

Long-Term Treatment With BRAF/MEK Inhibitors for Pleomorphic Xanthoastrocytoma Grade 3: A Case Report

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Keywords:

BRAF Mutation; BRAF/MEK Inhibitors; Pleomorphic Xanthoastrocytoma

List of Abbreviations:

PXA; Pleomorphic Xanthoastrocytoma; CNS: Central Nervous System Tumors; WHO: World Health Organization; PFS: Progression Free Survival; OS: Overall Survival; ECOG: Eastern Cooperative Oncology Group

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1. Abstract

1.1. Background

Pleomorphic xanthoastrocytoma grade 3 is rare disease classified as a distinct entity in WHO classification 2016. It is usually refractory to a standard therapy for high grade gliomas and has a dismal prognosis. About two thirds of patients have BRAFV600E mutation giving the opportunity for a targeted therapy. Due to scarce literature data the treatment is very challenging. Dual BRAF/MEK inhibition can lead to good disease control. This case is interesting because three WHO classifications and three diagnoses changed during the 10 years of the disease, but the emphasis here is on the BRAFV600E mutation and targeted therapy as a tissue-agnostic treatment.

1.2. Case Presentation

A 22-year-old female patient was diagnosed with pylocytic astrocytoma of posterior fossa. She was operated and followed-up. After four years tumor recurred locally and was classified as glioblastoma. On standard concomitant treatment with radiotherapy and temozolomide the tumor progressed and after revision of pathohistological examinations from both surgery pleomorphic xanthoastrocytoma with BRAFV600E mutation was diagnosed. In August 2019 she started with dabrafenib and trametinib in second line. After four months complete remission was achieved and was durable until December 2023. She was on therapy for 52 months.

1.3. Conclusions

Dual therapy with BRAF/MEK inhibitors for BRAFV600E mutant glioma can achieve durable complete response with very good tolerability and should be considered as a first line treatment. Together with previously published works, this case provides important insight into the disease course in rare high grade pleomorphic xanthoastrocytoma.

2. Introduction

Pleomorphic xanthoastrocytoma (PXA) accounts less than 0.3% of primary central nervous system tumors (CNS). The annual incidence is less than 0.7/100000 population [1]. Tumor is usually diagnosed at second life decade, mean age 26.3 years [2]. Usually the tumor arises in the temporal lobe but some reports described cases in the cerebellum, retina and spinal cord [3-5]. These tumors show the possibility of spreading through the cerebrospinal fluid. Immunohistochemical analyses with the antibodies against S100 protein and GFAP confirm strong and diffuse positivity supporting origin from the astrocyte lineage [6]. Weber et al. [7] used genomic hybridization to identify loss of chromosome 9 as the most common chromosomal change in 50 patient with PXA [7]. BRAF p.V600E mutation, the most frequent mutation in MAPK signaling pathway, has been identified in 38–80% of PXA [8]. Up to 25% of patients has mutations in p53 [9]. PXA has relatively favorable prognosis. In 1979 Kepel described PXA with high grade characteristics [10]. In the 2016

WHO classification (World Health Organization), PXA and anaplastic PXA are recognized as new variants of astrocytic tumors [11]. In new WHO classification from 2021 pleomorphic xanthoastrocytoma can be grade 2 or grade 3. High mitotic index (>5 mitosis/10 HPF) and tumor necrosis are negative prognostic features associated with decreased progression free survival (PFS) and overall survival (OS) [12]. Contrary, the presence of BRAFV600 mutation is associated with increased OS [13].

In this case report we will describe long-term disease control in patient with BRAFV600E positive glioma on dual therapy with BRAF/MEK inhibitors. We will show how diagnostic criteria change over the course of a 10-year disease, new classifications are introduced, and how all of this affects the choice of treatment.

