# Trametinib

Trametinib is a MEK inhibitor approved for treatment of melanoma. Therapeutic responses with Talimogene laherparepvec (T-VEC) are often limited, and BRAF/MEK inhibition is complicated by drug resistance.

Bommareddy et al., from Rutgers New Jersey Medical School, Rush University Medical Center, Rush University Medical Center, Massachusetts General Hospital, observed that the combination of T-VEC and trametinib resulted in enhanced melanoma cell death in vitro. Further, combination treatment resulted in delayed tumor growth and improved survival in mouse models. Tumor regression was dependent on activated CD8+ T cells and Batf3+ dendritic cells. They also observed antigen spreading and induction of an inflammatory gene signature, including increased expression of PD-L1. Triple therapy with the combination of T-VEC, MEK inhibition, and anti-PD-1 antibody further augmented responses. These data support clinical development of combination oncolytic viruses, MEK inhibitors, and checkpoint blockade in patients with melanoma [1].

## Case reports

A clinical phase I study reported significant shrinkage of plexiform neurofibromas following treatment with the MEK inhibitor selumetinib.

Vaassen et al., reported an 11-year-old NF1 patient with a large plexiform neurofibroma of the neck that had led to a sharp-angled kinking of the cervical spine and subsequent myelopathy. Although surgical stabilization of the cervical vertebral column was urgently recommended, the vertebral column was inaccessible due to extensive tumor growth. In this situation, treatment with the MEK inhibitor trametinib was initiated which resulted in a 22% reduction in tumor volume after 6 months of therapy and finally enabled surgery. These data show that MEK inhibitors may not lead to complete disappearance of NF1-associated plexiform neurofibromas but can be an essential step in a multimodal therapeutic approach for these tumors. The course of our patient suggests that MEK inhibitors are likely to play a significant role in providing a cure for one of the most devastating manifestations of NF1 [2].

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Hussain et al., present the case of an Anaplastic Pleomorphic Xanthoastrocytoma initially treated with the BRAF inhibitor vemurafenib. After progression trametinib was added to the regimen leading to radiographic improvement [3].

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Kondyli et al., described six children with sporadic pediatric low-grade glioma who were treated with trametinib, following progression under conventional therapies.

The median age at diagnosis was 2.3 years (y) old [range 11 months (m)-8.5 y old]. KIAA1549-BRAF fusion was identified in five cases, and hotspot FGFR1/NF1/PTPN11 mutations in one. All patients received at least one previous line of chemotherapy (range 1-4). The median time on treatment was 11 m (range 4-20). Overall, we observed two partial responses and three minor responses as best response; three of these patients are still on therapy. Treatment was discontinued in the patient with

progressive disease. The most frequent toxicities were minor to moderately severe skin rash and gastro-intestinal symptoms. Two patients had dose reduction due to skin toxicity. Quality of life was excellent with decreased hospital visits and a close to normal life.

Trametinib appears to be a suitable option for refractory pediatric low-grade glioma and warrants further investigations in case of progression [4].

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A 5-month-old boy who presented with giant congenital melanocytic nevus and hydrocephalus. MR imaging and CSF immunohistochemistry confirmed leptomeningeal melanosis.

The patient required placement of a right-sided ventriculoperitoneal shunt to control hydrocephalus. The patient tolerated the procedure well and was discharged home with normal neurological function. A presumptive diagnosis of NCM was made based on the MR characteristics, CSF cytology and clinical presentation. He received trametinib, a MAPK/Erk kinase inhibitor for 7 months. At 30 months of age, he developed left-sided weakness and status epilepticus requiring paediatric intensive care unit admission and ventilator support. The patient eventually succumbed to malignant transformation of leptomeningeal disease.

Cutaneous manifestations of NCM are usually congenital, and neurological manifestations develop early in life. Patients with large or multiple congenital nevi should therefore be investigated early to facilitate treatment. MR imaging is the investigation of choice which can further assist in performing biopsy. Symptomatic NCM is refractory to radiotherapy and chemotherapy and has a poor prognosis. A multidisciplinary approach is necessary in the management of NCM patients [5].

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5. Clin Cancer Res. 2018 Dec 15;24(24):6483-6494. doi: 10.1158/1078-0432.CCR-17-3384. Epub 2018 Jun 14.

