


Clinical response to pazopanib in a patient with endolymphatic sac tumor not associated with von Hippel-Lindau syndrome

Thomas Nelson^{*,1} , Jethro Hu², Serguei Bannykh³, Xuemo Fan³, Jeremy Rudnick² & Eric Vail⁴

¹Department of Neurology, Cedars-Sinai Medical Center, 127 S San Vicente Blvd, Suite A6600, Los Angeles, CA 90048, USA

²Division of Neuro-Oncology, Department of Neurology, Cedars-Sinai Medical Center, 127 S San Vicente Blvd, 6th Floor, Los Angeles, CA 90048, USA

³Division of Neuropathology, Department of Pathology, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048, USA

⁴Division of Molecular Pathology, Department of Pathology, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048, USA

*Author for correspondence: Tel.: +1 310 423 6472; thomas.nelson@cshs.org

Endolymphatic sac tumors (ELSTs) are rare, locally invasive, vascular tumors of the temporal bone. These lesions are associated with von Hippel-Lindau syndrome but may arise sporadically. Early surgical intervention is recommended to prevent permanent neurologic deficits; however, many ELSTs are unresectable or are subtotally resected due to neurovascular compromise. Chemotherapeutic salvage therapy in trials of neoplasms of associated syndromes has targeted angiogenesis with variable response. We present the case of a sporadic ELST, previously minimally responsive to bevacizumab, treated with pazopanib, a multi-kinase inhibitor and antiangiogenic, with good response. Cases such as our patient may demonstrate the utility of novel antiangiogenics in the treatment of these rare neoplasms, particularly when the tumor is unresectable or necessitates subtotal resection.

First draft submitted: 16 October 2019; Accepted for publication: 29 January 2019; Published online: 6 March 2020

Keywords: endolymphatic sac tumor • neuro-oncology • pazopanib • precision medicine • targeted therapy • tyrosine kinase inhibitor

Background

Endolymphatic sac tumors (ELSTs) are rare, large primary neoplasms of the temporal bone that are benign but locally invasive [1]. They arise from the endolymphatic sac or ducts of the inner ear, progressing slowly to erode adjacent structures including into the cerebellopontine angle (CPA). Common symptoms – secondary to involvement of the structures within the CPA – include progressive hearing loss, tinnitus, vertigo, headache, imbalance or ataxia and nausea/vomiting [2,3]. Hydrocephalus and its sequelae, from compression of the fourth ventricle, may be seen [4]. ELSTs have a female preponderance and are diagnosed in the first through eighth decades of life with a median age of presentation in the fourth decade [4,5]. These neoplasms are often associated with von Hippel-Lindau (vHL) syndrome but may also occur sporadically, with some cases due to somatic mutation of the *VHL* tumor suppressor gene [2,6–12]. Treatment is early resection to avoid permanent neurologic deficits, and complete resection is potentially curative [13,14]. Adjuvant radiotherapy may slow or stop progression of disease in patients undergoing subtotal resection, though regrowth has been seen in about half of patients [13,15]. There is no standard or established chemotherapeutic regimen, which is especially problematic for patients in whom resection is subtotal or not possible due to structural limitations or vascular compromise. However, a posited role of antiangiogenic agents such as sunitinib and bevacizumab in the management of vHL may provide alternative treatments for ELSTs [1,16,17]. For patients in whom these agents are ineffective or not tolerated, novel agents such as pazopanib – a multi-kinase inhibitor and angiogenic – may provide new avenues for treatment.



Figure 1. Post-contrast axial T1 image from July 2013 demonstrating left-sided tumor extending into the cerebellum, middle fossa and upper neck.

Case report

Our patient originally presented in 1997 at 20 years of age with several months of blurred vision and migraines. He was evaluated at an outside hospital with limited records available for review. Imaging at that time reportedly revealed a CPA mass, and he underwent a partial resection of this lesion. Initial tissue diagnosis was meningioma versus paraganglioma. In 2008, a repeat resection was attempted but was unsuccessful due to the hemorrhagic nature of the lesion. Tissue diagnosis at the outside institution was WHO grade I meningioma, meningothelial type.

