Letter to the Editor

rare tumors

Rare Tumors
Volume 15: 1–2

DOI: 10.1177/20363613231204798
journals.sagepub.com/home/rtu
Sage

Advancing precision oncology in metastatic colorectal cancer: The food and drug administration approval of foundation one liquid CDx as a companion diagnostic a correspondence

Syeda Shahnoor[1], Manahil Mansha[2], Solay Farhat[3], Adeena Maryyum[4], Adil Naseer Khan[5] and Abdul Moiz Khan[4]

Date received: 29 July 2023; accepted: 14 September 2023

Dear Editor,

Colorectal cancer (CRC) is the third most commonly diagnosed and the second most mortality-causing cancer worldwide.[1] Colorectal cancer develops through genetic and epigenetic changes that activate oncogenes, decrease tumor suppressor genes, and cause the disease to develop characteristic cancer traits. Mutation accumulation is fueled by genomic and epigenomic instability, which drives malignant transformation via aggressive cell selection and clonal growth.[2] BRAF mutations, particularly the V600E mutation, are observed in approximately 10% of colorectal cancer (CRC) patients. These mutations are more common in females, often found in right-sided tumors, and associated with advanced stage, mucinous histology, defective mismatch repair, and the serrated adenoma pathway. Compared to normal CRCs, patients with BRAF-mutated CRCs experience a worsened prognosis and demonstrate resistance to conventional treatment approaches.[3]

BRAF-mutated colorectal cancer (CRC) poses treatment challenges due to chemotherapy resistance. Combination therapies involving BRAF, MEK, and EGFR inhibitors are being explored, while further research targets Wnt and immunotherapy. In 2020, the FDA approved Encorafenib in combination with Cetuximab, as the first and the only treatment regimen for adult mCRC patients with a BRAF V600E mutation based on the BEACON CRC (NCT02928224) trial. This Phase 3 trial showed improved overall survival in patients with BRAF mutation, making it an important therapeutic advancement.[4] The approved CRC combination therapy combines both effects of the BRAF inhibitor (Encorafenib) with the epidermal growth factor receptor inhibitor EFGR (Cetuximab) in patients with the BRAF V600E mutation CRC.[4] Encorafenib acts to inhibit the activity of mutated BRAF proteins by blocking the abnormal signaling pathway in cancer cells, while Cetuximab acts as a monoclonal antibody that targets the overexpressed EFGR in CRC. Since the BRAF inhibition results in a rapid release of feedback-suppressed (EGFR)–mediated MAPK signaling, combining both drugs will synergistically inhibit tumor growth in BRAF V600E–mutant CRC.[5]

A significant recent advancement is the FDA approval of FoundationOne Liquid CDx on June 2023, a blood-based liquid biopsy test, as a companion diagnostic for determining the eligibility of patients with BRAF-V600E metastatic CRC (mCRC) for this combination therapy.[6] Utilizing targeted high throughput hybridization-based capture technology, FoundationOne Liquid CDx is a

[1]Department of Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan
[2]Islam Medical and Dental College, Sialkot, Pakistan
[3]Faculty of Medical Science, Lebanese University, Beirut, Lebanon
[4]Department of Internal Medicine, Ayub Medical College, Abbottabad, Pakistan
[5]Department of Gastroenterology, Ayub Medical College, Abbottabad, Pakistan

Corresponding author:
Solay Farhat, Faculty of Medical Sciences, Lebanese University, Beirut, Dekwaneh 1200, Lebanon.
Email: solayfarhat@gmail.com

qualitative next-generation sequencing-based in vitro diagnostic test capable of identifying and reporting gene substitutions, insertions and deletions, rearrangements, and copy number variations across 324 genes. It harnesses circulating cell-free DNA (cfDNA) extracted from anticoagulated peripheral whole blood plasma, collected in specialized FoundationOne tubes specifically designed for cfDNA analysis.[7] This vital companion diagnostics tool offers oncologists a validated, non-invasive genomic testing option for patients with metastatic solid tumors, with demonstrated efficacy as a companion diagnostic in prostate cancer (Olaparib and rucaparib), breast cancer (Alpelisib), and solid tumors (Entrectinib).[7] By aiding in the identification of specific mutations, FoundationOne Liquid CDx enables patients with mCRC BRAF V600E to benefit from expedited treatment initiation, particularly valuable for those unable to undergo tumor biopsy [6]. This regulatory milestone brings newfound hope to patients with BRAF-mutated CRC, offering them an approved treatment option tailored to their specific cancer type, coupled with a blood-based companion diagnostic.

Despite recent advances, the suggested revolutionary approach's dependence on circulating cell-free DNA (cfDNA) poses hurdles due to variable DNA fragment levels. False positive results, ambiguity in non-detection cases, and high costs necessitate the development of more sensitive, accessible, and cost-effective companion diagnostics for the timely diagnosis and personalized management of BRAF V600E-mutated metastatic colorectal cancers (mCRC). It is critical to address these restrictions through technological integration and artificial intelligence, as well as to investigate alternative biofluids and prioritize safety, accessibility, and cost. Large-scale research and clinical trials are required to establish clinical relevance, standardization, and consistent and reliable results.

Contributorship

Syeda Shahnoor, Manahil Mansha and Solay Farhat a wrote the draft. Adil Naseer Khan, Adeena Maryyum and Abdul Moiz Khan proofread it. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Abdul Moiz Khan https://orcid.org/0000-0001-9796-8867

References

1. Xi Y and Xu P. Global colorectal cancer burden in 2020 and projections to 2040. *Translational Oncology* 2021; 14(10): 101174.
2. Kuipers EJ, Grady WM, Lieberman D, et al. Colorectal cancer. *Nat Rev Dis Primers*. 2015; 1: 15065.
3. Caputo F, Santini C, Bardasi C, et al. BRAF-mutated colorectal cancer: clinical and molecular insights. *Int J Mol Sci*, 2019 16(21).
4. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E–Mutated Colorectal Cancer. *N Engl J Med* 2019; 81(17). Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1908075
5. Tabernero J, Grothey A, van Cutsem E, et al. Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON Study. *J Clin Oncol*. 2021 39(4): 273–284. Available from: https://pubmed.ncbi.nlm.nih.gov/33503393/
6. U.S. Food and Drug Administration (FDA). Approves foundation one®LiquidCDx as a Companion Diagnostic for Pfizer's BRAFTOVI® (encorafenib) in Combination With Cetuximab to Identify Patients With BRAF V600E alterations in metastatic colorectal cancer | foundation medicine. Available from: https://www.foundationmedicine.com/press-releases/f9b285eb-db6d-4f61-856c-3f1edb803937
7. FDA approves Foundation One Liquid CDx as diagnostic for Braftovi. Available from: https://www.medicaldevice-network.com/news/foundationone-liquid-cdx-diagnostic-braftovi/