography in 2009 showed no evidence of disease. In 2011, recurrent lesions were excised and she was treated with chemoradiotherapy with weekly carboplatin and paclitaxel and concurrent radiation therapy for 30 days (60 Gy in 30 fractions). Additional recurrent lesions were resected in 2013 and 2015.

An MRI in December 2016 revealed increasing size of masses in the right buccal and masticator space, left masticator space, scalp, as well as increased size of a

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on March 4, 2021 and published at ascopubs.org/journal/po on April 19, 2021; DOI <https://doi.org/10.1200/P0.20.00486>

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License 

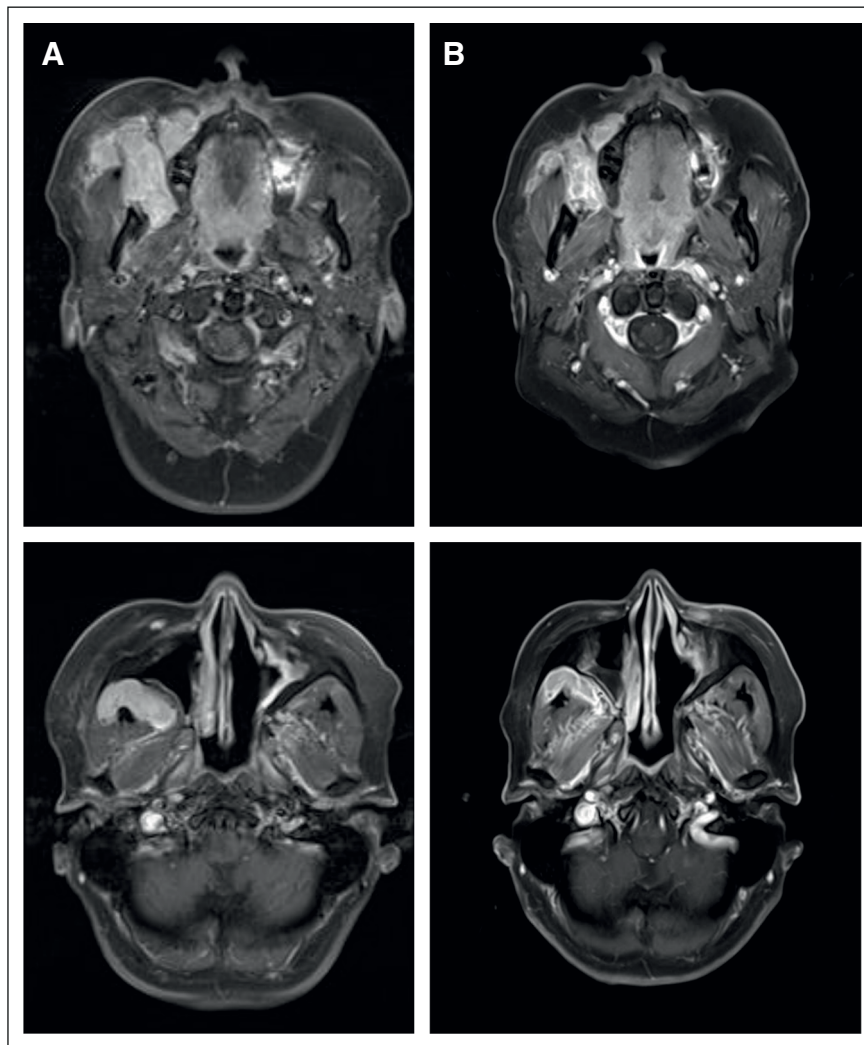


FIG 1. MRI with contrast—(A) before pazopanib (December 2016) and (B) after pazopanib (April 2017). Imaging report: (A) December 2016, Cerebral parenchyma: interval increase in vasogenic edema in bilateral frontal lobes in the background of gliosis, right greater than left. Extra-axial spaces: interval increase in size of dural-based masses seen in bilateral anterior cranial fossa floor. The right anterior cranial fossa lesion measures $2.0 \times 2.2 \text{ cm}^2$ (previously $1.7 \times 1.4 \text{ cm}^2$). It extends through the nearby craniotomy defect into the right anterior forehead scalp, which also demonstrates interval increase in size as well. The left anterior cranial fossa lesion measures $1.5 \times 1.6 \text{ cm}^2$ (previously $1.3 \times 2.3 \text{ cm}^2$). Calvarium or sinuses: interval increase in size of right buccal space and masticator space mass along the lateral wall of the right maxillary