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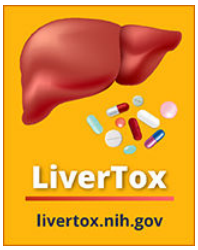


Dabrafenib

Updated: June 28, 2018.

OVERVIEW

Introduction

Dabrafenib is a selective inhibitor of mutated forms of BRAF kinase and is used alone or in combination with trametinib in the treatment of advanced malignant melanoma. Dabrafenib therapy is associated with transient elevations in serum aminotransferase during therapy, but has not been linked to instances of clinically apparent acute liver injury.

Background

Dabrafenib (da braf' e nib) is an orally available, small molecule inhibitor of certain mutated forms of BRAF kinase, a serine/threonine kinase that is frequently mutated in patients with malignant melanoma and other solid tumors. BRAF is an isoform of RAF, an early step in the mitogen-activated protein (MAP) kinase pathway which is an important cascade of kinases (RAS-RAF-MEK-ERK) that controls cell activation, growth and proliferation. Mutated forms of BRAF can cause dysregulation of cell growth resulting in tumor progression. Clinical trials of dabrafenib in patients with advanced melanoma have shown that it prolongs progression free survival in humans, but the effect seemed to be limited to patients with the BRAF V600E mutation. Dabrafenib was approved for use in the United States in 2013 and the combination of dabrafenib with trametinib (a inhibitor of MEK, a kinase active downstream of BRAF in the MAP kinase pathway) in 2014. Dabrafenib is currently indicated as a single agent for treatment of unresectable or metastatic melanoma with the BRAF V600E mutation, and in combination with trametinib for patients with advanced melanoma with BRAF V600E or V600K mutations. Dabrafenib is available in capsules of 50 and 75 mg under the brand name Tafinlar. The recommended dose is 150 mg orally twice daily. Common side effects include hyperkeratosis, skin rash, headache, fever, alopecia and peripheral neuropathy. Uncommon, but potentially severe side effects include serious skin toxicity including squamous cell carcinoma, venous thrombosis, cardiomyopathy, ocular toxicities and serious febrile reactions. Dabrafenib may cause a paradoxical stimulation of wild-type BRAF which may account for some of its adverse effects, including hyperkeratosis, squamous cell skin cancer and tumor progression in patients with melanoma that have BRAF-wild type mutations. The paradoxical effects of dabrafenib are less frequent when it is combined with trametinib.

Hepatotoxicity

Elevations in serum ALT levels were reported in 11% of patients treated with dabrafenib alone, but all elevations were above 5 times ULN. When dabrafenib was given in combination with trametinib, serum ALT elevations occurred in 35% to 42% of patients and were above 5 times ULN in 4%. Similarly, serum alkaline phosphatase elevations occurred in 26% of patients given dabrafenib alone, but in 60% to 67% given dabrafenib and

trametinib. These abnormalities were largely asymptomatic and fully reversible. There were no instances of clinically apparent acute liver injury or hepatic failure reported in prelicensure studies of dabrafenib and, since its approval and more wide spread use, there have been no published reports of dabrafenib hepatotoxicity.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the transient serum enzyme elevations during dabrafenib therapy is not known. Dabrafenib is metabolized in the liver largely through the cytochrome P450 pathway (CYP 3A4 and 2C8) and liver injury may be related to production of a toxic intermediate. Dabrafenib also induces CYP 3A4 and 2C8 activity and is susceptible to drug-drug interactions with agents that inhibit or induce or are metabolized by these hepatic drug metabolizing enzymes.

