Case Report

Corticosteroid-Refractory Myositis After Dual BRAF and MEK Inhibition in a Patient with BRAF V600E-Mutant Metastatic Intrahepatic Cholangiocarcinoma

Timothy P. DiPeri,1 Mehmet Demirhan,2,3 Daniel D. Karp,2 Siqing Fu,2 David S. Hong,2 Vivek Subbiah,2 Joann Lim,2 Leomar Y. Ballester,4,5 Jean H. Tayar,6 Maria E. Suarez-Almazor,6,7 Milind Javle,8 Funda Meric-Bernstam,1,2,9

1Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
2Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
3Department of Medicine, Elmhurst Hospital Center, Icahn School of Medicine at Mount Sinai, New York City, NY, USA
4Department of Pathology and Laboratory Medicine, University of Texas Health Science Center, Houston, TX, USA
5Department of Neurosurgery, University of Texas Health Science Center, Houston, TX, USA
6Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
7Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
8Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
9Department of Khalifa Institute for Personalized Cancer Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Address correspondence to Funda Meric-Bernstam (fmeric@mdanderson.org).

Sources of Support: This work was supported in part by the following: National Institute of Health (NIH) Training of Academic Surgical Oncologists (ST32CA009599-32), Sheikh Khalifa Bin Zayed Al Nahyan institute for Personalized Cancer Therapy, NIH/NCATS Center for Clinical and Translational Sciences (CCTS)/MD Anderson Translational Informatics (UL1 TR003167), and National Cancer Institute (NCI) Cancer Center Support (CORE) Grant (SP3CA016672-44). The Targeted Agent and Profiling Utilization Registry (TAPUR) trial (NCT02693535) was sponsored by the American Society of Clinical Oncology (ASCO).

Conflicts of Interest: Vivek Subbiah reports research funding/grant support for clinical trials from Roche/Genentech, Novartis, Bayer, GlaxoSmithKline, Nanocarrier, Vegenics, Celgene, Northwest Biotherapeutics, Berghhealth, Incyte, Fujifilm, Pharmamar, D3, Pfizer, Multivir, Amgen, Abbvie, Alfa-sigma, Agensys, Boston Biomedical, Idera Pharma, Inhibrx, Exelixis, Blueprint medicines, Lonox oncology, Medimmune, Altum, Dragonfly therapeutics, Takeda, National Comprehensive Cancer Network, NCI-CTEP, University of Texas MD Anderson Cancer Center, Turning Point Therapeutics, Boston Pharmaceuticals; travel support from Novartis, Pharmamar, ASCO, ESMO, Helsinn, Incyte. Consultancy/Advisory board: Helsinn, LOXO Oncology/Eli Lilly, R-Pharma US, INCYTE, QED pharma, Medimmune, Novartis, Relay Therapeutics, and Roche; and other support from Medscape. Funda Meric-Bernstam reports consulting fees from F. Hoffman-La Roche Ltd., Genentech Inc., Pfizer Inc. and sponsored research to the institution from Genentech Inc. The remaining authors have no relevant disclosures.

Received: Aug 28, 2021; Revision Received: Nov 13, 2021; Accepted: Nov 15, 2021

DiPeri TP, Demirhan M, Karp DD, et al. Corticosteroid-refractory myositis after dual BRAF and MEK inhibition in a patient with BRAF V600E-mutant metastatic intrahepatic cholangiocarcinoma. J Immunother Precis Oncol. 2022; 5:26–30. DOI: 10.36401/JIPO-21-18.

This work is published under a CC-BY-NC-ND 4.0 International License.

ABSTRACT

Intrahepatic cholangiocarcinoma is a rare malignancy, which is rich in actionable alterations. Genomic aberrations in the mitogen-activated protein kinase (MAPK) pathway are common, and BRAF exon 15 p.V600E mutations are present in 5–7% of biliary tract cancers (BTC). Dual inhibition of BRAF and MEK has been established for BRAF-mutated melanoma and lung cancer, and recent basket trials have shown efficacy of this combination in BRAF V600E-mutant BTCs. Here, we report on a patient with BRAF exon 15 p.V600E mutant metastatic intrahepatic cholangiocarcinoma who was started on BRAF and MEK inhibition with vemurafenib and combimetinib. Shortly thereafter, he developed debilitating myositis, which was refractory to corticosteroids, requiring therapeutic plasma exchange and intravenous immunoglobulin. We also review BRAF as a target in BTCs, relevant clinical trials, and adverse events associated with BRAF and MEK inhibition.