sinus extending along the right temporalis muscle. It demonstrates hypointense T1 and hyperintense T2 signals with solid enhancement. The lesion measures approximately $7.2 \times 3.7 \times 4.7 \text{ cm}^3$ (previously $6.2 \times 3.3 \times 3.5 \text{ cm}^3$). Interval increase in size of similar mass in left masticator space along temporalis muscles measuring $2.4 \times 1.0 \text{ cm}^2$ (previously $1.8 \times 0.8 \text{ cm}^2$). Interval increase in size of enhancing scalp lesion near the left anterior pinna measuring $1.8 \times 0.5 \text{ cm}^2$ (previously $1.4 \times 0.7 \text{ cm}^2$). (B) April 2017, Cerebral parenchyma: enhancing right frontal lobe lesion involves the brain parenchyma, dura, calvarium, and scalp, and has significantly decreased in size and currently appears non-mass-like. Similar-appearing lesion in the left frontal lobe has also decreased in size. Both of these lesions on the prior study were well-defined masses. Extra-axial spaces: no extra-axial collection. Calvarium or sinuses: nodular contrast enhancement within both inferior temporal fossa, decrease in size of the craniocaudal extent, the superficial muscular component on the right measures up to 3.4 cm in the AP dimension (previously about 4.4 cm). AP, anteroposterior; MRI, magnetic resonance imaging.

dural-based mass in the bilateral anterior cranial fossa floor and vasogenic edema in bilateral frontal lobes (Fig 1A). Her case was reviewed at a multidisciplinary tumor board, and it

was determined that these disease sites were no longer resectable. Using the Caris Molecular Intelligence platform (Caris Life Sciences, Phoenix, AZ), tumor specimen

