



# Treatment of periocular basal cell carcinoma with neoadjuvant vismodegib

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## ABSTRACT

**Purpose:** To report a case of a locally advanced periocular basal cell carcinoma treated with neoadjuvant Vismodegib therapy prior to surgery.

**Observations:** A 63-year-old female presented to the oculoplastics clinic with biopsy-proven basal cell carcinoma of the right periorbital region causing significant cicatricial ectropion of the right lower eyelid. The medial canthal lesion involved nearly the entire right lower eyelid with extension onto the cheek, the medial half of the right upper eyelid, the palpebral and bulbar conjunctiva, as well as the right lacrimal system. CT imaging was suggestive of involvement of the extraocular muscles and other post-septal tissues. Fortunately, the patient had no metastatic disease. The extent of the tumor would have necessitated aggressive resection to achieve surgical cure. However, the patient preferred to attempt globe-sparing therapy with a goal of preserving cosmesis as much as possible. Various treatment options were discussed with the patient, including the use of Vismodegib, and the patient elected to pursue this treatment strategy. The goal of Vismodegib treatment was to reduce the tumor size enough to permit surgical resection of all tumor without significantly affecting cosmesis. After 11 months of treatment with Vismodegib, the tumor size had reduced significantly to the point where surgical intervention with minimal disfigurement could be offered. The patient underwent multidisciplinary approach with Mohs micrographic excision of the tumor paired with oculoplastic reconstructive surgery resulting in negative margins and satisfactory cosmetic results.

**Conclusions and importance:** Although additional study is required regarding Vismodegib as a primary or adjuvant therapeutic approach to periorbital basal cell carcinoma, this case illustrates the potential usefulness of this drug as an option in this context. This case provides information that may help the comprehensive ophthalmologist or oculoplastic specialist in counseling patients with locally advanced periorbital basal cell carcinoma.

## 1. Introduction

Our goal in presenting this case is to illustrate that Vismodegib can be very helpful as an adjuvant to surgical resection in the context of locally advanced periorbital disease. Basal cell carcinoma is the most commonly diagnosed human cancer, typically occurring in persons of fair complexion over age 50, with men more commonly affected than women.<sup>1,2</sup> Periorbital basal cell carcinoma is generally treated with surgical excision with the addition of micrographic surgery to control margins when indicated. For tumors that may complicate traditional excision due to size, location, advancement, or metastasis Vismodegib may be of benefit as it was approved in 2012 for the treatment of adults with metastatic basal cell carcinoma, locally advanced basal cell carcinoma that has recurred following surgery, and those who are not candidates for surgery or radiation.<sup>3-6</sup> Aberrancies in the hedgehog signaling pathway are the causative pathogenesis of basal cell carcinoma, and Vismodegib, a small-molecule inhibitor of the hedgehog

pathway, in combination with surgical management, may be a useful therapeutic option.

### 1.1. Case report

A 63-year-old female presented to the oculoplastics clinic with a four-year history of a gradually enlarging lesion involving predominantly the right medial canthus. The patient at first attributed the non-healing right lower lid lesion to an abrasion inflicted by a tree branch. Subsequent biopsy by a dermatologist yielded the diagnosis of basal cell carcinoma. The patient was referred for Mohs excision, but she apparently was unable to follow this treatment course due to financial limitations. In this context, the patient presented to our oculoplastics clinic complaining of gradually worsening right-sided epiphora with intermittent blurry vision over the past several years. She also had been experiencing intermittent bleeding from the lesion and also had noted extension of the lesion to the upper eyelid. Aside from

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Fig. 1. The patient at presentation, both eyes.

mild refractive error, she otherwise had no other known past ocular history. The patient had a history of cerebral aneurysm repair in 2006 requiring a metal plate to close the surgical defect. This history precluded her from having magnetic resonance imaging. Otherwise, the remainder of her past medical and surgical history was non-contributory.

