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**Response to osimertinib in a colorectal cancer patient with an *EGFR* T790M mutation: A case report**

Buzard B *et al.* Osimertinib in colorectal cancer

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**Abstract**

BACKGROUND

Although common in lung cancer, somatic epidermal growth factor receptor (*EGFR*) mutations are rarely found in colorectal cancer, occurring in approximately 3% of cases. Treatment with anti-EGFR antibodies is commonplace, but *EGFR* tyrosine kinase inhibitors are not standard treatments in colorectal cancer. Here we report a case of sustained response to osimertinib in a colorectal cancer patient with an *EGFR* T790M mutation on cell-free DNA analysis.

CASE SUMMARY

A 72-year old woman with a past medical history of post-polio syndrome confined to a wheelchair, scoliosis and hypothyroidism presented with metastatic sigmoid colon adenocarcinoma with hepatic metastases. Next generation sequencing revealed a *RAS/RAF* wild-type, microsatellite stable, PD-L1 negative malignancy. Mutations in *TP3* and *APC* were also identified, as well as *EGFR* amplification. Cell-free DNA analysis revealed an *EGFR* T790M mutation. She was unable to tolerate first-line treatment with panitumumab, 5-fluorouracil and leucovorin, progressed on second-line treatment with trifluridine/tipiracil plus bevacizumab, and was unable to tolerate third-line treatment with regorafenib. She was started on fourth-line treatment with off-label osimertinib, with clinical response – decrease in size of hepatic metastases and a pericardial effusion. She remained on treatment with osimertinib for seven months.

CONCLUSION

This case shows the benefit of multi-gene sequencing assays to identify potential therapeutic options in patients with refractory disease.

**Key Words:** Colorectal cancer; Osimertinib; Epidermal growth factor receptor T790M; Precision oncology; Tyrosine kinase inhibitor; Case report

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**Core Tip:** Somatic epidermal growth factor receptor (*EGFR*) mutations are rarely found in colorectal cancer. Treatment with anti-EGFR antibodies is commonplace, but *EGFR* tyrosine kinase inhibitors are not standard in colorectal cancer. Here we report a case of sustained response to osimertinib in a metastatic colorectal cancer patient with an *EGFR* T790M mutation detected with cell-free DNA. She progressed on three lines of treatment, and received fourth-line treatment with off-label osimertinib, with clinical response. She received treatment with osimertinib for seven months. This case shows the benefit of multi-gene sequencing assays to identify potential therapeutic options in patients with refractory disease.

**INTRODUCTION**

Although common in lung cancer, somatic epidermal growth factor receptor (*EGFR*) mutations are rarely found in colorectal cancer, occurring in approximately 3% of cases[1]. Treatment with anti-EGFR antibodies is commonplace, but *EGFR* tyrosine kinase (TK) inhibitors (TKIs) are not standard treatments in colorectal cancer. Here we report a case of sustained response to osimertinib in a colorectal cancer patient with an *EGFR* T790M mutation on cell-free DNA analysis.

**CASE PRESENTATION**

***Chief complaints***

Our patient is a 72-year-old white female who presented with a chief complaint of right upper quadrant pain.

***History of present illness***

She was diagnosed with metastatic sigmoid colon adenocarcinoma with liver involvement in November 2020 (Table 1).

***History of past illness***

She was a former light smoker who quit 10 years before the diagnosis of colon cancer.

***Personal and family history***

The patient had a past medical history of post-polio syndrome confined to a wheelchair, scoliosis, and hypothyroidism.

***Physical examination***

Physical examination findings were significant for mild tenderness to palpation in the right upper quadrant without abdominal distention as well as chronic muscle wasting and decreased muscle tone secondary to post-polio syndrome. Her Eastern Cooperative Oncology Group (ECOG) performance status was 3.

