Targeted Treatment of Papillary Craniopharyngiomas Harboring BRAF V600E Mutations

Tareq A. Juratli, MD
Department of Neurosurgery, Divisions of Neuro-Oncology and Hematology/Oncology, Departments of Neurology and Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Department of Neurosurgery, Faculty of Medicine and Carl Gustav, Carus University Hospital, Technische Universität Dresden, Dresden, Germany

Pamela S. Jones, MD, MS, MPH
Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Nancy Wang, MD
Divisions of Neuro-Oncology and Hematology/Oncology, Departments of Neurology and Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Megha Subramanian, PhD
Divisions of Neuro-Oncology and Hematology/Oncology, Departments of Neurology and Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Simon J. B. Aylwin, FRCP, PhD
Department of Endocrinology, King's College Hospital, London, United Kingdom

Yazmin Odia, MD, MS
Miami Cancer Institute, Baptist Health South Florida, Miami, Florida

Craniopharyngiomas are primary brain tumors of the sellar region that are presumed to arise from embryologic remnants of Rathke's pouch.[1,2] Although craniopharyngiomas have a benign histology and the 10-year survival rate is higher than 90%, quality of life is frequently impaired by the involvement of neurohormonal structures, including the optic nerves, the pituitary gland, and the hypothalamus.[3,4] Complete surgical resection is attempted when possible, but partial resection is favored to preserve function when the tumor involves the hypothalamus. Radiation therapy is commonly used to manage residual tumor and recurrence.[5] Currently, US Food and Drug Administration–approved systemic treatments are not available for patients in whom craniopharyngiomas recur after surgery and radiation.

Craniopharyngiomas are divided into 2 main subtypes—adamantinomatous craniopharyngiomas and papillary craniopharyngiomas (PCPs)—that exhibit different clinical and molecular features (Table 1).[6,7]

A hallmark of PCPs is their supradiaphragmatic location. Surgical resection is challenging because of the proximity to critical structures and is typically performed via a traditional transcranial approach or an endoscopic endonasal approach.[8] The extent of resection varies with the tumor size and location. Despite the benign nature of these tumors, recurrences are common and necessitate further surgery or radiation. Consequently, morbidity due to neurological and endocrinological complications is high, with potentially devastating effects, including visual loss and hypothalamic dysfunction.[9,10]

BRAF Inhibitors in PCPs

Five years ago, we reported that nearly all PCPs have BRAF V600E (*BRAF*^{V600E}) mutations, which constitutively activate the mitogen-activated protein kinase signaling pathway.[7] *BRAF*^{V600E} mutations are recurrent aberrations in neoplasms such as melanoma that can demonstrate remarkable sensitivity to BRAF inhibitors.[11] Similarly, our group and others have published case reports of dramatic responses in patients with *BRAF*^{V600E}-mutant PCP treated with BRAF and/or mitogen-activated protein kinase kinase (MEK) inhibitors.

In this article, authors from all 5 previously published reports share their collective experience, provide updated follow-up on their patients, and thus generate an overview of all currently available information on targeted therapy in patients with *BRAF*^{V600E}-mutant PCP (Table 2).[12-16] We have also included information on an additional patient with PCP recently treated at Massachusetts General Hospital (patient PCP6). He was 21 years old when he presented with several months of intermittent headaches and progressive fatigue. He also reported difficulty in concentrating, weight gain, and nausea. An ophthalmologic evaluation identified visual field deficits, and brain magnetic resonance imaging (MRI) revealed an enhancing suprasellar mass. He underwent biopsy of the lesion, with pathology demonstrating *BRAF*^{V600E}-mutant PCP. The surgery was complicated by infarcts involving the right anterior choroidal artery territory as well as panhypopituitarism. One month after the operation, imaging revealed continued tumor growth. He was admitted to our institution and was started on dabrafenib and trametinib. Serial MRI scans over the course of 6 months demonstrated a significant reduction in the tumor size with corresponding improvements in his mental status and headaches (Fig. 1). This is the first example of successful neoadjuvant treatment