On presentation to our clinic, the patient's corrected distance visual acuity was 20/40–2 OD and 20/20 OS. Her pupillary exam was normal, alignment and motility were normal and visual fields were full to confrontation. Intraocular pressures were 14 OU. The external exam was remarkable for cicatricial ectropion of nearly the entire right lower lid with a firm, nodular mass that spared only the lateral 7 mm of the lid margin. As can be seen in Fig. 1, there were associated telangiectasias, madarosis, distortion of the eyelid architecture, and fistula formation from the nasolacrimal sac region. The lesion also involved about one-half of the medial right upper lid and the nasal bulbar conjunctiva. The upper lid component measured 15 mm × 25 mm and the lower lid component measured 20 mm × 35 mm (Figures, 1, 2, 3). Probing and irrigation of the nasolacrimal system revealed a discontinuous right upper canalicular system. The right lower eyelid punctum was obliterated and irrigation at the fistulous opening revealed no connection with the nose. There was a mild papillary reaction of the right upper lid and symblepharon formation from the lateral right lower lid to the temporal bulbar conjunctiva. The left eye conjunctiva and sclera were normal. There were mild punctate epithelial defects on the cornea and mild nuclear sclerosis OU, otherwise the anterior segment examination was unremarkable. Examination of the posterior segment revealed a few small drusen and some mild peripheral reticular pigmentary changes OU, but was otherwise unremarkable.



Fig. 2. The patient's right eye.



Fig. 3. The patient's right eye, lateral view.

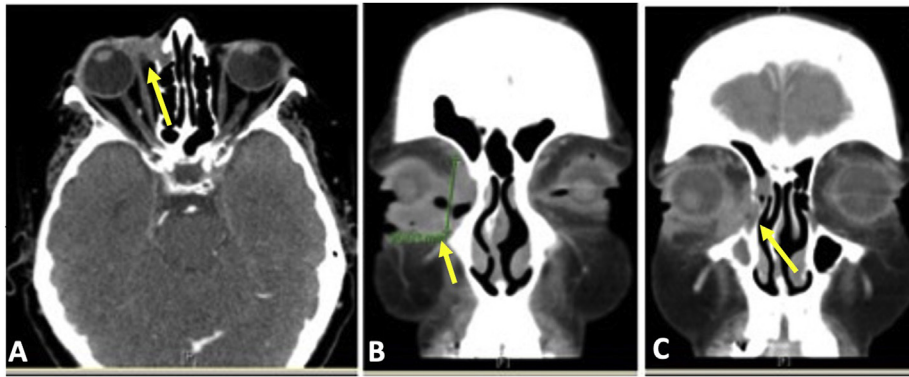
As shown in Figs. 4 and 5, CT imaging of the orbits with contrast demonstrated that the lesion had breached the anterior right lamina papyracea and nasolacrimal system, involving some of the extraocular muscles and post-septal orbital tissues. There was also apparent extension into the right maxillary sinus (Fig. 5).

### 1.2. Management options

Our patient expressed a strong desire to continue working if possible and wanted to try to preserve a normal facial appearance. The patient's case was evaluated by our institution's tumor board, including clinicians from Radiation Oncology, Hematology/Oncology and Otolaryngology. Endoscopic evaluation of the sinuses by Otolaryngology revealed no intranasal tumor and they felt that the apparent sinus extension on CT imaging may have been inflammatory reaction only. A full evaluation and workup by Oncology revealed no metastatic disease. Due to the locally advanced status of the patient's tumor, the possible need for disfiguring surgery such as orbital exenteration was discussed with her. The possibility of a globe sparing approach with resection of tumor following adjuvant radiation, with the accompanying risks of radiation optic neuropathy, retinopathy, dry eye, and infection were discussed. We also discussed the possibility of using Vismodegib to reduce tumor size enough for her to potentially be a candidate for globe-sparing surgery with improved cosmetic outcome. The patient ultimately decided to pursue this option and was started on 150mg Vismodegib by mouth daily, with regular evaluations by Oncology.

### 1.3. Patient's progress and treatment

Aside from minor fatigue, weight loss, and dysgeusia, our patient tolerated the Vismodegib therapy without major issues and has returned to clinic every 3 months for follow up evaluation. Her tumor size decreased significantly and CT imaging after 4 months of treatment demonstrated a significant decrease in radiodensity and soft tissue thickening involving the right medial canthus and lower lid. At 4 months follow up examination, the residual nodular lesions of the right upper lid measured 3mm vertically x 9mm horizontally, with associated madarosis. The residual nodular lesions of the right lower lid measured 5 mm vertically x 14mm horizontally, with associated madarosis (Fig. 6A). At 10 months, there was no longer any palpable nodularity of the lids, and the area of madarosis measured 10 mm along the right upper lid from the medial canthus (Fig. 6B). At approximately 12 months after the patient's initial presentation to our clinic and following 11 months of oral Vismodegib, the patient underwent Mohs micrographic excision of the right medial canthal basal cell carcinoma with same-day post-Mohs reconstruction of the right medial canthal defect which encompassed the medial half of the upper and lower eyelid. This