Keywords: cholangiocarcinoma, precision oncology, targeted therapy, myositis
INTRODUCTION

There has been growing interest in precision oncology, with the expectation that molecular profiling can help identify drivers of tumor growth, and thus, actionable alterations that can be targeted directly or indirectly with targeted therapy. It has been the hope that personalized cancer therapy with molecularly matched therapies will not only allow for greater antitumor efficacy but will also be less toxic. However, it should be noted that targeted therapies are associated with multiple adverse events, including those that are off-target, such as dermatologic reactions, hepatotoxicity, rhabdomyolysis, arthralgia, and ophthalmologic reactions as seen with BRAF and MEK inhibitors.[11–13]

Intrahepatic cholangiocarcinoma (ICC) is a rare malignancy that arises from the bile duct epithelial cells within the liver.[7] Unfortunately, many patients present with metastatic disease, and the 5-year survival for patients with unresectable ICC is less than 5–10%.[8,9] Increased molecular profiling of cholangiocarcinoma (CCA) has prompted evaluation of targeted therapies for these malignancies, which are rich in actionable mutations.[10] Large-scale sequencing studies have identified several targetable genetic alterations including FGFR2, ERBB2, IDH1, and BRAF, which have led to the development of various inhibitors currently under evaluation in multiple biomarker-selected clinical trials.[11–13]

BRAF, a serine/threonine protein kinase that activates the mitogen-activated protein kinase (MAPK) pathway, is an oncogenic driver in many human cancers.[14] Activating mutations at codon 600 results in constitutively active BRAF and aberrant MAPK signaling.[15] A recent multicohort basket study of the BRAF inhibitor vemurafenib in nonmelanoma BRAF V600E-mutant solid tumors in 172 patients with 26 unique cancer types, reported an overall response rate of 33% and median duration of response of 13 months.[16] Responses were observed in 13 unique cancer types, highlighting the importance of BRAF V600E as a driver. BRAF mutations are present in 5–7% of biliary tract cancers (BTC), and BRAF V600E-mutant ICC has been associated with worse overall survival.[15,17] Combination therapy with dual BRAF and MEK inhibition (BRAFi + MEKi) has been used to provide greater inhibition of the MAPK pathway and overcome resistance to BRAFi monotherapy.[18,19] Several case reports, and a recent phase II basket trial (NCT02034110), have shown responses with BRAFi + MEKi in patients with BRAF V600-mutant BTC.[19–21]

Here, we present a case of a man with BRAF V600E-mutant ICC who progressed on chemotherapy. He was then enrolled in the American Society of Clinical Oncology (ASCO) Targeted Agent and Profiling Utilization Registry (TAPUR) trial (ClinicalTrials.gov identifier: NCT02693535) and treated with vemurafenib and cobimetinib. Shortly thereafter, he developed debilitat-

CASE PRESENTATION

A 77-year-old man presented with metastatic ICC. Six months prior, he was diagnosed with a 6-cm right liver mass and underwent surgical resection, with pathology revealing CCA with sarcomatoid features (stage T1bN0M0). Relevant past medical history included use of rosvuvastatin at 40 mg by mouth (PO) once daily (QD). Genomic testing (Foundation One CDx) revealed a BRAF exon 15 p.V600E mutation along with CDKN2a loss, CDKN2b, PIK3CA H1047R, CDKN1A R48*, and PIM1 amplification. Subsequently, he received adjuvant capecitabine, which was discontinued after three cycles due to a drug-related rash. Restaging positron emission tomography–computed tomography revealed a 1.2-cm left upper lobe nodule and a biopsy specimen confirmed metastatic disease. He was transitioned to gemcitabine, cisplatin, and abraxane and received five cycles, with a best response of progressive disease. He was then enrolled in the TAPUR trial (ClinicalTrials.gov identifier: NCT02693535) based on his BRAF exon 15 p.V600E mutation and started on vemurafenib (960 mg PO twice daily [BID]) and cobimetinib (60 mg PO once daily [QD], 21 days on, 7 days off).

