BRAF/MEK Dual Inhibitors Therapy in Progressive and Anaplastic Pleomorphic Xanthoastrocytoma: Case Series and Literature Review

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ABSTRACT

Recurrent and anaplastic pleomorphic xanthoastrocytoma (r&aPXA) is a rare primary brain tumor that is challenging to treat. Two-thirds of PXA tumors harbor a BRAF gene mutation. BRAF inhibitors have been shown to improve tumor control. However, resistance to BRAF inhibition develops in most cases. Concurrent therapy with MEK inhibitors may improve tumor control and patient survival. In this study, we identified 5 patients diagnosed with BRAF-mutated PXA who received BRAF and MEK inhibitors over a 10-year interval at our institution. Patient records were evaluated, including treatments, adverse effects (AEs), outcomes, pathology, next-generation sequencing, and MRI. The median age was 22 years (range, 14–66 years), 60% male, and 60% anaplastic PXA. Median overall survival was 72 months (range, 19–112 months); 1 patient died of tumor-related hemorrhage while off therapy, and the other 4 experienced long-term disease control (21, 72, 98, and 112 months, respectively). Dual BRAF/MEK inhibitors were well tolerated, with only grade 1–2 AEs, including rash, neutropenia, fatigue, abdominal discomfort, and diarrhea. No grade 3–5 AEs were detected. A literature review was also performed of patients diagnosed with BRAF-mutated PXA and treated with BRAF and/or MEK inhibitors through August 2021, with a total of 32 cases identified. The median age was 29 years (range, 8–57 years) and the median PFS and OS were 8.5 months (range, 2–35 months) and 35 months (range, 10–80 months), respectively. The most common AEs were grade 1–2 fatigue and skin rash. Results of this case series and literature review indicate that dual-drug therapy with BRAF and MEK inhibitors for r&aPXA with BRAF V600E mutation may delay tumor progression without unexpected AEs.

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non–small cell lung cancer, papillary thyroid cancer, and central nervous system (CNS) neoplasms, including PXA.\textsuperscript{10–12}

Despite the encouraging response, resistance to BRAF inhibitors often emerges within months of starting treatment due to acquired reactivation of the MAPK pathway.\textsuperscript{13,14} Impeding MEK, which is downstream of BRAF, with an MEK inhibitor such as trametinib has demonstrated a dramatic and durable response in melanoma.\textsuperscript{15} Initiation of both inhibitors at the beginning of treatment may improve progression-free survival (PFS) and OS.

This report presents 5 cases of recurrent and anaplastic PXA (r&aPXA) with BRAF V600E mutations. Each patient received BRAF and MEK inhibitors concurrently, with distinctive clinical and radiologic outcomes.

**Methods**

Medical records from 2010 to 2021 at Memorial Hermann-Texas Medical Center were reviewed after approval of the Committee for the Protection of Human Subjects (HSC-MS-17-0967). Five patients diagnosed with r&aPXA who received BRAF and MEK inhibitors were identified. The data evaluated included age, sex, treatment received, adverse effects (AEs), outcomes, laboratory results, pathology findings, next-generation sequencing (NGS) results, and MRI features. We retrospectively analyzed AEs according to the CTCAE, version 5.0.

**Results**

Median age at diagnosis was 22 years (range, 14–66 years), 60% of the cohort was male, and 60% had grade III PXA. Timelines of MRIs and various treatments received, including BRAF/MEK inhibitors, for each patient are depicted in supplemental eFigures 1–5, available with this article at JNCCN.org.

**Case Series**

**Case 1**

A 14-year-old male from China was diagnosed with “rhabdoid meningioma” in June 2014 after craniotomy for a right temporal lobe lesion. He received XRT followed by multiple chemotherapy agents. In December 2015, he developed a scalp tumor that was resected, with pathology showing rhabdoid meningioma. He subsequently experienced tumor recurrence, which prompted further surgery and subsequent pharmacologic intervention (doxorubicin, ifosfamide, carboplatin, etoposide, cyclophosphamide, dac-tinomycin, vincristine).

In February 2017, he came to the United States seeking further therapy (Figure 2A–C). The previous surgical samples were evaluated by 2 independent neuropathologists, who determined that the specimens were anaplastic PXA, WHO grade III, with diffusely infiltrative rhabdoid morphology, positive for BRAF V600E mutation, with Ki67 >90%. In March 2017, MRI of the spine showed evidence of leptomeningeal disease (LMD) (supplemental eFigure 6) prompting spinal XRT (39.6 Gy), and subsequently treatment with TMZ and the BRAF inhibitor vemurafenib, in March 2017. The MEK inhibitor trametinib was added 2 months later.