The patient was overall stable until December 2012, when symptoms accelerated and he developed generalized weakness affecting the legs predominantly. From February to April 2013, the patient received radiation of the neck and brain at a total dose of 54 Gy. However, while receiving radiation treatment, the patient's weakness progressed to needing a cane for ambulation.

In July 2013, the patient established care with the neuro-oncology team at our institution for further management of his left skull base tumor. By then, his weakness had progressed, particularly in the left leg. Initial imaging is seen in [Figure 1](#).

At the time of initial consultation, the patient had received no chemotherapy. With a working diagnosis of nonresectable meningioma or paraganglioma, treatment was initiated with temozolomide with cycle 1 dosing of 50 mg/m² for 5 days, followed by monthly cycles of 200 mg/m² for 5 days each. This decision was guided by evidence of clinical response in several studies and case series [18–20]. Between July 2013 and August 2014, our patient received 14 cycles of temozolomide with minor/partial radiographic response and symptom stabilization by November 2013. He would later receive eight additional cycles of temozolomide at 200 mg/m², for a total of 22 cycles, from October 2016 to May 2017, after imaging in February 2016 revealed increased tumor burden.

Regular follow-up appointments, off treatment, occurred from March 2014 through early 2016. Symptoms were stable with only intermittent headaches reported. Interval MRI scans showed continued slow growth of his tumor, and the decision to begin treatment with bevacizumab was made. Twelve biweekly infusions of bevacizumab at 10 mg/kg occurred between June and December 2017.

In July 2017, the pathology department at our institution obtained slides from the patient's 2008 biopsy. Review of histology in our laboratory determined his tumor to be a papillary epithelial neoplasm most consistent with an ELST. There was no apparent necrosis, and the tissue was suboptimally preserved to recognize mitotic figures. No brain parenchyma was noted in the specimen. Our patient was referred to a geneticist for screening for *vHL*, and genetic testing did not demonstrate a germline *VHL* gene mutation. CT scans of the chest, abdomen and pelvis were negative for other neoplasms or vascular anomalies.

Unfortunately, in January 2018, our patient was hospitalized for epidural abscess and influenza. He underwent left mastoidectomy for biopsy and debridement, left ear canal tumor biopsy and redo left craniectomy with resection and

