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Trametinib in the treatment of melanoma

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Abstract

Introduction—Aberrant Mitogen Activated Protein Kinase (MAPK) pathway signaling is a hallmark of melanoma. Mitogen/Extracellular signal-regulated Kinase (MEK) 1/2 are integral components of MAPK signaling. Several MEK inhibitors have demonstrated activity as single agents and in combination with other therapies. Trametinib was the first MEK inhibitor approved for use in treatment of advanced *BRAF*^{V600} mutant melanoma as a single agent and in combination with BRAF inhibitor, dabrafenib.

Areas Covered—In this article, we discuss the underlying biology of MEK inhibition and its rationale in melanoma treatment with special emphasis on the clinical development of trametinib, from initial phase I studies to randomized phase II and III studies, both as monotherapy and in combination with other therapeutics. Furthermore, we briefly comment on trametinib for *NRAS* mutant and other non-*BRAF* mutant subsets of melanoma.

Expert Opinion—Trametinib is a novel oral MEK inhibitor with clinical activity in *BRAF*^{V600} mutant metastatic melanoma alone and in combination with dabrafenib. Trametinib is currently being explored in other genetic subsets as well, particularly those with *NRAS* mutations or atypical *BRAF* alterations. Furthermore, to maximize efficacy and overcome acquired resistance, studies evaluating the combination of trametinib with other targeted agents and immunotherapy are underway.

Keywords

Trametinib; GSK1120212; MEK inhibitor; melanoma; BRAF; NRAS; molecularly targeted therapy

1. Introduction:

1.1 Overview

Malignant melanoma is the most aggressive of the cutaneous malignancies. For decades, the treatment options for patients with advanced disease were limited with an estimated median overall survival of less than a year [1]. However, the treatment paradigm of metastatic melanoma has changed rapidly in recent years [2].

Melanoma can be classified into distinct molecular cohorts based on the underlying genetic alterations. *BRAF*^{V600} mutations are seen in 40–50% of all melanomas. A substitution of

valine for glutamine at this codon (V600E) occurs in nearly 90% of all *BRAF* mutant melanomas [3,4]. Following *BRAF*, *NRAS* mutations are frequently noted in 15–25% of all melanomas [5]. Other less common alterations include *KIT* mutations (1–2%), and mutations in *GNAQ* and *GNAI1* (80–90% of ocular melanomas) [6]. The remaining 30–35% of melanomas do not harbor recurrent alterations in these well-characterized driver genes. However, recently the *NFI* mutated or deleted (a potential driver mutation) subset overall appears to represent up to 12% melanomas and is found within the *BRAF*, *NRAS*, *CKIT* melanomas. Of note, certain mutations are notably associated with specific subtypes of melanomas such as *KIT* mutations seen in 15–20% of acral and mucosal melanoma [7]. Likewise, *GNAQ* and *GNAI1* mutations are seen in the large majority of uveal melanomas [8,9].

Among several MEK inhibitors in clinical development, Trametinib (GSK1120212, Mekinist™, GlaxoSmithKline, London) is the only MEK 1/2 inhibitor approved by FDA either as monotherapy or in combination with dabrafenib for the treatment of unresectable or metastatic *BRAF*^{V600E} or *BRAF*^{V600K} mutant melanoma.

1.2 Overview of the market

Improved understanding of genetic and molecular basis of melanoma has revolutionized treatment options for advanced melanoma leading to the approval of six new drugs in past 4 years including T cell regulatory immune therapies including the human anti-cytotoxic T lymphocyte antigen-4 (CTLA4) monoclonal antibodies (ipilimumab) [10], anti-programmed death-1 (PD-1) antibodies (pembrolizumab, nivolumab) [11] and targeted therapies against mitogen-activated protein kinase (MAPK) pathway including *BRAF* inhibitors (vemurafenib [12], dabrafenib [13]), MEK inhibitor (trametinib) [14] and recently the combination of *BRAF* and MEK inhibitors (dabrafenib with trametinib) [15]. In spite of these advances, the treatment of melanoma remains challenging in terms of treatment selection and appropriate sequencing of these drugs to achieve optimal outcomes.

In particular, there has been remarkable progress for the *BRAF* mutant subset of melanoma with the development of the selective *BRAF* and MEK inhibitors. *BRAF* inhibitors alone produce response rates in the range of 40–50% with a median progression free survival (PFS) of 6–7 months [12,13]. However, due to paradoxical activation of the MAPK pathway, some patients develop secondary cutaneous malignancies and almost all eventually develop acquired resistance via compensatory reactivation of the MAPK pathway or parallel signaling pathways. These resistance mechanisms include aberrant *BRAF* splicing, increase in *BRAF* copy number gains, mutations in *NRAS* or *MEK1/2*, *COT* overexpression, growth factor up regulation, and alterations in the PI3K/AKT pathway [16,17].

