Published in final edited form as:

Cardiovasc Toxicol. 2017 October ; 17(4): 487–493. doi:10.1007/s12012-017-9425-z.

Cardiovascular Effects of the MEK Inhibitor, Trametinib: A Case Report, Literature Review, and Consideration of Mechanism

Mary Banks¹, Karen Crowell², Amber Proctor³, and Brian C. Jensen^{1,4,5}

¹Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

²Health Sciences Library, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

³Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

⁴McAllister Heart Institute, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

⁵Division of Cardiology, University of North Carolina at Chapel Hill, 160 Dental Circle, CB 7075, Chapel Hill, NC 27599-7075, USA

Abstract

The MEK inhibitor trametinib was approved in 2013 for the treatment of unresectable or metastatic melanoma with a BRAF V600E mutation, the most common pathogenic mutation in melanoma. Trametinib blocks activation of ERK1/2, inhibiting cell proliferation in melanoma. ERK1/2 also protects against multiple types of cardiac insult in mouse models. Trametinib improves survival in melanoma patients, but evidence of unanticipated cardiotoxicity is emerging. Here we describe the case of a patient with metastatic melanoma who developed acute systolic heart failure after trametinib treatment and present the results of the literature review prompted by this case. A patient with no cardiac history presented with a 6.5-mm skin lesion and was found to have metastatic BRAF V600E melanoma. Combination treatment with trametinib and the BRAF inhibitor, dabrafenib, was initiated. The patient's pre-treatment ejection fraction was 55–60%. His EF declined after 13 days and that was 40% 1 month after treatment. Two months after initiating trametinib, he developed dyspnea and fatigue. We conducted a chart review in the electronic medical record. We conducted a PubMed search using trametinib/adverse effects AND (“heart failure” OR “left ventricular dysfunction” OR hypertension OR cardiotoxicity OR mortality). We also queried the FDA Adverse Events Reporting System for reports of cardiomyopathy, ejection fraction decrease, and left ventricular dysfunction associated with trametinib between January 1, 2013, and July 20, 2017. The literature search retrieved 19 articles, including clinical trials and case reports. Early clinical experience with the MEK inhibitor trametinib suggests that its clinical efficacy may be compromised by cardiotoxicity. Further studies in humans and animals are required to determine the extent of this adverse effect, as well as its underlying mechanisms.

Keywords

Protein kinase inhibitor; Cardiotoxicity; Antineoplastic agents; MAP kinase signaling system; Melanoma

Introduction

Persistent hyperactivation of the RAS–RAF–MEK–ERK pathway commonly contributes to carcinogenesis. Many of the recently developed cancer therapies target this pathway, including MEK inhibitors. Trametinib is a highly selective inhibitor of the tyrosine kinases mitogen-activated protein kinase kinase 1 and 2 (MEK 1 and MEK 2). In combination with the BRAF inhibitor, dabrafenib, trametinib prolongs life in patients with melanoma carrying an activating mutation in codon 600 of the BRAF gene (BRAF V600) [1]. The combination of dabrafenib and trametinib also received FDA approval for the treatment of BRAF V600 mutant non-small cell lung cancer in June 2017. Its efficacy in other tumor types, including kidney and breast cancer, is being explored actively in numerous clinical trials [2–6]. Trametinib generally is well tolerated, though can be associated with adverse effects on the cardiovascular system, including cardiomyopathy and hypertension. Here we report on a patient with BRAF V600E mutated melanoma who developed systolic heart failure after 1 month of trametinib treatment. We also review the extant literature on trametinib cardiotoxicity and discuss its potential underlying mechanisms.

Case Report

The patient was a 69-year-old man who was diagnosed with Stage IIIB melanoma with brain metastases and treated with dabrafenib and trametinib. He had a 50-packyear smoking history but no history of heart disease and no other cardiovascular risk factors. His pre-treatment echocardiogram was notable for an ejection fraction (EF) of 55–60%. The left ventricular internal diameter was 4.5 cm. There was mild left atrial enlargement. His baseline electrocardiogram (EKG) showed normal sinus rhythm with non-specific ST segment abnormalities and one premature ventricular contraction (PVC).