***Laboratory examinations***

Next-generation sequencing (NGS) covering over 600 genes was performed on the liver biopsy and revealed a *RAS/RAF* wild-type, microsatellite stable, PD-L1 negative malignancy. In addition, *TP53* and *APC* mutations and *EGFR* amplification with C-terminal deletion in exons 27-28 were discovered. Cell-free DNA analysis revealed an *EGFR* p.T790M exon 20 somatic mutation with a variant allele frequency (VAF) of 12.3%.

***Imaging examinations***

Computed tomography (CT) imaging revealed hepatic metastases at diagnosis.

**FINAL DIAGNOSIS**

She was diagnosed with metastatic sigmoid colon adenocarcinoma with liver involvement in November 2020 (Table 1).

**TREATMENT**

She desired to preserve her quality of life and minimize side effects and trips to the cancer center. With these goals in mind, she declined standard frontline treatment options, including FOLFOX and FOLFIRI. This patient was discussed at our molecular tumor board in December 2020. At that time, anti-EGFR antibody therapy was recommended as *EGFR* amplification was thought to be secondary to the *EGFR* exon 27-28 deletion and truncation of the C-terminal domain leading to a paradoxical, ligand-independent downstream activation of the MAPK pathway[2]. She initially received panitumumab, 5-fluorouracil, and leucovorin. However, shortly after receiving panitumumab, the patient complained of post-nasal drainage and difficulty swallowing. She declined further treatment with this regimen. Pursuant to her goals of minimizing time spent at the cancer center and using the least toxic regimen, she was transitioned to treatment with trifluridine/tipiracil plus bevacizumab in January 2021[3]. Imaging revealed treatment response with subsequent progression in November 2021, eleven months after initiation of treatment.

Subsequently, she was initiated on third-line treatment with regorafenib in December 2021. The patient experienced multiple treatment interruptions due to poor tolerability (primarily grade 3 hypertension), and the decision was made to stop regorafenib. Her case was re-presented at the molecular tumor board in January 2022. Recommendations at that time were to pursue clinical trial options for anti-EGFR therapy or off-label *EGFR* TKI therapy. An ECOG performance status of 3 precluded enrollment in local therapeutic clinical trials, and the patient expressed that she did not wish to travel. The decision was made to initiate off-label osimertinib.

She started osimertinib 80 mg daily in February 2022. The VAF of the *EGFR* T790M mutation was 13.3%. Two weeks after initiating osimertinib, the patient developed an acneiform rash on both cheeks. Oral minocycline was prescribed, and the rash improved within two weeks. Worsening fatigue and an elevated total bilirubin of 2.1 mg/dL were noted within the first month of therapy. Her fatigue improved, and bilirubin normalized by the start of cycle two without dose modifications. Between March and April of 2022, the patient developed grade 2 anemia and grade 2 thrombocytopenia, both of which were monitored. A CT chest, abdomen, and pelvis with contrast was obtained five weeks after initiating osimertinib and revealed a decrease in the size of liver metastases and an unchanged appearance of the primary sigmoid colon malignancy. The VAF of the *EGFR* T790M mutation was then 2.1%, which correlated with the response seen on imaging (Figure 1).

**OUTCOME AND FOLLOW-UP**

In June 2022, a CT scan revealed portal vein thrombosis, and apixaban was initiated. In addition, the osimertinib dose was reduced from 80 mg to 40 mg daily due to the aforementioned hematologic toxicities.

This same CT scan obtained five months after the initiation of osimertinib revealed further improvement in hepatic metastases with a decrease in the size of the dominant hepatic mass from 11.9 cm at the time of initiation of therapy to 8.4 cm (Figure 2). An echocardiogram revealed a decrease in the size of a pericardial effusion, which was present at the time of initiation of osimertinib. Subsequent imaging seven months after initiation of treatment revealed progression of hepatic metastases and new onset large volume ascites and peritoneal carcinomatosis. She decided to pursue hospice at this juncture and passed away two weeks later.

