# Gastrointestinal perforation following dabrafenib and trametinib administration in non-small cell lung carcinoma with BRAF V600E mutation: a case report and literature review

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**Research Article**

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## Abstract

Gastrointestinal perforation related to mitogen-activated protein kinase kinase (MEK) inhibitors has been reported previously; however, there has been no case report of such a condition in patients with non-small cell lung cancer (NSCLC). Herein, we report a case of small intestinal perforation secondary to dabrafenib and trametinib administration, but not related to tumor regression. A 62-year-old man with non-small cell lung cancer harboring BRAF V600E mutation was treated with dabrafenib and trametinib. Four months after the initiation of treatment, a small intestinal perforation was diagnosed. Dabrafenib and trametinib rechallenge was performed after gastrointestinal perforation. The patient responded well to therapy and did not experience recurrence of gastrointestinal perforation. To the best of our knowledge, this is the first report of gastrointestinal perforation in a patient with NSCLC treated with a MEK inhibitor. The mechanism and risk factors of trametinib-induced perforation are currently unknown. Physicians should be aware of such severe gastrointestinal side effects of trametinib.


## Introduction

V-raf murine sarcoma viral oncogene homolog B1 (BRAF) is a kinase positioned downstream of RAS in the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway [1]. Mutations in BRAF are most seen in melanomas, colon cancers, and thyroid cancers [2]. Among non-small cell lung cancers (NSCLCs), the frequency of BRAF mutations is relatively low at 1–3% of cases, with approximately half of them harboring the BRAF V600E mutation [1].

Dabrafenib is a potent kinase inhibitor of BRAF, selective for the V600E mutation. Trametinib is an inhibitor of mitogen-activated protein kinase kinase 1/2 (MEK1/2). Preclinical data suggest that inhibition of MEK suppresses the growth of tumors driven by BRAF mutations [3]. In clinical trials, combination therapy with dabrafenib plus trametinib showed high overall response rates in both previously treated and untreated patients with metastatic and *BRAF* V600E-positive NSCLC [4, 5]. Therefore, in the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines, dabrafenib plus trametinib is a standard therapy for stage Ⅳ NSCLC patients with BRAF V600E mutations [6, 7].

However, severe gastrointestinal toxicities of MEK inhibitors, such as gastrointestinal perforation, have been reported in melanoma and oral cavity squamous cell carcinoma patients [8–11]. Herein, we report a case with NSCLC who developed gastrointestinal perforation secondary to MEK inhibitor treatment.

## Case Report

A 62-year-old Japanese man presented to our hospital with upper abdominal pain. He was a former smoker, and had no history of drug allergy. He had no particular previous medical history other than *Helicobacter pylori* infection. A chest and abdominal computed tomography (CT) scan with contrast agent showed a mass in the right lower lobe of the lung, wall thickening of the jejunum, and swelling of the lymph nodes around the jejunum. A bronchoscopy was performed and pathological examination showed a poorly differentiated adenocarcinoma. Then, a small intestinal endoscopy was performed. An ulcer was discovered in the jejunum. The mucosal surface around the lesion was normal, which suggested a metastatic tumor. Pathological examination of a biopsy from the intestinal ulcer showed a poorly differentiated adenocarcinoma. Taken together, we diagnosed the patient as having lung adenocarcinoma with multiple distant metastases (cT2bN0M1c, stage Ⅳb, epidermal growth factor receptor mutation negative, anaplastic lymphoma kinase fusion negative, and c-ros oncogene 1 fusion negative) [12]. We initiated four courses of cisplatin (75 mg/m²) plus pemetrexed (PEM 500 mg/m²) as first-line therapy, followed by one cycle of PEM maintenance therapy. Four months after treatment initiation, a contrast-enhanced CT revealed intestinal lymphadenopathy and tumor enlargement, which we considered as progressive disease [13].

We then explored whether the BRAF V600E mutation was involved therein. Analysis of the lung lesion biopsy revealed the presence of this mutation, and we initiated treatment with the combination of 300 mg dabrafenib and 2 mg trametinib as second-line therapy. The Eastern Cooperative Oncology Group performance status of the patient was 1. A CT scan after 6 weeks of treatment revealed tumor regression, which we considered a partial response (PR) [13]. The patient showed grade 1 fever, but no diarrhea or abdominal pain, and there were no other side effects [14].

