Ameloblastoma is an uncommon tumor of odontogenic epithelium that rarely metastasizes but can recur locally despite wide surgical resections, resulting in cosmetic and functional abnormalities of the face and jaw (1). We present here a 40-year-old African American male diagnosed 30 years ago at another hospital with ameloblastoma of the left mandible. Despite an initial wide surgical resection and jaw reconstruction, he required three subsequent resections for recurrent disease, including removal of a 7.5 x 5.5 cm tumor mass 13 years ago and resection of separate 8.0 and 7.0 cm recurrent tumor masses 9 years ago. Seven years ago, he received involved field radiation therapy for biopsy-proven unresectable locally recurrent ameloblastoma. He did well for the next six years until gradual tumor regrowth in bilateral neck masses and in the region of his left mandible mandible reconstruction. CT imaging showed subcentimeter pulmonary nodules and a soft tissue mass obstructing the right bronchus as well as a contralateral hilar metastasis. He underwent bronchoscopic evaluation, and both a right middle lobe endobronchial mass and left inferior lingual endobronchial mass were positive for stage 4 metastatic ameloblastoma (Figure 1A). A cancer gene profile was obtained, detecting only the presence of a BRAF V600E mutation using a Clinical Laboratory Improvement Amendments (CLIA) certified test, and confirmatory cytoplasmic anti-BRAF V600E staining was detected on the biopsy sample by immunohistochemistry (Figure 1B).

The patient was aware of reports showing occasional tumor responses to standard systemic chemotherapy and that some patients could have an indolent clinical course in the absence of active treatments. However, because he was developing symptoms related to progressive disease and because there is poor overall survival with no established chemotherapy regimen for metastatic ameloblastoma (1), the patient was interested in pursuing therapy targeted to his newly discovered activating BRAF mutation.

GlaxoSmithKline approved our formal application to obtain the oral drugs dabrafenib at 150 mg twice daily and trametinib at 2 mg once daily under their compassionate use program. The Food and Drug Administration then approved our request for an Investigational New Drug application under their expanded access provision. Institutional review board approval and the patient’s informed consent were obtained prior to initiating treatment.

Within four days of starting the dual targeted oral therapy, the patient noted a subjective and then visible reduction in tumor volume in his face, oral cavity, and bilateral neck. Within two weeks of treatment, he noted an increase in energy level and improved subjective quality of life. We obtained a repeat PET CT scan eight weeks after starting treatment (Figure 1, C-F). This showed disappearance of fluorodeoxyglucose (FDG) activity in the lungs and reduction of the tumor mass in the face, jaw, and neck. This was associated with cosmetic improvement of his face and resolution of his oral pain. Chest and maxillofacial CT scans performed 20 weeks after starting treatment showed a persistent tumor response at all sites of prior disease (data not shown). He has experienced no apparent toxicity to date from this treatment.

This report raises several important points. First, ameloblastoma is over-represented in black males as compared with white males (2), and we might predict a reduced risk for dabrafenib-associated skin toxicity because of a lower burden of cutaneous cells bearing chronic UV-associated somatic mutations in patients of African descent. Second, while we were preparing to treat this patient, three studies totaling 136 cases of ameloblastoma were reported showing a frequency of BRAF mutations of 46% to 63% (3–5), with enrichment to 70% in mandibular ameloblastoma as in the case reported here. These data support the clinical significance and broad application of our treatment with an initial dramatic response. Third, it was not certain this patient would respond, because cases of colon cancer with the V600E allele are resistant to treatment because of epidermal growth factor receptor feedback (6) and possibly other mechanisms related to cooperating sequential mutations and undefined interactions related to the intestinal microenvironment. Similarly, it was not certain that the bilateral metastatic lung
tumor would respond similarly to recurrent tumor at the primary site. Our observation suggests the detection of V600E as a core driver event in ameloblastoma with important therapeutic opportunities despite previous treatment regimens over many years. Finally, following an eight-week treatment course, it is intriguing that a focus of FDG activity remains only in a region near the initial primary tumor presentation. This may be an indication of a relatively resistant tumor cell population and/or evidence for a discrete microenvironment niche that promotes and protects tumor viability rather than an idiosyncratic observation or a sign of poor drug penetration. We have noted cases of stage 4 lung adenocarcinoma treated with tyrosine kinase inhibitor therapy (TKI) where distant metastases disappear, but the primary lung tumor only partially responds and eventually shows signs of resistant disease. Accordingly, if safe and feasible, we and others have considered stereotactic radiation or other local treatments to the residual primary tumor and sites of oligometastatic disease after achieving maximal tumor reduction with TKI therapy to minimize the known high risk of eventual progression with resistant disease ([7] and data not shown). Whether this strategy is feasible and worthwhile in future cases remains to be seen.

In summary, we have confirmed that both primary and distant metastatic ameloblastoma carrying a V600E mutation respond dramatically to initial therapy with dual BRAF/MEK inhibition. Although cases of disseminated stage 4 ameloblastoma are exceedingly rare, this observation also suggests the possibility of neoadjuvant and/or adjuvant targeted therapy in localized ameloblastoma undergoing surgery to improve outcome and minimize functional and cosmetic morbidity.

Funding
This study was supported by the University of Florida College of Medicine Gatorade Fund (FJK).

References


