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Case Report

Precision Oncology in Duodenal Adenocarcinoma: A Case of Metastatic *BRAF* V600E-mutant Disease Treated with Encorafenib, Cetuximab, Chemotherapy, and Immunotherapy

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Abstract

Duodenal adenocarcinoma is a rare malignancy that is often managed with protocols extrapolated from colorectal cancer (CRC) due to limited disease-specific evidence. We present the case of a 28-year-old female with metastatic *BRAF* V600E-mutant, human epidermal growth factor receptor 2 (HER2)-positive, and programmed death-ligand 1 (PD)-positive duodenal adenocarcinoma. After progression on chemotherapy, anti-PD-1 immunotherapy, and anti-HER2 targeted therapy, she received a combination of encorafenib, cetuximab, folinic acid, 5-fluorouracil, and irinotecan, and atezolizumab, which resulted in marked regression of hepatic, lymphatic, and ovarian metastases. This case illustrates the potential value of comprehensive genomic profiling and suggests that CRC-derived targeted therapies may be considered in patients with small bowel adenocarcinoma with similar molecular alterations.

Keywords: *BRAF* V600E, case report, duodenal neoplasms, encorafenib

Introduction

Duodenal adenocarcinoma is a rare malignancy accounting for <1% of all gastrointestinal cancers.[1,2] It often presents with nonspecific symptoms, leading to delayed diagnosis and poor prognosis in advanced cases. The molecular landscape of small bowel adenocarcinoma (SBA) remains incompletely characterized, and systemic therapy is largely extrapolated from colorectal cancer (CRC) protocols due to limited evidence.[3] We report the case of a 28-year-old female with metastatic *BRAF* V600E-mutant, human epidermal growth factor receptor 2 (HER2)-positive, and programmed

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death-ligand 1 (PD-L1)-positive duodenal adenocarcinoma who had a sustained response to a tailored regimen of chemotherapy, immunotherapy, and targeted therapies, including encorafenib and cetuximab.

Case Report

A 28-year-old female with no prior medical disease or relevant family history presented with upper abdominal pain, decreased appetite, and unintentional weight loss for months. Physical examination revealed epigastric tenderness without palpable masses. Endoscopy revealed a mass in the second portion of the duodenum, and a biopsy confirmed duodenal adenocarcinoma. Computed tomography revealed hepatic metastases and regional lymphadenopathy [Figure 1]. The clinical stage was cT3N1M1. Immunohistochemistry (IHC) demonstrated proficient mismatch repair, with preserved expressions of MLH1, MSH2, MSH6, and PMS2. IHC also showed the overexpression of HER2 (IHC 2+) as confirmed by fluorescence *in situ* hybridization (FISH) amplification and positivity for PD-L1 with a combined positive score of 5 using the 28-8 clone. First-line treatment with capecitabine and oxaliplatin (CAPOX) plus nivolumab was initiated in September 2024.

Follow-up imaging in November 2024 showed a partial response with regression of the primary duodenal lesion and hepatic metastases. However, she subsequently developed obstructive symptoms requiring endoscopic placement of a duodenal stent, a common bile duct (CBD) stent, and a pancreatic duct stent. Imaging in January 2025 demonstrated disease progression with enlarged hepatic metastases and newly developed peritoneal seeding, indicating a progression-free survival (PFS) of approximately 4 months for the first-line nivolumab plus CAPOX regimen. She then received two cycles of second-line trastuzumab plus CAPOX and nivolumab; however, the disease still progressed with new ovarian metastases [Figure 2a and b], with a PFS of approximately 1.5 months for the second-line regimen. Repeat endoscopy showed tumor ingrowth into the pre-existing duodenal and CBD stents, causing luminal obstruction. A new duodenal stent was placed, and biopsy reconfirmed HER2 positivity (IHC 2+).