Trametinib (GSK1120212, JTP 74057, Mekinist™, GlaxoSmithKline, London), an oral MEK inhibitor also has activity in the *BRAF*^{V600} cohort. Trametinib demonstrated significantly improved response rates (22% vs. 8%) median PFS (4.8 months vs. 1.5 months) and 6 month OS (81% vs. 67%) compared with chemotherapy in a phase III clinical trial [14]. This single agent activity appears slightly inferior to single agent *BRAF* inhibition, and has led to somewhat infrequent use as monotherapy. By contrast, the combination of *BRAF* with MEK inhibitors resulted in more frequent responses and improved progression free

survival and overall survival compared to BRAF inhibitors alone [15,18,19]. Although the initial responses are more prolonged with the combination of BRAF and MEK inhibition (approximately 9–11 months), acquired resistance still occurs and usually involves MAPK reactivation [20,21]. The detailed mechanisms to overcome the resistance by complete blockade of the MAPK pathway are still being elucidated.

In addition, there is encouraging early clinical activity of other MEK inhibitors (binimetinib, RO4987655) alone and in combination with CDK4/6 inhibitors (palbociclib, LEE011) [22] and also emerging evidence of synergistic activity of trametinib in combination with metformin in *NRAS* mutant melanoma [23]. Furthermore, due to early signs of efficacy in *RAS* mutated tumors, presently the role of MEK inhibition is being actively explored in other *RAS* mutated tumors like non-small cell lung cancer, pancreatic, and hepatobiliary cancers.

1.3 Chemistry and Pharmacokinetics

Trametinib dimethyl sulfoxide ($C_{26}H_{23}FIN_5O_4$) is a highly potent reversible allosteric inhibitor of MEK 1 and 2 inhibitor with a molecular weight of 615.39 g/mol [24 25]. It is rapidly absorbed when orally administered. The peak plasma concentration (T_{max}) occurs in 1.5 hours with an absolute bioavailability of 72% [24]. In patients receiving a single oral dose of trametinib 2mg per day, the area under the curve (AUC) and mean peak plasma concentrations (C_{max}) of trametinib is 370 ngh/mL and 22.2 ng/ml respectively [26].

The systemic exposure to trametinib was decreased when the drug was administered with a high-fat meal. Trametinib dose administered with a high fat meal decreased C_{max} by 70% and AUC by 24% also prolonged T_{max} to 5.5 hours compared to the fasted state, which may decrease the drug effect [24]. Hence it is recommended that trametinib be administered on an empty stomach (1 hour before or 2 hours after food) [27]. Trametinib is 97 % bound to human plasma proteins, independent of its concentration. After a single dose of trametinib 2 mg in patients, the apparent volume of distribution (V_d) was 214 L.

The majority (80 %) of a radiolabelled dose of trametinib was recovered in the feces and less than 20 % of the dose was recovered in the urine. Less than 0.1% of the drug is eliminated as unchanged drug. The mean apparent plasma terminal elimination half-life of trametinib was 3.8 to 4.8 days, following a single oral dose of 2 mg in patients. The mean apparent clearance of trametinib is 4.9L/h. The trough concentrations ranged from a mean of 10.0 to 18.9 ng/mL [24].

1.4 Drug-Drug interactions

Trametinib is metabolized by non-cytochrome (CYP450) mediated mechanisms mainly involving deacetylation via hydrolytic enzymes alone or in combination with glucuronidation, therefore has very limited drug-drug interactions reported. At clinically relevant concentrations, trametinib is not a substrate for CYP enzymes, apical efflux transporters, P-glycoprotein, breast cancer resistance protein (BCRP), hepatic uptake transporters organic anion transporting polypeptide OATP1B1 and OATP1B3 [24].

At clinical concentrations, trametinib may inhibit CYP2C8 and induce CYP3A4, according to in vitro studies [24]; therefore, co-administration of the drug with CYP3A 4 and CYP2C8 substrates or substrates largely metabolized by these enzymes should be avoided [24]. It is known that dabrafenib is a substrate of both CYP2C8 and CYP3A4. The trametinib at 2mg dose when administered along with dabrafenib 150 mg twice a day resulted in a 23% increase in the AUC of dabrafenib without any change in the AUC of trametinib when compared with either drug alone suggesting minor inhibitory effect of trametinib on clearance of dabrafenib [15]. However, as dabrafenib is not routinely administered at the maximum tolerated dose the final recommended daily dosing of the combination remains the same [13,28].