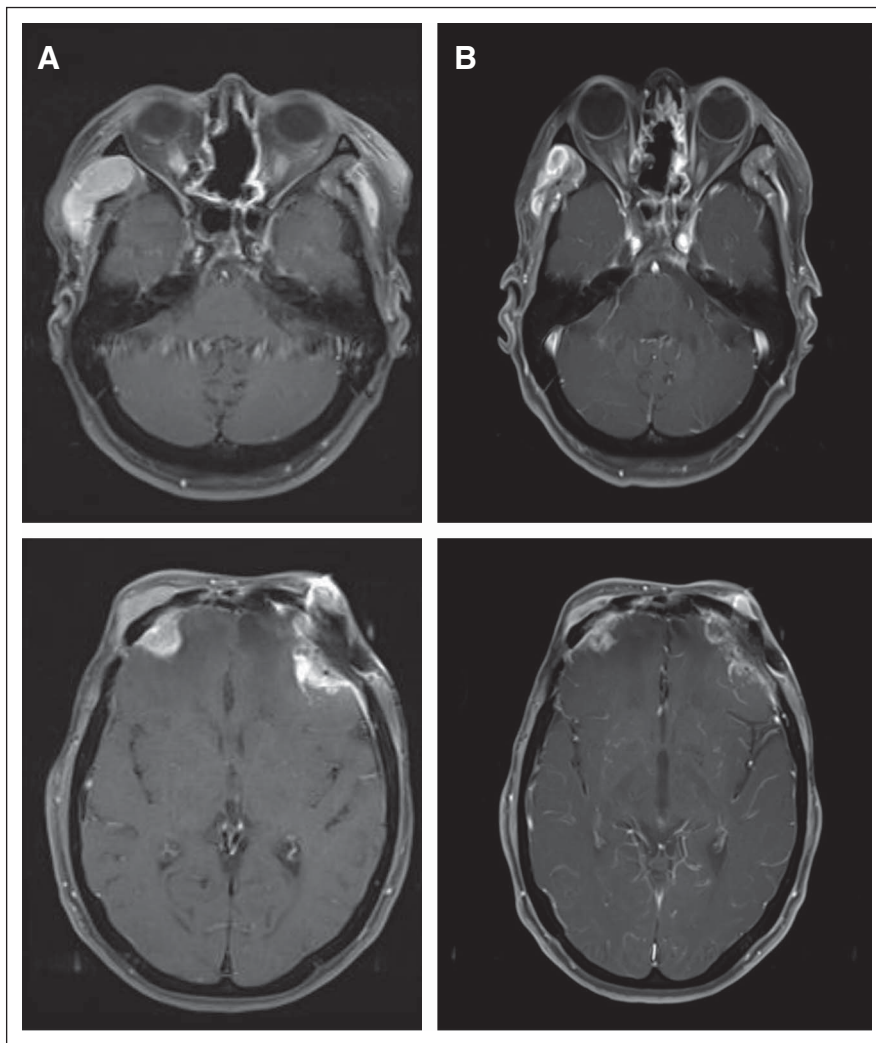


FIG 1. (Continued).

obtained in November 2015 was analyzed for 592 genes and revealed a presumed pathogenic mutation in fumarate hydratase (*FH*; Table 1). However, no clear actionable targets or applicable clinical trials were identified. By this time, the patient had a markedly swollen face, which was alarming to her.

The patient then started pazopanib 400 mg oral daily dose. Within a week, she noted rapid decrease in facial edema and size of the lesions on her forehead and right mouth. On therapy, she developed decreased appetite, fatigue, and myalgias as well as dryness in her hands, which led to a dose reduction of pazopanib to 200 mg daily. Follow-up MRI brain showed significant response at her disease sites consistent with partial response (Fig 1B). Her most recent surveillance imaging in October 2020 demonstrated stable disease. This represents durable partial response of metastatic esthesioneuroblastoma on pazopanib therapy for 4 years and ongoing. A timeline of her disease course and treatments is included in Figure 2. Written consent was

provided by the patient for publication of her clinical information and images as a case report.

DISCUSSION

As a rare malignancy, esthesioneuroblastoma currently has no defined treatment regimen. At diagnosis, multimodality therapy (surgery, radiation, and chemotherapy) is typically used. For recurrent or progressive disease, cytotoxic chemotherapy has been only modestly effective. Several recent case reports describe successful use of targeted therapy with small molecules and/or monoclonal antibodies in treatment of recurrent metastatic esthesioneuroblastoma (Table 2). Preusser et al⁶ reported on a 69-year-old man with massive progression of metastatic esthesioneuroblastoma following surgical resection and radiation therapy who achieved disease stabilization for 15 months with the TKI sunitinib before passing away from an unrelated traumatic injury. Wang et al³ used whole-exome sequencing to identify gene targets for treatment of a 44-year-old man with recurrent metastatic esthesioneuroblastoma

