Review

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Navigating the complexity of BRAF mutations in non-small cell lung cancer: current insights and future prospects

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ABSTRACT

There are many challenges that are faced in the treatment of Non-Small Cell Lung Cancer (NSCLC) due to the complexities associated with the tumor. Association of different types of mutations are one of the major complexities. Among these mutations, BRAF mutations are significantly gathering more attention due to their impact on disease progression and therapeutic response. This review provides an analysis of the current understanding of BRAF mutations in NSCLC, focusing on the molecular intricacies, clinical implications, and therapeutic advancements. The article explores the diverse spectrum of BRAF mutations, highlighting the prevalence of specific mutations such as V600E and non-V600E alterations. The review also highlights the intricate signalling pathways influenced by BRAF mutations, shedding light on their role in tumorigenesis and metastasis. Therapeutically, we critically evaluate the existing targeted therapies tailored for BRAF-mutant NSCLC, addressing their efficacy, limitations, and emerging resistance mechanisms. Furthermore, we outline ongoing clinical trials and promising investigational agents that hold potential for reshaping the treatment of NSCLC. This review provides comprehensive current information about the role of BRAF mutations in NSCLC. Understanding the molecular diversity, clinical implications, and therapeutic strategies associated with BRAF-mutant NSCLC is crucial for optimizing patient outcomes and steering the direction of future research in this evolving field.

Key words: NSCLC; thoracic cancer, malignancy, targeted therapy

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Introduction

Lung cancer, causing over a million deaths annually worldwide, is the primary contributor to cancer-related mortality. About 85% of patients with lung cancer are diagnosed with non-small cell lung cancer (NSCLC). The 5-year survival rate of NSCLC is approximately 17% [1]. The currently available treatment modalities available for NSCLC includes i) Chemotherapy drugs: i.e. cisplatin, carboplatin, paclitaxel, docetaxel, gemcitabine, vinorelbine, and etoposide. ii) Targeted drugs: these drugs are often the first treatment option for advanced NSCLC with a ROS1 (ROS proto-oncogene 1) rearrangement. Examples include entrectinib, crizotinib, and ceritinib. Lorlatinib is another option for patients with ROS1-mutated advanced NSCLC. iii) Immunotherapy drugs: these drugs include PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) immune checkpoint inhibitors. Some examples are nivolumab, pembrolizumab, ipilimumab, and tremelimumab [2].

Treatment options for NSCLC also depend on the stage of the cancer. For example, stage 0 NSCLC is usually curable with surgery alone, while stage I NSCLC may only require surgery. There are several mutations that occur in NSCLC that are currently the targets for numerous drugs. One of such mutations that we come across in NSCLC is that of BRAF. BRAF is a serine-threonine kinase and plays a major role in the mitogen-activated protein kinase (MAPK) pathways. BRAF mutations are found in different types of solid tumors, and in approximately 4% of NSCLC. NSCLC exhibits various BRAF mutation variants, with the prevalent form being V600E. About 2% of patients with NSCLC have mutations in BRAF gene and a significant number of them have a history of smoking [3].

With the availability of immunotherapy and targeted BRAF inhibitors, the overall survival rate has significantly improved in NSCLC patients. Combinatorial approaches, exploring anti-BRAF therapies targeting both MAPK signalling and the PI3K/mTOR pathway, have been extensively investigated to enhance treatment outcomes in BRAF-mutant NSCLC. Immunotherapy is proving to be a promising treatment for BRAF-mutated NSCLC, encompassing both V600E and non-V600E subtypes. Considering the established efficacy of combination RAS–RAF–MEK–ERK pathway inhibition targeted therapy and early indications of immune checkpoint inhibitor activity, careful consideration is essential in choosing the most suitable treatment for this specific patient group. However, resistance to BRAF inhibitors has emerged over time, necessitating an understanding of the underlying mechanisms to devise effective strategies for overcoming it. The comprehension of molecular resistance mechanisms to BRAF inhibitors is now crucial for optimizing clinical success, achieving enduring responses, and extending patient survival. One of the common causes of treatment failure is resistance to targeted agents. This occurs through various mechanisms which include secondary mutations, epigenetic changes, alterations of drugs metabolism and activation of compensatory pathways, fostering increased tumor cell survival. The elucidation of these mechanisms following BRAF inhibition is currently unfolding.