1.5 Pharmacodynamics

Trametinib is an allosteric kinase inhibitor of both isoforms of MEK. Trametinib directly binds to unphosphorylated MEK1 and MEK2 and inhibits their kinase activities with a half-maximum inhibitory concentration (IC₅₀) of 0.7–0.9 nmol/L [29]. It selectively inhibits MEK 1 and 2 without any inhibition noted when tested against more than 98 other kinases [30]. Further, it reversibly inhibits the RAF mediated phosphorylation thereby suppressing the downstream ERK signaling activity [31]. Inhibition of phosphorylated ERK, Ki-67 and increase in p27 were used as biomarkers of MEK inhibitor activity.

Trametinib induced rapid and sustained dephosphorylation of phosphorylated MEK in *BRAF*^{V600E} melanoma, HT-29 colon and other cancer cell lines, along with sustained tumor growth inhibition in xenograft tumors in nude mice [30]. At standard dosing of 2mg daily, trametinib produced dose-dependent changes in tumor biomarkers with a median change of 30% inhibition of phosphorylated ERK, 54% inhibition of Ki67 and an 83% increase of p27 [32].

Compared to other MEK inhibitors, trametinib had varied MEK binding affinity. Trametinib has lower binding affinity for MEK1/2 (IC₅₀ = 0.7 nM) than cobimetinib (IC₅₀ = 4.2 nM) [33]. Likewise, trametinib has also shown differential high sensitivity against BRAF (IC₅₀ = 0.3–0.85 nM) and NRAS mutant cell lines (IC₅₀ = 0.36–0.63 nM), as compared with wild type (IC₅₀ = 0.31–10 nM) melanoma cell lines [34].

2. Clinical Activity

2.1 Preclinical data

In cell lines and xenograft models of RAS mutated tumors, MEK was identified as potential therapeutic target based on the complete suppression of tumor growth in BRAF mutant xenografts and partial inhibition in RAS mutant tumors with use of selective MEK inhibitors [35]. Despite strong preclinical evidence, first and second generation MEK inhibitors such as CI-1040 and PD-0325901 either failed to show clinical activity or caused severe toxicities due to their narrow therapeutic window and simultaneous inhibition of MEK dependent non-tumor human tissues [36, 37]. Further enzymatic and cellular studies led to development of trametinib. Trametinib is a potent selective ATP noncompetitive allosteric inhibitor of MEK 1 and 2 kinases that prevents Raf-dependent phosphorylation of MEK and thus MAPK

pathway activation. In vitro, trametinib suppressed the tumor growth and had a favorable pharmacokinetic profile with a long circulating half-life and sustained suppression of p-ERK1/2 for more than 24 hours with greater antitumor effect among mutant BRAF or RAS tumors [31]. Based on this intriguing preclinical data, further clinical development of trametinib was undertaken.

2.1 Phase I trials

2.1.1 Trametinib Monotherapy—In a Phase I study, 206 patients with advanced solid tumors (including melanoma, non-small-cell lung cancer, colorectal cancer, and pancreatic cancers) were enrolled and treated with single agent trametinib [26]. Although the maximum tolerated dose in the study was 3 mg, 2 mg once daily was associated with better safety, tolerability and clinical activity and was the final recommended phase 2 dose. The dose-limiting toxicities (DLTs) were rash, diarrhea and central serous retinopathy. The common adverse events (any grade/grade 3 and 4) reported were skin rash (80/8%), diarrhea (42/<1%), peripheral edema (33/<1%), fatigue (29/4%), and nausea (28/0%). Other less common but notable side effects included ocular toxicities such as central retinal vein occlusion (15/<1%) and decreased cardiac ejection fraction (8/0%). No cutaneous squamous cell carcinomas were observed. Among all patients, objective tumor responses were noted in 10% with majority of responses in *BRAF* mutant melanomas.

Among melanoma patients, the response rates were significantly better in *BRAF* mutant melanoma (33%) compared to *BRAF* wild type tumors (10%) [32]. Although no objective responses were noted in *NRAS* mutant or uveal melanoma patients, approximately 27% (2 of 7) and 12% (2 of 16) had stable disease respectively [32].