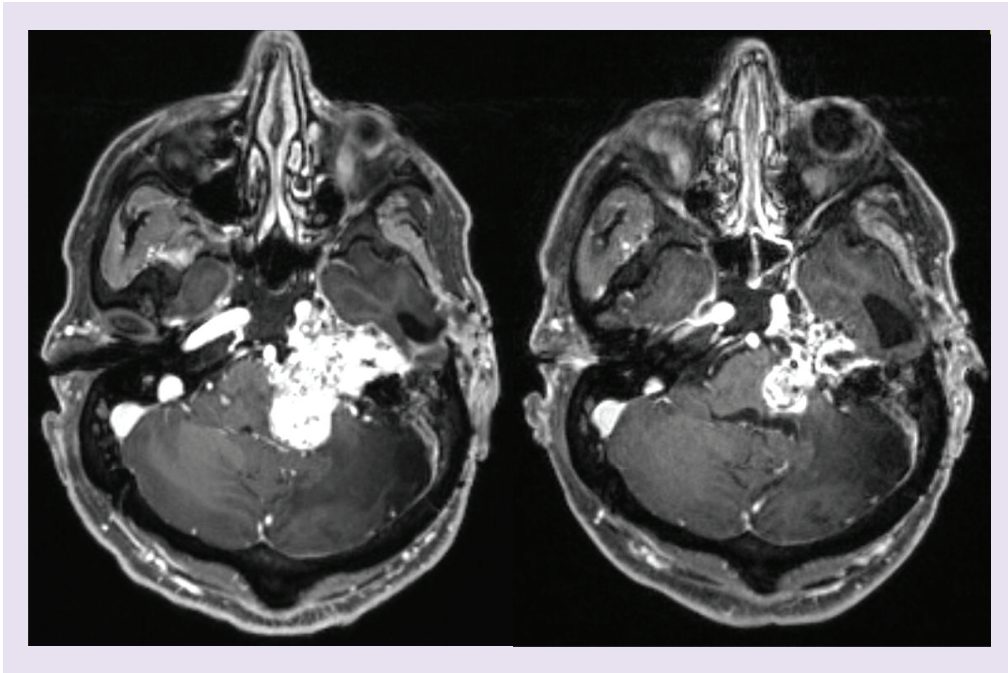


Figure 2. Radiographic response to pazopanib. Left is a post-contrast axial T1 MRI from October 2018 prior to initiation of pazopanib. Right is a post-contrast axial T1 MRI from April 2019 following initiation of pazopanib.

evacuation of abscess. The ear canal tumor biopsy demonstrated involvement by the ELST. A question posed during his January hospitalization was whether bevacizumab may have contributed, likely indirectly, to the formation of his abscess by impairing wound healing, possibly through decreased vascularization. Additionally, his tumor continued to enlarge while on this treatment as seen on follow-up MRI in April 2018, which revealed increasing tumor burden particularly of the intracranial component pressing on the left brachium pontis and brainstem.

In June 2018, partial embolization of arterial feeders to the tumor was performed with a reduction of more than 70% of the tumoral blush, though follow-up MRI in October 2018 was stable compared with July and April 2018, without reduction in tumor size.

Tissue from the January 2018 biopsy was sent for genetic analysis by Foundation One (Foundation Medicine, MA, USA), which demonstrated a somatic *VHL* L89R missense mutation, *TERT* promoter mutation –124C>T, stable microsatellite status, and low tumor mutation burden. There are currently no US FDA-approved targeted therapies for ELSTs; however, a Phase II trial of pazopanib by Jonasch *et al.* in 2018 demonstrated decreased tumor burden in patients with vHL-associated neoplasms. Given the association between vHL and ELST, as well as the suspected pathophysiology of these neoplasms, clinical response noted in these trials intimated a potential therapeutic response to pazopanib for our patient.

After discussing the risks, benefits and alternatives of this off-label application, treatment with pazopanib was initiated in November 2018 at a dose of 800 mg daily. This was well tolerated after a dose reduction to 400 mg daily in January 2019 given skin lightening and fatigue. Follow-up imaging demonstrated – as soon as December 2018 – significant reduction in tumor burden on this therapy. MRI brain comparing MRI in April 2019 to pretreatment imaging is seen in [Figure 2](#).

Discussion

A multisystem familial cancer syndrome, vHL is characterized by CNS hemangioblastomas, retinal hemangiomas, renal cell cancer of the clear cell type, renal or pancreatic cysts, pancreatic neuroendocrine tumors, pheochromocytomas and papillary cyst adenomas of the epididymis or broad uterine ligament; ELSTs have been reported in 9–16% of cases of vHL [2,6–8]. Conversely, in a series of 49 patients with diagnosed ESLTs, 24% had vHL [9]. Some cases of sporadic ELST have been associated with somatic mutation of the *VHL* tumor suppressor gene [10–12]. Treatment of ELST is primarily surgical, with complete resection being potentially curative [4,13]. There is an em-

phasis on early intervention as neurologic deficits may be permanent [13,14]. Adjuvant radiotherapy is not standard of care, though it has been shown to slow or stop progression of disease in half of patients undergoing subtotal resection [13,15]. The role of chemotherapeutic agents in the treatment of ELST is not clear, though patients in whom a subtotal resection is performed would benefit from nonsurgical interventions. To date, there have been no clinical trials of chemotherapeutic agents for ELST. Rather, the medications used in prior case reports are treatments studied in vHL alone, as an extension of the strong association between ELST and vHL. Given the highly vascular nature of tumors that form in vHL, including ELST, a putative mechanism for antiangiogenic agents such as sunitinib and bevacizumab in the management of this syndrome has been proposed and may provide alternative treatments for ELSTs [1,16,17].