Dual MAPK Inhibition Is an Effective Therapeutic Strategy for a Subset of Class II BRAF Mutant Melanomas.

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PURPOSE: Dual MAPK pathway inhibition (dMAPKi) with BRAF and MEK inhibitors improves survival in BRAF V600E/K mutant melanoma, but the efficacy of dMAPKi in non-V600 BRAF mutant tumors is

poorly understood. We sought to characterize the responsiveness of class II (enhanced kinase activity, dimerization dependent) BRAF mutant melanoma to dMAPKi. EXPERIMENTAL DESIGN: Tumors from patients with BRAF wild-type (WT), V600E (class I), and L597S (class II) metastatic melanoma were used to generate patient-derived xenografts (PDX). We assembled a panel of melanoma cell lines with class IIa (activation segment) or IIb (p-loop) mutations and compared these with WT or V600E/K BRAF mutant cells. Cell lines and PDXs were treated with BRAFi (vemurafenib, dabrafenib, encorafenib, and LY3009120), MEKi (cobimetinib, trametinib, and binimetinib), or the combination. We identified 2 patients with BRAF L597S metastatic melanoma who were treated with dMAPKi. RESULTS: BRAFi impaired MAPK signaling and cell growth in class I and II BRAF mutant cells. dMAPKi was more effective than either single MAPKi at inhibiting cell growth in all class II BRAF mutant cells tested. dMAPKi caused tumor regression in two melanoma PDXs with class II BRAF mutations and prolonged survival of mice with class II BRAF mutant melanoma brain metastases. Two patients with BRAF L597S mutant melanoma clinically responded to dMAPKi. CONCLUSIONS: Class II BRAF mutant melanoma is growth inhibited by dMAPKi. Responses to dMAPKi have been observed in 2 patients with class II BRAF mutant melanoma. These data provide rationale for clinical investigation of dMAPKi in patients with class II BRAF mutant metastatic melanoma.See related commentary by Johnson and Dahlman, p. 6107.

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6. J Pediatr Hematol Oncol. 2018 Oct;40(7):553-554. doi: 10.1097/MPH.0000000000001170.

Encephalocraniocutaneous Lipomatosis.

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A 5-year-old boy presented with worsening headaches for 3 months. On examination, he was found to have a hairless fatty tissue nevus of the scalp (nevus psiloliparus), subcutaneous soft tissue masses on the right side of his face, neck, mandible and right buttock and epibulbar dermoid of the right eye (choristoma) (). Magnetic resonance imaging revealed a large suprasellar mass, which was debulked and found to be a pilocytic astrocytoma. Testing was not performed for the BRAF/KIAA1549 fusion or BRAFV600E mutation. Seven years later, he was started on adjuvant chemotherapy for gradual tumor progression. Over the ensuing 3 years, he had further disease progression despite treatment with 3 frontline chemotherapy regimens: vinblastine, carboplatin/vincristine, and irinotecan/bevacizumab. Targeted sequencing of tissue from the right gluteal mass, revealed a mosaic activating FGFR1 c.1966A>G (p.Lys656Glu) mutation, absent in normal left gluteal tissue, confirming the diagnosis of encephalocraniocutaneous lipomatosis (ECCL), belonging to the family of RASopathies (including neurofibromatosis type I, Noonan syndrome, Costello syndrome), with constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, and an increased risk of developing neoplasms. He was started on trametinib, a MEK inhibitor, off-label, targeting the MAPK pathway downstream from FGFR1, with stable tumor size at last follow-up, after 6 months on therapy.

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7. Acta Neuropathol. 2018 May;135(5):757-777. doi: 10.1007/s00401-018-1830-2. Epub 2018 Mar 14.

Tumour compartment transcriptomics demonstrates the activation of inflammatory and odontogenic programmes in human adamantinomatous craniopharyngioma and identifies the MAPK/ERK pathway as a novel therapeutic target.

