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IN BRIEF

A New Indication for Dabrafenib *(Tafinlar)* and Trametinib *(Mekinist)* Combination Therapy

The oral kinase inhibitors dabrafenib (*Tafinlar* – GSK) and trametinib (*Mekinist* – Novartis) have received accelerated approval by the FDA for use together for a fifth indication: treatment of unresectable or metastatic solid tumors with a BRAF V600E mutation in patients ≥6 years old who have progressed following prior treatment and have no satisfactory alternative treatment options. The combination is not approved for treatment of colorectal cancer because of known intrinsic resistance to BRAF inhibition and dabrafenib is not approved for use in patients with wild-type BRAF melanoma, anaplastic thyroid cancer (ATC), or solid tumors.

MECHANISM OF ACTION – BRAF V600E mutations activate the mitogen-activated protein kinase (MAPK) pathway, including BRAF and mitogen-activated extracellular signal regulated kinase 1 (MEK1) and kinase 2 (MEK2), leading to cellular proliferation. Dabrafenib inhibits BRAF V600E and some other mutated forms of BRAF kinases. Trametinib inhibits MEK1 and MEK2 activity. The combination of dabrafenib and trametinib inhibits BRAF V600 mutation-positive tumor cells more than either drug alone.

CLINICAL STUDIES – Accelerated approval of the combination for the new indication was based on overall response and duration of response rates in open-label, multiple cohort trials in 131 adults and 36 children and previous studies in patients with melanoma and lung cancer. The new trials enrolled adults with BRAF V600E mutation-positive solid tumors, including low-grade glioma (LGG), high-grade glioma (HGG), biliary tract cancer, small intestine cancer, gastrointestinal stromal tumor, and anaplastic thyroid cancer. One trial enrolled 36 children with BRAF V600 refractory or recurrent LGG or HGG. The primary endpoint in all of the trials was overall response rate (ORR). A total of 54 (41%) of 131 adults in the trials had an objective response. Among the highest representative tumor types in the clinical trials, ORR was 46% for biliary tract cancer, 33% for HGG, and 50% for LGG. The ORR was 25% in children.[1-7]

Table 1. FDA-Approved Indications for Dabrafenib and Trametinib Combination Therapy

- Unresectable or metastatic melanoma with BRAF V600E or V600K mutations
- Adjuvant treatment of melanoma with BRAF V600E or V600K mutations and involvement of lymph nodes following complete resection
- Metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutations
- Locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutations and no satisfactory locoregional treatment options
- Unresectable or metastatic solid tumors with BRAF V600E mutations in patients ≥6 years old who progressed following prior treatment and have no satisfactory alternative treatment options

ADVERSE EFFECTS – Common adverse effects of dabrafenib/trametinib in the clinical trials included pyrexia, fatigue, gastrointestinal adverse effects, rash, chills, headache, hemorrhage, cough, myalgia, arthralgia, and edema. In children, dry skin, dermatitis acneiform, abdominal pain, and paronychia also occurred.

DRUG INTERACTIONS – Dabrafenib is an inducer of UDP-glucuronosyltransferases and multiple CYP isoenzymes, including CYP3A4, 2B6, 2C8, 2C9, and 2C19.[8] It may lower serum concentrations of midazolam, warfarin, dexamethasone, hormonal contraceptives, and many other drugs. Dabrafenib is primarily metabolized by CYP3A4 and 2C8; inhibitors or inducers of these enzymes may alter dabrafenib serum concentrations, resulting in loss of efficacy

or toxicity.[9] Drugs that increase gastric pH, such as proton pump inhibitors, H_2-receptor antagonists, or antacids, may reduce the bioavailability of dabrafenib. **Trametinib** does not affect CYP isoenzymes and has no clinically significant drug interactions.

PREGNANCY AND LACTATION – The combination of dabrafenib/trametinib can cause fetal harm. Both drugs were embryotoxic and teratogenic in animal studies. Females of reproductive potential should be screened for pregnancy before starting dabrafenib/trametinib; they should use an effective nonhormonal contraceptive method while taking the combination and for 4 months after the last dose. Male patients with female partners of reproductive potential should use condoms during treatment with the combination and for at least 4 months after the last dose.

No data are available on the effects of the combination on the breastfed infant or milk production. Women should not breastfeed during treatment with these drugs.

DOSAGE, ADMINISTRATION, AND COST – Dabrafenib is available in 50- and 75-mg capsules and trametinib is available in 0.5- and 2-mg tablets. The recommended dosage for all indications in adults is dabrafenib 150 mg orally twice daily in combination with trametinib 2 mg orally once daily; both drugs should be taken 1 hour before or 2 hours after a meal. The recommended dosage of both drugs in children is based on body weight. Children who weigh 26-37 kg should receive 75 mg of dabrafenib twice daily and 1 mg of trametinib once daily and those who weigh 38-50 kg should receive 100 mg of dabrafenib twice daily and 1.5 mg of trametinib once daily. A recommended dose of either drug has not been established in patients who weigh <26 kg. The labels of both drugs include dosage adjustments that should be made if adverse effects occur. A 30-day supply of *Tafinlar* and *Mekinist* for an adult costs about $25,518.[10]

CONCLUSION – In clinical trials in patients ≥6 years old with unresectable or metastatic solid tumors with a BRAF V600E mutation, about 40% of adults and 25% of children who received the oral kinase inhibitors dabrafenib *(Tafinlar)* and trametinib *(Mekinist)* achieved a response. ■

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