While on the 3-drug treatment, the patient developed a new cerebellar mass in April 2018 (Figure 2D–F). Subsequent MRI confirmed tumor progression, and in September 2018 his chemotherapy was changed to the second-generation BRAF inhibitor dabrafenib + lomustine. He was stable for 9 months. In January 2019, he received Gamma Knife (GK) stereotactic radiosurgery to the cerebellar tumor and fractionated XRT to the right temporalis muscle lesion while continuing therapy with dabrafenib + lomustine.

In September 2019, the patient developed severe myelosuppression, resulting in hospitalization and discontinuation of dabrafenib and lomustine. His scalp tumors were visibly enlarging while off therapy. He experienced clinical protocol.\textsuperscript{16} An MRI in December 2018 showed an enlarged enhancing mass, and follow-up MRI in March 2019 (Figure 1I, J) confirmed incremental progression after the patient began experiencing vision changes, dizziness, and ataxia.

TMZ was stopped in March 2019. The MEK inhibitor cobimetinib and the BRAF inhibitor vemurafenib were started in a planned staggered fashion in April 2019 and May 2019, respectively.

MRI 2 months later showed a decrease in enhancement along with the patient’s neurologic recovery (Figure 1K, L). At the time of writing in September 2021, the patient had continued on vemurafenib and cobimetinib for 28 and 29 months, respectively—except for short breaks (18 and 10 days, respectively) due to rash and neutropenia—without clinical or radiologic changes (Figure 1M, N). Results of pathology, NGS, and partial MRI were published previously by Dono et al.\textsuperscript{17}
deterioration with dysphagia and paraparesis, with MRI showing evidence of progression in October 2019 (Figure 2G–I).

In November 2019, encorafenib and binimetinib were initiated. Although MRI from December 2019 showed tumor progression, the majority of scalp soft tissue lesions were visibly stable (supplemental eFigure 6). The patient also reported significant improvement in nutrition and ambulation. Due to new bony metastases, nivolumab and ipilimumab were added in January 2020 while maintaining encorafenib and binimetinib.

While on this regimen for 4 months, with fatigue as the only AE, the patient experienced a slower tumor growth rate at extracranial sites (supplemental eFigure 6). His intracranial tumor remained stable (Figure 2J–L). In early July 2020, he developed partial paraplegia and dysphagia, with MRI evidence of cervical cord compression from an enlarging nonoperative cervical spinal mass. He was then transitioned to hospice and died shortly thereafter.

Case 3

A 28-year-old female presented in May 2012 for resection of a right frontal mass diagnosed as “glioblastoma multiforme (GBM)” with atypical features, positive for BRAF V600E mutation. She received XRT and TMZ per the Stupp protocol, and then enrolled in a clinical trial (Clinical-Trials.gov identifier: NCT01430351) in September 2012, undergoing treatment with TMZ, metformin, and mefloquine for 12 months. Follow-up MRI studies showed stable disease until 3 years later, and biopsy of the new enhancing mass in August 2015 was identified as “GBM” with BRAF V600E mutation. In September 2015 she entered a second clinical trial (NCT02034110) with the BRAF and MEK inhibitors dabrafenib and trametinib, respectively.

The patient remained stable for 4 more years (Figure 3A), until further tumor progression was confirmed by MRI in September 2019 while on both inhibitors (Figure 3B). She underwent a third surgery, with pathologic diagnosis of a PXA, WHO grade II, and Ki-67 of 32.6%. NGS showed BRAF V600E and RNF43 p.R389fs mutations (Figure 3C). While on both drugs, follow-up MRIs confirmed disease progression in December 2019 and January 2020.

The patient then transferred her care to our institution with MRI study (Figure 3D). Two neuropathologists reviewed her 3 separate surgical specimens and confirmed that all were aPXA. She stopped dual inhibitors in April 2020 when she began a washout period in preparation for LITT and planned initiation of third-generation of inhibitors. She developed profound left leg weakness 12 days after stopping both drugs. Given new MRI evidence of profound tumor progression (Figure 3E), she was no longer a candidate for LITT. Encorafenib and binimetinib were started concurrently, and the patient reported significant improvement in 1 week, with reduction of enhancement by MRI.
She experienced acne rash and abdominal discomfort, as she had with previous BRAF/MEK inhibitors therapy.