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Adamantinomatous craniopharyngiomas (ACPs) are clinically challenging tumours, the majority of which have activating mutations in CTNNB1. They are histologically complex, showing cystic and solid components, the latter comprised of different morphological cell types (e.g. β-catenin-accumulating cluster cells and palisading epithelium), surrounded by a florid glial reaction with immune cells. Here, we have carried out RNA sequencing on 18 ACP samples and integrated these data with an existing ACP transcriptomic dataset. No studies so far have examined the patterns of gene expression within

the different cellular compartments of the tumour. To achieve this goal, we have combined laser capture microdissection with computational analyses to reveal groups of genes that are associated with either epithelial tumour cells (clusters and palisading epithelium), glial tissue or immune infiltrate. We use these human ACP molecular signatures and RNA-Seq data from two ACP mouse models to reveal that cell clusters are molecularly analogous to the enamel knot, a critical signalling centre controlling normal tooth morphogenesis. Supporting this finding, we show that human cluster cells express high levels of several members of the FGF, TGFB and BMP families of secreted factors, which signal to neighbouring cells as evidenced by immunostaining against the phosphorylated proteins pERK1/2, pSMAD3 and pSMAD1/5/9 in both human and mouse ACP. We reveal that inhibiting the MAPK/ERK pathway with trametinib, a clinically approved MEK inhibitor, results in reduced proliferation and increased apoptosis in explant cultures of human and mouse ACP. Finally, we analyse a prominent molecular signature in the glial reactive tissue to characterise the inflammatory microenvironment and uncover the activation of inflammasomes in human ACP. We validate these results by immunostaining against immune cell markers, cytokine ELISA and proteome analysis in both solid tumour and cystic fluid from ACP patients. Our data support a new molecular paradigm for understanding ACP tumorigenesis as an aberrant mimic of natural tooth development and opens new therapeutic opportunities by revealing the activation of the MAPK/ERK and inflammasome pathways in human ACP.

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8. Pediatr Blood Cancer. 2018 May;65(5):e26969. doi: 10.1002/pbc.26969. Epub 2018 Jan 30.

Response to the BRAF/MEK inhibitors dabrafenib/trametinib in an adolescent with a BRAF V600E mutated anaplastic ganglioglioma intolerant to vemurafenib.

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Efficacy of BRAF V600E targeted therapies in brain tumors harboring the mutation has been shown in several case reports and is currently being studied in larger clinical trials. Monotherapy with vemurafenib has been associated with significant side effects, including rashes, papillomas, and squamous cell carcinomas. Here we describe an adolescent female with anaplastic ganglioglioma and significant skin reaction to vemurafenib with subsequent tumor response and tolerance to the BRAF/MEK inhibitor combination of dabrafenib and trametinib without recurrence of previous reaction.

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9. Pediatr Blood Cancer. 2018 May;65(5):e26917. doi: 10.1002/pbc.26917. Epub 2018 Jan 25.

Targeted therapy for infants with diencephalic syndrome: A case report and review of management strategies.

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Young children with emaciation caused by a hypothalamic glioma are considered to have diencephalic syndrome (DS), which is often poorly controlled with conventional treatment. We describe an infant with DS whose tumor progressed following chemotherapy. Biopsy was performed for molecular testing and demonstrated a BRAF fusion. Treatment with the MEK inhibitor trametinib for 18 months resulted in reduction of tumor size, normalization of his weight curve, and marked neurodevelopmental improvement. Our results build on earlier reports of using targeted agents for low-grade glioma, and we review the evolving management strategy for such patients in the era of precision medicine.

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10. J Pediatr Hematol Oncol. 2018 Aug;40(6):478-482. doi: 10.1097/MPH.0000000000001032.

Sustained Response to Targeted Therapy in a Patient With Disseminated Anaplastic Pleomorphic Xanthoastrocytoma.

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Pleomorphic xanthoastrocytoma is a rare brain tumor with unique high frequency of BRAF V600E mutation which is plausible for targeted therapy. The anaplastic variant has generally worse prognosis. We present an adolescent patient with a disseminated relapse of anaplastic pleomorphic xanthoastrocytoma following surgery, radiotherapy, and chemotherapy. She had a dramatic and prolonged response to a BRAF inhibitor (Dabrafinib) and later to addition of a MEK inhibitor (Trametinib) on tumor progression. With minimal side effects and a good quality of life, the patient is alive more than 2 years after initiation of targeted therapy. This experience confirms the potential role of targeted treatments in high-grade BRAF-mutated brain tumors.

