FDA Approves Tafinlar and Mekinist for Melanoma With Specific Mutations

People who received the combination treatment had a statistically significant improvement in relapse-free survival.

May 2, 2018 By Food and Drug Administration (FDA)

FDA approves dabrafenib plus trametinib for adjuvant treatment of melanoma with BRAF V600E or V600K mutations

On April 30, 2018, the Food and Drug Administration granted regular approval to dabrafenib (TAFINLAR, Novartis Pharmaceuticals Corp.) and trametinib (MEKINIST, Novartis Pharmaceuticals Corp.) in combination for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.

Approval was based on COMBI-AD (NCT01682083), an international, multi-center, randomized, double-blind, placebo-controlled trial in 870 patients with Stage III melanoma with BRAF V600E or V600K mutations, and pathologic involvement of regional lymph node(s). Patients were randomly allocated (1:1) to receive dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily or two placebos for up to 1 year.

The major efficacy outcome was relapse-free survival (RFS). RFS was defined as the time from randomization to disease recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first as assessed by the investigator. Patients who received the combination treatment had a statistically significant improvement in RFS compared with those receiving placebo. Patients in the combination arm experienced fewer recurrences/deaths at the time of data-cutoff: 38% (n=166), compared with 57% (n=248) in the placebo arm (hazard ratio 0.47; 95% confidence interval 0.39, 0.58; $p<0.0001$). The estimated median RFS was not reached for patients who received the combination therapy, compared with 16.6 months (95% CI: 12.7, 22.1) for those receiving placebo.

The most common adverse reactions in at least 20% of patients receiving the combination in the COMBI-AD trial were pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia. Adverse reactions resulting in discontinuation, dose reduction, or dose interruption of dabrafenib occurred in 25%, 35%, and 66% of patients, respectively; the most common for each were pyrexia and chills. Adverse reactions resulting in discontinuation and dose

interruption of trametinib occurred in 24% and 54% of patients respectively; the most common for each were pyrexia and chills. Adverse reactions leading to dose reduction of trametinib occurred in 23% of patients; the most common were pyrexia and decreased ejection fraction.

The recommended doses for the adjuvant treatment of melanoma are 150 mg of dabrafenib orally twice daily and 2 mg of trametinib orally once daily until disease recurrence or unacceptable toxicity, for up to one year.

Full prescribing information is available at:

Dabrafenib

PI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202806s008lbl.pdf
Trametinib PI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204114s007lbl.pdf

FDA granted this application priority review. Dabrafenib in combination with trametinib was granted breakthrough therapy designation and orphan drug designation for this indication. A description of FDA expedited programs is in the Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of any medicine and device to FDA's MedWatch Reporting System by completing a form online at http://www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178) or mailing the postage-paid address form provided online, or by telephone (1-800-FDA-1088).

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