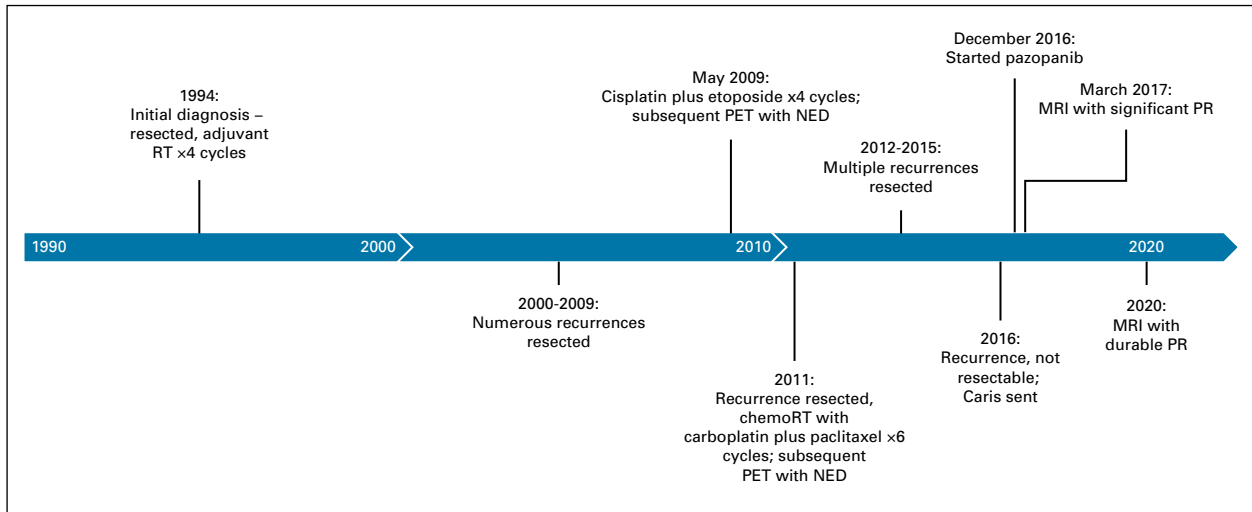


FIG 2. Clinical timeline. MRI, magnetic resonance imaging; NED, no evidence of disease; PET, positron emission tomography; PR, partial response; RT, radiotherapy.

following surgical resection, radiation therapy, and platinum-based chemotherapy who achieved clinical response with sunitinib and cetuximab. Dunbar et al² reported on a 60-year-old man with recurrent metastatic esthesioneuroblastoma following treatment 17 years earlier with surgical resection, radiation therapy, and both platinum-based and non-platinum-based chemotherapy who ultimately achieved stable disease for 22 months with the antiangiogenic agent bevacizumab. Kim et al¹⁴ reported on a 46-year-old man with an extensive locally infiltrating frontobasal tumor who underwent surgical resection and radiation therapy followed by cisplatin and etoposide with multiple subsequent recurrences who ultimately achieved prolonged partial remission with imatinib after his tumor was determined to be immunohistochemically positive for c-KIT. Fury et al¹⁵ conducted a phase I study using everolimus and cisplatin in patients with advanced solid tumors; the results included one subject with esthesioneuroblastoma previously treated with radiation who achieved prolonged stable disease. Gay et al¹⁰ performed comprehensive genomic profiling on samples from 41 cases of esthesioneuroblastoma, including one from a 49-year-old woman who underwent surgical resection and radiation therapy for disease of paranasal sinus with subsequent distant metastasis who

achieved stable disease for 2 years on pazopanib and docetaxel.

As precision medicine is increasingly used, use of targeted drugs for treating recurrent metastatic esthesioneuroblastoma is likely to increase. The antineoplastic effect of pazopanib and other multi-TKIs is presumably through inhibition of VEGF receptors and additional growth receptors involved in angiogenesis. Specifically in regards to the presented patient, we postulate that her significant response to pazopanib is related to her presumed pathogenic *FH* mutation. *FH* is an enzyme catalyzing the hydration of fumarate to malate in the Krebs cycle. Mutations of *FH* lead to accumulation of excess fumarate, which then inhibits hypoxia-inducible factor (HIF) prolyl hydroxylase. HIF prolyl hydroxylase facilitates ubiquitination and degradation of HIF; therefore, its inhibition results in stabilization and accumulation of HIF.^{16,17} *HIF* genes are involved in regulating angiogenesis through upregulation of downstream genes, which include VEGF.^{18,19} Increased VEGF transcription produced by this complex chain of inhibition and upregulation of genes in patients with *FH* mutations serves as an appealing therapeutic target for agents such as pazopanib, which inhibit VEGF receptors as part of their antiangiogenic mechanism. Although pazopanib predominantly exerts its effect through inhibition of VEGFR, platelet-derived growth factor receptor, and c-KIT, it was also shown to inhibit fibroblast growth factor receptor in vitro and it is plausible that this mechanism of action contributes to the antitumor effect in our case since she also harbors amplification of *FGF3* and *FGF4* ligands.²⁰