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11. Oncotarget. 2017 Sep 15;8(49):84697-84713. doi: 10.18632/oncotarget.20949. eCollection 2017 Oct 17.

Overcoming resistance to single-agent therapy for oncogenic BRAF gene fusions via combinatorial targeting of MAPK and PI3K/mTOR signaling pathways.

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Pediatric low-grade gliomas (PLGGs) are frequently associated with activating BRAF gene fusions, such as KIAA1549-BRAF, that aberrantly drive the mitogen activated protein kinase (MAPK) pathway. Although RAF inhibitors (RAFi) have been proven effective in BRAF-V600E mutant tumors, we have previously shown how the KIAA1549-BRAF fusion can be paradoxically activated by RAFi. While newer classes of RAFi, such as PLX8394, have now been shown to inhibit MAPK activation by KIAA1549-BRAF, we sought to identify alternative MAPK pathway targeting strategies using clinically relevant MEK inhibitors (MEKi), along with potential escape mechanisms of acquired resistance to single-agent MAPK pathway therapies. We demonstrate effectiveness of multiple MEKi against diverse BRAF-fusions with novel N-terminal partners, with trametinib being the most potent. However, resistance to MEKi or PLX8394 develops via increased RTK expression causing activation of PI3K/mTOR pathway in BRAF-fusion expressing resistant clones. To circumvent acquired resistance, we show potency of combinatorial targeting with trametinib and everolimus, an mTOR inhibitor (mTORi) against multiple BRAF-fusions. While single-agent mTORi and MEKi PLGG clinical trials are underway, our study provides preclinical rationales for using MEKi and mTORi combinatorial therapy to stave off or prevent emergent drug-resistance in BRAF-fusion driven PLGGs.

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Conflict of interest statement: CONFLICTS OF INTEREST None of the authors declare any conflict of interest.

12. CNS Oncol. 2017 Oct;6(4):291-296. doi: 10.2217/cns-2017-0006. Epub 2017 Oct 6.

Dabrafenib and trametinib in BRAFV600E mutated glioma.

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BRAFV600E mutations have been identified in a number of glioma subtypes, most frequently in pleomorphic xanthoastrocytoma, ganglioglioma, pilocytic astrocytoma, and epithelioid glioblastoma.

Although the development of BRAF inhibitors has dramatically improved the clinical outcome for patients with BRAFV600E mutant tumors, resistance develops in a majority of patients due to reactivation of the MAPK pathway. Addition of MEK inhibition to BRAF inhibition improves survival. Here we report successful treatment of two patients with BRAFV600E mutant pleomorphic xanthoastrocytoma using the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib.

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13. Int J Cancer. 2018 Jan 15;142(2):381-391. doi: 10.1002/ijc.31052. Epub 2017 Oct 4.

The impact of P-glycoprotein and breast cancer resistance protein on the brain pharmacokinetics and pharmacodynamics of a panel of MEK inhibitors.

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Mitogen/extracellular signal-regulated kinase (MEK) inhibitors have been tested in clinical trials for treatment of intracranial neoplasms, including glioblastoma (GBM), but efficacy of these drugs has not yet been demonstrated. The blood-brain barrier (BBB) is a major impediment to adequate delivery of drugs into the brain and may thereby also limit the successful implementation of MEK inhibitors against intracranial malignancies. The BBB is equipped with a range of ATP-dependent efflux transport proteins, of which P-gp (ABCB1) and BCRP (ABCG2) are the two most dominant for drug efflux from the brain. We investigated their impact on the pharmacokinetics and target engagement of a panel of clinically applied MEK inhibitors, in order to select the most promising candidate for brain cancers in the context of clinical pharmacokinetics and inhibitor characteristics. To this end, we used in vitro drug transport assays and conducted pharmacokinetic and pharmacodynamic studies in wildtype and ABC-transporter knockout mice. PD0325901 displayed more promising characteristics than trametinib (GSK1120212), binimetinib (MEK162), selumetinib (AZD6244), and pimasertib (AS703026): PD0325901 was the weakest substrate of P-gp and BCRP in vitro, its brain penetration was only marginally higher in Abcb1a/b;Abcg2-/- mice, and efficient target inhibition in the brain could be achieved at clinically relevant plasma levels. Notably, target inhibition could also be demonstrated for selumetinib, but only at plasma levels far above levels in patients receiving the maximum tolerated dose. In summary, our study recommends further development of PD0325901 for the treatment of intracranial neoplasms.