This paper offers an updated comprehensive overview of the role of BRAF mutations in NSCLC patients, referencing recent literature. The review details the biology of BRAF mutations, their significance in NSCLC, pharmacological inhibition, and provide an in-depth examination of current therapeutic targeting strategies. Additionally, we explore the mechanisms underlying therapeutic resistance, strategies to overcome resistance, and consider future prospects for BRAF-mutant NSCLC.

BRAF – Structure and physiology

Protein kinases are essential enzymes that play an integral part in protein phosphorylation. Kinases are involved in several cellular pathways that are instrumental in signal transduction and their nomenclature is based on the phosphorylating amino acid residue. Among them, serine-threonine kinases comprise the majority of kinases, BRAF, being one of them [4]. BRAF is made up of 766 amino acids. The BRAF gene (B-raf proto-oncogene) codes BRAF. The gene is located on chromosome 7 (7q34) [5].

Structure of BRAF protein

The BRAF protein comprises of three regions - CR1 is the RAS binding domain, CR2 is involved in regulatory domain and CR3 is the catalytic kinase domain (Figure 1) [6–9].

The N-terminal domain houses the CR1 region, spanning amino acids 155 to 290. Of particular significance within CR1 is the RAS GTP binding domain (RBD), positioned between amino acids 155 and 227. In its inactive state, the CR1 region, containing the RBD, acts in a self-inhibitory manner towards the kinase domain (CR3), thereby maintaining regulatory control over BRAF signalling and preventing its constitutive activation. The activation of the RBD within CR1, however, releases the inhibition on kinase activity, facilitating the initiation of BRAF signalling.

CR2 is a flexible hinge between CR1 and CR3, characterized by an abundance of serine and threonine residues. CR2 consists of amino acids 360 to 375.

The CR3 domain, spanning amino acids 457 to 717, comprises specific structural components, including the P-loop (amino acids 464–471), the αC helix (amino acids 492–504), the dimerization interface (DIF, amino acids 504–511), the catalytic loop (amino acids 574–581), the DFG motif (amino acids 594–596), and the activation segment (amino acids 594–623). Within the smaller N-lobe of CR3, the ATP binding site is located, featuring a P-loop responsible for stabilizing ATP and maintaining BRAF in an inactive state. In contrast, the larger C-lobe binds to the substrate protein. The inactivity of BRAF is preserved through the interaction between the activation segment, which includes an αC helix fostering RAS/RAF interaction and RAF dimerization, and the dimerization interface. The significance of the C-terminal end of CR3 lies in its pivotal role in binding substrate proteins, facilitated by the catalytic loop that enables the effective transfer of phosphate from ATP to BRAF substrates. In the C-terminal end of CR3, an obstructive DFG motif hinders the ATP binding pocket during BRAF inactivity, sustaining a stabilized open conformation. The activation segment within CR3 reinforces the inactive state through strong interactions with the P-loop. The catalytic center of RAF proteins is situated within the cleft between the N- and C-lobes. It is a crucial component of the mitogen-activated protein kinase (MAPK) signalling pathway [10–13].

RAS-RAF-MEK-ERK Signalling pathway

This pathway (Figure 2) plays a pivotal role in modulating cell proliferation, differentiation, and apoptosis in response to various other factors like cytokines, growth factors, hormones, and environmental stressors. Proteins undergo several chemical changes following translation which is referred to as post-translational modifications (PTM). It brings about changes in the physical, chemical and functional properties of the protein. PTM contributes to proteomic diversity. There are over 300 types of post-translational modifications that have been characterized in eukaryotic protein biosynthesis. Phosphorylation, acetylation,

