

Company

Pfizer Inc.

Drug or Device Name

Braftovi® Mektovi®

Category

Pharmaceutical

Compound/Technical Name

encorafenib, binimetinib

Trade Name

Braftovi® Mektovi®

Date of Approval

06/27/2018

Therapeutic Categories

Cancer

Indications

For use in combination in patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Background

Melanoma is a skin cancer that begins in the melanocytes, cells in the epidermis which produce melanin. It is the most lethal form of skin cancer due to its propensity to metastasize to vital organs, including the brain, lungs and liver. The incidence of malignant melanoma is increasing in the United States, with approximately 106,110 new cases and 7,180 melanoma-related deaths anticipated in 2021. Significant risk factors for melanoma include exposure to ultraviolet light, including a history of sunburns and tanning, dysplastic nevi and dysplastic nevus syndrome. Caucasians are at higher risk than other populations. While early-stage melanomas are treated by surgery with curative intent, the five-year survival rate for metastatic melanoma implicating distal organs is 27%.

The growth factor receptor/Ras/Raf/MEK/ERK axis is an important molecular driver of many human cancers. The overexpression of growth factor receptors and oncogenic mutations in Raf or Ras are implicated in various cancers. The dysregulation of this pathway leads to elevated phospho-ERK, which in turn phosphorylates and thereby activates cytosolic and nuclear proteins that regulate cell growth, survival, angiogenesis and differentiation. As these processes are all central to the cancer phenotype, inhibition of this pathway is a potential strategy for treating diverse cancers.

The dual specificity protein kinases MEK1/2 are the immediate upstream regulators of ERK phosphorylation. These proteins are the only widely accepted substrates of Raf proteins, and ERK 1/2

are the only known substrates for MEK1/2. This specificity formed the basis for significant cross-industry interest in MEK1/2 as an oncology target.

Approximately 50% of patients with metastatic melanoma have mutations in BRAF, and over 95% of these mutations are BRAF V600E. These mutations result in constitutive activation of BRAF protein, with a 500x increase in BRAF activity, and downstream signal transduction in the RAF/MEK/ERK pathway. Importantly this mutation is mutually exclusive with the BRAFV600 mutation. In a prospective study of 197 metastatic melanoma patients, BRAF mutations were associated with features of high-risk melanoma including truncal primary lesion, earlier age of onset, lack of chronic skin damage and shortened survival.

Treatment guidelines for BRAF-mutated metastatic melanoma include checkpoint inhibitor therapies or combination therapies with MEK and BRAF inhibitors, which have replaced BRAF inhibitor monotherapy as the standard of care. Although studies have shown that BRAF-targeted monotherapy with vemurafenib or dabrafenib is effective in BRAF-mutant melanoma, the duration of response is often limited, with resistance developing within 6 months. In an attempt to delay resistance to BRAF inhibition, the combination of BRAF and MEK inhibitors was investigated clinically in patients with advanced BRAF mutant melanoma. These trials demonstrated that the efficacy of BRAF/MEK combination therapy (dabrafenib/trametinib and vemurafenib/cobimetinib) was improved compared to either vemurafenib or dabrafenib alone.

Development

Encorafenib is a highly selective adenosine triphosphate (ATP)-competitive small-molecule RAF kinase inhibitor, which suppresses the RAS/RAF/MEK/ERK pathway in tumor cells expressing BRAF V600 mutations, including melanoma cell lines. In contrast, encorafenib was not anti-proliferative in the majority of BRAF wild-type cell lines.

Binimetinib is a potent and selective allosteric, ATP uncompetitive inhibitor of mitogen-activated protein kinase kinase (MEK) 1 and MEK 2. It is the first MEK inhibitor to demonstrate activity in NRAS mutation positive melanoma in a controlled pivotal trial (Dummer et al 2017). It is active in inhibiting phosphorylated extracellular signal-regulated kinase (pERK) and growth of BRAF mutated cancer cells in the low nanomolar range.

Encorafenib and binimetinib were developed as a doublet based on the scientific rationale that MAPK pathway reactivation is implicated in BRAF-inhibitor monotherapy resistance. Additionally, toxic effects associated with BRAF inhibition, notably secondary squamous-cell skin cancer and other skin toxicities, are caused by BRAF inhibitors paradoxically activating the wild-type BRAF kinase, promoting dimerization that triggers RAS-independent transactivation, and activation of the MAPK pathway in normal tissues.

The binimetinib discovery program began with allosteric MEK1/2 inhibitor leads that were published in the literature. Since all protein kinases depend on ATP binding for their enzymatic function, compounds that are uncompetitive with ATP are especially attractive starting points for kinase inhibitor programs, as they likely have higher selectivity for the desired kinase target. These compounds, exemplified by CI-1040 and PD-0325901, were taken forward into clinical studies but were discontinued from development. The poor solubility and metabolic stability of CI-1040 led to its discontinuation owing to poor target coverage in human clinical studies. Thus, the primary objective of the binimetinib team was to develop improved uncompetitive MEK1/2 inhibitors with enhanced pharmacokinetics.

The binimetinib team developed a pharmacophore model for MEK1/2 inhibition after studying the

structural similarity between these compounds and other published MEK1/2 inhibitors. This model revealed the crucial positioning of three hydrogen bond acceptors and two hydrophobic aromatic surfaces. Evaluating opportunities to incorporate these pharmacophoric features into an improved scaffold with lower lipophilicity led to replacement of the central aromatic ring with benzimidazole 1. This template showed excellent MEK enzyme potency but suffered from inhibition of cytochrome P450 3A4. Since most chemotherapeutic agents are used in combination, the team focused on removing this drug interaction liability by increasing steric bulk around the imidazole. The benzimidazole scaffold 2 was unique in preserving strong MEK1/2 inhibition while reducing CYP 3A4 liabilities. Alkylation at other positions on the benzimidazole ring was not tolerated, and while larger substituents could be accommodated at the N3 position, none provided a better balance of cellular potency and physicochemical properties. Exploration of the hydroxamate ester group led to the finding that small, polar aliphatic groups, such as in 3, yielded improved cellular potency and metabolic stability without significantly compromising permeability. Finally, optimization of the aryl amine led to the clinical candidate 4, binimetinib.