3. Case

A 22-year-old female patient started clinical workup in 2015 due to diplopia and headaches. General condition was excellent, ECOG 0 (Eastern Cooperative Oncology Group). Medical history and family history were insignificant. Laboratory tests were normal. She was diagnosed with a tumor of the posterior cranial fossa and gross total resection was performed. According to WHO classification from 2007 pathohistological examination showed pilocytic astrocytoma grade 1. Oncological treatment was not indicated. In 2019 tumor recurred locally (Figure 1A). After the brain surgery and subtotal resection according to WHO classification from 2016 the tumor was glioblastoma grade 4 with Ki-67 50%, 1p19q codeletion negative, MYCN neg, BRAF V600/2DD positive. From March to April 2019 patient was treated as for glioblastoma by concomitant chemoradiotherapy according to Stupp's protocol. Patient was irradiated with 3D-conformal technique with total dose 60 Gy on tumor bed concomitantly with temozolomide in dose 75 mg/m². Tumor samples from 2015 and 2019 were revised on Mayo Clinic (Rochester, Minnesota, USA). The histopathological and

molecular examination reclassified tumor to pleomorphic xanthoastrocytoma grade 2 in 2015 and anaplastic pleomorphic xanthoastrocytoma in 2019. In 2019 after concomitant setting of therapy brain MRI showed areas of contrast enhancement along the surgical cavity suspicious for tumor progression (Figure 1B). The patient deteriorated clinically and required corticosteroid therapy. Considering the last histological examination, BRAF/MEK dual inhibition started as second line therapy. Patient received dabrafenib (150 mg 2x/day) and trametinib (2 mg/day). After 4 months brain MRI showed complete response (Figure 1C), follow-up assessments by physical examination and laboratory tests were done every month and MRI every 3 months. Duration of response was 52 months. Patient received a total of 44 cycles of therapy in the period from July 2019 to November 2023. Therapy was well-tolerated with mild adverse events (grade 1 or 2) like fatigue, fever and rash only at the beginning of therapy. Brain MRI in November 2023 showed disease progression (Figure 1D). Spinal MRI was negative for spinal dissemination. Cerebrospinal fluid was negative for malignant cells. Due to neurological deterioration, patient was operated in November 2023. Subtotal resection was done and integrative diagnosis according to WHO classification from 2021 confirmed diagnosis of pleomorphic xanthoastrocytoma grade 3 (Figure 2). The term 'anaplastic' was no longer listed and replaced with 'grade 3'. Next Generation Sequencing by Foundation One CDx listed BRAF V600E mutation, CDKN2A/B loss and MET exon 14 alteration. Furthermore, the amplification of CUL4, FGF14 and IRS genes, which are involved in the control of cell growth and invasion, was determined. Microsatellite status and Tumor Mutational Burden (TMB) analysis do not indicate a benefit from immuno-oncology therapy. The patient continued with irinotecan plus bevacizumab and progressed after 4 cycle. Pan-RAF inhibitor tovorafenib was administered for 3 months but without response. The patient died with the clinical picture of tumor progression to the brainstem. Disease course is shown in timeline (Figure 3).