Outcome and Management

In using kinase inhibitors for treatment of cancer, monitoring of routine liver tests before starting and during therapy is warranted. Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) or elevations accompanied by jaundice or symptoms should lead to temporary cessation. Dabrafenib should not be restarted until the liver test abnormalities improve or resolve and then only with careful monitoring. There does not appear to be cross reactivity in risk for hepatic injury between dabrafenib and other inhibitors of the MAP kinase pathway and, in some situations, switching to another kinase inhibitor may be appropriate.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors; see also Trametinib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Dabrafenib – Tafinlar®

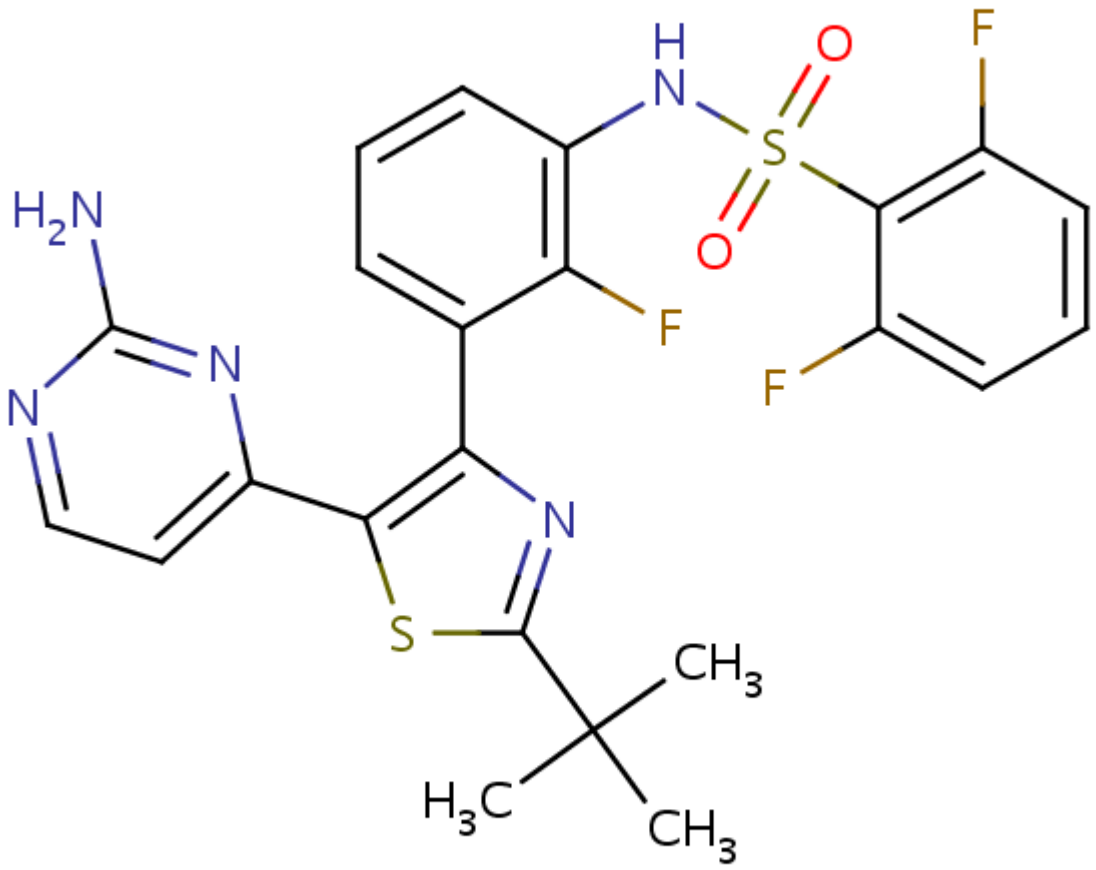
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Dabrafenib	1195765-45-7	C23-H20-F3-N5-O2-S2	

ANNOTATED BIBLIOGRAPHY

References updated: 28 June 2018

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of tyrosine kinase receptor inhibitors such as dabrafenib).

DeLeve LD. Erlotinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents discusses several tyrosine kinase inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not dabrafenib).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, Puzanov I, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13: 1087-95. PubMed PMID: 23051966.

(Among 255 patients with malignant melanoma metastatic to the brain, objective responses to dabrafenib occurred in 31-39% of patients with BRAF V600E, but in only 7-22% of those with V600K mutations; ALT elevations above 3 times ULN occurred in 2-4% of dabrafenib treated subjects).

Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, Rutkowski P, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380 (9839): 358-65. PubMed PMID: 22735384.