Comprehensive genomic profiling (CGP, ACTOnco®) of tumor tissue revealed *BRAF* V600E (variant allele frequency [VAF]: 33.3%), *TP53* C141Y (VAF: 23.9%), *MYC* and *CD79B* amplifications (copy number: 11 and 7, respectively), microsatellite stable (MSS) status, and low tumor mutational burden (1.3 mutations/Mb). Circulating tumor cell (CTC) profiling showed high expressions of vascular endothelial growth factor receptor 2, fibroblast growth factor receptor 3, PD-L1 (13.64%), and *BRAF* V600E (26.32%) [Figure 3], but low epidermal growth factor receptor (EGFR) and HER2 expressions. Based on these findings, third-line therapy with encorafenib, cetuximab, atezolizumab, and folinic acid, 5-fluorouracil, and irinotecan 9 (FOLFIRI) was initiated in March 2025. The treatment was well tolerated, with improved gastrointestinal symptoms and nutritional status. No grade ≥3 adverse events occurred. Imaging at 2 months showed marked regression of the hepatic, lymphatic, and ovarian metastases [Figure 2c and d], along with significant decreases in serum tumor markers [Figure 4]. She has now been on third-line therapy for 2 months with no disease progression and is still alive; a graphical timeline of the treatment course is presented in Figure 5.

Discussion

SBA is an uncommon gastrointestinal malignancy, with duodenal adenocarcinoma being the most prevalent subtype.[4] Despite a rising incidence, SBA remains a poorly understood malignancy, and the optimal systemic treatment for advanced disease is not well established. Current recommendations are largely based on retrospective data, with few prospective studies available. Most regimens are extrapolated from CRC protocols and often include combinations of oxaliplatin, irinotecan, 5-fluorouracil, folinic acid, and bevacizumab.[5]

In our case, CAPOX plus nivolumab was selected as the first-line therapy. This decision was supported by PD-L1 positivity (CPS 5, Dako 28-8 assay) and evidence from the CheckMate 649 and ATTRACTION-4 trials, which demonstrated the benefits of immunotherapy in PD-L1-positive upper gastrointestinal cancers.[6,7] Upon disease progression, trastuzumab was added to CAPOX and nivolumab based on the rationale of the KEYNOTE-811 trial,[8] but no clinical response was observed. Targeted therapies were reserved for later lines and guided by findings from CGP and CTC profiling, which identified a *BRAF* mutation and PD-L1 expression (13.6%). These findings supported a shift to third-line therapy with a combination of encorafenib, cetuximab, atezolizumab, and chemotherapy, which resulted in a marked and durable response.

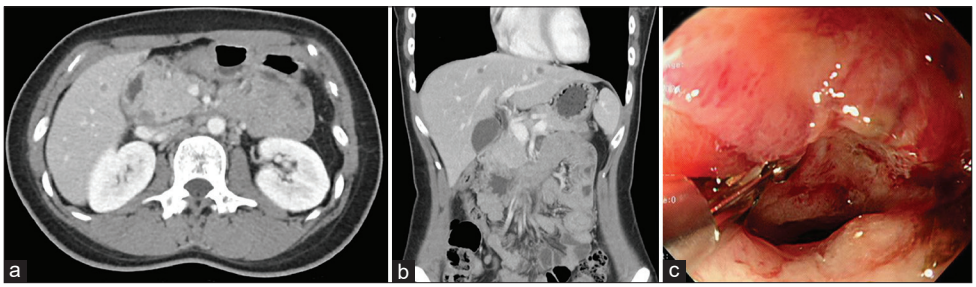

Figure 1: Initial imaging of metastatic duodenal adenocarcinoma. (a) Computed tomography (CT) demonstrating a primary duodenal mass. (b) CT showing liver metastases. (c) Endoscopy revealing an ulcerative tumor in the second portion of the duodenum

While the clinical significance of CTC-derived PD-L1 is still under investigation, it may provide complementary information when tissue biopsy is limited. PD-L1 assays differ by clone and drug association (e.g., 28-8/22C3 for PD-1 inhibitors vs. SP142/SP263 for PD-L1 inhibitors), which may affect the therapeutic response. Emerging real-world data suggest that switching from anti-PD-1 to anti-PD-L1 therapy can be beneficial in selected gastrointestinal cancers,[9] supporting our rationale for switching from nivolumab to atezolizumab.

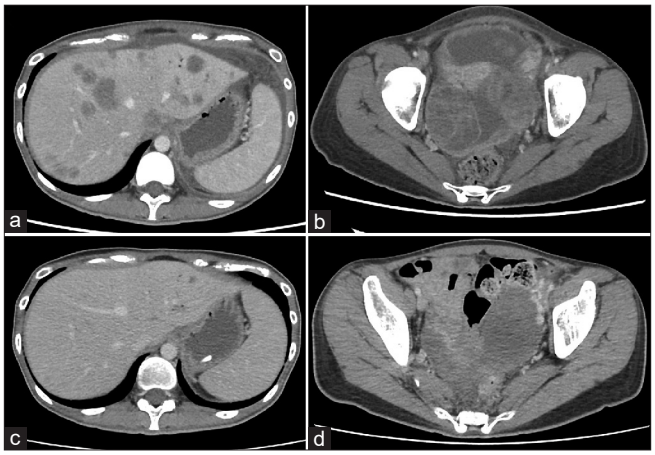

Figure 2: Images before and after third-line therapy. (a and b) Progressive duodenal tumor and liver metastases, with new ovarian and peritoneal metastases before third-line therapy. (c and d) Posttreatment images showing reduced liver and ovarian metastases