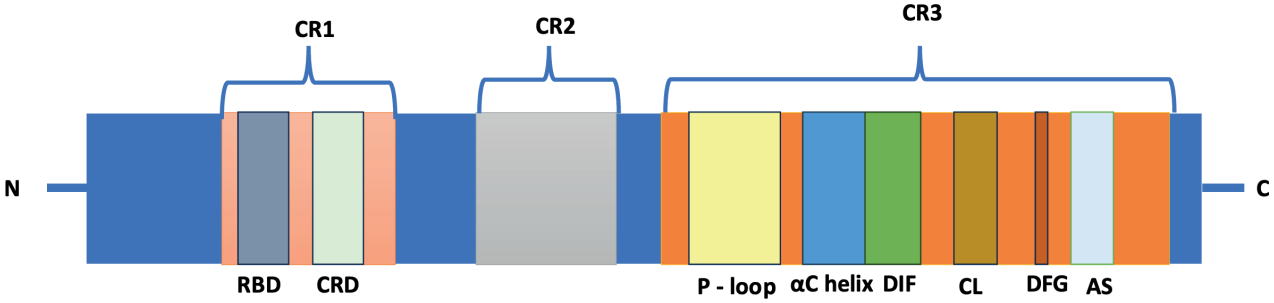

Figure 1. Schematic representation of BRAF Structure. The B-Raf protein, encoded by the BRAF gene, consists of distinct domains, including the N-lobe and C-lobe within the kinase domain, Ras-binding domain(RBD), cystine-rich domain (CRD) in (CR1), regulatory domain (CR2), and activation segment (CR3). The kinase domain contains crucial structural elements such as the P-loop, αC helix, dimerization interface (DIF), catalytic loop (CL), and DFG motif. These elements play essential roles in BRAF activation and downstream signalling within the MAPK pathway.