Two months later, MRI in June 2020 showed new tumor expansion (Figure 3G), and she underwent LITT in July 2020 (Figure 3H) followed by addition of nivolumab and ipilimumab. The patient experienced improvement in her neurologic status. Three months later, MRI in October 2020 showed new tumor progression (Figure 3I), for which salvage XRT (35 Gy in 10 fractions) was implemented while continuing the 4-drug chemotherapy (encorafenib/binimetinib/nivolumab/ipilimumab).

Shortly after finishing XRT in November 2020 (Figure 3J), the patient developed worsening of left hemiparesis and changes on MRI concerning for tumor versus necrosis. She added bevacizumab, which resulted in clinical and radiologic improvement (Figure 3K). While on the 5-drug regimen, there was no evidence of radiologic progression for 7
months (Figure 3L). Unfortunately, she then deteriorated gradually with left hemiplegia, hemianesthesia fatigue, ageusia, and dysphagia. In late August 2021 she stopped chemotherapy and entered hospice, and died in September 2021.

**Case 4**

A 66-year-old male presented in August 2019 with headaches, vision change, and ataxia. MRI demonstrated a right temporal lobe mass involving the right cavernous sinus and internal carotid artery (Figure 4A). He underwent subtotal resection (STR) with pathologic diagnosis as PXA, WHO grade II, with *BRAF* V600E mutation and Ki-67 of 10% to 12% (Figure 4B). His symptoms improved, but he declined adjuvant therapy with *BRAF* and MEK inhibitors.

In November 2019, he developed worsening vision and headaches. MRI revealed increased enhancement at the body of the corpus callosum and a new nodular enhancement in the precentral cortex (arrows in G). LITT was performed in July 2020, showing stable postablation changes (arrow in H). Follow-up MRI in October 2020 showed increase enhancement in the periventricular white matter, corpus callosum and septum pellucidum (arrows in I). MRI in December 2020 showed an increase enhancement at the corpus callosum and the ependymal linings of the bilateral lateral ventricles (arrows in J). Decrease in size and intensity of enhancement at the corpus callosum and bilateral lateral ventricles was noticed on follow-up scan in March 2021 (arrows in K), with stable radiologic changes seen on her last scan in July 2021 (arrows in L).

**Abbreviations:** aPXA, anaplastic pleomorphic xanthoastrocytoma; GTR, gross total resection of enhancing mass; LITT, laser interstitial thermal therapy; T1W, T1 weighted; XRT, radiotherapy.

*Encorafenib, binimetinib, nivolumab, ipilimumab.*

When MRI in February 2021 (Figure 4G) and March 2021 (Figure 4H) showed continued tumor progression, the patient ultimately agreed to start insurance preauthorization for dabrafenib + trametinib. In April 2021, MRI revealed increased enhancement at the corpus callosum and bilateral lateral ventricles (arrows in J). Decrease in size and intensity of enhancement at the corpus callosum and bilateral lateral ventricles was noticed on follow-up scan in March 2021 (arrows in K), with stable radiologic changes seen on her last scan in July 2021 (arrows in L).
for a new generation of BRAF and MEK inhibitors. Unfortunately, before starting the therapy, he developed a tumor-related hemorrhage (Figure 4H, I) and subsequent cerebral ischemia (Figure 4J). The patient was transitioned to hospice and then died.

Case 5
A 20-year-old male with progressively deteriorating vision of the left eye, worsening headache, and nausea was found to have a right parietal-occipital tumor with brainstem compression and obstructive hydrocephalus in December 2019. He underwent urgent external ventricular drain placement, and bilateral ocular nerve sheath fenestration followed by an STR craniotomy (Figure 5A, B). Pathology showed aPXA, WHO grade III, positive for BRAF V600E mutation and IDH1 wild-type, with a Ki67 of approximately 30%.

He was treated with fractionated XRT and TMZ in January 2020 per the Stupp protocol.16 Follow-up MRI showed shrinkage of his tumor (Figure 5C). In June 2020, due to tumor progression (Figure 5D), TMZ was discontinued and BRAF and MEK inhibitors were initiated, with vemurafenib in June 2020 and cobimetinib in July 2020. MRI in July 2020 showed decreased tumor size and stable adjacent FLAIR changes (Figure 5E). All of his symptoms had resolved except left eye blindness and left hemianopia of his right eye.