CGP is a valuable tool in the management of rare malignancies such as SBA, enabling the identification of actionable alterations to guide the choice of therapy.[10,11] In line with this, the NCCN recommends molecular testing as part of the initial workup for metastatic SBA.[5] Early CGP, ideally performed at the diagnosis of metastatic or unresectable disease, maximizes the opportunity for targeted therapy or immunotherapy.[12,13] Notably, although the overall prevalence of *BRAF* mutations in SBA is slightly higher than in colorectal or gastric cancer, the proportion of V600E mutations is lower compared to CRC.[14] In our case, CGP identified a *BRAF* V600E mutation, a level 1 actionable biomarker across multiple solid tumors, which was critical for tailoring therapy.[15] *BRAF* V600E is a

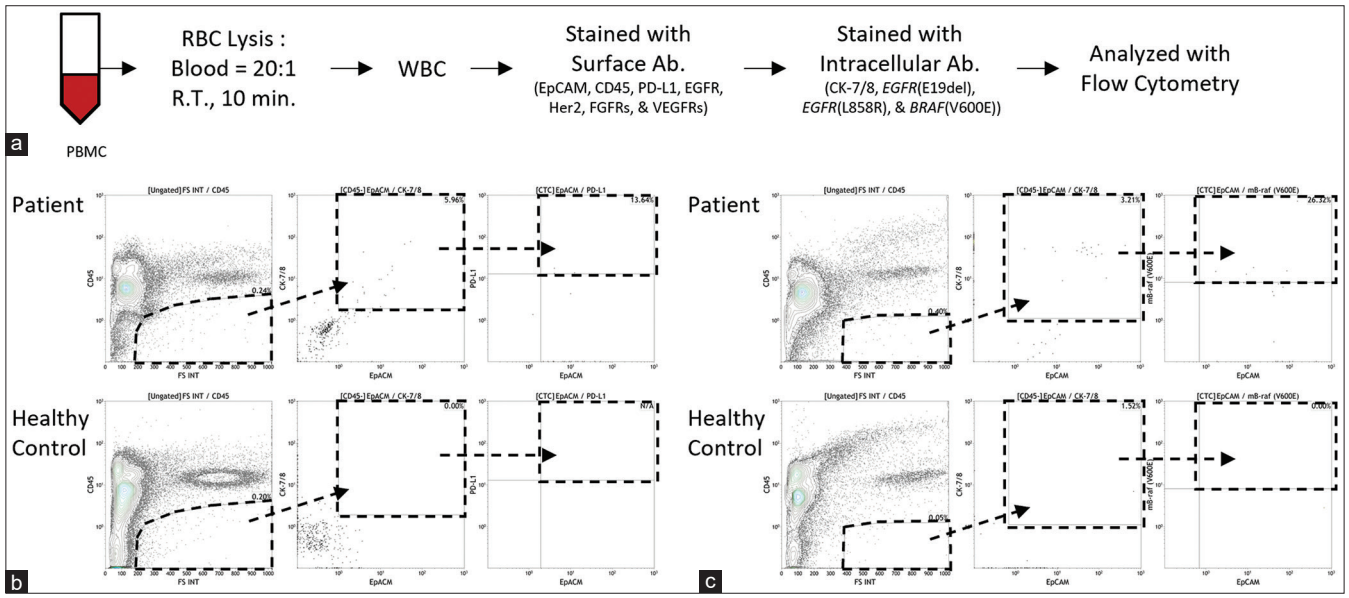

Figure 3: Flow cytometry analyses of circulating tumor cells (CTCs) before third-line therapy. (a) Schematic workflow of CTC detection by flow cytometry, including red blood cell lysis, surface staining, fixation/permeabilization, and intracellular staining. (b) Programmed death-ligand 1 and (c) *BRAF* V600E expression were assessed in gated CTCs (CD45–, EpCAM+, CK-7/8+) from the patient and healthy controls. Dashed arrows indicate gating strategies on representative biaxial plots