2.1.2 Trametinib with dabrafenib—Flaherty and colleagues conducted a phase I/II study of 247 patients with metastatic *BRAF*^{V600} mutated melanoma patients. The safety and pharmacokinetic activity was tested in first 85 patients (Phase I part) with variable doses of oral dabrafenib (75 or 150 mg twice daily) and trametinib (1, 1.5, or 2 mg daily) [15]. See section 2.2.2 for more details.

2.1.3 Trametinib in other malignancies—The efficacy of MEK inhibition has been explored in other tumors as well. In pancreatic adenocarcinoma, the clinical benefit rate was 50% including objective partial responses in 8% and some degree of tumor regression in 42% [26]. In NSCLC, 2 of 30 patients had partial responses. Temporary stabilization of tumor growth was also demonstrated occasionally in colorectal adenocarcinoma and other cancers [26]. Additionally, preclinical studies in human leukemic cells and primary mouse leukemia with *NRAS* mutations showed that trametinib reduced cell proliferation and prolonged survival. An early phase I trial showed promising clinical activity of trametinib in *NRAS* or *KRAS* mutant acute myeloid leukemia (AML) [38,39].

Based on the promising synergistic preclinical data of combined inhibition of MEK and PI3K/AKT/mTOR or cell cycle regulatory pathways, various early phase clinical trials of trametinib in combination with pan PI3K or AKT or mTOR or CDK inhibitors are currently ongoing [40,41]. In a phase 1b dose escalation study of 113 patients with RAS or BRAF mutant advanced solid tumors, the combination of trametinib with pan PIK3 inhibitor,

buparlisib (BKM120) is well tolerated and showed favorable activity especially in KRAS mutant ovarian cancer patients [42]. In contrast, both the combinations of trametinib with AKT inhibitor (afuresertib) or mTOR inhibitor (everolimus) were poorly tolerated and lacked clinical efficacy [43,44]. Other combinations such as gemcitabine were well tolerated in phase I setting but failed to show therapeutic efficacy in phase II studies [45,46].

2.2 Phase II trials

2.2.1 Trametinib Monotherapy—In a phase II open label study of metastatic *BRAF*^{V600} mutant melanoma treated with trametinib, the response rates and progression free survival were significantly better for BRAF inhibitor naïve patients. While patients with prior BRAF inhibitor therapy (N=40) had no responses, 25% of BRAF inhibitor-naïve patients had objective responses (N=57). Likewise the median progression free survival in BRAF inhibitor naïve patients was 4 months compared to 1.8 months in those with prior BRAF inhibitor treatment. These results establish lack of efficacy of MEK inhibition after progression on BRAF inhibitor therapy [47].

2.2.2 Trametinib and Dabrafenib—A phase II trial randomized 162 patients 1:1:1 to either combination therapy with dabrafenib and trametinib (150/1 or 150/2 mg) or dabrafenib monotherapy. The patients were allowed to cross over to combination (150/2) upon progression. The combination of trametinib with dabrafenib resulted in reduced incidence of cutaneous squamous-cell carcinoma (7% vs. 19%), but high rates of pyrexia (71% vs. 26%) compared to dabrafenib alone. Also, the combination group had higher response rates (76% vs. 54%; P=0.03) and prolonged median progression-free survival 9.4 vs. 5.8 months, HR= 0.39; P<0.001) [15].

In this study the efficacy of combination therapy in patients who progressed on prior BRAF inhibitor therapy was evaluated. The patients who received dabrafenib for more than 6 months had better response rates (26% vs.0%) and improved PFS (3.9 vs. 1.8 months; P=0.02) with the combination compared with those treated < 6 months of BRAF inhibitor therapy [48]. Thus combination treatment has modest clinical efficacy in patients with BRAF inhibitor-resistant melanoma and can be considered in patients with prior prolonged response to BRAF inhibition.

2.3 Phase III trials

2.3.1 Trametinib Monotherapy: METRIC study—In the open label phase III METRIC study, a total of 322 patients with metastatic *BRAF*^{V600E} or *BRAF*^{V600K} mutated melanoma were randomized to receive either trametinib 2mg once daily or chemotherapy (dacarbazine or paclitaxel). Trametinib significantly improved response rates and progression free survival (PFS) compared to chemotherapy (22% vs. 8% and 4.8 months vs. 1.5 months). Although nearly half of patients crossed over from chemotherapy to trametinib at progression, improved 6 month overall survival (OS) was noted with trametinib (81% vs. 67%) [14].