Binimetinib exhibits potent, ATP-uncompetitive activity against MEK1/2 (12 nM). As expected from its uncompetitive mechanism of kinase inhibition, binimetinib shows exquisite MEK1/2 selectivity, with no reported activity against a panel of 220 other serine/threonine kinases at concentrations as high as 20 μ M. Binimetinib inhibits basal and induced ERK phosphorylation in numerous cancer cell lines with IC50s as low as 5 nM. On the basis of data generated in preclinical models, binimetinib was advanced to clinical studies for advanced BRAF mutant metastatic melanoma as a single agent and in combination with encorafenib.

The combination of binimetinib and encorafenib was studied in the Phase III COLUMBUS trial, which enrolled 577 patients who received either 450 mg encorafenib once daily plus 45 mg binimetinib twice daily, or 300 mg encorafenib once daily or vemurafenib 960 mg twice daily. With a median follow-up of 32.1 months, median PFS was 14.9 months in the encorafenib + binimetinib group and 7.3 months in the vemurafenib group. An updated descriptive analysis revealed overall survival of 33.6 months for the encorafenib + binimetinib arm and 16.9 months for the vemurafenib arm. Compared with vemurafenib, the combination of encorafenib and binimetinib decreased the risk of death by 39% as well as increased in progression free survival (PFS) from 7.3 months (vemurafenib) to 14.9 months (encorafenib + binimetinib). The most frequently observed adverse events were diarrhea (38.5%), vomiting (31.8%), fatigue (29.7%) and arthralgia (28.6%) in the COMBO arm. Grade 3-4 toxicities included increased blood creatinine kinase (7.8%), pyrexia (3.6%), diarrhea (2.6%) and fatigue (2.1%). On the basis of these results, the FDA granted approval for binimetinib/encorafenib for the treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation in June, 2018. Please see important safety information and full prescribing information at www.braftovimektovi.com

Innovation

Vemurafenib was the first oral BRAF kinase-specific inhibitor showing a survival benefit in a Phase III clinical study of BRAF metastatic melanoma. Dabrafenib is another BRAF kinase-specific inhibitor that demonstrated efficacy as a monotherapy. Although tumor response rates with these two agents were excellent, Progression Free Survival (PFS) and Overall Survival (OS) were less promising. Tumors in some patients exhibited intrinsic resistance to these BRAF inhibitors, whereas others acquired resistance within a period of months. This resistance was associated with reactivation of the MAPK and PI3K-AKT pathways. Combining MEK inhibitors with BRAF inhibitors led to improved efficacy outcomes and decreased cutaneous toxicities associated with MAPK pathway reactivation. Class-specific side effects of BRAF inhibitors can be partially explained by paradoxical activation of the

MAPK pathway in BRAF wild type cells in various tissues. While V600-mutated BRAF acts as a constitutively active monomer and is specifically inhibited by BRAF inhibitors in its monomer form, wild type BRAF signaling is facilitated by dimerization as a homodimer or heterodimer with CRAF. The aforementioned BRAF inhibitors are not only incapable of inhibiting the dimeric form of BRAF, they promote formation of the dimer through allosterically induced conformational changes on the wild type protein, leading to activation of the MAPK pathway, especially in cells with preexisting RAS mutations. This paradoxical activation is thought to be responsible for cutaneous squamous cell carcinoma and other side effects mentioned above.

Encorafenib was developed with the goal of extending on-target binding time. The dissociation half-life of encorafenib is substantially increased (>30h) relative to other BRAF inhibitor agents (2h and 0.5h, respectively). This prolonged target engagement was confirmed in cellular washout studies and is associated with increased antiproliferative activity across a broad panel of tumor cell lines. Another consequence of this long pharmacodynamic half-life is the possibility of extended target inhibition long after elimination of the drug from plasma, resulting in a potentially greater therapeutic index related to off-target pharmacology. Preclinical studies have shown that encorafenib exhibits a lower incidence of paradoxical MAPK pathway activation relative to dabrafenib and vemurafenib. Encorafenib is a highly selective BRAF kinase inhibitor, with minimal activity across a panel of 99 other kinases, wherein activity was shown only against GSK3b and JNK2.

As of Q2 2023, nearly 15,000 patients in the US alone have been treated with either BRAFTOVI + MEKTOVI or BRAFTOVI + cetuximab with over 6,000 starting in the last two years.

In addition to its prevalence in metastatic melanoma, V600 mutant BRAF is also found in, 30% of low-grade serous ovarian cancers, 40-70% of papillary thyroid carcinomas and 7-8% of all solid tumors. The broad implication of BRAF mutations in human cancers prompted the study of Braftovi/Mektovi in other disease areas. For instance, this combination is currently in Phase 2 clinical studies for BRAF-mutant metastatic melanoma with brain metastasis, 1st-line and 2nd-line BRAF mutant metastatic non-small cell lung cancer.

Pubmed

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Attachments

- 1654019274BraftoviMektoviPrixGalienNom2022.docx
- 1654019319BraftoviMektoviPrixGalienNom2022.docx
- 1654019381BraftoviMektoviPrixGalienNom2022.docx
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