A routine surveillance echocardiogram 30 days after the initiation of treatment revealed a mildly decreased EF of 45–50% (Fig. 1) without segmental wall motion abnormalities. The left ventricular internal diameter at end diastole (LVIDd) was 4.9 cm. There was mild left atrial enlargement. His EKG revealed multiple PVCs but otherwise was unchanged from the previous study. He was taking only dabrafenib, lactulose, and oxycodone ER at the time. He denied any symptoms suggestive of heart failure, but his trametinib therapy was interrupted due to the decreased EF.

He returned for further evaluation 40 days after initiation of therapy (10 days after discontinuation of trametinib). A limited echocardiogram revealed an EF of 40% with no regional wall motion abnormalities and stable LVIDd. An EKG was not performed. He continued to deny any symptoms suggestive of heart failure. His trametinib was not resumed due to persistent contractile dysfunction.

Two months after the initiation of trametinib (30 days after its discontinuation), he was admitted to the hospital for management of acutely decompensated heart failure. He presented with progressive exertional dyspnea, orthopnea, and bilateral lower leg swelling. Physical examination revealed jugular venous distention, decreased breath sounds, and pitting pre-tibial edema. His NT pro-BNP was elevated at 404 pg/mL, but his cardiac troponin-I and creatine kinase-MB fraction were within normal limits. His echocardiogram revealed an ejection fraction of 40% with an LVIDd of 5.3 cm and persistent left atrial dilatation. A SPECT myocardial perfusion scan revealed no evidence of ischemia or prior infarction. He was diuresed to euvolemia and discharged on hospital day 3 with lisinopril 2.5 mg daily and furosemide 20 mg daily.

Three months after initiation of trametinib, he was admitted to the hospital with hemorrhagic conversion of cerebral metastasis. He was deemed a poor surgical candidate, and he declined palliative radiation therapy. At his request, he was discharged home with hospice care. No cardiovascular evaluation was undertaken during this hospitalization.

Discussion

Mechanism of Antineoplastic Action

The classical MAP kinase pathway involves the sequential activation of a member of the RAS family, followed by activation of a RAF family member, leading to activation of MEK1/2 with resultant phosphorylation of ERK1/2 (Fig. 2). The pathway initially is relatively linear, as RAF is narrowly selective for MEK1/2 and ERK1/2 is the only recognized substrate for MEK1/2 [7]. ERK1/2, on the other hand, phosphorylates over one hundred substrates, participating broadly in cell differentiation, proliferation, and metabolism [8]. The RAS–RAF–MEK–ERK signaling cascade is among the most frequently dysregulated pathways in carcinogenesis [2]. Inhibitors of this pathway, including MEK inhibitors, are among the most widely studied antineoplastic agents and are likely to see expanding clinical utilization in the coming years [2].

Trametinib is a highly selective allosteric inhibitor of MEK1 and MEK2 that potently and persistently inhibits of ERK1/2 activation in multiple cancer cell lines and xenograft tumor models [8]. In 2013, trametinib received FDA approval for the treatment of BRAF V600E/K-mutant melanoma, the first MEK inhibitor to be approved for any indication. The FDA approval followed the publication of the METRIC trial, a Phase III clinical trial demonstrating the benefit of trametinib in melanoma treatment [9]. METRIC compared trametinib with standard chemotherapy (dacarbazine or paclitaxel) in V600-mutated melanoma. The relative risk of death in the trametinib arm compared to the chemotherapy arm was 0.54 (95% CI, 0.32–0.92; $p=0.01$).