He first reported fatigue (grade 2) and anorexia (grade 1) 6 days after beginning treatment, and his cobimetinib dose was held the next week when his symptoms did not improve. On cycle 1 day 18, he presented with overwhelming fatigue (grade 2) and proximal upper or lower extremity weakness (grade 3), and was directed to the emergency department. Notably, no cutaneous lesions or rashes were observed. Admission labs were notable for elevated creatine kinase (CK) (3041 units/L), creatinine (1.66 mg/dL), transaminases (aspartate transaminase 137 units/L, alanine transaminase 68 units/L), alkaline phosphatase (362 units/L), aldolase (18.9 units/L), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP; 42, 53.6 mg/L), as well as several electrolyte derangements (potassium 2.7 mEq/L, sodium 135 mEq/L, calcium 8 mEq/L, phosphorous 2 mEq/L) and urine myoglobin more than 5000. Antinuclear antibody (ANA) titer was 1:160 with a speckled pattern. Autoantibody myositis panel and rheumatoid factor antibody (RF) was 1:160 with a speckled pattern. Autoantibody myositis panel and rheumatoid factor were within normal limits. Magnetic resonance imaging of the brain and spine were unremarkable. Cobimetinib, vemurafenib, and rosvuvastatin therapies were discontinued and methylprednisolone 80 mg PO BID was started given concern for a drug-related inflammatory or immune adverse event.

While his CK and Cr initially improved with intravenous (IV) fluids, he developed worsening muscle weakness with rising CK levels, which prompted initiation of high-dose pulse corticosteroids with methylprednisolone 500 mg intravenously three times daily (TID). He then underwent 5 days of therapeutic plasma exchange (PLEX) given concern for immune-mediated myositis (Figure). A biopsy procedure was performed of his left quadriceps, revealing severely distorted skeletal muscle with rare degenerative and necrotic fibers, macrophages,
rare B cells, and scattered T cells. His CK continued to rise, and he was started on a 4-day course of IV immunoglobulin (IVIG), which led to improvement of his CK levels and symptoms. Repeat ANA was 1:40 without ANA detected by immunofluorescence, CRP normalized, and ESR decreased to 25. Corticosteroids were tapered, and he was discharged home with improvement of his myositis (grade 2). Over the next several weeks, he reported worsening weakness requiring a wheelchair although his CK remained within normal limits. He unfortunately was unable to recover enough to receive additional anticancer therapy and died 1 month after discharge, 62 days after the last vemurafenib and MEKi treatment.

**DISCUSSION**

There is increasing awareness of BRAF V600E as a driver in several human cancers. A vemurafenib basket trial in BRAF V600E-mutant tumors reported an overall response rate of 33%, including two patients with CCA. Although myalgia is not uncommon with BRAFi + MEKi (14–19%), the diagnosis of myositis is much rarer, and was reported in only 1 of 247 patients enrolled in the coBRIM trial (ClinicalTrials.gov identifier: NCT01689519) evaluating the combination of vemurafenib and cobimetinib with the response secondary to MAPK pathway inhibition, in cancers other than CCA. However, even with targeted therapies that presumably hit the “Achilles heel” of the tumor, while relatively sparing the normal tissue, often there are adverse events.

Skeletal muscle-related adverse events have been reported with the use of MEKi monotherapy as well as the combination of BRAFi + MEKi (Table 1). Although myalgia is not uncommon with BRAFi + MEKi (14–19%), the diagnosis of myositis is much rarer, and was reported in only 1 of 247 patients enrolled in the coBRIM trial (ClinicalTrials.gov identifier: NCT01689519) evaluating the combination of vemurafenib and cobimetinib with V600E-mutant melanoma. Despite initial improvement of our patient’s CK and Cr with fluid resuscitation and corticosteroids, his symptoms worsened and CK levels continued to rise, which ultimately reversed only after PLEX and IVIG administration (Fig. 1).

There are several possible etiologies for myositis in this case, including immune-mediated necrotizing myositis, direct inhibitor effects on skeletal muscle, paraneoplastic syndromes, and statin-induced autoimmune myopathy. Oncogenic BRAF mutations have been associated with T cell suppression, and induction of the tumor–host immune response has been proposed as an off-target mechanism of MAPK inhibition. In several cancers, antigens have been identified that are morphologically similar to myoblasts, resulting in cross-reactivity of autoantibodies and resultant tissue damage. Interestingly, modulation of the FoxP3 transcription factor by MEKi has been proposed as a mechanism to reduce the activity of regulatory T cells. An amplified immune response secondary to MAPK pathway inhibition, in combination with cross-reactivity of autoantibodies, may explain the presentation of myositis in our case.
That being said, immune-mediated necrotizing myositis is often associated with antisignal recognition particle (SRP) antibodies and/or anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies, for which the former was normal, and the latter not evaluated. While the effects of MEK inhibition on normal myocytes has not been elucidated, inhibition may have effects on cell survival and homeostasis. A case report from Harrison et al. described a patient with metastatic melanoma on dabrafenib and trametinib who developed dermatomyositis refractory to corticosteroids but responded to IVIG. The absence of skin changes and anti-transcription intermediary factor 1 (TIF1) and/or anti-nuclear matrix protein (NXP) antibodies in our case make this diagnosis unlikely. Statin-induced autoimmune myopathy is also a consideration given our patient’s history of rosuvastatin use and necrotic muscle fibers on histopathology, although it is not commonly associated with infiltrating lymphocytes.