**DISCUSSION**

Our patient presented with metastatic colorectal cancer, which became refractory to treatment with trifluridine/tipiracil and bevacizumab. In addition, as described above, she had an intolerance to panitumumab and regorafenib. Cell-free DNA analysis revealed an *EGFR* T790M mutation. The patient's case was referred to our molecular tumor board, and the recommendation was to consider a trial of osimertinib. The patient had a response for over six months. While there is preclinical evidence for utilizing osimertinib in colon cancer, we could find only one clinical case report of using osimertinib in colon cancer[4,5].

The *EGFR* gene is located on chromosome 7p12-13 and encodes a transmembrane receptor composed of extracellular ligand binding and intracellular TK domains[6]. *EGFR* regulation is tightly controlled, and variations within the *EGFR* signaling pathway play a key role in solid tumor oncogenesis. Commercially available *EGFR* antagonists include the monoclonal antibodies (mAbs) panitumumab and cetuximab and act by preventing epidermal growth factor ligand binding to the external *EGFR* domain. *EGFR* mAbs are considered a standard of care in treating patients with metastatic colorectal cancer lacking activating mutations in *KRAS/NRAS* downstream of *EGFR*[7].

In contrast to these mAbs, *EGFR* TKIs block intracellular signaling cascades through competition with adenine triphosphate. While both approaches lead to the inhibition of *EGFR* autophosphorylation, TKI efficacy is restricted to cancers that carry *EGFR* mutations in the TK domain (exons 18-21). Still, these mutations are rarely seen in colorectal cancer[8]. Available TKIs against *EGFR* TK mutations are approved for non-small cell lung cancer and include first-generation agents gefitinib and erlotinib and second-generation agents afatinib and dacomitinib[9]. Osimertinib is the only approved third-generation *EGFR* TKI and has efficacy against *EGFR* T790M, a mutation resistant to first- and second-generation *EGFR* TKIs[10].

There are currently no guidelines to direct therapy selection in *EGFR*-mutated colorectal cancer. However, case reports exist describing the efficacy of erlotinib in *EGFR* mutant colorectal cancer[11,12]. More recently, a 50-year-old Japanese woman with an *EGFR* T790M lung lesion from a colorectal primary responded to osimertinib for 95 d[5]. The patient was noted positive for *RAS* mutant G13D at diagnosis, which is downstream of *EGFR*. Mutations of this pathway are established as strong negative predictive markers, and may preclude efficacy of these therapies. This patient also had an uncommon *EGFR* L861Q mutation compounded with the *EGFR* T790M at the time of osimertinib initiation. It is speculated by the authors the patient originally only had the *EGFR* L861Q mutation and the T790M was acquired during the clinical course prior to starting osimertinib. With one mutation acquired during the clinical course, it is possible another resistance mechanism was acquired after starting osimertinib. This hypothesis along with the *RAS* mutation are potential explanations for the short response time noted compared to our patient. However, such cases highlight the additional options afforded to these patients by utilizing multi-gene sequencing panels.

The use of NGS in metastatic colorectal cancers is becoming standard in an effort to identify additional therapeutic options in the refractory setting. However, guidelines currently recommend testing for only a limited set of genes, including *NRAS, KRAS, BRAF* V600E, and mismatch repair/ microsatellite instability, with consideration to test for *HER2* amplifications and *NTRK* fusions in the refractory disease setting[9].A retrospective review of 23 US-based oncology practices demonstrates that even these limited gene panels are underutilized; only 40% of patients underwent guideline-recommended genomic testing for any of these genomic markers, a rate that has not increased since 2013[13,14].

Cell-free DNA plays an increasingly pivotal role in minimal residual disease monitoring for individuals with colon cancer[15]. Both tumor-informed and tumor-agnostic approaches are being investigated[16]. The clinical case described in this paper demonstrates the prospect of using cell-free DNA for response assessment, in addition to standard tumor markers such as carcinoembryonic antigen, as illustrated in Figure 1.

Our patient had a response to osimertinib for over six months of therapy. The previously under-recognized factor of the time-related burden that patients undergoing oncologic treatments experience is coming to the forefront with recent research[17]. We customized her treatment to meet her goals of minimizing toxicity and time spent traveling to the cancer center. In alignment with these goals, most of her visits were performed virtually.

