

The Medical Letter[®]

on Drugs and Therapeutics

Volume 65

Published online April 17, 2023

Online
Article

IN THIS ISSUE

In Brief: Dabrafenib (*Tafinlar*) and Trametinib (*Mekinist*) for Glioma

Important Copyright Message

FORWARDING OR COPYING IS A VIOLATION OF U.S. AND INTERNATIONAL COPYRIGHT LAWS

The Medical Letter, Inc. publications are protected by U.S. and international copyright laws. Forwarding, copying, or any distribution of this material without permission to a nonsubscriber is prohibited.

Sharing a password with a nonsubscriber or otherwise making the contents of this site available to third parties is prohibited.

By accessing and reading the attached content I agree to comply with U.S. and international copyright laws and these terms and conditions of The Medical Letter, Inc.

For further information click: [Subscriptions](#), [Site Licenses](#), [Reprints](#)
or call customer service at: 800-211-2769

The Medical Letter®

on Drugs and Therapeutics

Volume 65

Published online April 17, 2023

Online
Article

IN THIS ISSUE

In Brief: Dabrafenib (*Tafinlar*) and Trametinib (*Mekinist*) for Glioma

IN BRIEF

Dabrafenib (*Tafinlar*) and Trametinib (*Mekinist*) for Glioma

The oral kinase inhibitors dabrafenib (*Tafinlar* – GSK) and trametinib (*Mekinist* – Novartis) have been approved by the FDA for use together for a sixth indication: treatment of low-grade glioma (LGG) with a BRAF V600E mutation in patients ≥ 1 years old who require systemic therapy.^{1,2} This combination is the first systemic therapy to be approved in the US for first-line treatment of LGG with a BRAF V600E mutation in pediatric patients. The FDA also approved new oral formulations of both drugs for patients who are unable to swallow dabrafenib capsules or trametinib tablets.

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STUDIES – FDA approval of the combination for the new indication was based on the results of an open-label trial (unpublished; summarized in the package insert) in 110 patients 1 to 17 years old with BRAF V600E mutation-positive LGG who required systemic therapy. Patients were randomized to receive dabrafenib plus trametinib or carboplatin plus vincristine. Treatment was continued until loss of clinical benefit or unacceptable toxicity occurred. The overall response rate (ORR) after at least 32 weeks of treatment, the primary endpoint, was statistically

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
- ▶ Low-grade glioma (LGG) with BRAF V600E mutations in patients >1 years old who require systemic therapy

significantly higher with dabrafenib/trametinib than with carboplatin/vincristine (46.6% vs 10.8%); most of the responses were partial responses. The duration of response was 23.7 months with dabrafenib/trametinib and not estimable with carboplatin/vincristine. Progression-free survival was also statistically significantly longer with dabrafenib/trametinib (20.1 months vs 7.4 months with carboplatin/vincristine).

ADVERSE EFFECTS – The most common adverse effects of dabrafenib and trametinib combination therapy in pediatric patients were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%), and dermatitis acneiform (23%). Decreased neutrophil counts and increased alanine aminotransferase and aspartate aminotransferase levels have been reported.

DRUG INTERACTIONS – Dabrafenib is an inducer of UDP-glucuronosyltransferases and multiple CYP isoenzymes, including CYP3A4, 2B6, 2C8, 2C9, and

2C19.³ It may lower serum concentrations of many drugs, including midazolam, warfarin, dexamethasone, and hormonal contraceptives. 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.⁴ Drugs that increase gastric pH, such as proton pump inhibitors, H₂-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 AND ADMINISTRATION – Dabrafenib is available in 50- and 75-mg capsules and 10-mg

tablets for oral suspension. Trametinib is available in 0.5- and 2-mg tablets and in an oral solution. The recommended doses of dabrafenib and trametinib for pediatric patients are based on body weight; dabrafenib is administered orally twice daily and trametinib is administered orally once daily until disease progression or unacceptable toxicity occurs. Children who weigh 26-37 kg should receive 75 mg of dabrafenib (capsules) twice daily and 1 mg of trametinib (tablets) once daily and those who weigh 38-50 kg should receive 100 mg of dabrafenib (capsules) twice daily and 1.5 mg of trametinib (tablets) once daily. The labels of dabrafenib tablets for oral suspension and trametinib oral solution contain recommended dosages for pediatric patients. Both drugs should be taken 1 hour before or 2 hours after a meal. ■