To our knowledge, this is the first report of steroid-refractory myositis in a patient receiving the combination of vemurafenib and cobimetinib, requiring PLEX and IVIG. It is essential for clinicians to be aware of skeletal muscle–related adverse events in the setting of dual BRAF and MEK inhibition.

REFERENCES

1. Binimetinib. Prescribing information. Array BioPharma Inc.; 2020. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/6c3408ac-d401-4925-8a03-26591abc240/spl-doc?hl=binimetinib. Revised October 2020. Accessed April 6, 2021.
2. Encorafenib. Prescribing information. Array BioPharma Inc.; 2020. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/235dfe38-0f0b-4037-b501-7a9f4294740c/spl-doc?hl=encorafenib.
3. Trametinib. Prescribing information. Novartis Pharmaceuticals Corporation; 2020. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/0002ad27-779d-42ab-83b5-bc65435412a1/spl-doc?hl=trametinib
4. Dabrafenib. Prescribing information. Novartis Pharmaceuticals Corporation; 2020. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/fee1e6b1-e1a5-4254-9fe-a70e08dbde6a/spl-doc?hl=dabrafenib
5. Cobimetinib. Prescribing information. Genetech, Inc.; 2018. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/c387579f-cced-4334-bd1e-7393ac1bd6e/spl-doc?hl=cobimetinib
6. Vemurafenib. Prescribing information. Genetech, Inc.; 2017. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/38eea320-7e0c-485a-bc30-98c3c45e2763/spl-doc?hl=vemurafenib
7. Putra J, de Abreu FB, Peterson JD, et al. Molecular profiling of intrahepatic and extrahepatic cholangiocarcinoma using next generation sequencing. Exp Mol Pathol. 2015;99:240–244.
8. Chong DQ, Zhu AX. The landscape of targeted therapies for cholangiocarcinoma: current status and emerging targets. Oncotarget. 2016;7:46750–46767.
9. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg. 2014;149:565–574.
10. Javle M, Bekaii-Saab T, Jain A, et al. Biliary cancer: utility of next-generation sequencing for clinical management. Cancer. 2016;122:3838–3847.
11. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. Hum Pathol. 2013;44:2768–2773.
12. Robertson S, Hyder O, Dodson R, et al. The frequency of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. Hum Pathol. 2013;44:2768–2773.
13. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF(V600)-mutant non-melanoma skin cancer: results from a phase II trial. Lancet Oncol. 2014;15:567–577.
14. Vemurafenib. Prescribing information. Genetech, Inc.; 2020. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/98c3c45e2763/spl-doc?hl=vemurafenib
15. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg. 2014;149:565–574.
16. Robertson S, Hyder O, Dodson R, et al. The frequency of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. Hum Pathol. 2013;44:2768–2773.
17. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF(V600)-mutant non-melanoma skin cancer. Lancet Oncol. 2014;15:567–577.
18. Vemurafenib. Prescribing information. Genetech, Inc.; 2017. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/38eea320-7e0c-485a-bc30-98c3c45e2763/spl-doc?hl=vemurafenib
19. Putra J, de Abreu FB, Peterson JD, et al. Molecular profiling of intrahepatic and extrahepatic cholangiocarcinoma using next generation sequencing. Exp Mol Pathol. 2015;99:240–244.
20. Chong DQ, Zhu AX. The landscape of targeted therapies for cholangiocarcinoma: current status and emerging targets. Oncotarget. 2016;7:46750–46767.
21. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg. 2014;149:565–574.
22. Robertson S, Hyder O, Dodson R, et al. The frequency of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. Hum Pathol. 2013;44:2768–2773.
23. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF(V600)-mutant non-melanoma skin cancer. Lancet Oncol. 2014;15:567–577.
24. Vemurafenib. Prescribing information. Genetech, Inc.; 2020. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/98c3c45e2763/spl-doc?hl=vemurafenib
25. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg. 2014;149:565–574.
26. Robertson S, Hyder O, Dodson R, et al. The frequency of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. Hum Pathol. 2013;44:2768–2773.
27. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF(V600)-mutant non-melanoma skin cancer. Lancet Oncol. 2014;15:567–577.
28. Vemurafenib. Prescribing information. Genetech, Inc.; 2020. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/98c3c45e2763/spl-doc?hl=vemurafenib
29. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg. 2014;149:565–574.
30. Robertson S, Hyder O, Dodson R, et al. The frequency of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. Hum Pathol. 2013;44:2768–2773.
31. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF(V600)-mutant non-melanoma skin cancer. Lancet Oncol. 2014;15:567–577.
32. Vemurafenib. Prescribing information. Genetech, Inc.; 2020. Accessed April 6, 2021. nctr-crs.fda.gov/fdlabel/services/spl/set-ids/98c3c45e2763/spl-doc?hl=vemurafenib
33. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg. 2014;149:565–574.
cholangiocarcinoma: dramatic clinical and radiological response with a confusing synchronic new liver lesion. *J Gastrointest Oncol*. 2017;8:E32–E38.