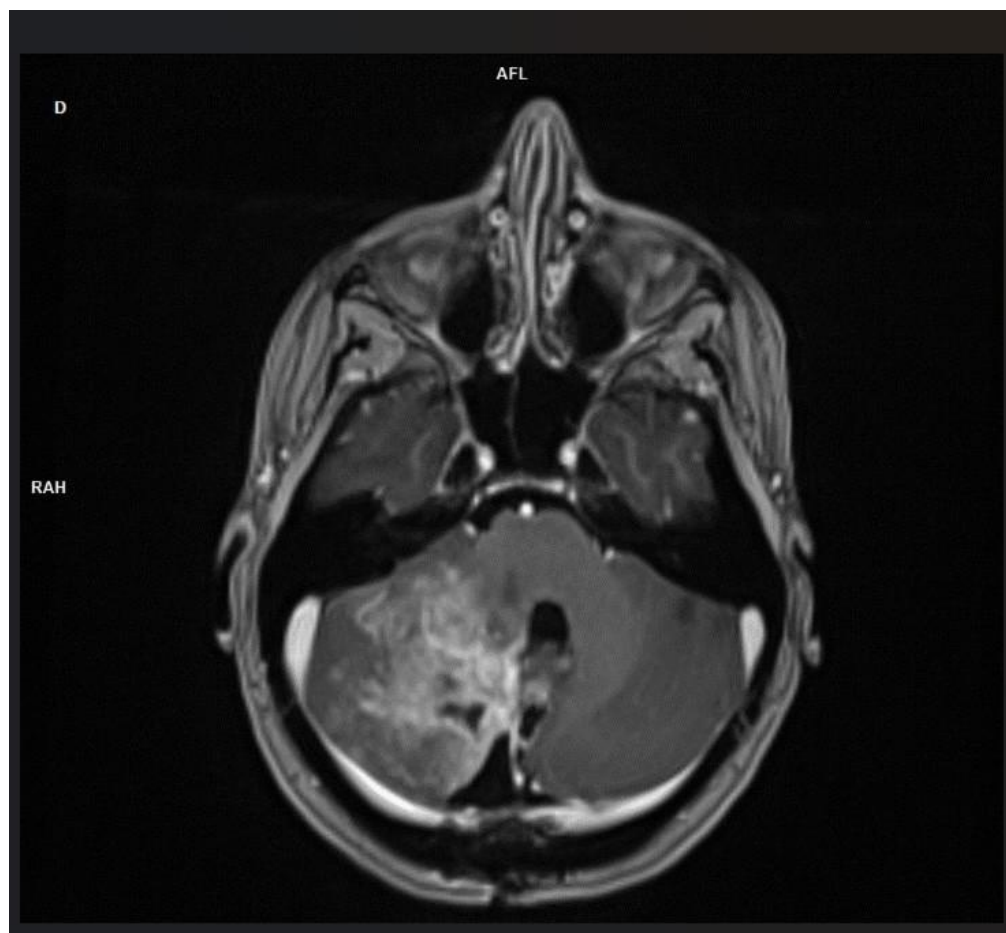


Figure 1: A: Post-gadolinium T1 weighted image. A large, thick fluid-containing cystic tumor with a thick, irregular, contrast-enhancing solid rim in the cerebellar vermis. Mild perifocal oedema, right more than left. There is moderate brainstem compression (2019, preoperative). B: Post-gadolinium T1 weighted image. An irregular residual tumor in the cerebellar vermis. Progression on chemoradiotherapy (2019). C: Post-gadolinium T1 weighted image. A post-treatment scar in the cerebellum, with a faint peripheral enhancement. No evidence of oedema nor mass effect. Complete response after initiation of BRAF/MEK inhibitors (2019). D: Post-gadolinium T1 weighted image. Progression of the infiltrative tumoral enhancement in the right-sided cerebellar hemisphere, with midbrain and fourth ventricle compression (2023, preoperative).