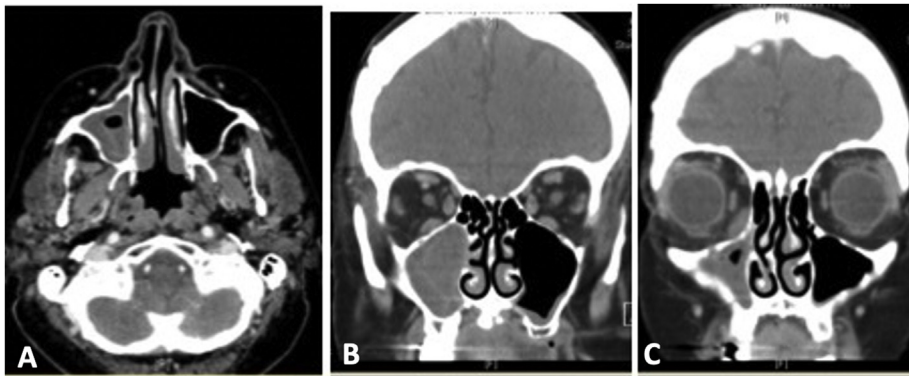


**Fig. 4. 4A:** CT imaging showed soft tissue mass (arrows) measuring 31mm (transverse) x 23mm (antero-posterior) x 26mm (craniocaudal), with involvement of anterior right lamina papyracea. There is an ulcerated soft tissue mass in the medial right orbit which measures up to 31 mm transverse by 23 mm AP by 26 cm craniocaudal. The medial most extent of this mass appears to breach the anterior right lamina papyracea and there is contiguous opacification of a right anterior ethmoid air cell.

**4B:** The inferomedial portion appears to breach the nasolacrimal duct with concern for tumoral extension into the duct. The superior extent of this lesion extends medially along the orbital wall with obliteration of the fat plane involving the inferior oblique.

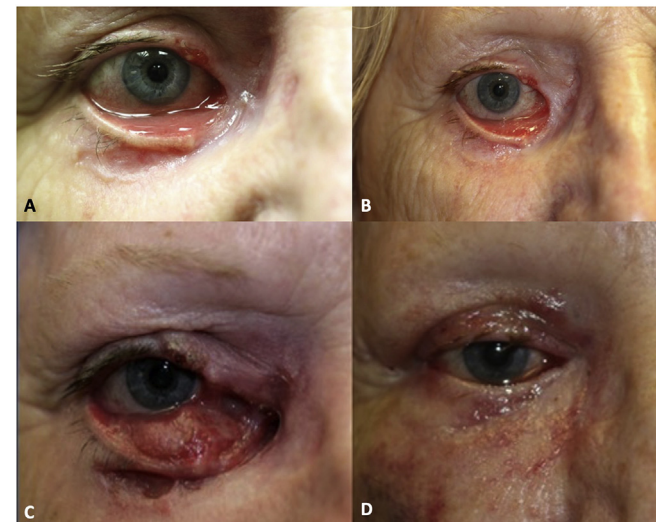
lique muscular origin, the myotendinous junction of the medial rectus muscle, and the tendon of the superior oblique muscle.

**4C:** The posterior aspect extends to involve the post septal soft tissues. The lateral most extent abuts the medial sclera, the right globe is otherwise unremarkable.



**Fig. 5. 5A:** The right orbital floor appears intact, but there is extensive mucosal thickening of the right maxillary sinus (also visible in **5B**)**5B:** There is mucosal opacification of the right maxillary ostium, the middle meatus is patent on the right.