Like other MEK inhibitors, trametinib is used most commonly in combination with other targeted agents as inhibition of MEK alone rarely provides therapeutically sufficient disruption of the aberrantly activated RAS–RAF–MEK–ERK cascade [2]. BRAF V600E is the most common oncogenic mutation in melanoma, followed by BRAF V600K, and both mutations have been identified in other malignancies [10]. Both mutations cause gain of BRAF's kinase function, leading to persistent hyperactivation of MEK1/2. Concomitant

inhibition of both BRAF and MEK very effectively abrogated tumor growth in preclinical models [11], serving as the basis for the COMBI-d [12] and COMBI-v [13] Phase III randomized controlled trials, which demonstrated superior efficacy of combination dabrafenib and trametinib therapy compared with BRAF inhibitor therapy alone for BRAF V600E mutated melanoma.

Literature Review

Our case prompted a review of the extant literature on trametinib cardiotoxicity. We conducted a PubMed search using trametinib/adverse effects AND (“heart failure” OR “left ventricular dysfunction” OR hypertension OR cardiotoxicity OR mortality). These search terms yielded 2 previous case reports, 10 clinical trials, and one general review of kinase inhibitor cardiovascular toxicity in which trametinib was mentioned. This search did not yield any previous reviews of trametinib-associated cardiovascular toxicity.

Our review indicated that cardiomyopathy is the most concerning trametinib-related adverse event, though hypertension also is a reported side effect and may be more common. One case report discussed an 11-year-old child who was treated with trametinib for neuroblastoma [14]. His EF was 74% prior to treatment, but declined to 45% on his first surveillance echocardiogram 13 days after initiation of trametinib. Trametinib subsequently was stopped 15 days after initiation of treatment when the patient developed shortness of breath. Thirty-seven days after withdrawal of trametinib, his EF had nearly normalized. Another case study described a 32-year-old patient who received trametinib for NRAS-mutant (Q61E) metastatic melanoma [15]. He presented to the hospital with coughing and dyspnea. He subsequently developed tachycardia, hypotension, and became hypoxic. He required intubation, vasopressors, and inotropic support with milrinone. His echocardiogram showed an EF of 11%. After stopping trametinib, his EF increased modestly to 18%. However, the patient died shortly thereafter due to brain metastases.

Several clinical trials have demonstrated cardiotoxicity due to trametinib (summarized in Table 1). A Phase 1 dose-escalation trial of trametinib for treatment of advanced melanoma reported decreased EF in 7% (6/97) of subjects [16]. A Phase 1B trial was conducted to assess the safety and dosing for trametinib and gemcitabine for the treatment of patients with solid tumors and low ECOG performance status [3]. In this trial, 8 (of 31) patients discontinued the treatment of trametinib and/or gemcitabine due to toxicities. One patient in the 2-mg dosing cohort experienced a reduction in EF that improved after the dose was reduced. After the EF recovered, full therapeutic dosing was resumed. However, the patient subsequently developed recurrent left ventricular contractile dysfunction associated with heart failure symptoms and trametinib was stopped altogether. A Phase 2 trial of trametinib and gemcitabine for pancreatic cancer reported that 10% of subjects experienced adverse cardiac events; 3% of subjects had Grade 3 cardiac events [17]. The nature of these events was not specified. A Phase 2 trial (www.accessdata.fda.gov, NCT01336634) of trametinib and dabrafenib in non-small cell lung cancer identified new onset cardiomyopathy in 9% (8/93) subjects, requiring discontinuation of treatment in 5% of those enrolled, though these data were not included in the published interim analysis [18]. In another Phase 2 trial of

trametinib in the treatment of melanoma, 3% (3/97) patients developed Grade 3 cardiomyopathy [19].