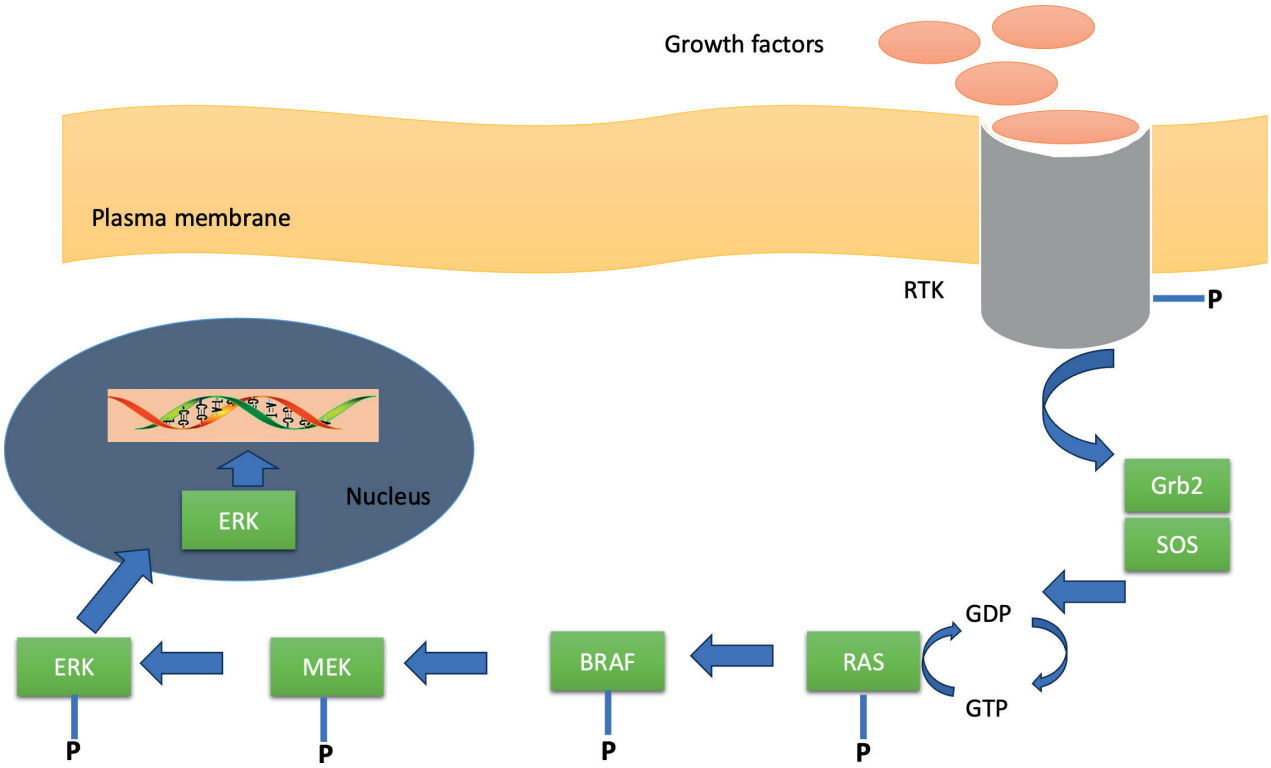

Figure 2: Ras-Raf-MEK-ERK pathway. Schematic representation of the RAS-RAF-MEK-ERK signaling pathway. Ligand binding, typically by growth factors, activates receptor tyrosine kinases (RTKs) leading to the phosphorylation and dimerization of the receptors. This event initiates a cascade of intracellular signaling, involving RAS activation, recruitment of RAF to the plasma membrane, and phosphorylation of MEK (Mitogen-Activated Protein Kinase/ERK Kinase). Subsequently, ERK (Extracellular Signal-Regulated Kinase) is activated and translocates to the nucleus, where it regulates gene expression associated with crucial cellular processes like proliferation, differentiation, and survival. The pathway is tightly regulated, and dysregulation can contribute to various diseases, particularly cancer.

glycosylation, succinylation ubiquitination, methylation and hydroxylation are some of the most witnessed post-translational modifications. Phosphorylation is one of the most important PTM which is required for regulating cell growth, differentiation and apoptosis [4,5]. While all members of the RAF kinase family, including A-Raf and C-Raf, exhibit the ability to phosphorylate Mitogen-Activated Protein Kinase/ERK Kinase (MEK), BRAF stands out with its notably robust activation capacity[14].

The process begins with binding ligands, such as growth factors, to receptor tyrosine kinases (RTKs). This interaction induces dimerization of the RTKs, resulting in the autophosphorylation of multiple tyrosine residues within the intracellular domain. Phosphorylated tyrosine residues serve as recognition sites for the SH2 domain of Grb2, facilitating their binding. This interaction activates SOS (Son of Sevenless), leading to the exchange of GDP for GTP on the RAS protein. The activated RAS-GTP then binds to the CR1 region of BRAF, initiating a conformational change that activates the BRAF kinase. Activated BRAF proteins can form dimers. Dimerization is often facilitated by the interaction between the RAF proteins and activated RAS. RAF dimers have increased kinase activity compared to monomers and are crucial for signal amplification. Activated BRAF kinases phosphorylate and activate MEK. MEK, in turn, phosphorylates and activates ERK (Extracellular Signal-Regulated Kinase). Activated ERK translocate to the nucleus and phosphorylates various transcription factors, leading to changes in gene expression. This nuclear signalling cascade regulates cellular responses such as proliferation, differentiation, and survival. The pathway is tightly

regulated by negative feedback mechanisms to prevent excessive signalling. ERK, once activated, can phosphorylate and inhibit upstream components, including RAF and RTKs, to attenuate the signal [11–13].

Role of BRAF in NSCLC

Mutations in BRAF

Among the three isoforms of RAF protein kinases (A, B and C), BRAF exhibits the strongest activity with the highest frequency of mutations. BRAF mutations can lead to the over-activation of MAPK signalling pathway leading to uncontrolled cell proliferation leading to the genesis of several cancers [15]. Mutations in BRAF are seen in an estimated 8% of cancers. Malignant melanoma, hairy cell leukemia, colorectal cancer, and thyroid carcinoma are the predominant cancers in which BRAF mutations are seen. BRAF mutations are seen in a small section of lung cancer patients [16].

