Editorial

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Celebrating a breakthrough: FDA endorses encorafenib plus binimetinib alongside two companion diagnostics for BRAV600E mutant metastatic non-small cell lung cancer

Haleema Qayyum Abbasi, MBBS[a], Malik Olatunde Oduoye, MBBS[b,*], Aman Goyal, MBBS[c]

Lung cancer, one of the most prevalent types of cancer and the leading cause of oncological fatalities not only in the United States but also worldwide, claimed over 150 000 lives in the United States in 2018[1]. It is categorized into two types: small-cell lung cancer and non-small cell lung cancer. Non-small cell lung cancer (NSCLC) constitutes 85% of all lung cancer cases and is classified as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma[2]. More than half of patients with NSCLC usually present at an advanced stage when the disease has already progressed beyond the lungs (distant metastasis). The chances of surviving stage IVA metastatic NSCLC over a 5-year period are ~10%, while for stage IVB, the survival rate is less than 1%, making it a significant global health concern[1]. The aim of this article is to improve the knowledge of the general public on the recently endorsed encorafenib plus binimetinib, along two companion diagnostics, for BRAFV600E mutant metastatic NSCLC.

Although rare (only 2–4%), NSCLC patients have mutations in the BRAF gene, most commonly a point mutation in codon 600[3]. Approximately half of these mutations are BRAFV600E. More common in females, those with a history of smoking, and in adenocarcinoma cases, activating mutations in BRAF result in sustained signaling in the MAK pathway, which is normally suppressed by negative feedback, leading to unregulated cell division and oncogenesis[4]. BRAFV600E mutated metastatic NSCLC is not only associated with poor prognosis but is also less responsive to chemotherapy and radiotherapy. Nonetheless, platinum-based chemotherapy was the treatment of choice until the encouraging results of the phase II trial (NCT01336634) led to the approval of dabrafenib in combination with trametinib as the standard of care for these patients[5,6]. Although this combination therapy is widely endorsed, it poses challenges, including short dissociation half-life (2 h for dabrafenib) and serious side effects, of which pyrexia is the most common, followed by hypertension and disturbed hepatic enzyme levels, necessitating the review of current treatment modalities and efforts for novel approaches offering improved results[7].

On 11 October, the United States Food and Drug Administration (FDA) approved encorafenib plus binimetinib as a first-line treatment for adult patients with metastatic NSCLC harboring BRAFV600E mutations, making a major leap in the treatment of the disease[8]. Encorafenib is a second-generation oral rapidly accelerated fibrosarcoma (RAF) kinase inhibitor with enhanced properties, such as high bioavailability and the ability to maintain prolonged inhibition of mutant BRAFV600E due to its extended dissociation half-life (> 30 h), setting it apart from other BRAF inhibitors such as dabrafenib that dissociate rapidly. This extended duration results in enhanced target inhibition and greater potency. Binimetinib is an oral selective mitogen-activated protein kinase (MEK) inhibitor[6]. When administered in combination, these drugs inhibit the action of proteins encoded by mutant genes and halt the growth and proliferation of cancer cells. FDA approval came shortly after this drug combination displayed promising results in a phase II multicenter PHAROS trial in terms of both efficacy and safety, with only minimal adverse effects in this patient population[6]. In this trial, encorafenib plus binimetinib demonstrated a robust 75% overall response rate (ORR) in the previously untreated group, and the median duration of response (DoR) and progression-free survival (PFS) were not estimable. In the previously treated group, the drug combination exhibited a 46% ORR, with a substantial median DoR of 16.7 months and a noteworthy median PFS of 9.3 months. Gastrointestinal disturbances and fatigue were the most common adverse effects[6].

Recently, the FDA granted approval to two companion diagnostics, FoundationOne CDx and FoundationOne Liquid CDx, to help in the identification and stratification of patients with metastatic BRAFV600E mutant NSCLC who may benefit from this treatment[9]. FoundationOne CDx is an advanced diagnostic tool that uses next-generation sequencing. It identifies substitutions, deletions, copy number alterations (CNAs) in more than 300 genes, gene rearrangements, microsatellite instability (MSI), and tumor mutational burden (TMB) using DNA from a tumor tissue sample[9,10]. FoundationOne Liquid CDx is a minimally

[a]Department of Internal Medicine, Ayub Medical College, Abbottabad, Pakistan, [b]Department of Medical Research Circle, Bukavu, Democratic Republic of the Congo and [c]Department of Internal Medicine, Seth GS Medical College and KEM Hospital, Mumbai, India

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Medical Research Circle (MedReC), Bukavu, Democratic Republic of the Congo. Tel.: +234 9035928801.
E-mail: malikolatunde36@gmail.com (M.O. Oduoye).