The Phase 3 trial METRIC found 7% incidence of cardiomyopathy in the trametinib arm, and 2 patients had Grade 3 cardiotoxicity that required discontinuation of the drug [9]. The EF of both patients normalized after discontinuation of trametinib treatment. The largest clinical trial of trametinib treatment was COMBI-v, an open-label Phase 3 randomized clinical trial comparing the combination of trametinib and dabrafenib with the BRAF inhibitor vemurafenib in 704 melanoma patients with V600E or V600K mutations [12]. Combination therapy resulted in 77% 1-year survival compared to 65% in the vemurafenib arm (HR = 0.69, $p=0.005$). Decreased ejection fraction was identified in 8% of subjects in the trametinib/dabrafenib arm and no patients in the vemurafenib arm. COMBI-d reported 4% incidence of cardiomyopathy in the trametinib/dabrafenib arm and 2% in the dabrafenib arm [13]. Collectively, these findings identify trametinib-associated cardiomyopathy as a relatively rare but important adverse event. The cardiotoxicity of combination trametinib/dabrafenib therapy appears to arise almost entirely from MEK inhibition.

One general toxicological review of multiple kinase inhibitors collected outcomes from assessment reports from the FDA, EU Committee for Medicinal Products for Human Use, postmarketing studies, and clinical trials [20]. The median time to decreased EF in the trametinib group was 63 days (range 16–156); it was 86 days (range 27–253) in patients who received both trametinib and dabrafenib group. The authors reported that across clinical trials, 11% of patients treated with trametinib developed cardiomyopathy, as defined by an EF decrease >10%. The authors found no evidence of cardiomyopathy that resulted from treatment with dabrafenib alone. Research AE (<http://www.researchae.com>), which aggregates postmarketing reports of adverse events, includes 4506 reports of trametinib toxicity; heart failure or decreased EF constituted 3.1% of these events.

Given the paucity of extant literature describing trametinib-induced cardiomyopathy, we requested postmarketing data from the FDA Adverse Events Reporting System (FAERS) database between the dates of January 1, 2013, and July 20, 2017. We reviewed the reports describing “cardiomyopathy” OR “left ventricular dysfunction” OR “ejection fraction decrease” OR “cardiac failure, congestive.” From over 5000 adverse event reports submitted during this time period, we identified 139 cases that pertained to trametinib-induced heart failure. The patients identified were 2–91 years of age, with a median age of 64 and three reports concerning patients younger than 18. The most common dose of trametinib referenced in the reports was 2 mg per day; however, there were 24 reports of cardiotoxicity occurring at lower doses. Ten of these reports were associated with a fatal event.

Not all trials reported cardiotoxicity due to trametinib. A Phase 1B trial aimed to investigate the safety and tolerability of trametinib and everolimus [21]. Sixty-seven patients with advanced solid tumors were included. In the trial, there were no significant cardiac events.

Trametinib also has been associated with hypertension. One small trial of cholangiocarcinoma therapy found mild hypertension in 64% of subjects (16 of 25) and more severe hypertension in 8% (2 of 25) [22]. Another Phase I study using trametinib and

the Akt inhibitor afuresertib demonstrated hypertension in 15% of subjects (3 of 20) [23]. A Phase 2 trial comparing trametinib with docetaxel for non-small cell lung cancer reported hypertension in 15% of subjects receiving trametinib (13 of 87) and no incident hypertension in the docetaxel group. The METRIC trial reported 15% incidence of hypertension (32 of 231 subjects), including a 12% incidence of Grade 3 hypertension in subjects receiving trametinib. Subjects receiving standard chemotherapy in METRIC had a 7% incidence (7 of 99 subjects) [9]. The incidence of hypertension in COMBIv was 26% in the trametinib/dabrafenib arm and 24% in the vemurafenib arm [12]. COMBI-d found 22% hypertension with trametinib/dabrafenib and 14% with dabrafenib alone [13]. Collectively, these findings suggest that trametinib can cause hypertension and that the risk is enhanced by combination therapy with dabrafenib.

Multiple kinase inhibitors have been associated with QT prolongation and increased risk of ventricular arrhythmias. For instance, a meta-analysis demonstrated increased relative risk of QTc prolongation treatment with kinase inhibitors that target the vascular endothelial growth factor receptor (RR 8.6, 95% confidence interval 4.92–15.2) [24]. One small study Phase 1 study of 35 patients with solid tumors examined whether trametinib can cause QT prolongation and found no difference in the corrected QT interval between trametinib and placebo using clinically relevant dosing [25].