BRAF mutations are of three classes (I, II and III). In Class I mutation, in the exon 15, valine is replaced with other amino acids. Based on the amino acid -glutamic acid, lysine, or arginine that replaces valine they are named V600 E, V600 K and V600 R respectively. This mutation enables BRAF to function constitutively without any ligand binding to it. This is the most frequently occurring BRAF mutation leading to uncontrolled cell proliferation. Class II and Class III are referred to as non-V600 E mutations. Class II mutation also enables constitutive activity of kinase but it is weaker compared to class I mutations. Class III mutations reduce the kinase activity or render it inactive. In Class I and II mutations, there is a gain of function whereas in Class III mutations, there is a loss of function [17]. As per a study done to check the prevalence of BRAF mutations across cancers from a large genomic database, it was seen that Class I, II and III mutations comprised of 62.1%, 16.5% and 17.7% of all cancers [18]. A minority of cases of BRAF fusions (<1%) are seen where the gene fuses with another and results in hybrid proteins. Currently, the drugs that are effective for NSCLC act against the V600E mutations.

Detection of BRAF mutations in NSCLC

BRAF V600E point mutation is a well-established predictive biomarker. The National Comprehensive Cancer Network guidelines (2018) advises testing for the BRAF V600E mutations as a part of routine testing in advanced NSCLC along with other important established predictive biomarkers [19]. Conventionally, single gene assay and real-time PCR are employed to detect mutation in a specific gene from the tumor tissue. However, the preferred method would be next-generation sequencing (NGS) which can analyze all classes of BRAF mutations in detail. It offers a powerful diagnostic tool by allowing the detection of multiple mutations across various genes simultaneously in a single test. NGS is sensitive in detecting low-frequency mutations, unlike conventional methods [20]. Liquid biopsy that utilizes body fluids can be opted in patients when tissue biopsy is not possible [21].

Treatment of BRAF mutated NSCLC

The management of BRAF-mutated NSCLC involves a combination of targeted therapies, chemotherapy, and immunotherapy, tailored to the specific mutation type and individual patient factors. Chemotherapy is usually indicated for patients with BRAF mutations who are not candidates for targeted therapy or have progressed on it. Common regimen includes Platinum-based doublets (e.g., carboplatin + pemetrexed or paclitaxel) [22]. Immunotherapy consists of immune checkpoint inhibitors (e.g., Pembrolizumab, Nivolumab) are used in patients with high PD-L1 expression or in combination with chemotherapy.

In patients with BRAF-mutated non-small cell lung cancer (NSCLC), targeted therapies are pivotal in improving outcomes. These therapies specifically target cancer cells with BRAF mutations, sparing normal cells, thus reducing side effects and improving patient outcomes. The choice of therapy depends on the mutation type, tumor stage, and the patient's overall condition. Targeted therapies are explained in detail below.

Monotherapy

BRAF gene is responsible for different cellular processes including differentiation and proliferation of cells. Any alteration in the BRAF gene leads to abnormal signaling which might even lead to different kinds of cancer including NSCLC. Though BRAF mutation accounts for approximately only 4% of all NSCLC, this amount is significant if the total number of patients suffering from NSCLC is taken into consideration [23]. BRAF mutation also leads to alterations in the tumor microenvironment, in addition to affecting the cellular signaling pathway. These alterations include increase in the activity of immunosuppressive mediators, decrease in the activity of immunostimulatory mediators, increased expression of vascular endothelium growth factor (VEGF), reduced activity of cytotoxic T cells and decrease in programmed cell death through pyroptosis [24]. Hence, it is theorized that drugs that inhibit the mutated BRAF kinase activity would be useful in treatment of NSCLC that are associated with BRAF gene mutations. The drugs that were tried are dabrafenib, vemurafenib and encorafenib. These drug act by attaching to ATP binding site of the BRAF gene and inhibiting BRAF kinase activity resulting in prevention of ERF phosphorylation and cellular proliferation. The cells get arrested in G1 phase of cell cycle and there is also enhanced apoptosis. These drug act primarily on BRAF V600E mutated NSCL [25]. Studies showed that treatment with these drugs did improve the objective response rate (ORR) and overall survival rate [26]. However, within 6 to 7 months of treatment initiation, it was observed that the disease progressed. It was also seen that there was a higher incidence of other cutaneous malignancies (primarily squamous cell carcinoma and keratoacanthoma) [27]. The reason for disease progression as well as hyperproliferative cutaneous reactions was attributed to reactivation of the MAPK pathway through different mechanisms after the primary BRAF signaling pathway was blocked. This leads to hyper signaling through the MAPK pathway [28]. Monotherapy is therefore not prescribed routinely.