**5C:** There is mild mucosal thickening of the left maxillary sinus, ostiomeatal unit on the left is patent.



**Fig. 6. 6A:** 4 months after initiation of Vismodegib.**6B:** 10 months after initiation of Vismodegib. **6C & D:** Before and after. These figures compare initial presentation (C) to 17 days post-op (D).

was accomplished using an advancement flap to close the right upper lid defect as well as a Tenzel semicircular flap from the right lateral canthus in conjunction with a medial rhomboid flap to close the medial right lower eyelid defect. The patient tolerated the procedure without difficulty and 17 days post operation, she reported stable vision with no complaints (**Fig. 6C & D**). The patient denied symptoms of epiphora at all post-operative visits and therefore the lacrimal system was not formally investigated. She continued to remain on Vismodegib and was followed by the Hematology/Oncology service. Approximately 10

months after surgery, Vismodegib was discontinued per Hematology/Oncology as there was no clinical evidence of active disease upon exam. The patient's only reported side effects during the course of the medication were fatigue, dysgeusia and weight loss. She completed a total of 21 months of Vismodegib. At her most recent follow up, 24 months after surgery, she continued to display no evidence of active disease upon exam.

## 2. Discussion

### 2.1. About the disease: basal cell carcinoma

Basal cell carcinomas (BCC) is a keratinocyte tumor that derives its name from their histological resemblance to the basal layer of the epidermis.<sup>1,7</sup> It is the most commonly diagnosed neoplasm in populations of European descent with fair complexion.<sup>1,2,8</sup> Most Basal cell carcinomas (BCCs) occur sporadically, but they rarely can be inherited as part of the basal cell nevus syndrome (BCNS or Gorlin syndrome).<sup>1</sup> Studies of tissues from patients with BCNS or sporadic BCC have revealed that the hedgehog (HH) signaling pathway is of central importance for BCC pathogenesis. Normally, the hedgehog pathway operates as a signaling system that begins during embryogenesis, controlling a range of cellular activities that aid in the regulation of cell growth and development.<sup>3,8,9</sup> It is the aberrant regulation of this pathway that results in uncontrolled proliferation of basal cells and carcinogenesis.<sup>1,4</sup> On the molecular level, the patched 1 (PTCH1) protein serves as a membrane-bound receptor for HH ligands. Biallelic inactivation of PTCH1 produces constitutive upregulation of HH signaling which has been found in a majority of cases of sporadic BCC while a subset are caused by activating mutations in SMO or other HH pathway mutations.<sup>1,4,8-10</sup> There are three families of extracellular HH ligands in mammals, sonic hedgehog, Indian hedgehog, and desert



hedgehog.<sup>1</sup> These HH ligands bind to the PTCH1 which relieves PTCH1's inhibition of smoothed homologue (SMO). SMO is a seven-transmembrane G protein-coupled receptor involved in nuclear localization of transcription factors that target gene induction.<sup>3,4,11</sup> Subsequently, SMO sends signals through a variety of interacting proteins including suppressor of fused (SUFU) protein which in turn results in the activation of the Gli family of transcription factors: GLI1, GLI2, and GLI3<sup>1,10,11</sup>. This leads to uncontrolled proliferation of basal cells. Although the majority of sporadic BCC cases involve a loss of PTCH1, TP53 (a tumor suppressor gene) mutations are present in about half of cases.<sup>12,13</sup>

The vast majority of BCCs are readily treated by surgical excision, however, in some cases, progression of these lesions renders the patient no longer a good candidate for surgical resection or radiation therapy.<sup>3,7,10</sup> Determination of the appropriate treatment approach for locally advanced or metastatic disease is a decision based upon physician expertise and experience, informed by the patient's goals and personal preferences.

## 2.2. Vismodegib

Vismodegib (GDC-0449, Genetech) is a synthetic, first-in-class, small-molecule inhibitor of SMO approved by the FDA in 2012 for treatment of locally advanced and metastatic BCC.<sup>3,4,6,14</sup> Erivance BCC was a phase 2 multicenter, multi-national, non-randomized, cohort study of 104 patients with metastatic (mBCC) or locally aggressive basal cell carcinoma (laBCC) evaluating the efficacy and safety of Vismodegib.<sup>3-7,10</sup> Patients received Vismodegib 150mg by mouth daily until there was evidence of disease progression, toxicity, or withdrawal from the study. The mean duration of treatment was approximately 10 months, the mean duration of response was 7.3 months (increased to 9.5 months at 2 years), and the objective response rate at 1 year for laBCC was 43% (48% at 2 years) and for mBCC was 30%.<sup>4,10</sup> The objective response rate was defined as a decrease in size by 30% either on exam or computed tomography imaging, or complete resolution of ulceration if present at baseline.<sup>4,10</sup> Responses were then classified as being either partial or complete. A complete response was defined as absence of residual basal cell carcinoma on assessment of a biopsy specimen.<sup>4</sup> There was complete response in 21% of subjects with laBCC. At 30 months, only 9 patients were still receiving treatment while 69 patients were in survival follow up. Additionally, at this time mean duration of response was 14.8 months for mBCC and 26.2 months for laBCC. The objective response rate for laBCC was 60.3% and for mBCC was 48.8%. Adverse events from the drug occurred in at least 20% of all patients, commonly involving muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, decreased appetite, and diarrhea.<sup>4,6,10</sup>