Bevacizumab is a humanized monoclonal antibody against VEGF-A, which is believed to be the primary driver of tumor angiogenesis [21,22]. This medication is a potent antiangiogenic used as single agent or in conjunction with other chemotherapeutics in the treatment of metastatic colorectal cancer, non-small-cell lung cancer, renal cell carcinoma, advanced ovarian cancer and recurrent glioblastoma [21]. Although VEGF-A is implicated in the formation of blood vessels, angiogenesis is complex and consists of signaling pathways that incorporate PGF, FGFs, PDGFs, angiopoietins, various cytokines, PDGF-BB, ephrin-B2 and NOTCH [23]. Therefore, it has been proposed that agents inhibiting more of these targets, or affecting downstream signaling cascades, would provide more robust antitumor effects. One such agent is pazopanib.

Pazopanib (Votrient; GlaxoSmithKline, London, UK) is a kinase inhibitor that targets several tyrosine kinases including VEGF receptors 1, 2 and 3, as well as PDGF alpha, beta and KIT [24,25]. This agent was approved by the US FDA in 2009 for the treatment of advanced renal cell carcinoma, and in 2012 extended its indications to include advanced soft tissue sarcoma in patients who had previously received other chemotherapy [26]. An illustration of the sites of action of pazopanib is seen in Figure 3.

Trials of pazopanib as single agent therapy for various neoplasms – within and outside the CNS – have demonstrated mixed response. In a Phase II trial by Iwamoto *et al.* in 2010, the safety and efficacy of pazopanib for recurrent glioblastomas was tested. Their primary end point for efficacy was progression-free survival at 6 months (PFS6). In these patients, despite tolerating the medication relatively well, the PFS6 rate was poor at 3%; this was significantly lower than trials of bevacizumab that demonstrated rates of 29–43% in a similar patient population [27,28]. Although the efficacy outcome was low, there was evidence that pazopanib did have *in situ* biological activity in this patient cohort [29]. Though not fully understood, the mechanism of tumor response may be due to normalization of abnormal tumor blood vessels rather than direct antiangiogenic or antitumor properties.

A Phase II trial of pazopanib as second-line therapy in patients with metastatic or locally unresectable renal clear cell carcinoma who had previously received single agent treatment with bevacizumab or sunitinib was conducted by Hainsworth *et al.* in 2013. In this study, 15 of 55 (27%) patients demonstrated objective response to pazopanib and another 27 (49%) had stable disease for a disease control rate of 76%. Of the 45 patients in whom disease progressed while on first line treatment, 10 (22%) demonstrated response with a disease control rate of 75% [30]. More recently, Jonasch *et al.* demonstrated in a Phase II, single center trial that patients with diagnosed vHL may see response to tumors of multiple organs when started on pazopanib therapy [31]. Of the 31 patients treated with pazopanib, 13 (42%) demonstrated objective response with the most pronounced effect in pancreatic lesions (9 of 17, 53%) and renal cell carcinomas (31 of 59, 52%); only 2 of 49 (4%) CNS hemangioblastomas demonstrated objective response [31]. These trials illustrate the treatment potential of pazopanib in patients with various tumor types, including those often associated with vHL.

Despite some promise seen with antiangiogenic therapies in patients with unresectable or partially resected ELSTs, treatment options remain limited. In our patient, diagnosed with his CPA neoplasm at age 20, the high vascularity of his lesion limited resection. Subsequent treatment with radiation therapy did not hinder growth and treatment response with temozolomide was transient. Bevacizumab likewise demonstrated only temporary disease control, and this therapy may have contributed indirectly to the development of an epidural abscess. Genetic testing did not identify a novel therapeutic target but was notable for a *VHL* L89R mutation. The clinical significance of the *VHL* L89R mutation is not characterized, and the effect on pVHL protein function is unknown. In a series of six patients with the *VHL* L89R mutation in the COSMIC database, five were associated with clear cell type renal cell carcinoma and one with CNS hemangioblastoma [32,33]; neither of these tumor types has been identified in our patient. With no specific genetic target and promising trials, pazopanib was initiated as third line therapy in our patient with significant reduction in tumor burden to date.