International Journal of Surgery (2024) 110:1894–1895

Received 10 November 2023; Accepted 21 December 2023

Published online 11 January 2024

http://dx.doi.org/10.1097/JS9.0000000000001044

invasive blood-based test that analyzes genomic changes using a blood sample and is an easy alternative for patients who are not eligible for the former[9]. The FDA approval of encorafenib plus binimetinib along with companion diagnostics marks a significant milestone for these patients, who, for the very first time, not only have pharmacotherapy but also two companion diagnostics tailored to their specific condition, a need previously unmet. It is a significant breakthrough in the field of oncology and is likely to pave the way for research on advanced and targeted treatment modalities and revolutionize treatment approaches, in addition to substantially reducing the global disease burden.

Despite the significant anticancer activity and acceptable safety profile, caution should be exercised when administering this combination therapy, particularly in pregnant women, as the drug has shown abortifacient effects in animals[11]. However, there is a lack of clinical data regarding its use in pregnant women. Therefore, women with reproductive potential should be educated by physicians, especially obstetricians and gynecologists, about the harmful effects of this therapy and advised to use contraceptive methods before starting the treatment. Moreover, immunization with live vaccines should be withheld during and 12 months following the treatment, as a weakened immune system might result in decreased vaccine effectiveness and limited protection, leaving patients vulnerable to severe infections[12]. The current body of information on the safety of this combination therapy is inadequate, and broadening it could facilitate more comprehensive updates to management guidelines, potentially enhancing patient outcomes. Large-scale prospective studies, multicenter randomized trials, systematic reviews, and meta-analyses are required to validate the safety and efficacy of this treatment regimen.

Ethics approval

It is not applicable to this letter to the editor.

Consent

It is not applicable to this letter to the editor.

Sources of funding

No funding was received for this letter to the editor.

Author contribution

H.Q.A.: conceptualization of ideas and data curation; H.Q.A., M.O.O., and A.G.: writing the initial draft, critical review, and comments; M.O.O.: writing, reviewing, editing, supervision, and funding acquisition.

Conflicts of interest disclosure

The authors have no conflicting interests to declare that are relevant to the content of this article.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Malik Olatunde Oduoye, https://orcid.org/0000-0001-9635-9891.

Data availability statement

Not applicable to this work.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgements

None.

References

[1] Simeone JC, Nordstrom BL, Patel K, *et al*. Treatment patterns and overall survival in metastatic non-small-cell lung cancer in a real-world, US setting. Future Oncol 2019;15:3491–502.
[2] Medscape. Non-Small Cell Lung Cancer (NSCLC): Practice Essentials, Background, Pathophysiology. Accessed 2 November 2023. https://emedicine.medscape.com/article/279960-overview#a3
[3] Lin Q, Zhang H, Ding H, *et al*. The association between BRAF mutation class and clinical features in BRAF-mutant Chinese non-small cell lung cancer patients. J Transl Med 2019;17:298.
[4] Riely GJ, Ahn MJ, Felip E, *et al*. Encorafenib plus binimetinib in patients with BRAFV600-mutant non-small cell lung cancer: phase II PHAROS study design. Future Oncol 2022;18:781–91.
[5] Planchard D, Smit EF, Groen HJM, *et al*. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol 2017;18:1307–16.
[6] Riely GJ, Smit EF, Ahn MJ, *et al*. Phase II, Open-label study of encorafenib plus binimetinib in patients with BRAF V600-mutant metastatic non-small-cell lung cancer. J Clin Oncol 2023;41:3700–11.
[7] König D, Prince SS, Rothschild SI. Targeted therapy in advanced and metastatic non-small cell lung cancer. An update on the treatment of the most important actionable oncogenic driver alterations. Cancers (Basel) 2021;13:804.
[8] U.S. Food & Drug Administration. FDA approves encorafenib with binimetinib for metastatic non-small cell lung cancer with a BRAF V600E mutation | FDA. Accessed 2 November 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-binimetinib-metastatic-non-small-cell-lung-cancer-braf-v600e-mutation
[9] Foundation Medicine. FDA Approves FoundationOne®CDx and FoundationOne®Liquid CDx as Companion Diagnostics for Pfizer's BRAFTOVI® (encorafenib) in Combination With MEKTOVI® (binimetinib) to Identify Patients with BRAF V600E Alterations in Metastatic NSCLC | Foundation Medicine. Accessed 2 November 2023. https://www.foundationmedicine.com/press-release/fda-approves-foundationonercdx-and-foundationonerliquid-cdx-companion-diagnostics
[10] Shahnoor S, Mansha M, Farhat S, *et al*. Advancing precision oncology in metastatic colorectal cancer: the food and drug administration approval of foundation one liquid CDx as a companion diagnostic a correspondence. Rare Tumors 2023;15:20363613231204798.
[11] Medscape. Braftovi (encorafenib) dosing, indications, interactions, adverse effects, and more. Accessed 2 November 2023. https://reference.medscape.com/drug/braftovi-encorafenib-1000232#6
[12] Priyanka, Chopra H, Choudhary OP. mRNA vaccines as an armor to combat infectious diseases. Travel Med Infect Dis 2023;52:102550.