The natural history, prognosis, and treatment of trametinib-induced cardiomyopathy have not been well established. Cardiomyopathy can occur within the first month of treatment or as late as 2 years after initiation [12, 18]. In the studies reviewed, many, but not all, patients experienced recovery of their EF after discontinuation of treatment. The potentially reversible nature of trametinib heart injury is consistent with observed patterns of response to other targeted therapies [26].

Management of trametinib-induced cardiotoxicity is not well defined. Novartis guidelines suggest withholding treatment for up to 4 weeks if the EF decreases by >10%, with rechallenge at a lower dose if the EF recovers. These guidelines suggest that trametinib treatment should be discontinued altogether for an EF decrease >20% or if symptomatic heart failure develops (www.accessdata.fda.gov). Neurohormonal antagonists such as ACE inhibitors and beta-blockers, which may promote recovery after trastuzumab-induced heart injury, have not been studied in the context of therapeutic MEK inhibition. However, the use of beta-blockers for management of trametinib-induced cardiomyopathy is biologically appealing. Myocardial beta-adrenergic receptor activation signals through both the cardioprotective MEK/ERK axis (as below) and the cardiotoxic p38 MAP kinase pathway [27, 28]. Theoretically, inhibiting MEK could shunt betaadrenergic signaling toward p38 [29, 30], hence augmenting the deleterious effects of MEK inhibition. Betablockers might attenuate these effects directly by inhibiting beta-adrenergic receptor-mediated p38 activation.

The MEK–ERK Axis is Cardioprotective

Trametinib is highly selective for MEK1/2 [8]; hence, the adverse cardiac effects likely result directly from suppression of ERK1/2 activation in the heart rather than off target effects. ERK1/2 has well-documented cardioprotective effects (reviewed in Ref. [31, 32]),

participating in protection against oxidative stress [33], adaptive hypertrophy [34], and anti-apoptotic protection against cytotoxic insults like anthracyclines [35].

There are no published studies on the cardiac effects of trametinib in animal models. Mice that lack ERK1/2 (ERK1/2^{-/-})—a genetic, rather than pharmacologic loss of function—have normal cardiac size and function, but are more susceptible to cardiomyocyte apoptosis and develop larger infarcts after coronary artery ligation [36]. Pressure overloading the hearts of ERK1/2^{-/-} mice with transverse aortic constriction leads to accelerated pathological cardiac hypertrophy and heart failure compared to wild-type littermate controls [37], but these defects can be rescued by overexpression of MEK1 [36, 37]. The observation that ERK null mice have phenotypically normal hearts at baseline, but are particularly susceptible to injury, may help to explain why trametinib cardiotoxicity does not occur with greater frequency in humans. It is conceivable that a second source of injury—hypertension, ischemia, or other toxic drug exposure—is required for cardiomyopathy to manifest. This “two-hit” hypothesis is true of other targeted therapies: mice treated with sorafenib have no evidence of cardiotoxicity, but develop accelerated heart failure after experimentally induced myocardial infarction [38]. Similarly, the likelihood of developing trastuzumab-induced cardiotoxicity is substantially higher in patients with cardiovascular comorbidities, such as the patient in our case report [39]. This enhanced susceptibility may become more evident as trametinib is administered to patients in the general population, who tend to be higher risk than those who are enrolled in clinical trials.

Conclusion

Trametinib is a highly selective MEK1/2 inhibitor that improves survival in patients with BRAF V600-mutated melanoma and is entering clinical trials for numerous other malignancies. Trametinib cardiotoxicity, typically manifest as cardiomyopathy, is relatively rare, but can cause symptomatic heart failure and necessitate discontinuation of otherwise effective antineoplastic therapy. This important adverse effect likely arises from inhibition of the cardioprotective effects of the MEK–ERK signaling axis.

Acknowledgments

Funding was provided by National Institutes of Health, Center for Advancing Translational Sciences (Grant No. UL1TR001111).