TABLE 1. Comparisons of Different Clinical and Molecular Features of Adamantinomatous and Papillary Craniopharyngiomas

	Adamantinomatous Craniopharyngiomas	Papillary Craniopharyngiomas
Age with highest prevalence	Bimodal: incidence peaks (5-15 and 40-60 y)	Primarily adults (40-55 y)
Location	Supra- and/or infradiaphragmatic	Mainly supradiaphragmatic
Calcifications	Frequently present	Rare
Tumor signaling pathway	Wnt pathway	MAPK pathway
Frequent genomic alterations	*CTNNB1* mutations	*BRAF*^{V600E} mutations

Abbreviations: CTNNB1, catenin β1; MAPK, mitogen-activated protein kinase.

in a patient with *BRAF*^{V600E}-mutant PCP. At the time of treatment, the tumors in patients PCP1 to PCP5 had recurred after they had undergone surgical resection(s) and/or radiation therapy, whereas treatment in PCP6 was performed after biopsy alone and without any other therapy; this highlights the potential of neoadjuvant treatment. Four patients (PCP1, PCP3, PCP4, and PCP6) received both BRAF and MEK inhibitors, whereas 2 patients (PCP2 and PCP5) received BRAF inhibitor monotherapy (vemurafenib or dabrafenib). Despite different treatment strategies, in all cases, complete or nearly complete tumor regression was achieved, mostly within just a few months after the start of treatment. Both solid and cystic components were responsive. The treatment was well tolerated in most cases, but therapy was temporarily held for 1 patient who developed a cerebrospinal fluid (CSF) leak (PCP2) and for another patient who developed pyrexia (PCP3).

In the patient who developed a CSF leak and meningitis (PCP2) while on vemurafenib monotherapy, the tumor had responded to therapy with a nearly complete response and regrew 3 months after treatment was discontinued because of the complications. Tumor control was again achieved with vemurafenib monotherapy but lasted only 7 months, after which the tumor progressed. A significant reduction in the performance status occurred after the CSF leak, so further active treatment was considered inappropriate, and she died 6 months after treatment was discontinued. In 1 patient (PCP1), a dramatic response was achieved after only 1 month of BRAF/MEK inhibitor dual therapy, after which the remaining tumor was resected, and the area was treated with radiation. The patient was well 12 months later and was subsequently lost to follow-up. Similarly, a substantial treatment response was achieved in another patient (PCP4) with BRAF/MEK inhibitor dual therapy, and the residual tumor was treated with radiation. This patient was tumor-free and remained on dual therapy with dabrafenib and trametinib at the time of this writing. In 1 case (PCP5), minimal tumor remained after 9 months of targeted monotherapy with dabrafenib, at which point treatment was discontinued. With the patient off therapy, the tumor had not recurred 18 months later. The dramatic responses achieved in these cases highlight the transformative potential of BRAF-targeted therapy for patients with PCP. The most recently treated patient (PCP6) had a rapid response in the form of an approximately 80% to 90% reduction of the solid and cystic portions within 6 months.

Although these 6 cases are highly informative for guiding patient treatment, uncertainty remains concerning the optimal timing, the particular agents (single-agent or dual therapy) to be used, and the duration of treatment. A combination of dabrafenib and trametinib has been used most frequently (4 of 6 patients); however, more data are needed to decide on the optimal drug combination. The ongoing multicenter phase 2 Alliance A071601 trial (NCT03224767) of vemurafenib and cobimetinib for patients with biopsy-proven residual or recurrent PCP should provide additional information to help to inform patient management.

