Case Report

A case of class 3 *MEK1* mutated metastatic colorectal cancer with a non-durable tumor marker response to MEK and ERK inhibitors

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Abstract: Class 3 *MEK1* mutations disrupt the negative regulatory helix region of *MEK1* and drive constitutive activation of both pMEK and pERK that is independent of RAF and of MEK phosphorylation. Targeting MEK with trametinib resulted in mixed clinical responses in class 3 *MEK1* mutated Langerhans cell histiocytosis (LCH). The ERK inhibitor, ulixertinib, demonstrated limited anti-tumor activity in non-characterized *MEK1* mutated solid tumors, with 2 out 4 patients experiencing stable disease (SD). Here, we present the case of a 52-year-old female with metastatic colon cancer harboring a *MEK1*E102_I103del (class 3 mutation) who progressed on standard chemotherapy and showed no response to the MEK inhibitor trametinib, the ERK inhibitor ulixertinib, and the combination of ulixertinib and the anti-EGFR antibody panitumumab. Despite progressive disease (PD), the patient exhibited a steep but short-lived tumor marker response to MEK and ERK inhibition, suggesting the emergence of early mechanisms of resistance to MAPK pathway inhibition. This report presents the first case in the literature investigating a MEK inhibitor and an ERK inhibitor (alone and in combination with anti-EGFR therapy) in metastatic colorectal cancer harboring a class 3 *MEK1* mutation (E102-I103 deletion).

Keywords: *MEK1* mutation; MEK inhibitor; ERK inhibitor; anti-EGFR

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Case presentation

A 52-year-old female presented with obstructive symptoms and abdominal pain, which led to a diagnosis of descending colon adenocarcinoma with metastatic disease to the lungs, liver and retroperitoneal lymph nodes. Left hemicolectomy revealed a poorly differentiated adenocarcinoma with signet-ring and mucinous features. She received first-line chemotherapy with FOLFOX for 5 cycles with stable disease (SD) as best response. In the interim, next generation sequencing (NGS) of her primary tumor by FoundationOne® (Gene List: https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx, Foundation Medicine, Inc., Cambridge, MA, USA) revealed a microsatellite stable, *KRAS* and *NRAS* wild type, *BRAF* wild type, *IDH1* R132c [mutation allele frequencies (MAF) 22.18%] mutation, FANCG loss exons 5–14, *GNAS* R201H (MAF, 38.69%), and a*MEK1* (E102-I103del, MAF, 21.87%) mutation. Given the lack of *RAS* and *BRAF* mutations and the concerns about prior anastomotic micro-perforation, panitumumab was added to her treatment regimen. She progressed after an additional 4 cycles of FOLFOX plus panitumumab chemotherapy. Given her refractoriness to first-line chemotherapy and emerging case reports of *MEK1* mutated tumors responding to MEK inhibitor, she was treated with trametinib (1-3). She experienced a short-lived decline in CA19.9 (*Figure 1A*). Unfortunately, she had progressive disease (PD) on CT scan after 3 months of trametinib treatment. She was then