References

1. Lugowska I, Kosela-Paterczyk H, Kozak K, & Rutkowski P (2015). Trametinib: A MEK inhibitor for management of metastatic melanoma. *OncoTargets and Therapy*, 8, 2251–2259. [PubMed: 26347206]
2. Zhao Y, & Adjei AA (2014). The clinical development of MEK inhibitors. *Nature Reviews Clinical Oncology*, 11, 385–400.
3. Infante JR, Papadopoulos KP, Bendell JC, Patnaik A, Burris HA, 3rd, Rasco D, et al. (2013). A phase 1b study of trametinib, an oral mitogen-activated protein kinase kinase (MEK) inhibitor, in combination with gemcitabine in advanced solid tumours. *European Journal of Cancer*, 49, 2077–2085. [PubMed: 23583440]

4. Bridgeman VL, Wan E, Foo S, Nathan MR, Welti JC, Frentzas S, et al. (2016). Preclinical evidence that trametinib enhances the response to antiangiogenic tyrosine kinase inhibitors in renal cell carcinoma. *Molecular Cancer Therapeutics*, 15, 172–183. [PubMed: 26487278]
5. Pervere LM, Rakshit S, Schrock AB, Miller VA, Ali SM, Velcheti V (2017). Durable response to combination of dabrafenib and trametinib in BRAF V600E-mutated non-small-cell lung cancer. *Clinical Lung Cancer*, 18(3), e211–e213. [PubMed: 28024926]
6. Cho H, Matsumoto S, Fujita Y, Kuroda A, Menju T, Sonobe M, et al. (2017). Trametinib plus 4-methylumbelliferone exhibits antitumor effects by ERK blockade and CD44 downregulation and affects PD-1 and PD-L1 in malignant pleural mesothelioma. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*, 12(3), 477–490.
7. Roskoski R, Jr. (2012). MEK1/2 dual-specificity protein kinases: Structure and regulation. *Biochemical and Biophysical Research Communications*, 417, 5–10. [PubMed: 22177953]
8. Gilmartin AG, Bleam MR, Groy A, Moss KG, Minthorn EA, Kulkarni SG, et al. (2011). GSK1120212 (JTP-74057) is an inhibitor of MEK activity and activation with favorable pharmacokinetic properties for sustained in vivo pathway inhibition. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 17, 989–1000. [PubMed: 21245089]
9. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al. (2012). Improved survival with MEK inhibition in BRAF-mutated melanoma. *The New England Journal of Medicine*, 367, 107–114. [PubMed: 22663011]
10. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. (2002). Mutations of the BRAF gene in human cancer. *Nature*, 417, 949–954. [PubMed: 12068308]
11. Solit DB, Garraway LA, Pratilas CA, Sawai A, Getz G, Basso A, et al. (2006). BRAF mutation predicts sensitivity to MEK inhibition. *Nature*, 439, 358–362. [PubMed: 16273091]
12. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. (2015). Improved overall survival in melanoma with combined dabrafenib and trametinib. *The New England Journal of Medicine*, 372, 30–39. [PubMed: 25399551]
13. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, deBraud F, Larkin J, et al. (2015). Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*, 386, 444–451. [PubMed: 26037941]
14. Modak S, Asante-Korang A, Steinherz LJ, & Grana N (2015). Trametinib-induced left ventricular dysfunction in a child with relapsed neuroblastoma. *Journal of Pediatric Hematology/ oncology*, 37, e381–e383. [PubMed: 26181424]
15. Tseng D, Mason XL, Neilan TG, & Sullivan RJ (2016). Cardiogenic shock and respiratory failure in a patient with metastatic melanoma receiving trametinib therapy. *The Oncologist*, 21, 1136–1137. [PubMed: 27388234]
16. Falchook GS, Lewis KD, Infante JR, Gordon MS, Vogelzang NJ, DeMarini DJ, et al. (2012). Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: A phase 1 dose-escalation trial. *The Lancet Oncology*, 13, 782–789. [PubMed: 22805292]
17. Infante JR, Somer BG, Park JO, Li CP, Scheulen ME, Kasubhai SM, et al. (2014). A randomised, double-blind, placebo-controlled trial of trametinib, an oral MEK inhibitor, in combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas. *European Journal of Cancer*, 50, 2072–2081. [PubMed: 24915778]
18. Planchard D, Besse B, Groen HJ, Souquet PJ, Quoix E, Baik CS, et al. (2016). Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: An open-label, multicentre phase 2 trial. *The Lancet Oncology*, 17, 984–993. [PubMed: 27283860]
19. Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, Sosman JA, et al. (2013). Phase II study of the MEK1/MEK2 inhibitor trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 31, 482–489. [PubMed: 23248257]
20. Shah RR, & Morganroth J (2015). Update on cardiovascular safety of tyrosine kinase inhibitors: With a special focus on QT interval, left ventricular dysfunction and overall risk/benefit. *Drug Safety*, 38, 693–710. [PubMed: 26008987]