In September 2020, MRI showed an overall decrease of enhancement but a tiny nodular enhancement at the posterior periphery of the resection cavity (Figure 5F), prompting GK radiosurgery while continuing vemurafenib and cobimetinib. Two months after, in November 2020, MRI showed transient increase in enhancement of the GK treated area, which was likely GK treatment-related, and he continued with dual-inhibitor therapy without neurologic decline (Figure 5G).

At the time of this report in September 2021, he had been taking BRAF and MEK inhibitors for 15 and 14 months, respectively, with stable clinical and imaging results (Figure 5H, I). The only AE he experienced was facial erythema with sun exposure.

Adverse Effects
Dual BRAF and MEK inhibitors were well tolerated, with grade 1–2 AEs including transient skin rash, fatigue,
abdominal discomfort, neutropenia, and diarrhea. All symptoms were reversible. Among the 5 patients in our cohort, 4 were able to tolerate dual therapy without significant AEs, except for fatigue and skin sensitivity to sun. No grade 3–4 AEs were detected (supplemental eTable 1).

Literature Review

Literature review through PubMed was performed for publications through August 2021 that included adult and pediatric patients diagnosed with BRAF-mutated r&aPXA who were treated with BRAF and/or MEK inhibitors. A total of 32 cases (including 7 from the BASKET study) were identified, as summarized in supplemental eTable 1. Median age was 29 years (range, 8–57 years), with 15 males and 17 females.

The number of prior surgeries (unknown in the BASKET study) were none in 2 patients, 1 in 6 patients, and 2 in 10 patients, whereas 7 patients had ≥3 resections. In all but 2 cases, XRT (details unknown) was used at least once, 13 (41%) patients had second XRT, 15 (47%) had initial chemotherapy, and 14 (44%) had salvage treatment. Median PFS was 8.5 months (range, 2–35 months) for the 25 cases without the BASKET study subjects from the literature review and 5.7 months for the BASKET study. Median OS was 35 months (range, 10–80 months) among the same 25 cases and not reached in the BASKET study. The most common AEs were grade 1–2 fatigue and skin rash.

Discussion

An increasing number of reports support the use of BRAF and MEK inhibitors in treating r&aPXA. Our literature search identified 32 cases, which were summarized along with our 5 patients (supplemental eTable 1).2,6,7,8,11,12,14,15,18–30 Most had radiographically documented tumor progression while on standard of care (SoC) regimen before starting targeted therapy.

It is impossible to conclude superiority across described regimens based on case reports and retrospective reviews. However, promising clinical and radiologic outcomes are noted. Patients on BRAF inhibitor monotherapy in 32 published cases demonstrated up to 35 months (median, 7 months) of stable disease, 2 patients receiving...
adjunct MEK inhibitor at a later time experienced up to 21 months of stable disease, and those on dual concomitant therapy experienced up to 23 months (median, 11 months) of stable disease (supplemental eTable 1). The trend of drug usage developed over time, with dual inhibitors now being initiated relatively routinely. This shift in the treatment algorithm may correlate with improved outcomes and synergistic potential of dual BRAF and MEK inhibitors.

Knowledge of the specific BRAF mutation is important for the proper selection of BRAF and MEK inhibitors. BRAF mutations have been grouped into 3 classes: class I comprises V600E mutations resulting in low RAS activity; class II includes BRAF fusions and non-V600E mutations, leading to increased ERK activation with decreased RAS activity; and class III have impaired and/or absent kinase activity. Class III mutations might not respond to BRAF inhibitors, making MEK inhibitors a more optimal option.13 Our cohort of 5 patients with class I mutation demonstrated the benefit of using dual BRAF and MEK therapy on PXA intracranial tumor control. Four patients experienced long-term disease control (21, 72, 98, and 112 months, respectively); 2 of them remain on dual therapy at the time of writing, and 1 died of systemic PXA progression while the intracranial PXA tumor remained stable (Case 2). The elderly patient (Case 4) experienced short-term disease stability for 5 months, but died of tumor progression and stroke complications while waiting for initiation of second-generation inhibitor therapy. The patient experiencing the longest period of stable disease (Case 3; 112 months) had a final episode of clinical deterioration while on the 5-drug therapy, and died shortly after stopping treatment (supplemental eFigure 3).