This case shows the benefit of large panel multi-gene sequencing assays to identify potential therapeutic options in patients with refractory disease. Molecular tumor boards are integral in identifying patients appropriate for a targeted therapy approach and procuring these much-needed therapies. As demonstrated in this case, precision medicine holds promise to tailor patient treatments to align with their goals and expectations.

**CONCLUSION**

This case shows the benefit of large panel multi-gene sequencing assays to identify potential therapeutic options in patients with refractory disease. Molecular tumor boards are integral in identifying patients appropriate for a targeted therapy approach and procuring these much-needed therapies. As demonstrated in this case, precision medicine holds promise to tailor patient treatments to align with their goals and expectations.

**REFERENCES**

1 **Kim N**, Cho D, Kim H, Kim S, Cha YJ, Greulich H, Bass A, Cho HS, Cho J. Colorectal adenocarcinoma-derived EGFR mutants are oncogenic and sensitive to EGFR-targeted monoclonal antibodies, cetuximab and panitumumab. *Int J Cancer* 2020; **146**: 2194-2200 [PMID: 31290142 DOI: 10.1002/ijc.32499]

2 **Park AK**, Francis JM, Park WY, Park JO, Cho J. Constitutive asymmetric dimerization drives oncogenic activation of epidermal growth factor receptor carboxyl-terminal deletion mutants. *Oncotarget* 2015; **6**: 8839-8850 [PMID: 25826094 DOI: 10.18632/oncotarget.3559]

3 **Van Cutsem E**, Danielewicz I, Saunders MP, Pfeiffer P, Argilés G, Borg C, Glynne-Jones R, Punt CJA, Van de Wouw AJ, Fedyanin M, Stroyakovskiy D, Kroening H, Garcia-Alfonso P, Wasan H, Falcone A, Fougeray R, Egorov A, Amellal N, Moiseyenko V. First-line trifluridine/tipiracil + bevacizumab in patients with unresectable metastatic colorectal cancer: final survival analysis in the TASCO1 study. *Br J Cancer* 2022; **126**: 1548-1554 [PMID: 35440667 DOI: 10.1038/s41416-022-01737-2]

4 **Guo L**, Huang S, Wang X. PUMA mediates the anti-cancer effect of osimertinib in colon cancer cells. *Onco Targets Ther* 2017; **10**: 5281-5288 [PMID: 29138581 DOI: 10.2147/OTT.S139382]

5 **Yanagisawa A**, Kinehara Y, Kijima R, Tanaka M, Ninomiya R, Jokoji R, Tachibana I. Metastatic Lung Tumors from Colorectal Cancer with EGFR Mutations That Responded to Osimertinib. *Intern Med* 2023; **62**: 769-773 [PMID: 35871578 DOI: 10.2169/internalmedicine.0002-22]

6 **Mitsudomi T**, Yatabe Y. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. *FEBS J* 2010; **277**: 301-308 [PMID: 19922469 DOI: 10.1111/j.1742-4658.2009.07448.x][](https://sci-hub.se/10.1111/j.1742-4658.2009.07448.x)

7 **Cai WQ**, Zeng LS, Wang LF, Wang YY, Cheng JT, Zhang Y, Han ZW, Zhou Y, Huang SL, Wang XW, Peng XC, Xiang Y, Ma Z, Cui SZ, Xin HW. The Latest Battles Between EGFR Monoclonal Antibodies and Resistant Tumor Cells. *Front Oncol* 2020; **10**: 1249 [PMID: 32793499 DOI: 10.3389/fonc.2020.01249]

8 **Altunel E**, Aljamal AA, Mantyh J, Deak K, Glover W, McCall SJ, Datto M, Strickler J, Hsu DS. Characterization of the Epidermal Growth Factor Receptor T790M Mutation in Colorectal Cancer. *JCO Precis Oncol* 2018; **2**: 1-7 [PMID: 35135168 DOI: 10.1200/PO.18.00194]