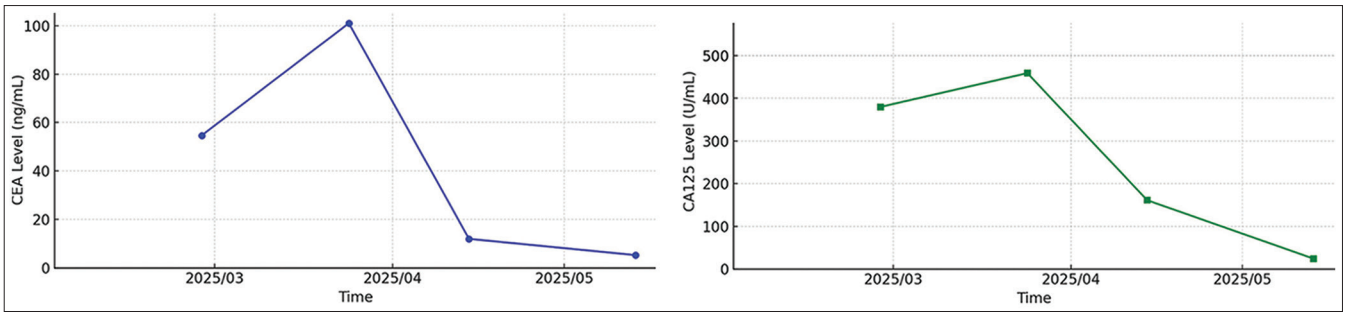

Figure 4: Change of serum CEA and CA125 levels following third-line therapy

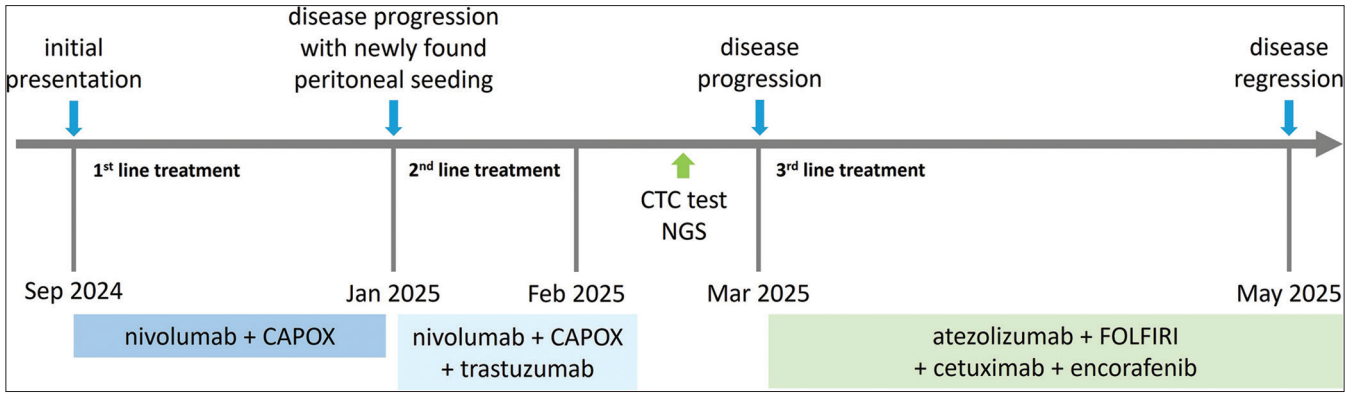

Figure 5: Timeline of the patient's treatment course. CTC: Circulating tumor cell; NGS: Next-generation sequencing; CAPOX: Capecitabine and oxaliplatin; FOLFIRI: Folinic acid, 5-fluorouracil, and irinotecan