In addition, the remarkable responses in patients PCP1 to PCP5 with recurrent disease and in PCP6 with neoadjuvant treatment after biopsy signal the potential for using targeted therapy before any surgery. Algorithms for discriminating PCPs from adamantinomatous craniopharyngiomas have been proposed on the basis of retrospective analyses of MRI data.[17-19] Such approaches

Elham Rostami, MD, PhD
Section of Neurosurgery, Department of Neuroscience, Uppsala University, Uppsala, Sweden; Department of Neuroscience, Karolinska Institute, Stockholm, Sweden

Olafur Gudjonsson, MD, PhD
Section of Neurosurgery, Department of Neuroscience, Uppsala University, Uppsala, Sweden

Brian L. Shaw, BS
Divisions of Neuro-Oncology and Hematology/Oncology, Departments of Neurology and Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Daniel P. Cahill, MD, PhD
Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Evanthia Galanis, MD
Division of Medical Oncology, Department of Oncology, Department of Molecular Medicine, Mayo Clinic, Rochester, Minnesota

Fred G. Barker II, MD
Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Sandro Santagata, MD, PhD
Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Priscilla K. Brastianos, MD
Divisions of Neuro-Oncology and Hematology/Oncology, Departments of Neurology and Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

TABLE 2. Overview of Currently Available and Updated Information on Targeted Therapy in Patients With *BRAF*^{V600E}-Mutant PCP

Case No.	Age, y/Sex	Histology and Molecular Status	Tumor Size Before Treatment, cm	Initial Treatment	Agents	Regimen	Response	Reference
PCP1	39/male	rPCP, *BRAF*^{V600E} mutant	4.4 × 2.7 × 4.2	Multiple surgeries	Dabrafenib and trametinib	150 mg bid and 2 mg bid	PR (85% decrease) after 1 mo	12
PCP2	57/female	rPCP, *BRAF*^{V600E} mutant	2 × 3 × 2	Multiple surgeries	Vemurafenib	960 mg bid	Near CR after 3 mo	13
PCP3	65/male	rPCP, *BRAF*^{V600E} mutant	2.15 × 2.64 × 2.2	Multiple surgeries	Dabrafenib and trametinib	150 mg bid and 2 mg qd	PR (91% decrease) after 4 mo	14
PCP4	47/female	rPCP, *BRAF*^{V600E} mutant	2.6 × 2.3 × 3.2	Surgery and RTx	Dabrafenib and trametinib	150 mg bid and 2 mg qd	CR after 7 mo	15
PCP5	52/male	rPCP, *BRAF*^{V600E} mutant	1.9 × 1.8 × 1	Surgery and RTx	Dabrafenib	150-225 mg qd	CR after 9 mo	16
PCP6	21/male	Residual PCP, *BRAF*^{V600E} mutant	3.1 × 2.6 × 2.3	Surgery (biopsy)	Dabrafenib and trametinib	150 mg bid and 2 mg qd	PR (>80% decrease) after 6 mo	Recent case

Abbreviations: bid, twice daily; CR, complete response; PCP, papillary craniopharyngioma; PR, partial response; qd, every day; rPCP, recurrent papillary craniopharyngioma; RTx, radiation therapy.

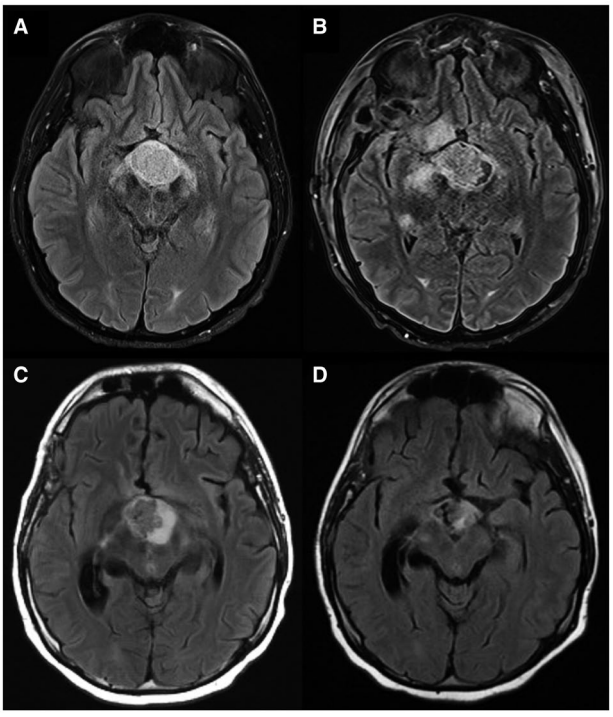

Figure 1. T2/fluid-attenuated inversion recovery–weighted magnetic resonance imaging sequences demonstrating a cystic and solid suprasellar mass: (A) on initial presentation, (B) after subtotal resection, (C) after 2 weeks of dabrafenib and trametinib, and (D) after 6 months of therapy.