Dual therapy

As it was observed that there was disease progression and adverse effects due to activation of the MAPK pathway, hence, MEK inhibitors were tried along with BRAF inhibitors. Dual treatment led to overcoming the resistance to BRAF inhibitors and prevented the development of cutaneous adverse effects. Combination therapy was useful in blocking even the BRAF wild type tumor cells [29]. MEK inhibitors include trametinib and binimetinib. The FDA approved combinations for metastatic NSCLC with BRAF V 600E mutations include dabrafenib + trametinib and encorafenib + binimetinib. FDA has approved the combination therapies (Table 1) based on positive results obtained in the BRF113928 and

Table 1. FDA approved targeted therapy combinations for NSCLC associated with BRAF V600E mutations.

Combination Name	Date of approval	Clinical trial evidence for approval	Indication	Dose	Common adverse effects
Dabrafenib and Trametinib	22 June 2017	BRF113928	Adults with Metastatic non-small cell lung cancer with BRAF V600E mutation. Approved for children less than 6 years on 22 June 2022	Dabrafenib 150mg orally twice daily and Trametinib 2mg orally once daily. One hour before or 2 hours after food	Pyrexia, fatigue, nausea, headache, myalgia, chills, rash, hemorrhage
Encorafenib and Binimetinib	11 Oct 2013	PHAROS trial	Adults with metastatic NSCLC with BRAFV600E mutation	Encorafenib 450mg orally once daily and Binimetinib 45mg orally twice daily. Need not be taken empty stomach	Fatigue, nausea, diarrhoea, musculoskeletal pain, abdominal pain, visual impairment, constipation, dyspnea, hair thinning, rash, cough, bleeding

PHAROS clinical trials [30,31] . There are other trials (COMBI-d, COMBI-V) that have also supported the results, in metastatic malignant melanoma patients positive for BRAF V600E mutations [32,33]. A multi-centric real-world study has also confirmed better ORR and prolonged overall survival rate in BRAF mutated NSCLC patients with the combination therapy compared to individual therapy or any other first line agent [34]. The combination therapy is well tolerated except for the increase in gastrointestinal side effects [35]. Most of the adverse effects observed are usually seen during initiation of treatment and they are reduced later. Hence, monitoring patients is very important during this phase. As per the latest oncology guidelines for NSCLC, dabrafenib and trametinib dual therapy has been recommended as the first line treatment for metastatic NSCLC with BRAF V600E mutations [36–38]. Since BRAF mutations are less common, it is difficult to find large number of patients for phase III clinical trials for comparing these drugs with the standard of care. Hence, treatment is usually recommended based on phase I/II trials.

Triple therapy

As the BRAF kinase pathway is involved in numerous immunological functions in the body and BRAF mutations are known to cause significant immunological changes in the body, hence addition of an immunotherapy to the BRAF/MEK inhibitors would theoretically improve the tumor environment and T cell response. Immunotherapy as monotherapy is also being tested in BRAF mutated NSCLC [39]. A triple drug regimen consisting of vemurafenib (BRAF inhibitor) + cobimetinib (MEK inhibitor) + atezolizumab (check point inhibitor) is already approved by the US-FDA for patients with BRAF V600E mutated metastatic malignant melanoma based on the results of IMspire150 trial [40]. However, efficacy of the triple drug combination in NSCLC is yet to be established.