He presented to our hospital 4 months after the commencement of dabrafenib and trametinib with abdominal pain and vomiting. A CT scan revealed bowel perforation, free air, and ascites (Fig. 1). Emergent abdominal surgery was performed, revealing a perforation in the jejunum (Fig. 2a, red arrow). A tumor was found distant from the perforation and adherent to the mesentery of the sigmoid colon (Fig. 2a, yellow arrow). The affected region of the small intestine was resected.

From the pathological analysis, there was no evidence of malignancy at the perforation site (Fig. 2b). On the anal side, we found tumor cell proliferation from the mucosa to the submucosa, which suggested metastatic lung cancer (Fig. 2c, enclosed in yellow arrows). We examined

the remaining intestinal specimen; however, there were no abnormal findings, such as ulceration, scarring, intestinal fragility, and blood vessel abnormality. The patient recovered and was discharged 16 days after the surgery. He resumed dabrafenib and trametinib therapy (same doses) 32 days post-surgery, and experienced no recurrence of gastrointestinal perforation. Overall, his best response was deemed a PR, and his progression-free survival was 439 days.

## Discussion

This report describes a case of small intestinal perforation secondary to dabrafenib and trametinib administration. Severe gastrointestinal toxicities of MEK inhibitors, such as gastrointestinal perforation and colitis, have been reported in melanoma patients in clinical trials and case reports. In a phase Ⅱ study of patients with neuroblastoma RAS viral oncogene homolog (NRAS)-mutated advanced melanoma treated with binimetinib (MEK162, a potent, selective inhibitor of MEK1 and MEK2), one (3%) of 30 patients in the NRAS-mutated group had a small intestinal perforation [10]. In another retrospective analysis of patients with melanoma treated with MEK inhibitors (cobimetinib, trametinib, or binimetinib), two (1.7%) of 117 patients developed colonic perforations [8].

We searched PubMed for related articles published before September 2020. The clinical features of the patients in previously reported clinical trials and case reports are summarized in Table 1 [8–11]. Among these cases, four were of melanoma, one oral cavity squamous cell carcinoma, and our case NSCLC. The intervals between the initiation of MEK inhibitors and the onset of perforation ranged from 7 days to 5.5 months. Four cases received trametinib, one case received cobimetinib, and another case received binimetinib. In two of the six cases, the patient had a history of intestinal disease. Therefore, a history of intestinal disease could be a possible risk factor for gastrointestinal perforation.

Importantly, in this case, the perforation occurred in a non-tumor area, and was not related to tumor regression. Some previous reports suggested that MEK inhibitors block the Ras-ERK-MEK pathway; this increases cell proliferation and induces mucosal damage leading to severe gastrointestinal toxicity [8]. Clinically, in this patient, metastasis to the small intestine caused bowel obstruction, which could have partly caused the bowel perforation. However, we believe that mucosal damage from trametinib was the main reason for the perforation based on previously reported cases and the clinical course.

There are few case reports describing rechallenge with MEK inhibitors after gastrointestinal perforation, and we did not know whether we could successfully rechallenge after gastrointestinal perforation had occurred. In this case, we rechallenged with dabrafenib and trametinib, as his tumor was well-controlled by tyrosine kinase inhibitors, and there was no apparent fragility or abnormality in his resected tissue. Fortunately, the patient did not experience recurrence of gastrointestinal perforation until we finished the administration of dabrafenib and trametinib, and a good therapeutic effect was achieved thereafter. The precise mechanism and risk factors of MEK inhibitor-induced gastrointestinal perforation are currently unclear, and the matter of rechallenge is inconclusive. Further study is warranted to understand this adverse effect.

## Conclusion

Physicians should be wary of secondary gastrointestinal toxicities such as perforation in NSCLC patients carrying BRAF V600E mutations while treating them with MEK inhibitors.

## Abbreviations


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### Competing interests

Dr. Sato and Dr. Tomii have received lecture fees from Novartis Pharma K.K. (Tokyo, Japan). All remaining authors have no conflicts of interest to declare. We wish to confirm that there are no other known conflicts of interest associated with this publication. Further, there was no significant financial support for this work that could have influenced its outcome.

### Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Consent for publication

Informed consent was obtained from the patient.

### Availability of data and materials

All related datas are presented in this paper, further inofrmation or datas are available on a reasonable request.

### Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yuri Shimada, Yuki Sato, Ryo Tachikawa and Shigeo Hara. The first draft of the manuscript was written by Yuri Shimada and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Declarations

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# Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yuri Shimada, Yuki Sato, Ryo Tachikawa and Shigeo Hara. The first draft of the manuscript was written by Yuri Shimada and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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## Table

Table 1. Characteristics of patients with gastrointestinal perforation secondary to MEK inhibitor treatment

| | Age/Sex | Underlying disease | Onset | MEK inhibitor | Concomitant antitumor agent | Perforation site | Intestinal metastasis presence or absence | History of intestinal diseases | Rechallenge | Outcome | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 49/F | melanoma | 5.5 months | cobimetinib | vemurafenib | large intestine | unknown | ulcerative colitis | no | survival | [8] |
| 2 | 63/M | melanoma | 7 days | trametinib | dabrafenib | large intestine | unknown | diverticulum of large intestine | no | survival | [8] |
| 3 | 63/F | melanoma | 2 months | trametinib | dabrafenib | small intestine | presence | no | rechallenge | survival | [9] |
| 4 | unknown | melanoma | unknown | binimetinib | no | small intestine | unknown | unknown | unknown | unknown | [10] |
| 5 | unknown | oral cavity squamous cell carcinoma | 7 days | trametinib | no | duodenum | unknown | unknown | unknown | unknown | [11] |
| 6 | 62/M | non-small cell lung cancer | 4 months | trametinib | dabrafenib | small intestine | presence | no | rechallenge | survival | our case |