(Among 250 patients with metastatic melanoma and BRAF mutations, progression free survival was longer with dabrafenib than dacarbazine therapy [5.1 vs 2.7 months], but side effects were more frequent with dabrafenib and included skin toxicity, fever, fatigue, arthralgias and headache; no mention of ALT elevations or hepatotoxicity).

Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, Hamid O, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet 2012; 379 (9829): 1893-901. PubMed PMID: 22608338.

(Among 184 patients with various advanced malignancies [156 with melanoma] treated with dabrafenib in varying doses, responses occurred only in patients with BRAF mutations, the optimal dose appeared to be 150 mg twice daily and dose limiting side effects include cutaneous squamous cell carcinoma [11%], fatigue and fever).

Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, Hamid O, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012; 367: 1694-703. PubMed PMID: 23020132.

(Among 247 patients with metastatic melanoma and BRAF V600 mutations, progression free survival was prolonged by the combination of trametinib and dabrafenib compared to dabrafenib alone [mean 9.2 and 9.4 months vs 5.8 months]; most side effects were more common with the combination, but cutaneous squamous cell carcinoma was less [2% and 7% vs 19%]; no mention of hepatotoxicity or ALT elevations).

Dabrafenib (Tafinlar) and trametinib (Mekinist) metastatic melanoma. Med Lett Drugs Ther 2013; 55 (1422): 62-3. PubMed PMID: 23917385.

(Concise review of mechanism of action, efficacy, safety and cost of dabrafenib with or without trametinib for metastatic melanoma shortly after their approval in the US; no mention of ALT elevations or hepatotoxicity).

King AJ, Arnone MR, Bleam MR, Moss KG, Yang J, Fedorowicz KE, Smitheman KN, et al. Dabrafenib; preclinical characterization, increased efficacy when combined with trametinib, while BRAF/MEK tool combination reduced skin lesions. PLoS One 2013; 8: e67583. PubMed PMID: 23844038.

(Review of the development, mechanism of action and efficacy of dabrafenib, a specific inhibitor of V600E mutant BRAF; no discussion of hepatotoxicity).

Ascierto PA, Minor D, Ribas A, Lebbe C, O'Hagan A, Arya N, Guckert M, et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J Clin Oncol 2013; 31: 3205-11. PubMed PMID: 23918947.

(Among 92 patients with metastatic melanoma and BRAF mutations treated with dabrafenib, confirmed responses occurred in 59% with BRAF V600E, but only 13% with V600K; adverse events occurred in 93% of patients and included arthralgia, hyperkeratosis, fever, fatigue, headache and nausea; but no mention was made of ALT elevations or hepatotoxicity).

Ballantyne AD, Garnock-Jones KP. Dabrafenib: first global approval. Drugs 2013; 73: 1367-76. PubMed PMID: 23881668.

(Review of structure, mechanism of action, pharmacology, efficacy and safety of dabrafenib given alone or in combination with trametinib, mentions ALT elevations occurred in 2% and 5% of patients in one clinical study).

Spraggs CF, Xu CF, Hunt CM. Genetic characterization to improve interpretation and clinical management of hepatotoxicity caused by tyrosine kinase inhibitors. Pharmacogenomics 2013; 14: 541-54. PubMed PMID: 23556451.

(Review of genetic associations of serum ALT and bilirubin elevations during therapy with tyrosine kinase inhibitors, focusing on lapatinib and pazopanib).

Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf 2013; 36: 491-503. PubMed PMID: 23620168.

(Review of the hepatotoxicity of 18 tyrosine kinase inhibitors approved for use in cancer in the US as of 2013; dabrafenib is not discussed).

Johnson DB, Flaherty KT, Weber JS, Infante JR, Kim KB, Kefford RF, Hamid O, et al. Combined BRAF (Dabrafenib) and MEK inhibition (Trametinib) in patients with BRAFV600-mutant melanoma experiencing progression with single-agent BRAF inhibitor. J Clin Oncol 2014; 32: 3697-704. PubMed PMID: 25287827.