Mutation of *FH* in esthesioneuroblastoma was previously reported.²¹ Although confirmation by germline genetic testing would be needed, the high percentage of our patient's tumor cells containing an *FH* mutation suggests a germline mutation, although she does not have a personal or family history suggestive of a germline *FH* defect. To

TABLE 1. Summary of Caris Findings

Gene	Aberration (% Tumor Cells)	Method
CCND1	Amplified	NGS
CDH1 exon 14 D756Y	Mutated, variant of unknown significance (16)	NGS
FGF3	Amplified	NGS
FGF4	Amplified	NGS
FH exon 10 K477dup	Mutated, presumed pathogenic (85)	NGS
TUBB3	Positive (65)	IHC

Abbreviations: FH, fumarate hydratase; IHC, immunohistochemistry; NGS, next-generation sequencing.

TABLE 2. Use of Biological Agents in the Literature

Reference	Treatment at Diagnosis	Treatment(s) for Progressive or Recurrent Disease	Patient Outcome
Preusser et al ⁶	Surgery	Radiation, surgery, sunitinib (TKI)	SD for 15 months with sunitinib (died from unrelated traumatic injury)
Wang et al ³	Surgery; radiation; and ifosfamide, cisplatin, and etoposide	Sunitinib and cetuximab (EGFR inhibitor)	Clinical response for > 4 months with sunitinib and cetuximab
Dunbar et al ²	Surgery and radiation	Cisplatin and etoposide, surgery and temozolomide, docetaxel and irinotecan, bevacizumab (VEGFR inhibitor)	SD for 22 months with bevacizumab
Kim et al ¹⁴	Surgery, radiation, and adjuvant cisplatin and etoposide	Surgery, imatinib (TKI)	Prolonged partial remission for 50 months with imatinib
Fury et al ¹⁵	Radiation	Everolimus (mTOR inhibitor) and cisplatin	Prolonged SD with everolimus and cisplatin
Gay et al ¹⁰	Surgery and radiation	Everolimus; pazopanib (TKI) and docetaxel	SD for 24 months with pazopanib and docetaxel
Spengler et al (current study)	Surgery and radiation	Surgery, cisplatin, and etoposide; radiation, carboplatin, and paclitaxel; pazopanib (TKI)	Prolonged partial remission for 48 months to date with pazopanib

Abbreviations: EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

date, she has enjoyed a durable partial response for 48 months. If she experiences progressive disease, the next line of treatment could include a selective inhibitor of circulating VEGF such as bevacizumab, in keeping with our suspicion that her current prolonged disease control is through an antiangiogenic pathway.

Case reports and cohort studies add to the growing fund of knowledge and are valuable in real-world management of this rare malignancy after recurrence. They suggest that biologic targeted therapies can have a durable impact on even heavily pretreated patients with esthesioneuroblastoma.

AFFILIATIONS

¹Department of Hematology/Oncology, Penn State Milton S. Hershey Medical Center, Hershey, PA

²Department of Radiation Oncology, Geisinger Medical Center, Danville, PA

CORRESPONDING AUTHOR

Marianne Spengler, MD, Department of Hematology/Oncology, Penn State Health Milton S. Hershey Medical Center, 500 University Dr, Hershey, PA 17036-9341; e-mail: mspengler@pennstatehealth.psu.edu.

AUTHOR CONTRIBUTIONS

Conception and design: Marianne Spengler, Megan Wheelden, Joseph J. Drabick

Administrative support: Joseph J. Drabick

Provision of study materials or patients: Joseph J. Drabick

Collection and assembly of data: Marianne Spengler, Megan Wheelden, Joseph J. Drabick

Data analysis and interpretation: Marianne Spengler, Megan Wheelden, Heath B. Mackley, Joseph J. Drabick

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](http://OpenPayments)).

Joseph J. Drabick

Consulting or Advisory Role: Sanofi/Aventis

No other potential conflicts of interest were reported.