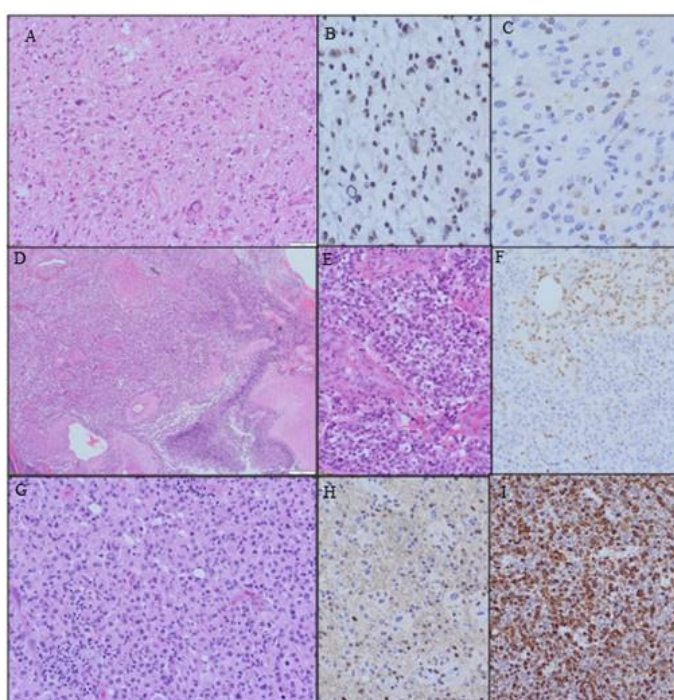


Figure 2: In first biopsy from 2015 (A; HE) partial loss of ATRX positivity can be seen (B, C; ATRX). Biopsy from 2019 shows areas of necrosis (D; HE) and endothelial proliferation (E; HE), with complete loss of ATRX positivity (F; ATRX). In the last biopsy from 2023, there is a diffuse infiltration of the cerebellar tissue by tumor cells which have a loss of ATRX positivity and are positive for BRAF (I; BRAF VE1). In 2019 tumor samples from 2015 and 2019 were analyzed using the BRAF/NRAS Mutation Test (LSR), which found the mutation V600E/ E2/D BRAF gene.

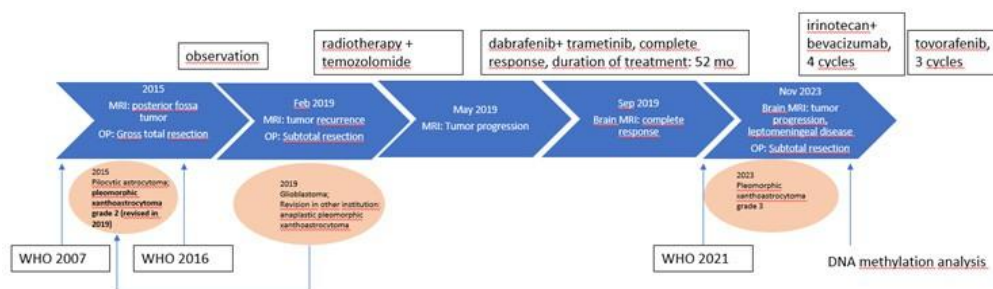


Figure 3: Timeline of disease course, changes in WHO classification and diagnosis of disease.

4. Discussion

Due to the course of the disease of 10 years in our patient, three WHO classifications were in use (2007, 2016, 2021) and tumor was reclassified and renamed three times, from pilocytic astrocytoma, glioblastoma to pleomorphic xanthoastrocytoma. These changes have naturally influenced the choice of therapeutic options. The introduction of molecular diagnostics in CNS tumors has established a classification that is more data-based and objective. In this way, new diagnostic tests can change the initial diagnosis of the tumor, or found new clinical entities. In our case, final histological diagnosis was PXA based on histological features as an essential diagnostic criterion and desirable criteria such as BRAF mutation and homozygous deletion of CDKN2A and CDKN2B. DNA methylation analysis is a recently developed diagnostic method and is recommended from international committees for brain tumor diagnostics. Due to lack of quality sample for analysis DNA methylation was not possible to perform. Looking back, it is not of crucial importance because, as we can see, the diagnosis can change several times during the long disease trajectory. In this case, the emphasis is on the BRAF status, because based on this finding, the patient received targeted therapy, in this case dabrafenib and trametinib, which have the status of tissue-agnostic targeted therapy. In low-prevalence tumors such as BRAFV600E-mutant glioma, it is difficult to give an evidence-based answer about optimal treatment. Although PXA has a relatively good prognosis, this is not the case with its high grade variant. According to the literature, the 5-year median survival is 57%.¹⁴ PXA grade 2 can transform to higher grade either to PXA grade 3 or epitheloid variant of glioblastoma. BRAF mutations, as a part of RAS/RAF/MEK/ERK signaling pathway, are grouped into classes I to III based on dimerization status, RAS-dependence and kinase activity levels. Class I are activating signaling as RAS-independent monomers (V600), class II as RAS-independent dimers (codons 597/601) and class III as RAS-dependent dimers with impaired kinase activity (codons 594/596). First generation BRAF inhibitors are effective for class I monomers and has less efficacy against BRAF-mutant dimers.¹⁵ BRAFV600E mutation has great therapeutic significance. BRAF alteration activates MAPK signal pathway which can result in cancer development promotion. Dual inhibition of this cascade with BRAF and MEK inhibitors led to paradigm change in several tumor types with positive BRAF alteration. BRAF inhibitors selectively bind to V600E mutated B-Raf proteins and inhibit MEK activation in the MAPK/ERK signaling

