

Impressive response to dual *BRAF* and MEK inhibition in patients with *BRAF* mutant intrahepatic cholangiocarcinoma—2 case reports and a brief review

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Abstract: Intrahepatic cholangiocarcinoma (ICC) typically presents at an advanced stage and is associated with a poor oncological outcome. The median survival for metastatic ICC is less than 1 year with standard chemotherapy. ICC is associated with distinct oncogenic drivers including *IDH* (isocitrate dehydrogenase), *HER-2* (human epidermal growth factor 2), and *BRAF* (v-Raf murine sarcoma viral oncogene homolog B), which may benefit from matching targeted therapies. Hereby we report 2 cases of *BRAF* V600E refractory ICC treated with dual *BRAF* and MEK inhibitors (dabrafenib and trametinib) with excellent clinical and radiological response to therapy and with protracted duration of disease control. Our first patient achieved CR (complete remission) at 6 months of treatment with ultimate disease progression at 9 months. The second patient achieved a PR (partial response) at 2 months from starting treatment and remains progression free at 5 months. Our results confirm the activity of dual *BRAF* and MEK targeting in *BRAF* mutated ICC, adding further support to 3 additional case-reports in the literature. Dual targeting appears superior to other case reports with *BRAF* inhibition alone and appear favorable to historic data with cytotoxic chemotherapy. Given the poor outlook and refractoriness of *BRAF* mutant ICC, future studies should focus on early integration of *BRAF*/MEK inhibition.

Keywords: Intrahepatic cholangiocarcinoma (ICC); *BRAF*; MEK; dabrafenib; trametinib

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Introduction

Molecular analysis in patients with cholangiocarcinoma has been studied increasingly and has shown marked diversity in the frequency of targetable oncogenic driver mutations. One such aberration is mutation in *BRAF* (v-Raf murine sarcoma viral oncogene homolog B) which is one of the downstream signals in MAPK (Mitogen-activated protein kinases) pathway. Here we report 2 cases of *BRAF* mutant intrahepatic cholangiocarcinoma (ICC) refractory to initial chemotherapy treated with dual *BRAF* and MEK inhibition exhibiting excellent durable clinical and radiological response.

Case presentation

Case 1

A 49-year-old female presented with abdominal bloating and increasing discomfort in June 2014. She was evaluated by imaging and was found to have a large left lobe liver tumor. Fine needle aspiration cytology (FNAC) was consistent with adenocarcinoma. Her CA19-9 (carbohydrate antigen 19.9) and carcinoembryonic antigen (CEA) serum tumor markers and liver function tests were unremarkable. A [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan showed a left lobe liver mass