22. Zhu AX, Borger DR, Kim Y, et al. Genomic profiling of intrahepatic cholangiocarcinoma: refining prognosis and identifying therapeutic targets. *Ann Surg Oncol*. 2014;21:3827–3834.

23. Cohen Aubart F, Emile JJ, Carrat F, et al. Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). *Blood*. 2017;130:1377–1380.

24. Leijen S, Middleton MR, Tresca P, et al. Phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of the MEK inhibitor RO4987655 (CH4987655) in patients with advanced solid tumors. *Clin Cancer Res*. 2012;18:4794–4805.

25. Grimaldi AM, Simeone E, Festino L, Vanella V, Strudel M, Ascierto PA. MEK inhibitors in the treatment of metastatic melanoma and solid tumors. *Am J Clin Dermatol*. 2017;18:745–754.

26. Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2016;17:1248–1260.

27. Ebert PJR, Cheung J, Yang Y, et al. MAP kinase inhibition promotes T cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. *Immunity*. 2016;44:609–621.

28. Harrison SR, Tew A, Steven N, Fisher BA. Steroid refractory dermatomyositis following combination dabrafenib and trametinib therapy. *Rheumatology (Oxford)*. 2018;57:1497–1499.

29. Lieske NV, Tonby K, Kvale D, Dyrrhol-Riise AM, Tasken K. Targeting tuberculosis and HIV infection-specific regulatory T cells with MEK/ERK signaling pathway inhibitors. *PLoS One*. 2015;10:e0141903.

30. Anquetil C, Boyer O, Wenes N, Benveniste O, Allenbach Y. Myositis-specific autoantibodies, a cornerstone in immune-mediated necrotizing myopathy. *Autoimmun Rev*. 2019;18:223–230.

31. Gauci ML, Laly P, Leonard-Louis S, et al. Focal necrotizing myopathy with ‘dropped-head syndrome’ induced by cobimetinib in metastatic melanoma. *Melanoma Res*. 2017;27:511–515.

32. Babu S, Li Y. Statin induced necrotizing autoimmune myopathy. *J Neurol Sci*. 2015;351:13–17.

33. Schreuer M, Jansen Y, Planken S, et al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAF(V600)-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. *Lancet Oncol*. 2017;18:464–472.

34. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367:1694–1703.

35. Nakamichi S, Nokihara H, Yamamoto N, et al. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. *Invest New Drugs*. 2015;33:641–651.

36. Arend RC, Davis AM, Chmiczewski P, et al. EMR 20006-012: A phase II randomized double-blind placebo controlled trial comparing the combination of pimasertib (MEK inhibitor) with SAR245409 (PI3K inhibitor) to pimasertib alone in patients with previously treated unresectable borderline or low grade ovarian cancer. *Gynecol Oncol*. 2020;156:301–307.

37. Cohen RB, Aamdal S, Nyakas M, et al. A phase I dose-finding, safety and tolerability study of AZD8330 in patients with advanced malignancies. *Eur J Cancer*. 2013;49:1521–1529.

38. Heinzerling L, Eigentler TK, Fluck M, et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. *ESMO Open*. 2019;4:e000491.