well-known oncogenic driver that has been shown to activate the mitogen-activated protein kinase (MAPK) pathway in various tumors, including melanoma, nonsmall cell lung cancer, thyroid cancer, CRC, and gliomas.[16-18] Although BRAF inhibitors have shown efficacy in various types of tumor, tumor-specific feedback mechanisms such as activation of receptor tyrosine kinases and reactivation of the ERK pathway may affect the response to anti-BRAF therapy. In melanoma, combining a MEK inhibitor with a BRAF inhibitor has been shown to overcome the resistance mechanisms of anti-BRAF and improve response rate, PFS, and overall survival.[19] However, in CRC, monotherapy with BRAF inhibitors is largely ineffective due to EGFR-driven MAPK pathway reactivation, necessitating the combination of BRAF and EGFR inhibition.[20,21] EGFR blockade has therefore become an essential component of treatment for *BRAF* V600E-mutant CRC. The recent phase III BREAKWATER study demonstrated that first-line therapy with encorafenib (BRAF inhibitor), cetuximab (EGFR inhibitor), and chemotherapy outperformed standard regimens and achieved a 60% objective response rate, and subsequently, the regimen received accelerated FDA approval for *BRAF* V600E-mutant metastatic CRC.[22] Although no large clinical trials have focused on BRAF-mutant SBA, the ROAR basket trial included three SBA patients with *BRAF* V600E mutations treated with dabrafenib and trametinib, two of whom achieved objective responses.[23] While dabrafenib and trametinib have received accelerated FDA, tumor-agnostic approval, they have not been studied in combination with EGFR inhibition or chemotherapy in gastrointestinal malignancies. These findings along with the molecular similarity between SBA and CRC supported the use of a CRC-derived regimen in our patient, with a combination of encorafenib, cetuximab, FOLFIRI, and atezolizumab.

Another actionable alteration identified in our case was HER2 overexpression. In the DESTINY-PanTumor02 basket trial, the HER2-targeted antibody–drug conjugate of trastuzumab deruxtecan demonstrated clinical benefits across multiple tumor types with HER2 IHC 3+ or IHC 2+/FISH+ status, particularly among IHC 3+ tumors, leading to accelerated approval by the FDA.[24] However, in our case, after anti-HER2 therapy, CTC profiling revealed a low HER2 expression and no HER2 amplification on CGP, suggesting biomarker evolution and the limited efficacy of continued HER2-targeted therapy. Moreover, coexisting BRAF mutations may reduce the efficacy of HER2-directed therapy in gastrointestinal malignancies, as concurrent RAS/RAF mutations are associated with lower HER2 amplification and diminished response to HER2-targeted agents.[25,26] These findings underscore the complementary role of CTC analysis when tissue rebiopsy is not feasible or declined.

Notably, the addition of immunotherapy in this MSS and low TMB case may have contributed to the observed therapeutic synergy. Although MSS and low TMB are generally associated with a limited response to immune checkpoint inhibitors, emerging evidence suggests that combining immunotherapy with targeted agents and chemotherapy may enhance efficacy in certain molecular subgroups.[27,28] Preliminary data from an early-phase trial evaluating encorafenib, cetuximab, and nivolumab in patients with MSS, *BRAF* V600E-mutant metastatic CRC demonstrated encouraging clinical activity. A randomized phase II trial (SWOG S2107 and NCT05308446) is currently underway to further investigate this combination.

In conclusion, this case illustrates the importance of genomic profiling in guiding treatment decisions for rare cancers such as SBA. Identifying actionable targets such as *BRAF* V600E and HER2 enables a personalized therapeutic strategy that can provide meaningful clinical benefits, even in the setting of heavily pretreated disease. Expanding access to molecular diagnostics and including SBA patients in clinical trials are essential to improve outcomes for patients with this understudied malignancy.

Declaration of patient consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her