will require further refinement and testing in prospective studies. Further diagnostic approaches, including the detection of BRAF mutations in serum, may contribute to preoperative diagnostic evaluations. Circulating BRAF in the blood of a patient with a PCP (PCP2) was previously reported.[12] This liquid biopsy approach would allow not only the noninvasive detection of BRAF mutations but also monitoring of treatment responses. However, until such noninvasive techniques can be demonstrated to be reliable, the diagnosis of a papillary subtype of craniopharyngioma will be made through biopsy, histology review, and molecular assessment. A feasible strategy may be conservative biopsy of a craniopharyngioma that has radiological features suggestive of the papillary subtype with the potential for targeted therapy. In the future, if achievable with high sensitivity and specificity, the noninvasive or minimally invasive diagnosis of PCP would lead to neoadjuvant targeted therapeutic approaches that could further reduce the significant lifelong morbidity associated with these challenging neoplasms beyond what has already been achieved for patients with recurrent disease.

Summary

PCPs are characterized by the presence of *BRAF*^{V600E} mutations, which are emerging as a useful guide for diagnosis and treatment decision making. The ongoing multicenter phase 2 Alliance A071601 trial is evaluating the efficacy of BRAF and MEK inhibitors for patients with PCP. With continued successful responses, we propose that BRAF (and MEK) inhibitors be evaluated for the neoadjuvant treatment of patients with PCP.

This study was conducted according to the guidelines of the Declaration of Helsinki and has been approved by the local ethics committee of our faculty.

The last 3 authors contributed equally to this article.

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CONFLICT OF INTEREST DISCLOSURES

Yazmin Odia reports grants from Bristol-Myers Squibb and grants and other from Novocure outside the submitted work. She also reports advising roles for Novocure and Abbvie. Daniel P. Cahill reports receiving honoraria from Merck and Lilly outside the submitted work. Eva Galanis reports research funding from Bristol-Myers Squibb, Genentech, Merck, and Tracon and personal fees from Celgene, KIYATEC, Tactical Therapeutics, and Oncorus outside the submitted work. Sandro Santagata is a consultant for RareCyte. Priscilla K. Brastianos reports honoraria for consulting from Tesaro, Lilly, Angiochem, and Genentech-Roche; speaker's honoraria from Genentech-Roche and Merck; and research funding (to Massachusetts General Hospital) from Merck and Pfizer. The other authors made no disclosures.

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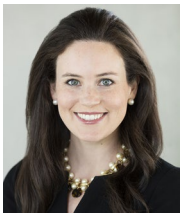
Author Bios

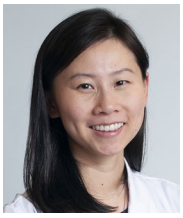
Tareq A. Juratli, MD

Tareq A. Juratli is an assistant professor of neurosurgery at Carl Gustav Carus University Hospital in Dresden, Germany. He completed a 2.5-year postdoctoral fellowship at Massachusetts General Hospital in Boston. His research focuses on investigating genomic alterations and molecular mechanisms in brain tumors.

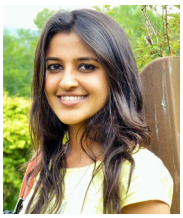


Pamela S. Jones, MD, MS, MPH

Pamela S. Jones is a neurosurgeon at Massachusetts General Hospital in Boston who cares for people with all types of brain tumors, including glioblastomas, low- and high-grade gliomas, metastatic brain tumors, and skull base tumors such as meningiomas and pituitary tumors and craniopharyngiomas.