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14. Acta Neurochir (Wien). 2017 Nov;159(11):2217-2221. doi: 10.1007/s00701-017-3311-0. Epub 2017 Sep 16.

Recurrent papillary craniopharyngioma with BRAFV600E mutation treated with neoadjuvant-targeted

therapy.

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Craniopharyngiomas are histologically benign but locally aggressive tumors in the sellar region that may cause devastating neurological and endocrine deficits. They tend to recur following surgery with high morbidity; hence, postoperative radiotherapy is recommended following sub-total resection. BRAFV600E mutation is the principal oncogenic driver in the papillary variant of craniopharyngiomas. Recently, a dramatic tumor reduction has been reported in a patient with BRAFV600E mutated, multiply recurrent papillary craniopharyngioma using a combination therapy of BRAF inhibitor dabrafenib and MEK inhibitor trametinib. Here, we report on near-radical reduction of a growing residual BRAFV600E craniopharyngioma using the same neoadjuvant therapy.

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15. Expert Rev Anticancer Ther. 2017 Apr;17(4):347-356. doi: 10.1080/14737140.2017.1296764. Epub 2017 Mar 1.

Radiosurgery/stereotactic radiotherapy in combination with immunotherapy and targeted agents for melanoma brain metastases.

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INTRODUCTION: The clinical landscape of advanced melanoma drastically changed after the introduction of both targeted therapies and immunotherapy. This rapid development in systemic therapies led to a change in the management of patients with brain metastases, with the subsequent need to re-assess the role of local therapies, in particular stereotactic radiosurgery (SRS). Areas covered: In this non-systematic review, we report on the current knowledge on the use of SRS in combination with immunotherapy and BRAF/MEK inhibitors for patients with melanoma brain metastases, as well as ongoing trials in this field. Expert commentary: It is now more common to observe patients with melanoma brain metastases with better performance status and prolonged life expectancy. A combination of targeted therapy and immunotherapy, in different sequences, has been shown to be feasible and well tolerable, on the basis of retrospective reports. Additional data from ongoing prospective trials are however needed to confirm or not these findings and better explore the efficacy of the combination.

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16. Cancer Treat Rev. 2017 Feb;53:25-37. doi: 10.1016/j.ctrv.2016.11.013. Epub 2016 Dec 19.

Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review.

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BACKGROUND AND PURPOSE: Both stereotactic radiotherapy (SRT) and immune- or targeted therapy play an increasingly important role in personalized treatment of metastatic disease. Concurrent application of both therapies is rapidly expanding in daily clinical practice. In this systematic review we summarize severe toxicity observed after concurrent treatment. MATERIAL AND METHODS: PubMed and EMBASE databases were searched for English literature published up to April 2016 using keywords “radiosurgery”, “local ablative therapy”, “gamma knife” and “stereotactic”, combined with “bevacizumab”, “cetuximab”, “crizotinib”, “erlotinib”, “gefitinib”, “ipilimumab”, “lapatinib”, “sorafenib”, “sunitinib”, “trastuzumab”, “vemurafenib”, “PLX4032”, “panitumumab”, “nivolumab”, “pembrolizumab”, “alectinib”, “ceritinib”, “dabrafenib”, “trametinib”, “BRAF”, “TKI”, “MEK”, “PD1”, “EGFR”, “CTLA-4” or “ALK”. Studies performing SRT during or within 30days of targeted/immunotherapy, reporting severe (⩾Grade 3) toxicity were included. RESULTS: Concurrent treatment is mostly well tolerated in cranial SRT, but high rates of severe toxicity were observed for the combination with BRAF-inhibitors. The relatively scarce literature on extra-cranial SRT shows a potential risk of increased toxicity when SRT is combined with EGFR-targeting tyrosine kinase inhibitors and bevacizumab, which was not observed for cranial SRT. CONCLUSIONS: This review gives a best-possible overview of current knowledge and its limitations and underlines the need for a timely generation of stronger evidence in this rapidly expanding field.

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17. J Neurosurg Pediatr. 2017 Mar;19(3):319-324. doi: 10.3171/2016.9.PEDS16328. Epub 2016 Dec 23.