cascade. Combination of BRAF and MEK inhibitors block the aberrant activation of mutated BRAF in the RAF-MEK-ERK pathway. Study VE-BASKET was the initial proof of vemurafenib efficacy in BRAFV600 positive primary brain tumors. Twenty-four patients with glioma were included, 7 with PXA. Responses were confirmed in all glioma subgroups, with PXA subgroup achieving best results. Response rate was 25% and median PFS 5.5 months. After 39.1 months of follow-up the only patient that continue with vemurafenib after the time of study closure has PXA and was not treated with radiotherapy or chemotherapy before.¹⁶ Phase 2 Basket study included BRAFV600E-mutant low-grade and high-grade tumors and showed a clinical benefit in patients treated with dabrafenib and trametinib.¹⁷ In NCI-MATCH (EAY131-H) trial dabrafenib and trametinib were evaluated in tumors containing BRAFV600E mutation, including one PXA. In second line setting they showed durable disease control.¹⁸ The new pan-RAF inhibitor like recently approved tovorafenib can inhibit dimers and target BRAF non-V600 mutations which opens up the possibility of further research.¹⁹ Our patient showed a long-term clinical response on BRAF/MEK inhibitors in second line therapy that lasted for 52 months what is consistent with previously published data in small number of patients. A similar case is described in literature, where a patient diagnosed with PXA received dabrafenib and trametinib in third line of treatment and had a stable disease for 4 years.²⁰ The only longer patient survival was described in paper by Schmidt et al. where a 28-year-old patient was diagnosed with BRAF positive PXA grade 3 and lived for 11 years at the time of completion of the study.²¹ In June 2022, the Food and Drug Administration approved dabrafenib and trametinib for the treatment of patients with unresectable or metastatic solid tumors with BRAFV600E mutation in second line treatment of patients with no satisfactory alternative treatment options. We searched the PubMed until December 2023 using the keywords “anaplastic” and “grade 3” combined with “pleomorphic xanthoastrocytoma”. 93 patients with PXA grade 3 were identified. Considering the rarity of the diagnosis, the found cases are a very heterogeneous group of tumors, treated in the first line with chemotherapy, radiation or BRAF/ MEK inhibitors. Accordingly, the survival results are very different and it is difficult to draw consistent conclusions. As dabrafenib and trametinib are registered for patients after progression to standard therapy, the question is whether in high grade PXA, which is rare and has no standardized therapeutic options, we should wait for progression to the first line which

actually does not exist or should we start immediately with targeted treatment if we have a targetable mutation. It is similar with other tumors where targeted therapy is started immediately if there are positive predictive biomarkers. Encouraged by the approval of BRAF/MEK inhibitors as tissue agnostic therapy, we selected here and analyzed patients with PXA grade 3 who received targeted therapy upfront. We found 7 patients with PXA grade 3 who received BRAF inhibitors or BRAF/MEK inhibitors in the first line of systemic therapy.^{20, 22-26} The patients were aged from 18 to 66 years. One patient had previously received irradiation. Patients were treated with dabrafenib+trametinib,²² cobimetinib+vemurafenib,²⁰ only dabrafenib,²³ only vemurafenib,¹⁶ vemurafenib+trametinib,²⁴ only vemurafenib, and then dabrafenib and trametinib after progression and only vemurafenib and then trametinib after progression.^{25,14} Survival was 5, 26, 10, months,^{20, 23, 24} and PFS 54, 24 and 10 months (OS was not recorded).^{22, 25, 14} Patient treated with only vemurafenib was on treatment 39.1 months and was ongoing at study closure.¹⁶ Since different combinations of BRAF/MEK inhibitors were used there is question if there are differences between them and which would be the best combination. The advantages of early dual inhibition may include tumor shrinkage, improved quality of life by avoiding adverse events associated with conventional chemotherapy. Since rare brain tumors have uncertain response to radiation and temozolomide, it should be considered to introduce targeted dual therapy in the first line of adjuvant treatment or as neoadjuvant therapy in diffuse glial tumors. Several years of experience using BRAF/MEK inhibitors in other indications have led to a good knowledge of the safety profile. Adverse events of dabrafenib and trametinib are mild. The most common are chills and pyrexia of grade 1 (29%) or 2 (29%). Grade 3 was reported in 5% and grade 4 less than 1%.²⁶ In the phase II clinical study of dabrafenib plus trametinib the most common grade 3 or grade 4 adverse events, were pyrexia (3%) and headache (2%).²⁷