In addition to Erivance, the EAS Study was an open-label, 2-cohort study that investigated the effect of 150mg of oral Vismodegib in 120 BCC patients with advanced BCC inappropriate for radiotherapy or surgery.<sup>7,14</sup> The STEVIE study was a multicenter, open-label trial designed to assess the safety of a daily dose of 150mg of oral Vismodegib in 468 patients with laBCC and 31 with mBCC.<sup>11</sup> The sites of advanced BCC involvement in the EAS and STEVIE studies included but were not limited to the lung, skin, lymph node, bone, and liver.<sup>11,14</sup> Of note, these studies did not specify the proportion of patients that had a periocular site of skin involvement by BCC, specifying involvement only as of the "head" or "face". However, findings from these studies demonstrated similar results to those from Erivance.<sup>7</sup>

Guidelines for inoperability based on the tumor, node, and metastasis classification scheme have been proposed by a panel from the American Joint Committee on Cancer for eyelid carcinoma. The panel recommends that "eyelid tumors of stages T3a (defined as a tumor > 20mm in greatest dimension, or any tumor that invades adjacent ocular or orbital structures, or any tumor with perineural tumor invasion), T3b, and T4 not appropriate for radical local therapy be assessed for possible systemic therapy with vismodegib".<sup>3</sup> Of note, the panel was

sponsored by Roche(Genentech) and consisted of oncologists, dermatologists, and radiation oncologists but no ocular oncologists or oculoplastics specialists were present on this panel. Notwithstanding, based on the current evidence there is reason to support use of vismodegib in clinical situations such as those with which our patient presented. In our patient, vismodegib made later surgical cure possible, concomitantly facilitating a cosmetically acceptable outcome.

In a study performed by Gonzalez et al., the 7 of 8 patients who showed response neoadjuvant Vismodegib prior to Mohs micrographic surgery were disease free after a mean follow up of 12.4 months.<sup>15</sup> There have been other studies reported in the literature examining the use of Vismodegib for periocular BCC however, follow up periods in the literature have been limited.<sup>5,6,16-21</sup> Due to the limitation of follow-up, a conclusion cannot be drawn yet whether long-term complications exist or if Vismodegib truly improves rates of disease-free survival. Further studies are clearly needed.

Although our patient has remained free of any evidence of tumor recurrence or new tumor formation, there have been reports of new onset keratoacanthomas after Vismodegib treatment. Aasi et al. report two observational cases of patients without histories of squamous cell carcinoma who developed keratoacanthomas after Vismodegib treatment for locally advanced basal cell carcinomas.<sup>22</sup> New tumor formation or the possibility of tumor recurrence should be incorporated in the physician's discussions with their patients.

## 3. Conclusions

In summary, we report a case of periorbital basal cell carcinoma treated with 11 months of Vismodegib therapy resulting in significant reduction of the tumor size, making the patient a good surgical candidate. The combination of Mohs micrographic surgery and oculoplastics reconstructive surgery resulted in negative margins and satisfactory cosmetic results. Additional study is needed regarding the efficacy of Vismodegib as a long-term therapeutic approach and as adjuvant therapy to periorbital basal cell carcinoma. However, this case illustrates a therapeutic approach that can usefully inform the counseling of patients presenting with locally advanced periorbital BCC.

### 3.1. Patient consent

- The patient consented to publication of the case in writing.
- The patient consented to the use of photos and personal information in writing

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### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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### Declaration of competing interest

The following authors have no financial disclosure: MGS, LBP, JHT.

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