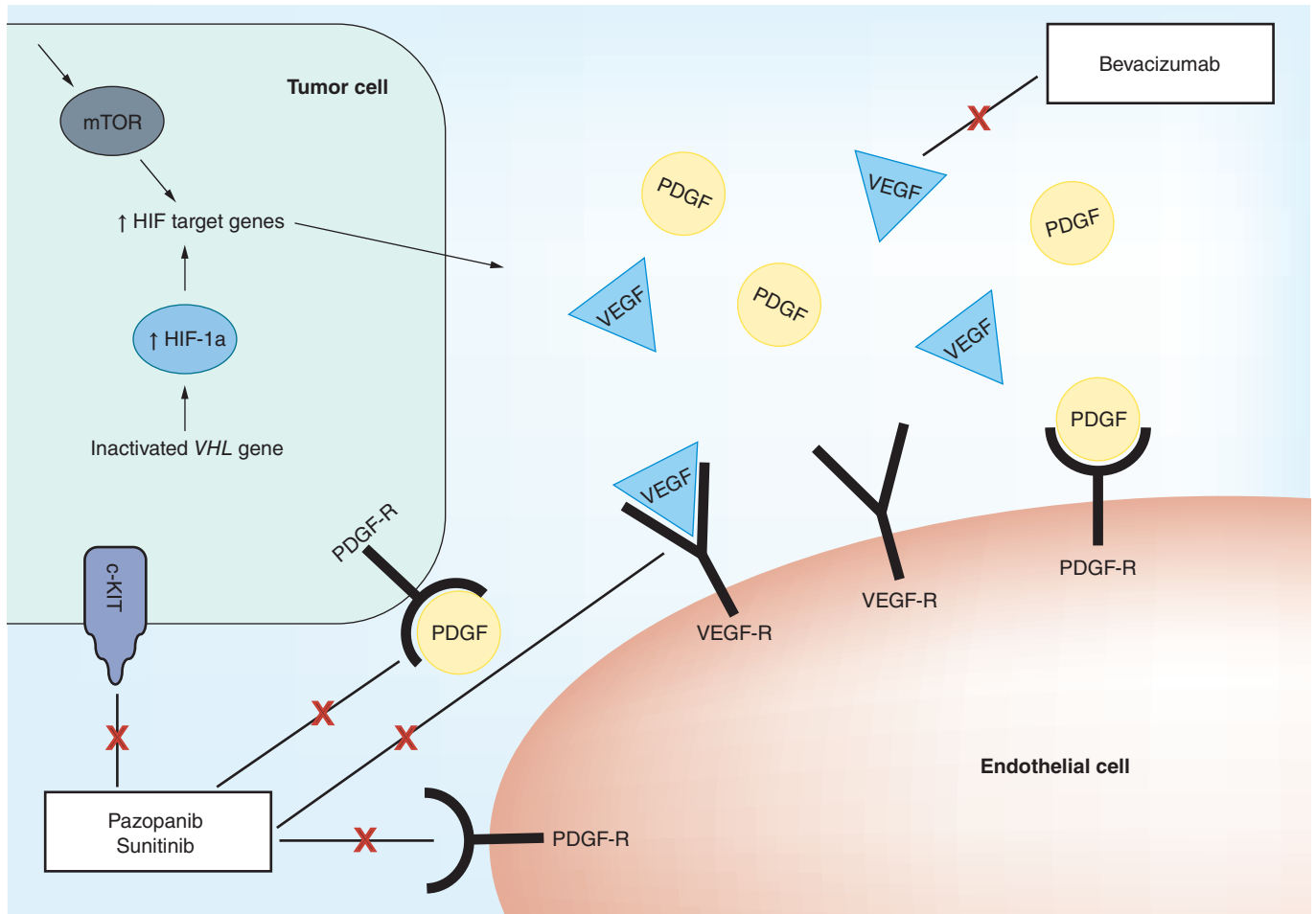


Figure 3. Sites of action of notable antiangiogenic agents.