There are many questions that should be answer in a clinical trial or a systematic analysis: what is real effectiveness of radiotherapy and chemotherapy with temozolomide, is there a benefit of using BRAF/MEK inhibitors in first line, is combination better than single agent, what is the best combination, can radiotherapy be omitted in selected cases, is there role for neoadjuvant therapy with BRAF/MEK inhibitors. In the case of such rare tumors, the existence of international registries is imposed as a necessity that would significantly facilitate the treatment of patients due to a better insight into the biology of the disease.

5. Conclusions

Patients with BRAFV600E-mutated glioma should be treated with BRAF and MEK inhibitors with a high likelihood of durable response and acceptable toxicity profile. There is growing evidence in literature data for the use of these inhibitors in first line treatment. Despite changes in tumor classification over the long course of the disease, molecular markers are most important in the era of tissue-agnostic targeted therapy.

References

1. Ida CM, Rodriguez FJ, Burger PC. Pleomorphic Xanthoastrocytoma: Natural History and Long-Term Follow-Up. *Brain Pathol.* 2015; 25(5): 575-86.
2. Giannini C, Scheithauer BW, Burger PC. Pleomorphic xanthoastrocytoma: what do we really know about it? *Cancer.* 1999; 85: 2033-2045.
3. Gil- Gouveia R, Cristino N, Farias JP, Trindade A, Ruivo NS, Pimentel J. Pleomorphic xanthoastrocytoma of the cerebellum: illustrated review. *Acta Neurochir.* 2004; 146: 1241-1244.
4. Nakamura M, Chiba K, Matsumoto M, Ikeda E, Toyama Y. Pleomorphic xanthoastrocytoma of the spinal cord. Case report. *J. Neurosurg. Spine.* 2006; 5: 72-75.
5. Zarate JO, Sampaioles R. Pleomorphic xanthoastrocytoma of the retina. *Am J Surg Pathol.* 1999; 23: 79-81.
6. Hirose T, Ishizawa K, Sugiyama K, Kageji T, Ueki K, Kannuki S. Pleomorphic xanthoastrocytoma: a comparative pathological study between conventional and anaplastic types. *Histopathology.* 2008; 52: 183-193.
7. Weber RG, Hoischen A, Ehrler M. Frequent loss of chromosome 9, homozygous CDKN2A/p14 (ARF)/CDKN2B deletion and low TSC1 mRNA expression in pleomorphic xanthoastrocytomas. *Oncogene.* 2007; 26: 1088-1097.
8. Nakajima N, Nobusawa S, Nakata S. BRAFV600E, TERT promoter mutations and CDKN2A/B homozygous deletions are frequent in epithelioid glioblastomas: a histological and molecular analysis focusing on intratumoral heterogeneity. *Brain Pathol.* 2018; 28: 663-673.
9. Nasuha NA, Daud AH, Ghazali MM. Molecular genetic analysis of anaplastic pleomorphic xanthoastrocytoma. *Asian J Surg.* 2003; 26(2): 120-125.
10. Kepes JJ, Rubinstein J. Pleomorphic xanthoastrocytoma: a distinctive meningocerebral glioma of young subjects with relatively favorable prognosis, *Eng F Cancer.* 1979; 44: 1839-1852.
11. Louis DN, Perry A, Reifenberger G. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 2016; 131: 803-820.
12. Byun J, Hong SH, Kim Y-H, Kim JH, Kim CJ. Peritumoral edema affects the prognosis in adult pleomorphic xanthoastrocytoma: retrospective analysis of 25 patients. *World Neurosurg.* 2018; 114: e457-e467.
13. Ida CM, Rodriguez FJ, Burger PC. Pleomorphic xanthoastrocytoma: natural history and long-term follow-up. *Brain Pathol.* 2015; 25: 575-586.
14. Hussain F, Horbinski CM, Chmura SJ, Yamini B, Lukas RV. Response to BRAF/MEK inhibition after progression with BRAF inhibition in a patient with anaplastic pleomorphic xanthoastrocytoma. *Neurologist.* 2018; 23: 163-166.
15. Planchard D, Sanborn RE, Negrao MV, Vaishnavi A, Smit EF. BRAFV600E-mutant metastatic NSCLC: disease overview and treatment landscape. *NPJ Precis Oncol.* 2024; 16: 8(1):90.
16. Kaley T, Touat M, Subbiah V. BRAF Inhibition in BRAFV600-Mutant Gliomas: Results From the VE-BASKET Study. *J Clin Oncol.* 2018; 36(35): 3477-3484.