NSCLC with a non-v600 BRAF mutation treatment

The treatment for non-small cell lung cancer (NSCLC) with non-V600 BRAF mutations can be challenging due to the limited data available. However, several strategies may be considered: i. Targeted therapy: While specific targeted therapies for non-V600 mutations are not as well-established, some evidence suggests that agents targeting other pathways, such as MEK inhibitors (e.g., trametinib), may be effective in certain cases. ii. Chemotherapy: standard chemotherapy regimens can still be a viable option for patients with non-V600 mutations, often combined with other agents based on the individual patient's tumor characteristics. iii. Immune checkpoint inhibitors: Agents such as pembrolizumab or nivolumab may be considered, particularly if there is high PD-L1 expression. These treatments have shown efficacy in various subtypes of NSCLC. Participation of these patients in clinical trials can provide access to emerging therapies and combinations tailored to specific mutations, including those with non-V600 BRAF alterations [41].

Drug resistance

Targeting BRAF and downstream MEK pathway is the current strategy for treatment of BRAF mutant NSCLC and is shown to produce significant therapeutic benefit. However, most of the patients develop disease progression within 1 year [42]. Resistance to targeted therapy poses a challenge to achieving a cure in NSCLC [43]. Studies related to resistance to targeted drugs in NSCLC are limited [44]. Most of the studies published are those of malignant melanoma. It was seen that approximately 50% of patients develop resistance within a year to monotherapy with dabrafenib [45] or vemurafenib [46] and also to combination therapy with Encorafenib + Binimetinib [47]. Studies have shown that usually the resistance to targeted therapy is due to enhancement in the signalling of the ERK bypassing the block caused by BRAF kinase. It has been noticed that there is amplification in ERK signalling when there is BRAF splice variants (16%), BRAF gene amplification (13%), NRAS/KRAS (20%) and MEK1/2 mutations (7%) [48,49]. These occur independent of BRAF action. In addition to the counter regulatory enhancement in the ERK pathway, the other major pathway through which resistance can develop is by PI3K-AKT activation observed following use of BRAF inhibitors in malignant

melanoma [42]. The MATCH-R trial evaluated those with BRAFV600E NSCLC along with acquired resistance to BRAF/MEK inhibitors. Three patients who progressed on dabrafenib-trametinib combination had acquired mutations in MEK1 K57N, NRAS (v-RAS) Q61R and KRAS (rat sarcoma virus) Q61R. A PTEN frameshift mutation was seen in a patient progressing while on dabrafenib therapy alone [50]. In most cases, secondary resistance to dual inhibition of BRAF and MEK involves reactivation of the MAPK pathway and ERK signalling, though the mechanisms are more complicated in the case of resistance to dual therapy as compared to monotherapy [42,50–52]. It is valuable to identify acquired resistance mechanisms to develop novel therapeutic agents, customize treatment, and improve patient outcomes.

Future prospects

Lung cancer, particularly NSCLC, remains a formidable challenge in oncology, prompting a continual search for novel therapeutic strategies. Among the various molecular alterations implicated in NSCLC, BRAF mutations have gained attention, and recent clinical trials are shedding light on promising avenues for the future. One such avenue is the Phase Ib/II clinical trial assessing the combination of HLX208, a potent BRAF V600E inhibitor, with serplulimab, an anti-PD-1 antibody. This trial aims to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of this innovative combination in advanced NSCLC patients harbouring the BRAF V600E mutation [53]. The significance of this trial lies in its potential to expand the repertoire of treatment options for a subset of NSCLC patients who exhibit this specific, commonly encountered genetic alteration. Concurrently, an observational Phase II study investigates a unique combination involving aspirin with Trametinib and Dabrafenib in advanced NSCLC patients carrying the BRAF V600E mutation. Building on previous findings that suggested aspirin might enhance the efficacy of osimertinib, this study endeavours to delineate the safety and efficacy of this unconventional therapeutic approach [54]. By leveraging the insights gained from previous studies, which demonstrated prolonged progression-free survival with aspirin, the trial seeks to establish a rationale for incorporating aspirin into the treatment paradigm for BRAF-mutant NSCLC.