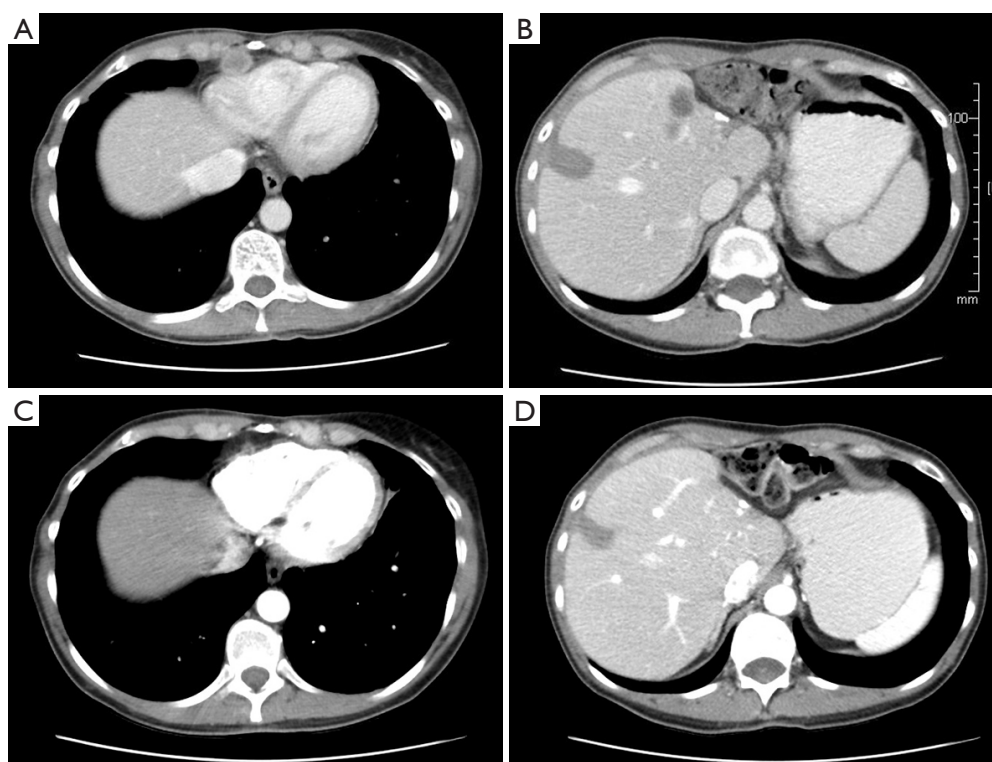


Figure 1 BRAF mutant intrahepatic cholangiocarcinoma (ICC) (case 1). (A) CT showing enlarged pericardial lymphadenopathy before dabrafenib + trametinib; (B) CT showing liver recurrence at hepatectomy margin before dabrafenib + trametinib. Note the RFA site in the right lobe of liver; (C) CT showing resolution of pericardiac lymph node after 5 months of dabrafenib + trametinib; (D) CT showing complete response in hepatic recurrence after 5 months of dabrafenib + trametinib.

with no evidence of extra hepatic disease. Colonoscopy was unremarkable. She underwent a left hepatectomy with dissection of celiac nodes and cystic duct in July 2014. Post operative histopathological examination revealed a 7.3-cm moderately differentiated ICC, with direct tumor invasion to local adjacent extra hepatic structures, perineural invasion, and with 3 out of 4 positive lymph nodes (Tumor Node Metastasis stage pT3N1—Stage IVA). No loss of mismatch repair protein (MMR) expression was noted by immunohistochemistry. In view of her high risk of disease recurrence, she received five 3-week cycles of gemcitabine and cisplatin adjuvant chemotherapy. Repeat imaging after cycle 5 (4 months) revealed a new 1 cm right liver lobe lesion with new periportal and portacaval nodes and a pericardial lymph node enlargement. She underwent radiofrequency ablation (RFA) to the liver lesion and was switched to second line single-agent capecitabine. Repeat computerized tomography (CT) scan following 3 cycles of capecitabine (2 months) revealed new liver lesions and progressive lymph node enlargement in the pericardial region (*Figure 1A,B*).

Foundation One comprehensive genomic analysis was performed on her original resection specimen and confirmed a *BRAF V600E* mutation. She was started on dabrafenib 150 mg PO BID (twice a day) and trametinib 2 mg PO QD (once a day) in May 2015. Follow-up imaging studies confirmed a partial response after 6 weeks of treatment and a complete clinical response after 5 months of treatment (RECIST 1.1) (*Figure 1C,D*). At 9 months of treatment, CT imaging confirmed recurrence of disease in the pericardial node and periportal/portacaval lymph nodes and new right pleural disease. Treatment with dabrafenib and trametinib was discontinued.