BRAF and MEK inhibitor regimen has potential utility not only in primary CNS tumor control but also as palliative treatment of aggressive systemic PXA. The patient in Case 2 had several metastatic lesions that significantly impacted his quality of life. BRAF- and MEK-targeted therapy allowed him a period of clinical improvement. Similarly, a recently published case demonstrated that encorafenib significantly reduced chest wall and spinal PXA metastases.30 Unfortunately, the patient developed disease at other sites while on therapy. Early initiation of dual-inhibitor therapy can also be an option for tumors located in eloquent areas of the brain. In Case 4, use of this strategy to treat a mass close to the optic nerve avoided or delayed potential AEs from XRT.

Interpretation of outcomes following BRAF- and MEK-targeted therapy can be complicated by pseudoprogression. Although its incidence remains low in low-grade astrocytic tumors, such as PXA WHO grade II, this phenomenon can mimic tumor progression in patients with GBM who have received XRT and TMZ.31 Two of our patients were noted to have MRI progression within a few months following treatment with the Stupp protocol and prior to initiation of BRAF and MEK inhibitors. Their subsequent improvement could be unrelated to the therapeutic benefit of the inhibitors. This is less likely, given that the patient in Case 1 was deteriorating while on TMZ and her immediate improvement clinically and by MRI would not be possible without the dual inhibitors. The significant worsening while off dual inhibitors for 12 days and subsequent dramatic improvement after starting a third generation of dual inhibitors, seen in Case 3, resulted from the absence and then readministration of BRAF and MEK inhibitors, respectively. Moreover, Pearson correlation analysis demonstrates no relationship between age and PFS or age and OS, respectively (supplemental eFigures 7 and 8). Although BRAF/MEK inhibitors play a major role, we cannot exclude that other therapies, including LITT, GK, salvage radiation, and chemotherapy, may contribute to the improved PFS and OS results.

Optimal medical intervention is a fine balance between benefit and potential harm. There is evidence that dual therapy can reduce cutaneous toxicity of BRAF inhibitor.27 Dual BRAF and MEK inhibitors were well tolerated in our patients, with only grade 1–2 AEs. Most symptoms subsided over time while continuing the dual therapy, except in Case 4, and no grade 3–5 AEs were detected. A limitation to our study is that the AEs were evaluated retrospectively from patients’ medical records, as outlined in supplemental eTable 1. It remains likely that some symptoms may have not been adequately documented.

Establishing evidence-based guidelines to maximize the value of BRAF and MEK inhibitors for PXA remains a challenge, but evidence is mounting to support the use of BRAF and MEK inhibitors concurrently. The up-front combination of inhibitors could be more effective than sequential use of MEK inhibitors after tumor progression while on BRAF inhibitor monotherapy.23 Further molecular studies may help in understanding the synergistic action and if the combination may delay the development of tumor resistance.

Given the low prevalence of PXA, performing clinical trials for r&apXA to answer management questions is difficult. Because there is no uniform chemotherapy SoC based on clinical trial results, providers often select medications based on retrospective data. Application of BRAF and/or MEK inhibitors against activating BRAF mutations, such as V600E, in patients with r&apXA has generated provocative and promising results (supplemental eTable 1). It is reasonable to try dual inhibitors after XRT, either before or after subsequent tumor progression and prior to use of traditional chemotherapy. The benefits of early dual-inhibitor application may be multiple. The high likelihood of shrinking and/or curtailing tumor growth can improve patient function and quality of life while avoiding myelosuppression associated with traditional chemotherapy. BRAF and MEK inhibitors are also in the convenient per os formulation and the adverse effects in most patients are mild and reversible. Three generations of BRAF/MEK
inhibitors are available and may be selected based on tolerance and treatment effect. Although complete results are yet to be published, targeted drug therapy trials examining the utility of BRAF and MEK inhibitors are ongoing (ClinicalTrials.gov identifiers: NCT02684058, NCT03975829, NCT03919071, NCT01430351, NCT03973918). One study (NCT02034110) using dabrafenib and trametinib on rare tumors with BRAF mutation is showing a durable clinical benefit in BRAF V600E-mutant low- and high-grade gliomas.32 The patient in Case 3, who was initially misdiagnosed and treated as having GBM, entered this clinical trial and was stable for 48 months while on the protocol. Trametinib is also being studied in combination with cyclin-dependent kinase inhibitors (NCT03434262). A recent NCI-MATCH (EAY131-H) trial (NCT02465060) evaluated dabrafenib and trametinib in tumors containing the BRAF V600E mutation, including one PXA, after progression on SoC, and showed durable disease control.33 Further efforts to understand drug efficacy and mechanisms of drug resistance are also being conducted through surgical specimen analysis (NCT03593993).