21. Tolcher AW, Bendell JC, Papadopoulos KP, Burris HA, 3rd, Patnaik A, Jones SF, et al. (2015). A phase IB trial of the oral MEK inhibitor trametinib (GSK1120212) in combination with everolimus in patients with advanced solid tumors. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, 26, 58–64. [PubMed: 25344362]
22. Shroff RT, Yarchoan M, O'Connor A, Gallagher D, Zahurak ML, Rosner G, et al. (2017). The oral VEGF receptor tyrosine kinase inhibitor pazopanib in combination with the MEK inhibitor trametinib in advanced cholangiocarcinoma. *British Journal of Cancer*, 116(11), 1402–1407. [PubMed: 28441383]
23. Tolcher AW, Patnaik A, Papadopoulos KP, Rasco DW, Becerra CR, Allred AJ, et al. (2015). Phase I study of the MEK inhibitor trametinib in combination with the AKT inhibitor afuresertib in patients with solid tumors and multiple myeloma. *Cancer Chemotherapy and Pharmacology*, 75, 183–189. [PubMed: 25417902]
24. Ghatalia P, Je Y, Kaymakcalan MD, Sonpavde G, & Choueiri TK (2015). QTc interval prolongation with vascular endothelial growth factor receptor tyrosine kinase inhibitors. *British Journal of Cancer*, 112, 296–305. [PubMed: 25349964]
25. Patnaik A, Tolcher A, Papadopoulos KP, Beeram M, Rasco D, Werner TL, et al. (2016). Phase 1 study to evaluate the effect of the MEK inhibitor trametinib on cardiac repolarization in patients with solid tumours. *Cancer Chemotherapy and Pharmacology*, 78, 491–500. [PubMed: 27392790]
26. Thakur A, & Witteles RM (2014). Cancer therapy-induced left ventricular dysfunction: Interventions and prognosis. *Journal of Cardiac Failure*, 20, 155–158. [PubMed: 24378722]
27. Hu LA, Chen W, Martin NP, Whalen EJ, Premont RT, & Lefkowitz RJ (2003). GIPC interacts with the β_1 -adrenergic receptor and regulates β_1 -adrenergic receptor-mediated ERK activation. *The Journal of Biological Chemistry*, 278, 26295–26301. [PubMed: 12724327]
28. Sabri A, Pak E, Alcott SA, Wilson BA, & Steinberg SF (2000). Coupling function of endogenous α_1 - and β -adrenergic receptors in mouse cardiomyocytes. *Circulation Research*, 86, 1047–1053. [PubMed: 10827134]
29. Marber MS, Rose B, & Wang Y (2011). The p38 mitogen-activated protein kinase pathway—a potential target for intervention in infarction, hypertrophy, and heart failure. *Journal of Molecular and Cellular Cardiology*, 51, 485–490. [PubMed: 21062627]
30. Kerkela R, & Force T (2006). P38 mitogen-activated protein kinase: A future target for heart failure therapy? *Journal of the American College of Cardiology*, 48, 556–558. [PubMed: 16875983]
31. Fischer P, & Hilfiker-Kleiner D (2007). Survival pathways in hypertrophy and heart failure: The gp130-STAT3 axis. *Basic Research in Cardiology*, 102, 279–297. [PubMed: 17530315]
32. Rose BA, Force T, & Wang Y (2010). Mitogen-activated protein kinase signaling in the heart: Angels versus demons in a heart-breaking tale. *Physiological Reviews*, 90, 1507–1546. [PubMed: 20959622]
33. Aikawa R, Komuro I, Yamazaki T, Zou Y, Kudoh S, Tanaka M, et al. (1997). Oxidative stress activates extracellular signal-regulated kinases through Src and Ras in cultured cardiac myocytes of neonatal rats. *The Journal of Clinical Investigation*, 100, 1813–1821. [PubMed: 9312182]
34. Bueno OF, & Molkentin JD (2002). Involvement of extracellular signal-regulated kinases 1/2 in cardiac hypertrophy and cell death. *Circulation Research*, 91, 776–781. [PubMed: 12411391]
35. Lou H, Danelisen I, & Singal PK (2005). Involvement of mitogen-activated protein kinases in adriamycin-induced cardiomyopathy. *American Journal of Physiology Heart and Circulatory Physiology*, 288, H1925–H1930. [PubMed: 15772336]
36. Lips DJ, Bueno OF, Wilkins BJ, Purcell NH, Kaiser RA, Lorenz JN, et al. (2004). MEK1-ERK2 signaling pathway protects myocardium from ischemic injury in vivo. *Circulation*, 109, 1938–1941. [PubMed: 15096454]
37. Purcell NH, Wilkins BJ, York A, Saba-El-Leil MK, Meloche S, Robbins J, et al. (2007). Genetic inhibition of cardiac ERK1/2 promotes stress-induced apoptosis and heart failure but has no effect on hypertrophy in vivo. *Proceedings of the National Academy of Sciences of the United States of America*, 104, 14074–14079. [PubMed: 17709754]
38. Duran JM, Makarewich CA, Trapanese D, Gross P, Husain S, Dunn J, et al. (2014). Sorafenib cardiotoxicity increases mortality after myocardial infarction. *Circulation Research*, 114, 1700–1712. [PubMed: 24718482]