The landscape of BRAF-mutant NSCLC is further explored in a Phase II study designed to assess the efficacy and safety of neoadjuvant and adjuvant targeted therapy. Specifically, patients with stage IB-IIIA NSCLC harbouring BRAF V600 mutations are treated with dabrafenib plus trametinib [55]. This trial not only delves into the efficacy of this targeted therapy but also considers the optimal sequencing of therapeutic modalities, combining neoadjuvant and adjuvant strategies to comprehensively address the disease spectrum. In a Phase 1/2 open-label multicenter trial, the investigation of CFT1946 as a standalone treatment and in conjunction with trametinib was initiated [56]. The primary objectives of this trial encompass the assessment of safety, tolerability, and early efficacy of CFT1946 in individuals diagnosed with solid tumors harbouring the BRAF V600 mutation. The study is designed to comprehensively evaluate the therapeutic potential of CFT1946, exploring both monotherapy and combination strategies, thereby aiming to offer a nuanced comprehension of its effectiveness within the context of BRAF-mutant NSCLC.

The BDTX-4933-101 trial represents a first-in-human, open-label, Phase 1 dose escalation, and expansion cohort study evaluating the safety, tolerability, and antitumor activity of BDTX-4933 [57]. The study population encompasses adults with recurrent advanced/metastatic NSCLC harboring KRAS non-G12C mutations or BRAF mutations. This trial not only investigates the safety profile and antitumor activity of BDTX-4933, but also explores the potential efficacy of this novel agent in the context of BRAF-mutant NSCLC. Moreover, a multicenter, open-label Phase II study focuses specifically on the Chinese patient population, evaluating the safety and tolerability of encorafenib monotherapy in patients with advanced metastatic solid tumors harbouring BRAF V600E mutations. This study recognizes the importance of studying therapeutic responses in diverse patient populations, considering potential variations in treatment outcomes. In another Phase II study, the efficacy and safety of avutometinib (VS-6766) versus

its combination with defactinib are being investigated in subjects with KRAS and BRAF mutant NSCLC following treatment with an appropriate platinum-based regimen and an approved immune checkpoint inhibitor (CPI) [58]. This trial capitalizes on the growing understanding of the interplay between different signaling pathways, aiming to optimize therapeutic responses through combination strategies.

Adding to this growing body of evidence, a phase II trial assesses the combination of the BRAF inhibitor encorafenib with the MEK inhibitor binimetinib in patients with BRAF V600E-mutant metastatic NSCLC [59]. This trial is crucial in elucidating the synergistic effects of combined BRAF and MEK inhibition in the specific subset of NSCLC patients with BRAF V600E mutations. Another single-arm, open, multicenter Phase II study evaluates the efficacy and safety of HL-085 capsules combined with vemurafenib in the treatment of BRAF V600E mutated patients with unresectable locally advanced or metastatic NSCLC, aiming to contribute insights into the potential of HL-085 capsules as part of the treatment armamentarium for BRAF V600E mutated NSCLC [60].

Conclusion

In conclusion, through an in-depth exploration of recent literature, we have elucidated the multifaceted aspects of BRAF mutations, starting from their biological underpinnings to their clinical significance in NSCLC patients. The array of ongoing clinical trials reflects the dynamic landscape of research in BRAF-mutant NSCLC. These trials, collectively, hold the promise of shaping the future of treatment paradigms for NSCLC patients harbouring BRAF mutations. The insights gained from these studies may not only enhance our understanding of the underlying biology of BRAF-mutant NSCLC, but also pave the way for more personalized and effective therapeutic approaches, ultimately improving patient outcomes. Through continued research and collaborative efforts, the landscape of BRAF-mutant NSCLC is poised for further elucidation, offering new avenues for improving patient outcomes and ultimately advancing the field of precision oncology.

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