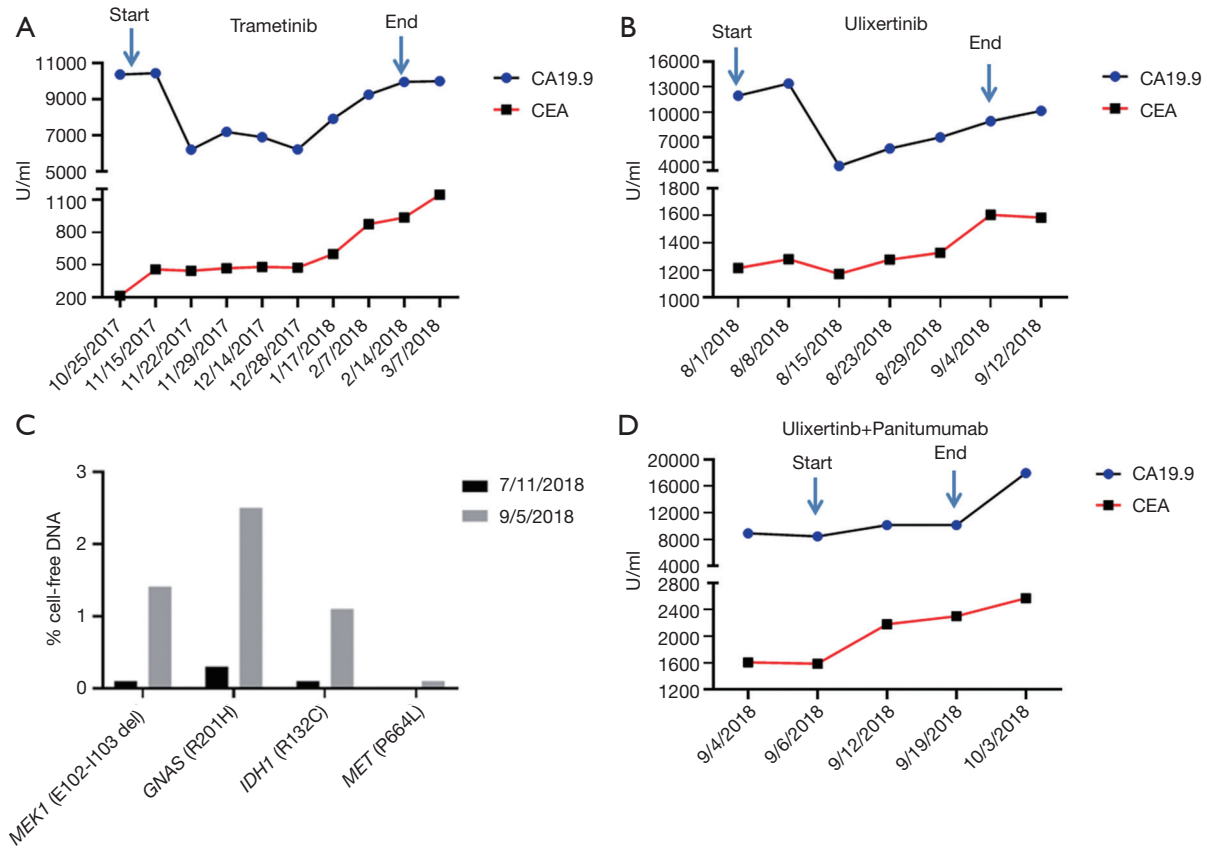

Figure 1 Tumor markers and cfDNA changes following treatment. (A) CA19.9 and CEA levels following trametinib treatment. Trametinib was started on 11/7/2017 and ended on 2/14/2018; (B) CA19.9 and CEA levels following ulixertinib treatment. Ulixertinib was started on 8/1/2018, and ended on 9/4/2018; (C) cfDNA alterations before and after ulixertinib monotherapy; (D) CA19.9 and CEA level following ulixertinib plus panitumumab treatment. Ulixertinib plus panitumumab were started on 9/6/2018 and ended on 9/19/2018. cfDNA, cell-free DNA.

treated with FOLFIRI plus bevacizumab with SD as best response, followed by PD at after 5 months of treatment. Given emerging pre-clinical data characterizing *MEK1* (E102_I103) mutation as a class 3 *MEK1* mutation with relative resistance to MEK inhibitors and with sensitivity to ERK inhibitors, we treated our patient on a single-patient Investigational New Drug (IND)-exempt clinical trial of the ERK inhibitor, ulixertinib (BVD-523) (4-6). The study was approved by City of Hope Investigational Review Board (IRB #18278). Ulixertinib was administrated orally twice-daily at the previously recommended phase II dose of 600 mg PO BID (6). Two weeks after initiation of ulixertinib, the patient experienced a more robust, but short-lived, decline in CA19.9 (*Figure 1B*). The treatment was well-tolerated with mild to moderate nausea, fatigue, and dry skin (grade 1). Unfortunately, she experienced a subsequent surge in tumor markers and radiographic progression following 6 weeks of treatment. Meanwhile, digital NGS of cell-free DNA (cfDNA) carried out by Guardant360 cfDNA assay (Gene List: http://www.guardant360.com/, Guardant Health, Redwood City, CA, USA) revealed an increased proportion of *MEK1* cfDNA (0.095589–1.41%), *GNAS* R201H cfDNA (0.3–2.5%), *IDH1* R132C cfDNA (0.1–1.1%), and *MET* (non-detectable–0.1%), with the detection of a synonymous *PIK3CA* mutation, which suggests increased tumor load and tumor evolution but without clear explanation of the resistance mechanisms (*Figure 1C*). Given the concern that the rapid acquired resistance was related to compensatory EGFR phosphorylation, we amended her clinical trial to allow for the combination of ulixertinib plus panitumumab. Following IRB approval and after obtaining patient consent, ulixertinib was continued at 600 mg PO BID in combination

with panitumumab 6 mg/kg given intravenously every 2 weeks. Unfortunately, this treatment was poorly tolerated with refractory nausea and vomiting requiring admission following 2 weeks of treatment. Imaging studies at the time of admission did not show any obstructive findings and her disease burden was noted to be unchanged in this short period of treatment. Given the intolerance to protocol treatment and lack of disease regression or tumor marker decline (*Figure 1D*) with ulixertinib plus panitumumab, the patient was taken off study. She was subsequently treated with trifluridine/tipiracil with rapid disease progression and death.