39. Chavez-MacGregor M, Zhang N, Buchholz TA, Zhang Y, Niu J, Elting L, et al. (2013). Trastuzumab-related cardiotoxicity among older patients with breast cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 31, 4222–4228. [PubMed: 24127446]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1. Ejection fraction declined after trametinib treatment. The patient underwent surveillance echocardiography 13 and 30 days after starting trametinib for treatment of BRAF V600-mutated melanoma

Fig. 2.

RAS–RAF–MEK–ERK pathway is activated in many types of cancer. Trametinib inhibits MEK1/2, blocking the activation of ERK1/2. Dabrafenib and vemurafenib inhibit RAF activation. Trametinib and dabrafenib are used in combination to treat BRAF V600 mutated melanoma

Table 1

Summary of trametinib-associated cardiovascular toxicity in clinical trials

References	Regimen	Cardiac events	Incidence (%)	Subjects treated
[3]	Trametinib and gencitabine	Decreased EF	3	31
[16]	Trametinib	Decreased EF	7	97
[19]	Trametinib	Decreased EF	3	97
[17]	Trametinib and gencitabine	Cardiac-related events	3	160
[9]	Trametinib	Decreased EF	7	214
[12]	Trametinib and dabrafenib	Decreased EF	8	350
[13]	Trametinib and dabrafenib	Decreased EF	4	209
[9]	Trametinib	HTN	15	214
[12]	Trametinib and dabrafenib	HTN	26	350
[13]	Trametinib and dabrafenib	HTN	22	209
[23]	Trametinib and afuresertib	HTN	15	20