Report of effective trametinib therapy in 2 children with progressive hypothalamic optic pathway pilocytic astrocytoma: documentation of volumetric response.

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Brain tumors are the most common solid tumor in childhood, and astrocytomas account for the largest proportion of these tumors. Increasing sophistication in genetic testing has allowed for the detection of specific mutations within tumor subtypes that may represent targets for individualized tumor treatment. The mitogen-activating protein kinase (MAPK) pathway and, more specifically, BRAF

mutations have been shown to be prevalent in pediatric pilocytic astrocytomas and may represent one such area to target. Herein, the authors describe 2 cases of inoperable, chemotherapy-resistant pediatric pilocytic astrocytomas with a documented response to trametinib, an MAPK pathway inhibitor. While these cases were not treated in the setting of a clinical trial, their data support further ongoing clinical trial investigation to evaluate the safety and efficacy of this agent in pediatric low-grade gliomas.

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18. J Neurooncol. 2016 Oct;130(1):211-219. Epub 2016 Aug 16.

Clinical utility and treatment outcome of comprehensive genomic profiling in high grade glioma patients.

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Genomic research of high grade glioma (HGG) has revealed complex biology with potential for therapeutic impact. However, the utilization of this information and impact upon patient outcome has yet to be assessed. We performed capture-based next generation sequencing (NGS) genomic analysis assay of 236/315 cancer-associated genes, with average depth of over 1000 fold, to guide treatment in HGG patients. We reviewed clinical utility and response rates in correlation to NGS results. Forty-three patients were profiled: 34 glioblastomas, 8 anaplastic astrocytomas, and one patient with anaplastic oligodendroglioma. Twenty-five patients were profiled with the 315 gene panel. The median number of identified genomic alterations (GAs) per patient was 4.5 (range 1-23). In 41 patients (95 %) at least one therapeutically-actionable GA was detected, most commonly in EGFR [17 (40 %)]. Genotype-directed treatments were prescribed in 13 patients, representing a 30 % treatment decision impact. Treatment with targeted agents included everolimus as a single agent and in combination with erlotinib; erlotinib; afatinib; palbociclib; trametinib and BGJ398. Treatments targeted various genomic findings including EGFR alterations, mTOR activation, cell cycle targets and FGFR1 mutations. None of the patients showed response to respective biologic treatments. In this group of patients with HGG, NGS revealed a high frequency of GAs that lead to targeted treatment in 30 % of the patients. The lack of response suggests that further study of mechanisms of resistance in HGG is warranted before routine use of biologically-targeted agents based on NGS results.

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19. World J Surg Oncol. 2016 Sep 1;14(1):235. doi: 10.1186/s12957-016-0965-7.

Primary cerebral malignant melanoma in insular region with extracranial metastasis: case report and review literature.

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BACKGROUND: Primary brain melanomas are very infrequent and metastasis outside central nervous system very uncommon. There are some cases in the literature about primary melanoma in the temporal lobe; nevertheless, the insular location has never been described. CASE PRESENTATION: The patient presented as left insular intraparenchymal hematoma with multiple bleedings. Complementary tests did not show any tumoral nor vascular pattern in relation with these bleedings. A complete surgical resection was performed, and the diagnosis of malignant melanoma, with BRAF mutation, was obtained after histology exam. Extension studies were negative for skin or mucous melanoma. 18F-FDG PET/CT was performed and a metastatic lymph node was found. The diagnosis was primary brain melanoma with extracerebral metastasis. Dabrafenib 150 mg/12 h was the only chemotherapy during 5 months. After that, Trametinib 2 mg/24 h was added to the treatment. Eighteen months after surgery, the patient is independent, with stable situation, and without new metastasis. CONCLUSIONS: Although malignant melanomas have poor prognosis, total surgical resection and new therapies are increasing the overall survival and improving quality of life. In a patient with suspected brain melanoma, in spite of having extracerebral metastasis, aggressive treatment may be considered.

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20. Melanoma Res. 2016 Aug;26(4):382-6. doi: 10.1097/CMR.0000000000000250.

Initial experience with combined BRAF and MEK inhibition with stereotactic radiosurgery for BRAF mutant melanoma brain metastases.