The sites of action of pazopanib may in part explain our patient's improved response to this therapy. In particular, disruption of tyrosine kinase signaling cascades rather than scavenging VEGF-A – the mechanism of bevacizumab – may provide longer-term reduction in tumor burden. Additionally, there may be decreased development of resistance to this therapy. The authors acknowledge that this is a single case report and that no clinical trial has yet been performed to assess the response of ELSTs to pazopanib therapy. Given the rare nature of this condition, a prospective clinical trial is likely not feasible. There remains a dearth of available systemic therapies for vHL syndrome, but as more trials are conducted, the frontiers of treatment options for vHL that may extend to ESLT will continue to shift.

Summary points

- Nonsurgical treatment options for patients with endolymphatic sac tumors remain limited.
- However, there is demonstrated potential for antiangiogenic agents in our patient and previous case series.
- In our patient, treatment with pazopanib, a tyrosine kinase inhibitor with antiangiogenic properties, has resulted in decreased lesional burden that may provide evidence for a novel therapy for endolymphatic sac tumors.

Acknowledgments

The authors would like to thank their friends and colleagues who supported the writing of this case report.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient for the inclusion of their medical and treatment history within this case report.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

- Alkhotani A, Butt B, Khalid M, Binmahfoodh M, Al-Said Y. Endolymphatic sac tumor at the cerebellopontine angle: a case report and review of literature. *Int. J. Surg. Case Rep.* 58, 162–166 (2019).
- Choo D, Shotland L, Mastroianni M *et al.* Endolymphatic sac tumors in von Hippel-Lindau disease. *J. Neurosurg.* 100(3), 480–487 (2004).
- Manski TJ, Heffner DK, Glenn GM *et al.* Endolymphatic sac tumors: a source of morbid hearing loss in von Hippel-Lindau disease. *JAMA* 277(18), 1461–1466 (1997).
- Rodrigues S, Fagan P, Turner J. Endolymphatic sac tumors: a review of the St. Vincent's hospital experience. *Otol. Neurotol.* 25(4), 599–603 (2004).
- Wenig BM, Heffner DK. Endolymphatic sac tumors: fact or fiction? *Adv. Anat. Pathol.* 3(6), 378–387 (1996).
- Choyke PL, Glenn GM, Walther MM, Patronas NJ, Linehan WM, Zbar B. von Hippel-Lindau disease: genetic, clinical, and imaging features. *Radiology* 194(3), 629–642 (1995).
- Maher ER, Yates JRW, Harries R *et al.* Clinical features and natural history of von Hippel-Lindau disease. *Q. J. Med.* 77(2), 1151–1163 (1990).
- Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. *J. Neurosurg.* 98(1), 82–94 (2003).
- Diaz RC, Amjad EH, Sargent EW, LaRouere MJ, Shaia WT. Tumors and pseudotumors of the endolymphatic sac. *Skull Base* 17(06), 379–393 (2007).
- Hamazaki S, Yoshida M, Yao M *et al.* Mutation of von Hippel-Lindau tumor suppressor gene in a sporadic endolymphatic sac tumor. *Hum. Pathol.* 32(11), 1272–1276 (2001).
- Husseini ST, Piccirillo E, Taibah A, Paties CT, Almutair T, Sanna M. The Gruppo Otologico experience of endolymphatic sac tumor. *Auris Nasus Larynx* 40(1), 25–31 (2013).
- Poletti AM, Dubey SP, Barbò R *et al.* Sporadic endolymphatic sac tumor: its clinical, radiological, and histological features, management, and follow-up. *Head Neck* 35(7), 1043–1047 (2013).
- Hansen MR, Luxford WM. Surgical outcomes in patients with endolymphatic sac tumors. *Laryngoscope* 114(8), 1470–1474 (2004).
- **Case series illustrates outcomes of surgical and adjuvant radiotherapy interventions.**
- Lonser RR, Kim HJ, Butman JA, Vortmeyer AO, Choo DI, Oldfield EH. Tumors of the endolymphatic sac in von Hippel-Lindau disease. *N. Engl. J. Med.* 350(24), 2481–2486 (2004).
- Megerian CA, McKenna MJ, Nuss RC *et al.* Endolymphatic sac tumors: histopathologic confirmation, clinical characterization, and implication in von Hippel-Lindau disease. *Laryngoscope* 105(8), 801–808 (1995).
- Jimenez C, Cabanillas ME, Santarpia L *et al.* Use of the tyrosine kinase inhibitor sunitinib in a patient with von Hippel-Lindau disease: targeting angiogenic factors in pheochromocytoma and other von Hippel-Lindau disease-related tumors. *J. Clin. Endocrinol. Metab.* 94(2), 386–391 (2009).
- **Highlights the use of antiangiogenic agents for von Hippel-Lindau (vHL).**
- Jonasch E, McCutcheon IE, Waguespack SG *et al.* Pilot trial of sunitinib therapy in patients with von Hippel-Lindau disease. *Ann. Oncol.* 22(12), 2661–2666 (2011).
- **Highlights the use of antiangiogenic agents for vHL.**
- Bravo EL, Kalmadi SR, Gill I. Clinical utility of temozolomide in the treatment of malignant paraganglioma: a preliminary report. *Horm. Metab. Res.* 41(9), 703–706 (2009).