(Among 71 patients with refractory melanoma with BRAF V600 mutantations treated with the combination of dabrafenib and trametiinib, the objective response rate was 13-15% and all patients had at least one adverse event, which were severe in 4 and fatal in 2, but none were liver related).

Rutkowski P, Blank C. Dabrafenib for the treatment of BRAF V600-positive melanoma: a safety evaluation. Expert Opin Drug Saf 2014; 13: 1249-58. PubMed PMID: 25014231.

(Review of the safety of dabrafenib in treatment of melanoma, lists 23 common adverse effects of dabrafenib, but not ALT elevations or hepatotoxicity).

Amaria RN, Kim KB. Dabrafenib for the treatment of melanoma. Expert Opin Pharmacother 2014; 15: 1043-50. PubMed PMID: 24720932.

(Review of the rationale behind the development of dabrafenib, its mechanism of action, pharmacology, preclinical activity and basis for efficacy in malignant melanoma; no mention of ALT elevations or hepatotoxicity).

Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014; 371: 1877-88. PubMed PMID: 25265492.

(Among 423 pateints with advanced melanoma [with BRAF V600E or V600K mutations] treated wtih dabrafenib with or without trametinib, progression free survival was slightly better with the combination [9.3 vs 8.8 months], while adverse events tended to be more common and more severe with the combination, ALT elevations occurring in 11% vs 5% and rising above 5 times ULN in 2% vs <1%; no mention of clinically apparent hepatotoxicity).

Flaherty DC, Hoffner BW, Lau BJ, Hamid O, Faries MB. Hepatic hemorrhage as a consequence of rapid response to combined targeted therapy in metastatic melanoma. J Surg Oncol 2015; 112: 844-5. PubMed PMID: 26503563.

(49 year old woman with metastatic melanoma and liver involvement developed severe abdominal pain and hemoperitoneum from rupture of hepatic metstases after 3 doses of dabrafenib and trametinib, recovering with conservative management and able to restart the same chemotherapeutic regimen).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 were attributed to antineoplastic agents [5.5%], 3 of which were attributed to kinase inhibitors [imatinib, lapatinib], but none to dabrafenib or trametinib).

Anker CJ, Grossmann KF, Atkins MB, Suneja G, Tarhini AA, Kirkwood JM. Avoiding severe toxicity from combined BRAF inhibitor and radiation treatment: consensus guidelines from the Eastern Cooperative Oncology Group (ECOG). Int J Radiat Oncol Biol Phys 2016; 95: 632-46. PubMed PMID: 27131079.

(Guidelines to the use of BRAF kinase inhibitors mentions that hepatic toxicity is low and may be caused by hepatic radiation).

Planchard D, Besse B, Groen HJM, Souquet PJ, Quoix E, Baik CS, Barlesi F, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol 2016; 17: 984-93. PubMed PMID: 27283860.

(Among 59 patients with previously treated, refractory NSCLC [with BRAF V600E mutation], treated with dabrafenib and trametinib, the overall response rate was 63% and adverse events were common, but ALT elevations occurred in only 3 patients [6%] and were above 5 times ULN in only 1; there were no serious liver related adverse events).

Knispel S, Zimmer L, Kanaki T, Ugurel S, Schadendorf D, Livingstone E. The safety and efficacy of dabrafenib and trametinib for the treatment of melanoma. Expert Opin Drug Saf 2017: 1-15. PubMed PMID: 29050517.

(Review of the structure, mechanism of action, clinical efficacy and safety of dabrafenib and its combination with trametinib as therapy for metastatic melanoma; no specific discussion of hepatotoxicity).

Long GV, Eroglu Z, Infante J, Patel S, Daud A, Johnson DB, Gonzalez R, et al. Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma who received dabrafenib combined with trametinib. J Clin Oncol 2017 Oct 9: JCO2017741025. PubMed PMID: 28991513.

(Among 99 patients enrolled in a trial of dabrafenib and trametinib, 18 survived for at least 5 years and no new safety issues arose; no mention of ALT levels or hepatotoxicity).

