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
**Case 1**

- **Diagnosis:** PXA in 7/2013
- **Treatment:** GTR in 7/2013
- **MRI:** PXA progression in 4/2018, and TMZ stopped in 3/2019
- **Additional Treatments:**
  - MEK inhibitor
  - MRI showed PXA progression and underwent LITT in 8/2018
  - MRI showed PXA progression and underwent LITT in 8/2018

**Timeline:**
- 57 months
- Recurrent PXA and underwent 2nd GTR in 4/2018
- 2 months
- MRI showed PXA progression and underwent LITT in 8/2018
- 2 months
- XRT and concurrent TMZ per Stupp protocol in 10/2018
- 5 months

**Abbreviations:** COB, cabimetinib; GTR, gross total resection of enhancing mass; LITT, laser interstitial thermal therapy; PXA, pleomorphic xanthoastrocytoma; TMZ, temozolomide; VMF, vemurafenib; XRT, radiotherapy.

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**Case 2**

- **Diagnosis:** "rhabdoid meningioma" in China in 6/2014
- **Treatment:** GTR + XRT in 6/2014
- **MRI:** showed T11–L4 LMD in 3/2017
- **Additional Treatments:**
  - Added NIV and IPI while maintaining ENC and BIN in 1/2020
  - MRI showed enlarged cerebellar mass in 4/2019

**Timeline:**
- 32 months
- Diagnosis changed to aPXA in United States in 2/2017
- 1 month
- MRI showed T11–L4 LMD in 3/2017
- 2 months
- MEK inhibitor TRAM added in 5/2017
- 11 months
- Enrolled in clinical trial (NCT01430351) with TMZ, metformin, and mefloquine in 9/2012
- 4 months
- MRI showed enlarged mass of cervical spine in 10/2015

**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.

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**Case 3**

- **Diagnosis:** "GBM" with atypical features in 5/2012
- **Treatment:** XRT + TMZ in 5/2012−6/2012
- **MRI:** showed tumor progression in 9/2019
- **Additional Treatments:**
  - Added BVZ in 10/2020

**Timeline:**
- 35 months
- MRI showed tumor progression in 7/2015 and biopsy identified as "GBM" in 8/2015
- 35 months
- MRI showed tumor progression and regimen changed to ENC and BIN in 4/2020
- 3 months
- MRI showed tumor expansion in 5/2020

**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.

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5 drugs: ENC, BIN, NIV, IPI, BVZ.
3 months Worsening vision/headaches and MRI showed increased enhancement in 11/2019

MRIs showed tumor progression in 9/2020 and 10/2020

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

Tumor progression by MRI in 2/2021 and intratumor hemorrhage in 3/2021

Patient self-stopped COB and VMF in 4/2020 due to GI symptoms and weight loss

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

MRI showed tumor progression in 9/2020 and 10/2020

Tumor progression by MRI in 2/2021 and intratumor hemorrhage in 3/2021

Patient transitioned to hospice and died in 3/2021

4 months

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

Worsening vision/headaches and MRI showed increased enhancement in 11/2019

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

Patient self-stopped COB and VMF in 4/2020 due to GI symptoms and weight loss

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

MRI showed tumor progression in 9/2020 and 10/2020

Tumor progression by MRI in 2/2021 and intratumor hemorrhage in 3/2021

Patient transitioned to hospice and died in 3/2021

1 month

Chemotherapy and concurrent TMZ per Stupp protocol in 1/2020–2/2020

MRI showed tumor progression in 9/2020, except one area treated with GK

Stable and in remission since 11/2021

4 months

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

XRT and concurrent TMZ per Stupp protocol in 1/2020–2/2020

MRI showed tumor progression, TMZ stopped, VMF and COB started in 6/2020 and 7/2020, respectively

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

Stable and in remission since 11/2021

4 months

10 months

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.

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.
**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.
eFigure 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.

eFigure 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.
**eTable 1. Summary of Results of Patients With PXA Who Received BRAF and MEK Inhibitors**

<table>
<thead>
<tr>
<th>Age at</th>
<th>Gender</th>
<th>IDH</th>
<th>Histology</th>
<th>BRAF</th>
<th>MEK</th>
<th>Surgery</th>
<th>chemotherapy</th>
<th>RT</th>
<th>Adverse Effects</th>
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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCNU, carbamoyl; BIN, binimetinib; BVZ, bevacizumab; CCNU, lomustine; COB, cobimetinib; CR, complete response; CTX, chemotherapy; DAB, dabrafenib; DC, dendritic cell vaccine; DU, details unavailable; ENC, encofensib; 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; 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.

*Patient deceased at this time mark. 
*Reported at this time of given article publication, patient alive; conventional therapy. 
*Conventional therapy: DU. 
*Additive PFS.