## Figures

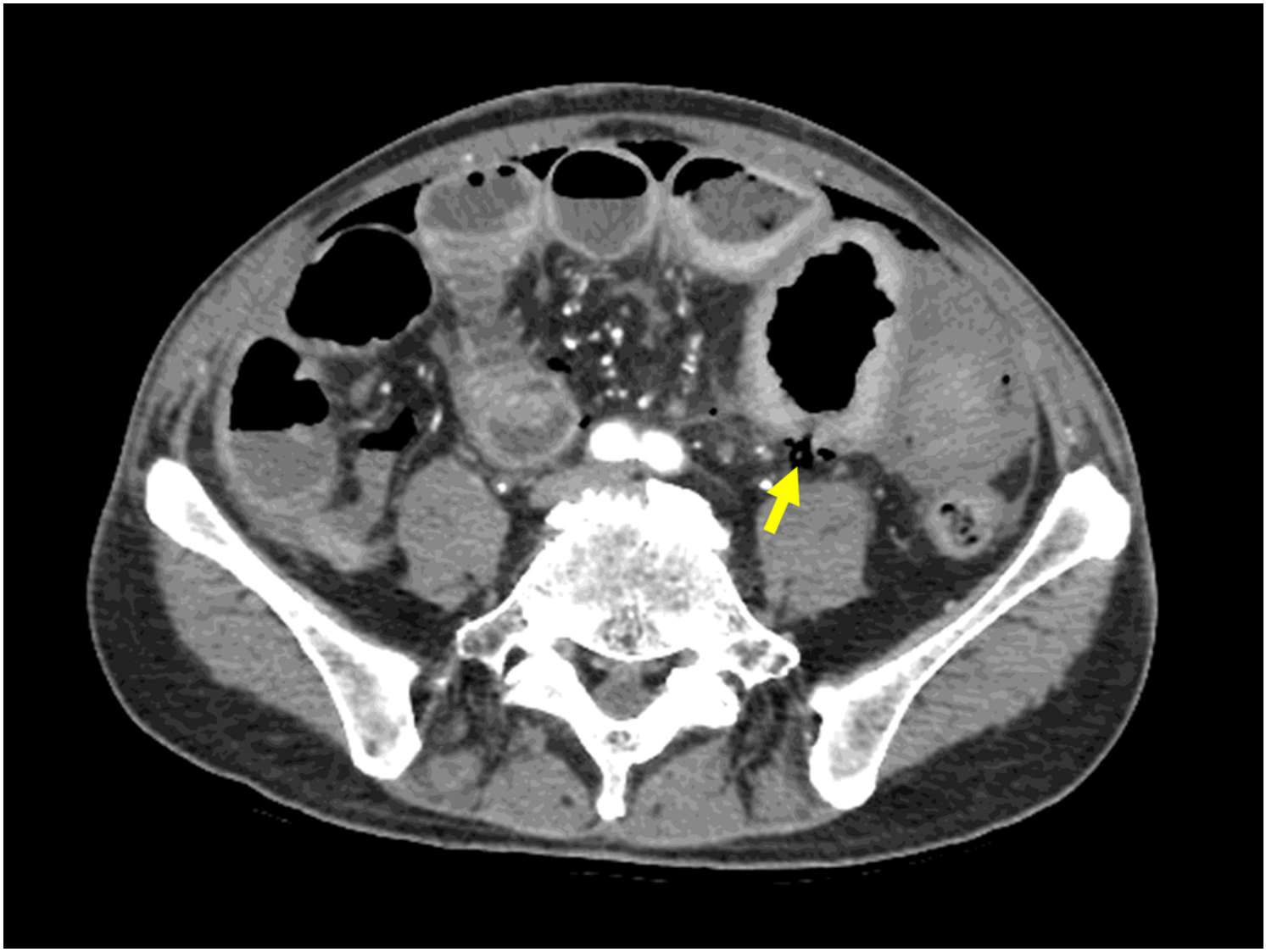

**Figure 1**

Computed tomography (CT) scans 4 months after the commencement of dabrafenib and trametinib therapy shows perforation in the small intestine (yellow arrow).

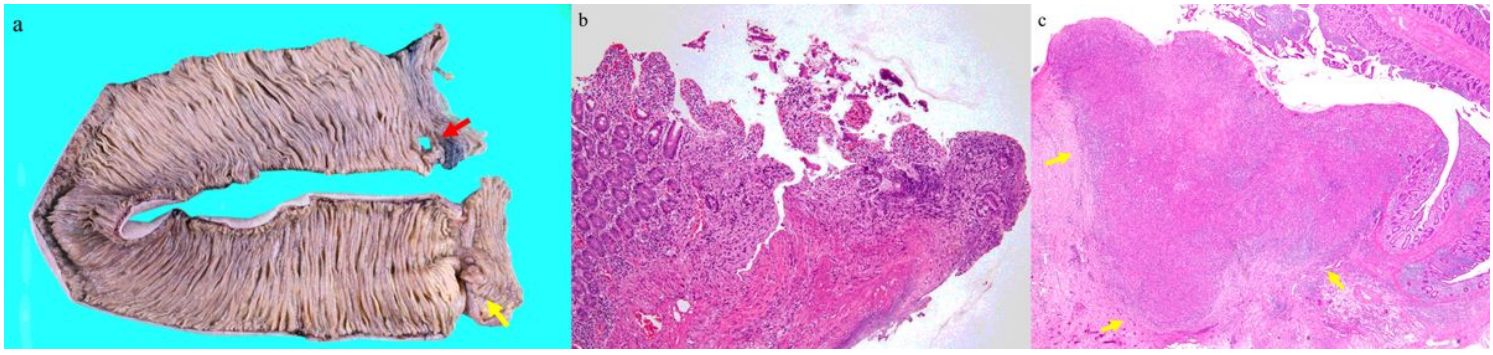


**Figure 2**

Surgical specimen and histopathology of the resected lesion (a) Surgical specimen of the resected lesion Perforation in the jejunum was found at 10 cm from the ligament of Treitz (red arrow). A tumor was found in the jejunum at 60 cm from the ligament of Treitz, and adhering to the mesentery of the sigmoid colon (yellow arrow). (b) Histopathology of the specimen on the oral side There were no tumor cells in the perforation and jejunum epithelium (hematoxylin and eosin; magnification, 100×). (c) Histopathology of the specimen on the anal side There were proliferating tumor cells (enclosed in yellow arrows) from the mucosa to the submucosa (hematoxylin and eosin; magnification, 20×).