name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12-49.
2. Aparicio T, Zaanan A, Svrcek M, Laurent-Puig P, Carrere N, Manfredi S, *et al*. Small bowel adenocarcinoma: Epidemiology, risk factors, diagnosis and treatment. Dig Liver Dis 2014;46:97-104.
3. Pedersen KS, Raghav K, Overman MJ. Small bowel adenocarcinoma: Etiology, presentation, and molecular alterations. J Natl Compr Canc Netw 2019;17:1135-41.
4. Overman MJ, Hu CY, Kopetz S, Abbruzzese JL, Wolff RA, Chang GJ. A population-based comparison of adenocarcinoma of the large and small intestine: Insights into a rare disease. Ann Surg Oncol 2012;19:1439-45.
5. NCCN Clinical Practice Guidelines in Oncology: Small Bowel Adenocarcinoma (Version 3.2025); 2025. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1495. [Last accessed on 2025 May 19].
6. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, *et al*. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.
7. Kang YK, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, *et al*. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): A randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022;23:234-47.
8. Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, *et al*. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: Interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet 2023;402:2197-208.
9. Lai KC, Chen YH, Hung YP, Chiang NJ, Chen MH, Chen SC. Efficacy and safety of durvalumab rechallenge in advanced hepatocellular carcinoma patients refractory to prior anti-PD-1 therapy. Hepatol Int 2024;18:1804-14.
10. Mosele MF, Westphalen CB, Stenzinger A, Barlesi F, Bayle A, Bièche I, *et al*. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: A report from the ESMO precision medicine working group. Ann Oncol 2024;35:588-606.
11. Yu D, Wang J, Zheng B, Yuan M, Gu D, Chen R, *et al*. Comprehensive genomic profiling of small bowel adenocarcinoma by tissue and plasma biopsy. Genomics 2024;116:110766.
12. Matsubara J, Mukai K, Kondo T, Yoshioka M, Kage H, Oda K, *et al*. First-line genomic profiling in previously untreated advanced solid tumors for identification of targeted therapy opportunities. JAMA Netw Open 2023;6:e2323336.
13. Hagio K, Kikuchi J, Takada K, Tanabe H, Sugiyama M, Ohhara Y, *et al*. Assessment for the timing of comprehensive genomic profiling tests in patients with advanced solid cancers. Cancer Sci 2023;114:3385-95.
14. Schrock AB, Devoe CE, McWilliams R, Sun J, Aparicio T, Stephens PJ, *et al*. Genomic profiling of small-bowel adenocarcinoma. JAMA Oncol 2017;3:1546-53.
15. Ahronian LG, Sennott EM, Van Allen EM, Wagle N, Kwak EL, Faris JE, *et al*. Clinical acquired resistance to RAF inhibitor combinations in BRAF-mutant colorectal cancer through MAPK pathway alterations. Cancer Discov 2015;5:358-67.
16. Planchard D, Smit EF, Groen HJ, Mazieres J, Besse B, Helland Å, *et al*. Dabrafenib plus trametinib in patients with previously untreated BRAF (V600E)-mutant metastatic non-small-cell lung cancer: An open-label, phase 2 trial. Lancet Oncol 2017;18:1307-16.
17. Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JH, Soria JC, *et al*. Dabrafenib plus trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer: Updated analysis from the phase II ROAR basket study. Ann Oncol 2022;33:406-15.
18. Salama AK, Li S, Macrae ER, Park JI, Mitchell EP, Zwiebel JA, *et al*. Dabrafenib and trametinib in patients with tumors with BRAF (V600E) mutations: Results of the NCI-MATCH trial subprotocol H. J Clin Oncol 2020;38:3895-904.
19. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, *et al*. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30-9.
20. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, *et al*. Unresponsiveness of colon cancer to BRAF (V600E) inhibition through feedback activation of EGFR. Nature 2012;483:100-3.
21. Corcoran RB, Ebi H, Turke AB, Coffee EM, Nishino M, Cogdill AP, *et al*. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. Cancer Discov 2012;2:227-35.
22. Elez E, Yoshino T, Shen L, Lonardi S, Van Cutsem E, Eng C, *et al*. Encorafenib, cetuximab, and mFOLFOX6 in BRAF-mutated colorectal cancer. N Engl J Med 2025;392:2425-37.
23. Subbiah V, Kreitman RJ, Wainberg ZA, Gazzah A, Lassen U, Stein A, *et al*. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: The phase 2 ROAR trial. Nat Med 2023;29:1103-12.
24. Meric-Bernstam F, Makker V, Oaknin A, Oh DY, Banerjee S, González-Martín A, *et al*. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: Primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol 2024;42:47-58.
25. Pizzamiglio M, Soulabaille A, Lahlou W, Pilla L, Zaanan A, Taieb J. Advances and challenges in targeted therapies for HER2-amplified colorectal cancer. Eur J Cancer 2025;222:115471.
26. Zhang R, Su C, Jia Y, Xing M, Jin S, Zong H. Molecular mechanisms of HER2-targeted therapy and strategies to overcome the drug resistance in colorectal cancer. Biomed Pharmacother 2024;179:117363.
27. Baraibar I, Mirallas O, Saoudi N, Ros J, Salvà F, Tabernero J, *et al*. Combined treatment with immunotherapy-based strategies for MSS metastatic colorectal cancer. Cancers (Basel) 2021;13:6311.
28. Gandini A, Puglisi S, Pirrone C, Martelli V, Catalano F, Nardin S, *et al*. The role of immunotherapy in microsatellites stable metastatic colorectal cancer: State of the art and future perspectives. Front Oncol 2023;13:1161048.