Conclusions

Patients with BRAF V600E–mutated r&PXA that is refractory to standard or salvage treatments can be treated with dual BRAF and MEK inhibitors with a high likelihood of durable response and tolerable AEs. There is growing support for the concurrent and adjuvant use of these inhibitors to improve PFS and OS. Further investigations are warranted, including clinical trials of dual-inhibitor therapy to treat BRAF V600E–mutated PXA.

References

24. Lukas RV, Merrell RT. BRAF inhibition with concomitant tumor treating fields for a multiply progressive pleomorphic xanthoastrocytoma. CNS Oncol 2018;7:CN510.


Supplemental online content for:

**BRAF/MEK Dual Inhibitors Therapy in Progressive and Anaplastic Pleomorphic Xanthoastrocytoma: Case Series and Literature Review**

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**eFigure 1:** Case 1: Timeline of Diagnosis, Treatment Received, and Duration of Each Treatment Period
**eFigure 2:** Case 2: Timeline of Diagnosis, Treatment Received, and Duration of Each Treatment Period
**eFigure 3:** Case 3: Timeline of Diagnosis, Treatment Received, and Duration of Each Treatment Period
**eFigure 4:** Case 4: Timeline of Diagnosis, Treatment Received, and Duration of Each Treatment Period
**eFigure 5:** Case 5: Timeline of Diagnosis, Treatment Received, and Duration of Each Treatment Period
**eFigure 6:** Lumbar MRI and Head Photographs From Case 2
**eFigure 7:** Pearson Correlation of Age Versus Progression-Free Survival
**eFigure 8:** Pearson Correlation of Age Versus Overall Survival

**eTable 1:** Summary of Results of Patients With PXA Who Received BRAF and MEK Inhibitors
COB and VMF started in 4/2019 and 5/2019, respectively.
Stable and remission since 9/2021.
XRT and concurrent TMZ per Stupp protocol in 10/2018.

MRI showed PXA progression and TMZ stopped in 3/2019.

Case 1 was diagnosed with PXA and underwent GTR in 7/2013.

MRI showed PXA progression and underwent LITT in 4/2018.

Case 2 was diagnosed with “rhabdoid meningioma” and underwent GTR + XRT in China in 6/2014.

MRI showed a new cerebellar mass in 4/2018.

Case 3 was diagnosed with “GBM” with atypical features and received XRT + TMZ per Stupp protocol in 5/2012–6/2012.

MRI showed tumor progression in 9/2019.

MRI showed new tumor progression and started salvage XRT in 10/2020.

**eFigure 1.** Case 1: Timeline of diagnosis, treatment received, and duration of each treatment period.
Abbreviations: COB, cobimetinib; GTR, gross total resection of enhancing mass; LITT, laser interstitial thermal therapy; PXA, pleomorphic xanthoastrocytoma; TMZ, temozolomide; VMF, vemurafenib; XRT, radiotherapy.

Case 2 was diagnosed with “rhabdoid meningioma” and underwent GTR + XRT in China in 6/2014.

MRI showed a new cerebellar mass in 4/2018.

Severe myelosuppression. DAB and CCNU were discontinued in 9/2019.

Patient transitioned to hospice, died 2 weeks later.

**eFigure 2.** Case 2: Timeline of diagnosis, treatment received, and duration of each treatment period.
Abbreviations: aPXA, anaplastic pleomorphic xanthoastrocytoma; BIN, binimetinib; CCNU, lomustine; DAB, dabrafenib; ENC, encorafenib; GK, Gamma Knife; GTR, gross total resection of enhancing mass; IPI, ipilimumab; LMD, leptomeningeal disease; NIV, nivolumab; TMZ, temozolomide; TRAM, trametinib; VMF, vemurafenib; XRT, radiotherapy.