Long GV, Hauschild A, Santinami M, Atkinson V, Mandalà M, Chiarion-Sileni V, Larkin J, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017; 377: 1813-23. PubMed PMID: 28891408.

(Among 870 patients with Stage III, resected malignant melanoma treated with dabrafenib and trametinib or placebo for at least 1 year, relapse free survival was greater with the combination therapy [58% vs 39%], although adverse events were greater and included ALT elevations in 15% vs 1% that were above 5 times ULN in only one patient on the combination therapy; no mention of serious liver related serious adverse events).

Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, Chiarion-Sileni V, et al. Dabrafenib plus trametinib in patients with BRAF (V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol 2017; 18: 863-73. PubMed PMID: 28592387.

(Among 125 patients with malignant melanoma and brain metastases [with BRAF V600 mutation] treated with dabrafenib and trametinib, intracranial response were achieved in 44-59% and the most common adverse events were fever and headache; while ALT elevations occurred in 12 patients [10%], none were above 5 times ULN).

Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol 2017; 28: 1631-9. PubMed PMID: 28475671.

(Further follow up of patients enrolled in a long term extension of a trial of dabrafenib monotherapy vs combination with trametinib [Long 2014] showed continued benefit of the combination with a survival of 44% vs 32% at 3 years, with ALT elevations in 13% vs 6% which rose above 5 times ULN in 2% vs <1%; no mention of clinically apparent liver injury).

Shroff RT, Yarchoan M, O'Connor A, Gallagher D, Zahurak ML, Rosner G, Ohaji C, et al. The oral VEGF receptor tyrosine kinase inhibitor pazopanib in combination with the MEK inhibitor trametinib in advanced cholangiocarcinoma. Br J Cancer 2017; 116: 1402-7.

(Among 25 patients with advanced, refractory cholangiocarcinoma treated with pazopanib and trametinib for an average of 12 weeks, the objective response rate was 5% and adverse events were common including elevated liver tests in 44% resulting in dose interruption in 1 patient, but without clinically apparent liver injury).

Planchard D, Smit EF, Groen HJM, Mazieres J, Besse B, Helland Å, Giannone V, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF (V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol 2017; 18: 1307-16. PubMed PMID: 28919011.

(Among 36 patients with metastatic NSCLC treated with dabrafenib and trametinib, the objective response rate was 64% and all patients had at least one adverse event including 6 [17%] with ALT elevations which were above 5 times ULN in 4 [11%], but none were associated with jaundice or symptoms).

Martín Algarra S, Soriano V, Fernández-Morales L, Berciano-Guerrero MÁ, Mujika K, Manzano JL, Puértolas Hernández T, et al. Dabrafenib plus trametinib for compassionate use in metastatic melanoma: A STROBE-compliant retrospective observational postauthorization study. Medicine (Baltimore) 2017; 96: e9523. PubMed PMID: 29384960.

(Among 135 patients with metastatic melanoma treated with dabrafenib and trametinib in a Spanish open access program, the overall response rate was 68% and adverse events included skin reactions [42%], fever, weakness, arthralgia and diarrhea; no mention of ALT elevations or hepatotoxicity).

Bunchorntavakul C, Reddy KR. Drug hepatotoxicity: newer agents. Clin Liver Dis 2017; 21: 115-34. PubMed PMID: 27842767.

(Review of the hepatotoxicity of recently approved medications including kinase inhibitors such as imatinib, erlotinib, lapatinib, pazopanib, ponatinib, nilotinib, sorafenib, sunitinib and regorafenib, but does not mention dabrafenib or trametinib).

Amaria RN, Prieto PA, Tetzlaff MT, Reuben A, Andrews MC, Ross MI, Glitza IC, et al. Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. Lancet Oncol 2018; 19: 181-93. PubMed PMID: 29361468.

(Among 17 patients with surgically resected melanoma given adjuvant dabrafenib and trametinib or standard of care treatment, progression free survival was greater with the kinase inibitors [20 vs 3 months] and adverse events were mostly fever, fatigue, headache and diarrhea; ALT or AST elevations occurred in only 3 patients [23%] which were all below 5 times ULN).