Discussion

Mutations in *MEK1* occur in approximately 1–2% of colorectal cancer patients, and have been characterized as oncogenic (7,8). Preclinical studies confirm that *MEK1* activating mutations are sufficient to transform intestinal epithelial cells and facilitate the formation of high-grade adenocarcinoma (9). *MEK1* mutations have been classified into 3 classes. Class 1 *MEK1* mutations are RAF-dependent and are the least activating. Class 2 *MEK1* mutations are activating in nature but can be upregulated further by upstream RAF. Class 3 *MEK1* mutations (ΔL98-I103, ΔI99-K104, ΔE102-I103, ΔI103-K104) lead to auto-phosphorylation of MEK which is independent of RAF and are associated with the highest level of downstream ERK phosphorylation (4). Class 3 *MEK1* mutations are mutually exclusive with other mutations that activate MAPK signaling, and are therefore considered driver mutations. In addition, class 3 mutations promote tumor formation in mice more efficiently than class 1 and class 2 mutations, suggesting that this class is the most oncogenic amongst *MEK1* mutations (4). Among solid tumors, *MEK1* mutations have been best characterized in non-small cell lung cancer (NSCLC), where class 2 mutations (K57N and Q56P) were the most common and were associated with a worse outcome in the setting of metastatic disease (10).

Gao *et al*. have previously demonstrated the relative resistance of class 3 *MEK1* mutations to MEK inhibition (4). Prior to Gao's report, we treated our patient with trametinib, and her disease indeed progressed after 3 months of trametinib. However, trametinib was associated with complete remission in a case of class 3 *MEK1* mutation (ΔE102-I103) Langerhans cell histiocytosis (LCH) and with PD in another class 3 *MEK1* mutation (ΔL98- K104) LCH patient (3,11). Complete responses to MEK inhibitors have also been described in two cases with histiocytic sarcoma and serous ovarian cancer, both harboring class 2 *MEK1* mutations (1,2).

Given this patient's resistance to multiple lines of chemotherapy and to trametinib, and in light of pre-clinical and clinical work suggesting benefit from ERK inhibition (4,6). We treated our patient with ulixertinib alone and added panitumumab to ulixertinib at the time of progression, on a single patient IND-exempt clinical trial. In line with our expectations, treatment with ulixertinib resulted a steeper decline in CA19.9 than with trametinib, but this response was short lived and disease progression was recorded four weeks after starting ulixertinib. CEA and CA19.9 tumor markers are often elevated in the setting of metastatic colorectal cancer. Comparative studies between CEA and imaging studies show a very strong correlation between CEA response and imaging response. Combining with the initial decline of CEA and subsequent rise in those markers, our results suggest an initial response with rapid onset of acquired resistance to ERK inhibition (12). Circulating cfDNA assays showed an emergent *PIK3CA* mutation at the time of resistance. This specific mutation causes a synonymous alteration which is not likely the underlying mechanism of resistance. Adding panitumumab to her treatment did not reverse this resistance, which suggests that the mechanism of resistance is not likely limited to compensatory EGFR phosphorylation. Unfortunately, no serial tumor biopsies were obtained during treatment, making the mechanistic evaluation of resistance more challenging.

Disparity in sensitivity to *BRAF* inhibitors between melanoma and colorectal cancer suggests primary tumor heterogeneity despite harboring identical *BRAF* mutations (13,14). This case highlights similar heterogeneity in response to MEK or ERK inhibitors within *MEK1* mutated tumors and highlights the need of better pre-clinical models to guide drug development in this rare molecularly defined subgroup. While similar mutations to our case have responded to MEK inhibition in the setting of LCH, no clinical response was noted in our case with either MEK inhibitors or ERK inhibitors +/– anti-EGFR. The initial response in tumor markers followed by rapid disease progression suggests rapid compensatory mechanisms that bypass in MEK and ERK inhibition in CRC. Future studies investigating ERK or MEK inhibitors in tumors harboring *MEK1* mutations should include robust correlative studies and PDX modeling to better delineate the various mechanisms of resistance and to develop better rational

combinations for this patient population.

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None.

Footnote

Conflicts of Interest: M Fakih: Amgen [Honoraria, Advisory/Consultancy, Speaker Bureau/Expert Testimony, Research Grant (Institution)], Array (Advisory/Consultancy), Bayer (Advisory/Consultancy), Astra Zeneca [Research Grant (Institution)], Novartis [Research Grant (Institution)]. C Wang, J Sandhu have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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