Case 3 was diagnosed with “GBM” with atypical features and received XRT + TMZ per Stupp protocol in 5/2012–6/2012.

MRI showed tumor progression in 9/2019.

MRI showed new tumor progression and started salvage XRT in 10/2020.

**eFigure 3.** Case 3: Timeline of diagnosis, treatment received, and duration of each treatment period.
Abbreviations: aPXA, anaplastic pleomorphic xanthoastrocytoma; BIN, binimetinib; BVZ, bevacizumab; DAB, dabrafenib; ENC, encorafenib; GBM, glioblastoma multiforme; IPI, ipilimumab; LITT, laser interstitial thermal therapy; NIV, nivolumab; TMZ, temozolomide; TRAM, trametinib; XRT, radiotherapy.

*5 drugs: ENC, BIN, NIV, IPV, BVZ.*
**eFigure 4.** Case 4: Timeline of diagnosis, treatment received, and duration of each treatment period.

Abbreviations: COB, cobimetinib; ENC, encorafenib; GI, gastrointestinal; PXA, pleomorphic xanthoastrocytoma; STR, subtotal resection; VMF, vemurafenib; XRT, radiotherapy.

**Case 4** was diagnosed with PXA and underwent STR in 8/2019.

3 months: Worsening vision/headaches and MRI showed increased enhancement in 11/2019.

1 month: COB and VMF started in 12/2019 and 1/2020, respectively.


Fractionated XRT from 5/2020 to 6/2020 due to tumor progression.

4 months: MRIs showed tumor progression in 9/2020 and 10/2020.


1 week: Patient transitioned to hospice and died in 3/2021.

**eFigure 5.** Case 5: Timeline of diagnosis, treatment received, and duration of each treatment period.

Abbreviations: aPXA, anaplastic pleomorphic xanthoastrocytoma; COB, cobimetinib; GK, Gamma Knife; TMZ, temozolomide; VMF, vemurafenib; XRT, radiotherapy.

**Case 5** was diagnosed with aPXA and underwent STR in 12/2019.


4 months: MRI showed tumor progression in 9/2020 and 10/2020.

2 months: MRI showed overall decrease of enhancement in 9/2020, except one area treated with GK.

Stable and in remission since 11/2021.

10 months: MRI showed overall decrease of enhancement in 9/2020, except one area treated with GK.
**eFigure 6.** Lumbar MRI and head photographs from Case 2. (A) Sagittal and (B) axial view post-contrast MRI of lumbar spine in 5/2017. (A) Sagittal lumbar, T1 with contrast MRI revealed heterogeneously intradura (arrows) and extradura (arrowhead) enhancements between T11–L4 as well as regional LMD. (B) Axial view of lumbar, T1 with contrast MRI showed intra-dura (arrows) and soft tissue enhancement (arrowhead) between T12–L1. (C–G) Progression of extracranial disease in the soft tissue of the neck and the craniofacial metastases. (C) Extracranial soft tissue metastases at the right frontotemporal scalp and right frontal bone in 10/2019. (D) Slowed progression of previously mentioned masses during XRT, with a treated and dried ulcer with granulation tissue in the right temporalis area. (E) Extracranial masses in right parotid and right neck with hyperpigmentation/dried desquamation after completion of palliative XRT. (F, G) Scalp photographs show progression of right frontotemporal scalp masses with stable right temporal fossa dried ulcer.

Abbreviations: LMD, leptomeningeal disease; XRT, radiotherapy.
**Figure 7.** Pearson correlation of age vs PFS of the (A) 5 cases, (B) 26 cases* from the literature, and (C) combined 26 + 5 cases. Abbreviation: PFS, progression-free survival.

*Including 7 cases from the BASKET study.

**Figure 8.** Pearson correlation of age vs OS of the (A) 5 cases, (B) 11 cases* from the literature, and (C) combined 11 + 5 cases. Abbreviation: OS, overall survival.