Case 2

A 71-year-old lady presented with vague right sided abdominal discomfort of 3 to 4 months duration with associated anorexia and weight loss in August 2015. Her past medical history was significant for cardiac dysrhythmia requiring pacemaker placement and mild chronic obstructive

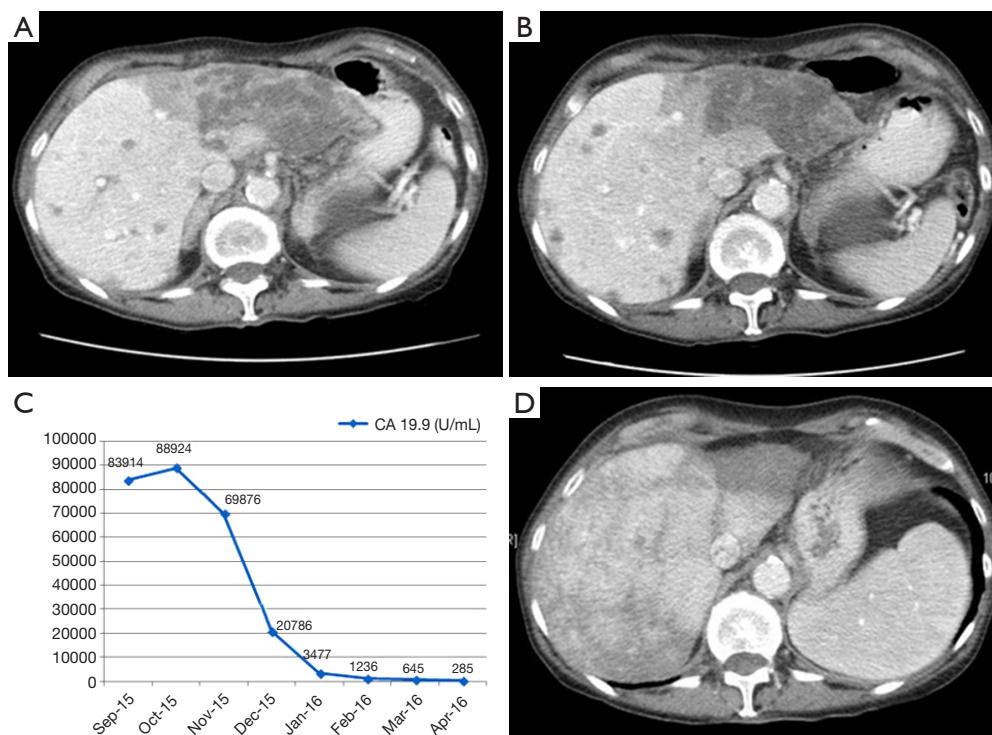


Figure 2 BRAF mutant intrahepatic cholangiocarcinoma (case 2). (A) CT showing hepatic cholangiocarcinoma with predominant left lobe disease at baseline; (B) CT after 3 cycles of gemcitabine plus cisplatin chemotherapy showing unchanged left lobe liver lesion with increased number of right lobe liver lesions; (C) CA19.9 response dabrafenib + trametinib; (D) CT showing marked regression of left lobe liver lesion and complete response to right lobe lesions following 5 months of dabrafenib + trametinib. Note: Increased vascularity corresponding to probably worsening chronic liver disease.

pulmonary disease (COPD). CT scan of the abdomen and pelvis showed a 7.8 cm infiltrative mass in the left lobe of liver and other too numerous to count smaller metastases in both lobes of liver (August 2015, *Figure 2A*). CA19.9 levels were elevated at 84,000 U/mL. Her liver enzymes and other biochemical parameters were unremarkable. Colonoscopy and Esophagogastroduodenoscopy (EGD) were unremarkable. FNA biopsy was consistent with ICC, with CK7+, CK19+, CK20-, CDX.2-, and TTF1-. She received gemcitabine and cisplatin chemotherapy for 3 cycles followed by re-staging CT scans, which confirmed progressive disease in the liver (November 2015, *Figure 2B*). Foundation One was performed on her initial diagnostic biopsy and confirmed a *BRAF V600E* mutation. She was started on dabrafenib 150 mg PO BID and trametinib 2 mg PO QD starting November 2015. Her CA19.9 levels dropped dramatically in the next six weeks (*Figure 2C*). Her last scan was done 5 months after initiation of *BRAF/MEK* inhibitors (April 2016, *FIG2d*) and confirms a partial response to treatment.