19. Chamberlain MC, Tsao-Wei DD, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. *Neurology* 62(7), 1210–1212 (2004).
20. Hadoux J, Favier J, Scoazec JY *et al.* SDHB mutations are associated with response to temozolomide in patients with metastatic pheochromocytoma or paraganglioma. *Int. J. Cancer* 135(11), 2711–2720 (2014).
21. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature* 473(7347), 298–307 (2011).
22. Claesson-Welsh L, Welsh M. VEGFA and tumour angiogenesis. *J. Intern. Med.* 273(2), 114–127 (2013).
23. Lambrechts D, Lenz HJ, de Haas S, Carmeliet P, Scherer SJ. Markers of response for the antiangiogenic agent bevacizumab. *J. Clin. Oncol.* 31(9), 1219–1230 (2013).
24. Harris PA, Bolor A, Cheung M *et al.* Discovery of 5-[[4-[(2, 3-dimethyl-2 H-indazol-6-yl) methylamino]-2-pyrimidinyl] amino]-2-methyl-benzenesulfonamide (Pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. *J. Med. Chem.* 51(15), 4632–4640 (2008).
25. Kumar R, Knick VB, Rudolph SK *et al.* Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol. Cancer Ther.* 6(7), 2012–2021 (2007).
26. US Food and Drug Administration. Votrient (pazopanib): prescribing Information (2019). www.accessdata.fda.gov/drugsatfda_docs/label/2015/022465s020lbl.pdf
27. Friedman HS, Prados MD, Wen PY *et al.* Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J. Clin. Oncol.* 27(28), 4733–4740 (2009).
28. Kreisl TN, Kim L, Moore K *et al.* Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J. Clin. Oncol.* 27(5), 740–745 (2009).
29. Iwamoto FM, Lamborn KR, Robins HI *et al.* Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American Brain Tumor Consortium Study 06-02). *Neuro Oncol.* 12(8), 855–861 (2010).
30. Hainsworth JD, Rubin MS, Arrowsmith ER, Khatcheressian J, Crane EJ, Franco LA. Pazopanib as second-line treatment after sunitinib or bevacizumab in patients with advanced renal cell carcinoma: a Sarah Cannon Oncology Research Consortium Phase II Trial. *Clin. Genitourin. Cancer* 11(3), 270–275 (2013).
31. Jonasch E, McCutcheon IE, Gombos DS *et al.* Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, Phase II trial. *Lancet Oncol.* 19(10), 1351–1359 (2018).
- **A Phase II, single center trial of pazopanib in patients with diagnosed vHL that demonstrated response of multiple tumor types to this agent.**
32. Tate J, Bamford S, Jubb H *et al.* COSMIC: the catalogue of somatic mutations in cancer. *Nucleic Acids Res.* 47(D1), D941–D947 (2019).
33. COSMIC. Mutation overview – VHL p.L89R (2019). <https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=14404>