1. Dabrafenib (Tafinlar) and trametinib (Mekinist) for metastatic melanoma. *Med Lett Drugs Ther* 2013; 55:62.
2. In brief: A new indication for dabrafenib (Tafinlar) and trametinib (Mekinist) combination therapy. *Med Lett Drugs Ther* 2023; 65:e26.
3. H Yin et al. Inhibition of human UDP-glucuronosyltransferase enzyme by dabrafenib: implications for drug-drug interactions. *Biomed Chromatogr* 2021; 35:e5205.
4. Inhibitors and inducers of CYP enzymes, P-glycoprotein, and other transporters. *Med Lett Drugs Ther* 2023 January 25 (epub). Available at: medicalletter.org/downloads/CYP_PGP_Tables.pdf.

PRESIDENT: Mark Abramowicz, M.D.; **VICE PRESIDENT, EDITOR IN CHIEF:** Jean-Marie Pflomm, Pharm.D.; **ASSOCIATE EDITORS:** Susan M. Daron, Pharm.D., Amy Faucard, MLS, Michael P. Viscusi, Pharm.D. **CONSULTING EDITORS:** Joanna Esterow, PA-C, Mordechai Sacks, DMSc, PA-C, Brinda M. Shah, Pharm.D., F. Peter Swanson, M.D.

CONTRIBUTING EDITORS: Carl W. Bazil, M.D., Ph.D., Columbia University College of Physicians and Surgeons; Ericka L. Crouse, Pharm.D., B.C.P.P., C.G.P., F.A.S.H.P., F.A.S.C.P., Virginia Commonwealth University; Vanessa K. Dalton, M.D., M.P.H., University of Michigan Medical School; Eric J. Epstein, M.D., Albert Einstein College of Medicine; David N. Juurlink, BPhm, M.D., Ph.D., Sunnybrook Health Sciences Centre; Richard B. Kim, M.D., University of Western Ontario; Sandip K. Mukherjee, M.D., F.A.C.C., Yale School of Medicine; Dan M. Roden, M.D., Vanderbilt University School of Medicine; Esperance A.K. Schaefer, M.D., M.P.H., Harvard Medical School; Neal H. Steigbigel, M.D., New York University School of Medicine; Arthur M. F. Yee, M.D., Ph.D., F.A.C.R., Weill Medical College of Cornell University

MANAGING EDITOR AND DIRECTOR OF CONTENT OPERATIONS: Susie Wong; **EDITORIAL ASSISTANT:** Karrie Ferrara

FULFILLMENT AND SYSTEMS MANAGER: Cristine Romatowski; **EXECUTIVE DIRECTOR OF SALES:** Elaine Reaney-Tomaselli

EXECUTIVE DIRECTOR OF MARKETING AND COMMUNICATIONS: Joanne F. Valentino; **INTERIM PUBLISHER:** Jean-Marie Pflomm, Pharm.D.

Founded in 1959 by Arthur Kallet and Harold Aaron, M.D.

Copyright and Disclaimer: The Medical Letter, Inc. is an independent nonprofit organization that provides healthcare professionals with unbiased drug prescribing recommendations. The editorial process used for its publications relies on a review of published and unpublished literature, with an emphasis on controlled clinical trials, and on the opinions of its consultants. The Medical Letter, Inc. does not sell advertising or receive any commercial support. No part of the material may be reproduced or transmitted by any process in whole or in part without prior permission in writing. The Medical Letter, Inc. does not warrant that all the material in this publication is accurate and complete in every respect. The Medical Letter, Inc. and its editors shall not be held responsible for any damage resulting from any error, inaccuracy, or omission.

Subscription Services

Address:

The Medical Letter, Inc.
145 Huguenot St. Ste. 312
New Rochelle, NY 10801-7537
www.medicalletter.org

Customer Service:

Call: 800-211-2769 or 914-235-0500
Fax: 914-632-1733
E-mail: custserv@medicalletter.org

Permissions:

To reproduce any portion of this issue,
please e-mail your request to:
permissions@medicalletter.org

Subscriptions (US):

1 year - \$159; 2 years - \$298;
3 years - \$398. \$65 per year
for students, interns, residents,
and fellows in the US and Canada.
Reprints - \$45 per issue or article

Site License Inquiries:

E-mail: SubQuote@medicalletter.org
Call: 800-211-2769
Special rates available for bulk
subscriptions.