REFERENCES

- Purohit B, Winder T, Maggio EM, et al: Aggressive primary olfactory neuroblastoma of the sphenoclivar region: A case report and literature review. *Laryngoscope* 125:822-825, 2015
- Dunbar EM, Pumphrey PK, Bidari S: Unexpectedly durable palliation of metastatic olfactory neuroblastoma using anti-angiogenic therapy with bevacizumab. *Rare Tumors* 4:e33, 2012
- Wang L, Ding Y, Wei L, et al: Recurrent olfactory neuroblastoma treated with cetuximab and sunitinib: A case report. *Medicine (Baltimore)* 95:e3536, 2016

4. Abdelmeguid AS: Olfactory neuroblastoma. *Curr Oncol Rep* 20:7, 2018
 5. Sohrabi S, Drabick JJ, Crist H, et al: Neoadjuvant concurrent chemoradiation for advanced esthesioneuroblastoma: A case series and review of the literature. *J Clin Oncol* 29:e358-e361, 2011;
 6. Preusser M, Hutterer M, Sohm M, et al: Disease stabilization of progressive olfactory neuroblastoma (esthesioneuroblastoma) under treatment with sunitinib mesylate. *J Neurooncol* 97:305-308, 2010
 7. Turri-Zanoni M, Maragliano R, Battaglia P, et al: The clinicopathological spectrum of olfactory neuroblastoma and sinonasal neuroendocrine neoplasms: Refinements in diagnostic criteria and impact of multimodal treatments on survival. *Oral Oncol* 74:21-29, 2017
 8. Ozsahin M, Gruber G, Olszyk O, et al: Outcome and prognostic factors in olfactory neuroblastoma: A rare cancer network study. *Int J Radiat Oncol Biol Phys* 78:992-997, 2010
 9. Marinelli JP, Janus JR, Van Gompel JJ, et al: Esthesioneuroblastoma with distant metastases: Systematic review & meta-analysis. *Head Neck* 40:2295-2303, 2018
 10. Gay LM, Kim S, Fedorchak K, et al: Comprehensive genomic profiling of esthesioneuroblastoma reveals additional treatment options. *Oncologist* 22:834-842, 2017
 11. Frampton JE: Pazopanib: A review in advanced renal cell carcinoma. *Target Oncol* 12:543-554, 2017
 12. Chellappan DK, Chellian J, Ng ZY, et al: The role of pazopanib on tumour angiogenesis and in the management of cancers: A review. *Biomed Pharmacother* 96:768-781, 2017
 13. Nakano K, Takahashi S: Current molecular targeted therapies for bone and soft tissue sarcomas. *Int J Mol Sci* 19:739, 2018
 14. Kim S, Atta JR, Bergmann L, et al: Imatinib mesylate as second-line treatment in a c-kit-positive esthesioneuroblastoma. *J Clin Oncol* 29, 2011 (suppl 15; abstr e12513)
 15. Fury MG, Sherman E, Haque S, et al: A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors. *Cancer Chemother Pharmacol* 69:591-598, 2012
 16. Sudarshan S, Linehan WM, Neckers L: HIF and fumarate hydratase in renal cancer. *Br J Cancer* 96:403-407, 2007
 17. Choi Y, Keam B, Kim M, et al: Bevacizumab plus erlotinib combination therapy for advanced hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma: A multicenter retrospective analysis in Korean patients. *Cancer Res Treat* 51:1549-1556, 2019
 18. Morris MR, Maina EN, Morgan NV, et al: Molecular genetic analysis of FH-1, FH, and SDHB candidate tumour suppressor genes in renal cell carcinoma. *J Clin Pathol* 57:706-711, 2004
 19. Bai T, Wang D, Yang, X: Role of hypoxia-inducible factor in clear cell renal cell carcinoma and its application in targeted therapy. *Int J Clin Exp Med* 10:9909-9917, 2017
 20. McCormack PL: Pazopanib: A review of its use in the management of advanced renal cell carcinoma. *Drugs* 74:1111-1125, 2014
 21. Topcagic J, Feldman R, Ghazalpour A, et al: Comprehensive molecular profiling of advanced/metastatic olfactory neuroblastomas. *PLoS One* 13:e0191244, 2018
-