17. Wen PY, Stein A, van den Bent M. Dabrafenib plus trametinib in patients with BRAF V600E-mutant low grade and high grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. *The Lancet Oncol.* 2022; 23 (1): 53-64.
18. Salama AKS, Li S, Macrae ER. Dabrafenib and trametinib in patients with tumors with BRAFV600E mutations: results of the NCIMATCH Trial Subprotocol H. *J Clin Oncol.* 2020; 38: 3895-3904.
19. Kilburn LB, Khuong-Quang DA, Hansford JR. The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial. *Nat Med.* 2024; 30: 207-217.
20. Kata K, Rodriguez-Quintero JC, Arevalo OD. BRAF/MEK Dual Inhibitors Therapy in Progressive and Anaplastic Pleomorphic Xanthoastrocytoma: Case Series and Literature Review. *J Natl Compr Canc Netw.* 2022; 20(11): 1193-1202.e6
21. Schmidt Y, Kleinschmidt-DeMasters BK, Aisner DL, Lillehei KO, Damek D. Anaplastic PXA in adults: case series with clinicopathologic and molecular features. *J Neurooncol.* 2013; 111(1): 59-69.
22. Arbour G, Ellezam B, Weil AG. Upfront BRAF/MEK inhibitors for treatment of high-grade glioma: A case report and review of the literature. *Neurooncol Adv.* 2022; 19; 4(1): vdac174.
23. Usualieva A, Pierson CR, Kavran CA. Primary Meningeal Pleomorphic Xanthoastrocytoma With Anaplastic Features: A Report of 2 Cases, One With BRAF(V600E) Mutation and Clinical Response to the BRAF Inhibitor Dabrafenib. *J Neuropathol Exp Neurol.* 2015; 74(10): 960-9.
24. Leaver KE, Zhang N, Ziskin JL, Vogel H, Recht L, Thomas RP. Response of metastatic glioma to vemurafenib. *Neurooncol Pract.* 2016; 3(4): 268-271.
25. Brown NF, Carter T, Kitchen N, Mulholland P. Dabrafenib and trametinib in BRAFV600E mutated glioma. *CNS Oncol.* 2017; 6(4): 291-296.
26. Brown NF, Carter T, Mulholland P. Dabrafenib in BRAFV600-mutated anaplastic pleomorphic xanthoastrocytoma. *CNS Oncol.* 2017; 6(1): 5-9.
27. Hussain F, Horbinski CM, Chmura SJ, Yamini B, Lukas RV. Response to BRAF/MEK Inhibition After Progression with BRAF Inhibition in a Patient with Anaplastic Pleomorphic Xanthoastrocytoma. *Neurologist.* 2018; 23(5): 163-166.