*There were only 11 cases with known OS among the 32 cases from the literature.
**Table 1. Summary of Results of Patients With PXA Who Received BRAF and MEK Inhibitors**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>BRAF Inhibitor</th>
<th>MEK Inhibitor</th>
<th>Surgery</th>
<th>Radiation</th>
<th>Response</th>
<th>Additional Adverse Events</th>
<th>BRAF Resistance</th>
<th>MEK Inhibitor Resistance</th>
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<th>MEK Inhibitor</th>
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<th>Response</th>
<th>Additional Adverse Events</th>
<th>BRAF Resistance</th>
<th>MEK Inhibitor Resistance</th>
<th>PFS (mo)</th>
<th>OR (HR)</th>
<th>Adverse Events</th>
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<tr>
<td>Hofer et al, 2016</td>
<td>26</td>
<td>M</td>
<td>DAB</td>
<td>DABDM</td>
<td>GTR</td>
<td>6 Gy (5)</td>
<td>DAB</td>
<td>forall adenosine nucleotides</td>
<td>Grade 1: Photosensitivity, xerosis, fatigue, weight loss</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>20</td>
<td>1.5</td>
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<tr>
<td>Brown et al, 2017</td>
<td>27</td>
<td>M</td>
<td>DAB</td>
<td>DABDM</td>
<td>GTR</td>
<td>13 Gy</td>
<td>DAB</td>
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<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>17</td>
<td>1.5</td>
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<tr>
<td>Finch et al, 2017</td>
<td>29</td>
<td>M</td>
<td>DAB</td>
<td>DABDM</td>
<td>GTR</td>
<td>13 Gy</td>
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<td>forall adenosine nucleotides</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>21</td>
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<td>Amayiri et al, 2017</td>
<td>30</td>
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<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>24</td>
<td>1.5</td>
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<tr>
<td>Kata et al, 2018</td>
<td>31</td>
<td>M</td>
<td>DAB</td>
<td>DABDM</td>
<td>GTR</td>
<td>13 Gy</td>
<td>DAB</td>
<td>forall adenosine nucleotides</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
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<td>1.5</td>
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<td>Hofer et al, 2019</td>
<td>32</td>
<td>M</td>
<td>DAB</td>
<td>DABDM</td>
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<td>DAB</td>
<td>forall adenosine nucleotides</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
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<td>13 Gy</td>
<td>DAB</td>
<td>forall adenosine nucleotides</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>Grade 1: Fatigue, rash, nausea, vomiting</td>
<td>32</td>
<td>1.5</td>
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(continued on next page)
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<tr>
<th>Study/Author</th>
<th>WHO Grade</th>
<th>Primary Location</th>
<th>Age at Diagnosis (y)</th>
<th>Gender</th>
<th>IDH</th>
<th>MGMT</th>
<th>Surgery (no. if multiple)</th>
<th>Chemotherapy</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
<th>Adverse Effects</th>
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<td>Kata et al, 2022</td>
<td>II</td>
<td>L temporal</td>
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<td>U GTR</td>
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<td>—</td>
<td>57</td>
<td>Increased enhancing tumor</td>
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<tr>
<td></td>
<td>III</td>
<td>R temporal</td>
<td>14</td>
<td>M</td>
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<td>U DU</td>
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<td>R frontal</td>
<td>28</td>
<td>F</td>
<td>M</td>
<td>M</td>
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<td>R parietal</td>
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<td>M</td>
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<td>STR</td>
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</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCNU, carmustine; BIN, binimetinib; BVZ, bevacizumab; CCNU, lomustine; COB, cobimetinib; CR, complete response; CTX, chemotherapy; DAB, dabrafenib; DC, dendritic cell vaccine; DU, details unavailable; ENC, encorafenib; F, female; 4 drugs: ENC/BIN/NIV/IPI; GK, Gamma Knife; GTR, gross total resection of enhancing mass; IDH, isocitrate dehydrogenase; INR, international normalized ratio; IPI, ipilimumab; L, left; LINAC, linear accelerator; LITT, laser interstitial thermal therapy; LMD, leptomeningeal disease; M, male; Meth, methylated; MGMT, methylguanine methyltransferase; NIV, nimustine; OS, overall survival; PCV, procarbazine/CCNU/vincristine; PD, progressive disease; PFS, progression-free survival; PR, partial response; PT, prothrombin time; PXA, pleomorphic xanthoastrocytoma; R, right; STR, subtotal resection; TMZ, temozolomide; TRAM, trametinib; TTF, tumor treating fields; U, unmethylated; VMF, vemurafenib; W, wild-type; XRT, radiotherapy.

aPatient deceased at this time mark.
bReported at this time of given article publication, patient alive; conventional therapy.
cConventional therapy: DU.
dConventional therapy: dacarbazine/cisplatin/etoposide/cyclophosphamide/doxatumomab/vinleucovorin.