Nancy Wang, MD
Nancy Wang is a neuro-oncologist at Massachusetts General Hospital in Boston. She has a special interest in treating patients with brain metastases as well as primary brain tumors.



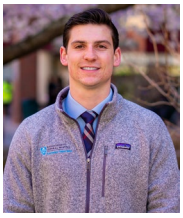
Megha Subramanian, PhD
Megha Subramanian is a postdoctoral fellow in the laboratories of Priscilla K. Brastianos and Daniel P. Cahill in Boston, Massachusetts. She received her PhD in neuroscience from Johns Hopkins School of Medicine and her BS in biology from the University of Virginia.

Simon J. B. Aylwin, FRCP, PhD
Simon J. B. Aylwin is the lead clinician for the regional pituitary team at King's College Hospital London in the United Kingdom and an expert in endocrine oncology. He has published extensively on pituitary and other endocrine-related tumors.

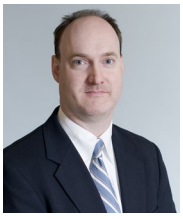
Yazmin Odia, MD, MS
Yazmin Odia has served as the lead physician of medical neuro-oncology at the Miami Cancer Institute at Baptist Health South Florida since 2016. At Baptist Health South Florida, she also serves on the scientific review committee for the Miami Cancer Institute and on the Neuroscience Research Fund review committee.

Elham Rostami, MD, PhD
Elham Rostami is a consultant neurosurgeon and associate professor for the Department of Neurosurgery at Uppsala University Hospital in Sweden. She completed her MD and PhD at the Karolinska Institute in Stockholm, Sweden. Her current research area covers neuro-oncology and neurotrauma.

Olafur Gudjonsson, MD, PhD
Olafur Gudjonsson is a senior consultant neurosurgeon. He graduated from the University of Iceland in 1983 and completed his neurosurgical training and PhD at Uppsala University Hospital in Sweden, where he is currently the chief of skull base surgery and the head of the Department of Neurosurgery.

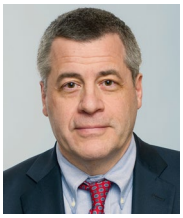


Brian L. Shaw, BS
Brian L. Shaw currently works as a clinical research coordinator II in neuro-oncology at Massachusetts General Hospital in Boston while applying to medical school.

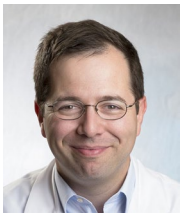


Daniel P. Cahill, MD, PhD
Daniel P. Cahill holds the Tawingo Chair in Neurosurgery at Massachusetts General Hospital in Boston and is an associate professor at Harvard Medical School. His research focuses on precision medicine in brain tumors.

Evanthia Galanis, MD
Evanthia Galanis is a professor of oncology and the Sandra J. Schulze Professor of Novel Therapeutics at the Mayo Clinic in Rochester, Minnesota. She is also the chair of the Department of Molecular Medicine at the Mayo Clinic and Chair of the Neurooncology Committee of the Alliance for Clinical Trials in Oncology.



Fred G. Barker II, MD
Fred G. Barker II is a professor of neurosurgery at Massachusetts General Hospital in Boston. He specializes in the surgical treatment of central nervous system and skull base tumors, including acoustic neuromas, craniopharyngiomas, and meningiomas.



Sandro Santagata, MD, PhD
Sandro Santagata is an assistant professor of pathology at Brigham and Women's Hospital in Boston, Massachusetts, where he practices neuropathology. His laboratory investigates molecular mechanisms of tumorigenesis and identifies strategies for treating patients with brain tumors.

Priscilla K. Brastianos, MD
Priscilla K. Brastianos is an assistant professor at Harvard Medical School and is the director of the Central Nervous System Metastasis Center at Massachusetts General Hospital in Boston. Her research focuses on understanding the genomic mechanisms that drive progression in primary and metastatic brain tumors.