As of this report, the patient continues on treatment with ongoing clinical benefit.

Discussion

Cholangiocarcinoma (CCA) is one of the most fatal malignancies in the field of pancreatico-hepatobiliary tumors. Based on the SEER database, the 5-year overall survival is 15% and 2% for stage I (localized) and stage IV disease, respectively (1). The median survival of metastatic CCA is approximately one year with currently approved systemic therapies (2). There is an unmet need for new strategies and treatment options for metastatic CCA. One such strategy relies on the stratification of cholangiocarcinoma into distinct molecular subgroups, with matching targeted therapies. These molecular subgroups include *BRAF*, *ERBB2*, *IDH1 & 2* and *FGFR* aberrations (3). These molecular aberrations have been shown to be targetable, and are the subject of several ongoing or planned clinical trials. In this reports, we focus

on two cases of ICC with *BRAF* mutation and demonstrate impressive clinical activity for a combination of *BRAF* and MEK inhibitors, dabrafenib and tramatenib.

BRAF mutations are more common in ICC than extrahepatic cholangiocarcinoma or gallbladder cancer (4,5). The frequency of *BRAF* mutations in ICC have ranged between 1% to 22% among various cases series or population studies. The frequency appears to be underestimated when assessed by immunohistochemistry studies in comparison to PCR (6,7). In addition, the variations in the reported frequency may be related to differences in PCR techniques and Next Generation Sequencing (NGS) as well as distinct differences in the study populations. Irrespective of the true frequency, *BRAF* mutant cholangiocarcinoma appears to be a distinct molecular subtype of biliary cancers that can be associated with aggressive behavior and chemotherapy resistance, as demonstrated in our cases. The targeting of this subgroup of patients with single agent *BRAF* inhibitors has been associated with modest clinical responses and short duration of disease control. In a study by Hyman *et al.*, single agent vemurafenib was associated with a 12% objective response rate in *BRAF* mutant cholangiocarcinoma (1 out of 8 patients had PR) (8). Several other solid tumors with *BRAF* mutation have shown a benefit from combining *BRAF* and MEK inhibitors. Randomized phase III clinical trials have shown superiority of *BRAF* plus MEK inhibitors to *BRAF* inhibitors alone in *BRAF* mutant melanoma (9). In addition, a study of dabrafenib plus tramatenib shows more favorable responses and progression free survival in comparison to another study with vemurafenib alone in patients metastatic *BRAF* mutant colorectal cancer (10).

In view of improved efficacy of dual *BRAF* and MEK inhibition in melanoma and colorectal cancer, we elected to treat our patients with *BRAF* mutant ICC with a combination of dabrafenib and tramatenib. Both cases were characterized by refractoriness to first-line standard chemotherapy with gemcitabine and cisplatin and with aggressive clinical behavior. Dramatic and durable responses to dabrafenib and tramatenib were recorded and included a complete clinical response and an ongoing partial response. Our results are in line with 3 additional case reports of dabrafenib and tramatenib in *BRAF* mutant ICC. These include 2 cases with a clinical benefit from MDACC (not detailed) and one case with a PR lasting more than 8.5 months from Penn University (11,12). While ideal, the conduct of future conclusive first-line phase III randomized clinical trials of dual *BRAF*/MEK inhibitors

against gemcitabine plus cisplatin will be challenging. However, several Basket studies are currently evaluating combinations of *BRAF* and MEK inhibitors in non-melanoma and non-colorectal cancer *BRAF*-V600E mutated tumors (NCT02034110, NCT01713972, NCT01902173). Additional data from these prospective clinical trials will help confirm the activity of dual MEK/*BRAF* inhibition as a standard approach in *BRAF*-mutant cholangiocarcinoma.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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