9 **Marin-Acevedo JA**, Pellini B, Kimbrough EO, Hicks JK, Chiappori A. Treatment Strategies for Non-Small Cell Lung Cancer with Common EGFR Mutations: A Review of the History of EGFR TKIs Approval and Emerging Data. *Cancers (Basel)* 2023; **15** [PMID: 36765587 DOI: 10.3390/cancers15030629]

10 **Remon J**, Steuer CE, Ramalingam SS, Felip E. Osimertinib and other third-generation EGFR TKI in EGFR-mutant NSCLC patients. *Ann Oncol* 2018; **29**: i20-i27 [PMID: 29462255 DOI: 10.1093/annonc/mdx704]

11 **Yarom N**, Jonker DJ. The role of the epidermal growth factor receptor in the mechanism and treatment of colorectal cancer. *Discov Med* 2011; **11**: 95-105 [PMID: 21356164]

12 **Li Y**, Zhang HB, Chen X, Yang X, Ye Y, Bekaii-Saab T, Zheng Y, Zhang Y. A Rare EGFR-SEPT14 Fusion in a Patient with Colorectal Adenocarcinoma Responding to Erlotinib. *Oncologist* 2020; **25**: 203-207 [PMID: 32162810 DOI: 10.1634/theoncologist.2019-0405]

13 **Gutierrez ME**, Price KS, Lanman RB, Nagy RJ, Shah I, Mathura S, Mulcahy M, Norden AD, Goldberg SL. Genomic Profiling for KRAS, NRAS, BRAF, Microsatellite Instability, and Mismatch Repair Deficiency Among Patients With Metastatic Colon Cancer. *JCO Precis Oncol* 2019; **3** [PMID: 32923867 DOI: 10.1200/PO.19.00274]

14 **Iyer P**, Deng M, Handorf EA, Nakhoda S, Dotan E. Assessing Oncologists' Adoption of Biomarker Testing in Metastatic Colorectal Cancer Using Real-World Data. *JNCI Cancer Spectr* 2022; **6** [PMID: 36149298 DOI: 10.1093/jncics/pkac065]

15 **Venook AP**. Colorectal Cancer Surveillance With Circulating Tumor DNA Assay. *JAMA Netw Open* 2022; **5**: e221100 [PMID: 35258585 DOI: 10.1001/jamanetworkopen.2022.1100]

16 **Gong J**, Hendifar A, Gangi A, Zaghiyan K, Atkins K, Nasseri Y, Murrell Z, Figueiredo JC, Salvy S, Haile R, Hitchins M. Clinical Applications of Minimal Residual Disease Assessments by Tumor-Informed and Tumor-Uninformed Circulating Tumor DNA in Colorectal Cancer. *Cancers (Basel)* 2021; **13** [PMID: 34572774 DOI: 10.3390/cancers13184547]

17 **Gupta A**, Jensen EH, Virnig BA, Beg MS. Time-Related Burdens of Cancer Care. *JCO Oncol Pract* 2022; **18**: 245-246 [PMID: 34709950 DOI: 10.1200/OP.21.00662]

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**Figure Legends**

图表, 折线图

描述已自动生成

**Figure 1 Serial cell-free DNA analyses and carcinoembryonic antigen levels over time.** Osimertinib was initiated in February 2022, and imaging in April 2022 confirmed treatment response with a decrease in size of the hepatic metastases. CEA: Carcinoembryonic antigen; CEGFR: Epidermal growth factor receptor; VAF: Variant allele frequency.

**Table 1 Timeline of events**

|  |  |
| --- | --- |
| **Date** | **Event** |
| November 2020 | Diagnosed with metastatic colon adenocarcinoma and started on panitumumab, 5-fluorouracil and leucovorin |
| January 2021 | Switched to trifluridine/tipiracil |
| November 2021 | Disease progression on CT imaging |
| December 2021 | Switched to regorafenib |
| February 2022 | Switched to osimertinib |
| November 2023 | Died |



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