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The combined use of the BRAF inhibitor dabrafenib and MEK inhibitor trametinib has been found to improve survival over dabrafenib alone. The management of melanoma brain metastases continues to present challenges. In this study, we report our initial experience in the management of melanoma brain metastases with stereotactic radiosurgery (SRS) with the use of BRAF and MEK inhibitors. We identified six patients treated with SRS for 17 brain metastases within 3 months of BRAF and MEK inhibitor administration. The median planning target volume was 0.42 cm (range: 0.078-2.08 cm). The median treatment dose was 21 Gy (range 18-24 Gy). The median follow-up of all lesions from SRS was 10.6 months (range 5.8-28.5 months). One lesion was found to undergo local failure 21.7 months following SRS treatment. The median overall survival was 20.0 months (range 6.1-31.8 months) from the time of SRS treatment and 23.1 months (range: 12.1-30.9 months) from the date of BRAFi and MEKi administration. There was no evidence of increased nor unexpected toxicity with the two modalities combined. In this initial experience of melanoma brain metastases treated with BRAF and MEK inhibition with SRS, we find the two modalities can be combined safely. These outcomes should be assessed further in prospective evaluations.

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21. J Natl Cancer Inst. 2015 Oct 23;108(2). pii: djv310. doi: 10.1093/jnci/djv310. Print 2016 Feb.

Dramatic Response of BRAF V600E Mutant Papillary Craniopharyngioma to Targeted Therapy.

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We recently reported that BRAF V600E is the principal oncogenic driver of papillary craniopharyngioma, a highly morbid intracranial tumor commonly refractory to treatment. Here, we describe our treatment of a man age 39 years with multiply recurrent BRAF V600E craniopharyngioma using dabrafenib (150mg, orally twice daily) and trametinib (2mg, orally twice daily). After 35 days of treatment, tumor volume was reduced by 85%. Mutations that commonly mediate resistance to MAPK pathway inhibition were not detected in a post-treatment sample by whole exome sequencing. A blood-based BRAF V600E assay detected circulating BRAF V600E in the patient's blood. Re-evaluation of the existing management paradigms for craniopharyngioma is warranted, as patient morbidity might be reduced by noninvasive mutation testing and neoadjuvant-targeted treatment.

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22. Am J Case Rep. 2014 Oct 12;15:441-3. doi: 10.12659/AJCR.890875.

A case of intracranial hemorrhage caused by combined dabrafenib and trametinib therapy for metastatic melanoma.

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BACKGROUND: Combination therapy with BRAF V600E inhibitor dabrafenib and MEK inhibitor trametinib significantly improves progression-free survival of patients with BRAF V600-positive metastatic melanoma, but their use can be associated with life-threatening toxicities. We report the case of a patient receiving dabrafenib and trametinib for metastatic melanoma who developed intracranial hemorrhage while on therapy. Combination therapy with dabrafenib and trametinib improves progression-free survival of patients with BRAF V600-positive metastatic melanoma. Nevertheless, it is associated with an increased incidence and severity of any hemorrhagic event. To the best of our knowledge, this is the first report of intracranial hemorrhage with pathological confirmation. CASE REPORT: We present the case of a 48-year-old man with metastatic melanoma of

unknown primary site. He had metastases to the right clavicle, brain, liver, adrenal gland, and the right lower quadrant of the abdomen. He progressed on treatment with alpha-interferon. He was found to have a 4.5-cm mass in the left frontotemporal lobe and underwent gross total resection followed by adjuvant CyberKnife stereotactic irradiation. He was subsequently started on ipilimumab. Treatment was stopped due to kidney injury. He was then placed on dabrafenib and trametinib. He returned for follow-up complaining of severe headache and developed an episode of seizure. MRI showed a large area of edema at the left frontal lobe with midline shift. Emergency craniotomy was performed. Intracranial hemorrhage was found intra-operatively. Pathology from surgery did not find tumor cells, reported as organizing hemorrhage and necrosis with surrounding gliosis; immunohistochemistry for S100 and HMB45 were negative. CONCLUSIONS: This case demonstrates the life-threatening adverse effects that can be seen with the newer targeted biological therapies. It is therefore crucial to maintain a high index of suspicion when patients on this combination therapy present with new neurologic symptoms.

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