2.3.2 Trametinib and Dabrafenib—In the phase III COMBI-d trial, 423 patients with newly diagnosed advanced *BRAF*^{V600E} or *BRAF*^{V600K} mutated melanoma were treated

with either dabrafenib plus trametinib or to dabrafenib plus placebo. The progression-free survival was significantly prolonged with the combination compared with dabrafenib alone (9.3 versus 8.8 months). The objective response rate was also significantly improved (67 versus 51 percent) with the combination [18]. Interestingly, the combination treatment group had decreased incidence of cutaneous squamous cell carcinoma (2% vs. 9%) and more frequent pyrexia (51% vs. 28%) chills (28% vs. 16%), diarrhea (24% vs. 14 %) and hypertension (22% vs. 14 %) compared to dabrafenib alone group. Dose interruptions were significantly more frequent with the combination, mainly due to fevers and chills [18].

Another phase III study compared dabrafenib plus trametinib with vemurafenib (COMBI-V) and found significantly improved outcomes with the combination (1 year OS 72% vs. 65%; HR=0.69; P=0.005 and median PFS 11.4 vs. 7.3 months; HR=0.56; P<0.001, respectively). Likewise, the objective response rate was also superior in the combination group (64% vs. 51%; P<0.001). The incidence of adverse events was similar in both groups but cutaneous squamous-cell carcinoma and keratoacanthoma were significantly less common in the combination group compared with vemurafenib group (1% vs. 18%) [19].

3. Trametinib in *NRAS* Mutant Melanoma

NRAS mutant melanomas are the second most common molecular cohort representing nearly 15–25% of all melanomas [49]. Unlike mutant BRAF, mutant NRAS activates downstream CRAF, MEK, and ERK in the MAP kinase pathway bypassing BRAF. Therefore selective BRAF inhibitors are unlikely to have any effect on the NRAS mutant melanomas [5].

MEK inhibition, by contrast, may have a role in treating *NRAS* mutant melanoma. Trametinib was associated with stable disease in 2 of 7 patients treated in the phase I clinical trial [32]. In a phase II study of binimetinib (MEK162), 6 of 30 patients (20%) had partial responses in NRAS mutant melanoma [50].

Recently, in a phase I PACMEL study, the combination of trametinib with paclitaxel in BRAF wild type melanoma demonstrated a 40% partial response rate and median OS of 14 months [51]. Notably, 4 of 6 patients with *NRAS*-mutant melanoma experienced a response.

In addition to alterations in the MAPK pathway, cell cycle checkpoint dysregulation is also frequently noted in melanoma. In a phase 1b/2 study of the combination of binimetinib with selective CDK4/6 inhibitor LEE011 in NRAS mutant melanoma, 7 of 21 patients had partial responses (33%) and >80% of patients had some degree of tumor regression [22]. Currently early phase trials evaluating the combination of trametinib with the CDK4/6 inhibitor palbociclib are also underway.

Furthermore, strong preclinical evidence suggests dual inhibition of PI3K/AKT/mTOR pathway along with MAPK pathway is important in NRAS mutant melanoma [52]. However, simultaneous inhibition of both the key pathways might be clinically challenging [53]. Recently, the combination of trametinib with metformin (which indirectly inhibits the PI3K/AKT/mTOR pathway) showed synergistic activity in *NRAS* mutant cell lines as well as in xenograft tumor models [23]. Combined inhibition of MEK and ERK also appears to

be a promising strategy in *NRAS*-mutant pre-clinical models [54]. Rationally designed targeted therapies combinations including trametinib may play a major role in the therapy of *NRAS* mutant melanoma in the future.

4. Trametinib in *BRAF*^{V600}/*NRAS* Wild Type Melanoma

Despite rapid developments in *BRAF* mutant melanoma, no targeted therapy options exist for patients with *BRAF/NRAS* wild type melanoma. Preclinical evidence suggests activity of trametinib in *BRAF/NRAS* wild type melanoma cell lines with or without loss of *NFI* (~12% of melanomas) [55,56]. In the early phase I study, trametinib monotherapy resulted in partial responses (10%) in wild type melanoma patients as well [32]. Intriguingly several responses in patients with atypical *BRAF* mutations have been noted. Specifically, pre-clinical data, early trametinib studies, and a retrospective series the uncommon *BRAF* K601E and L597 mutations are sensitive to trametinib [32,47,57,58]. A phase II study of trametinib in patients with atypical *BRAF* mutations and fusions is now ongoing.

Although trametinib monotherapy may play a role in some subsets (e.g. atypical *BRAF* mutations), combinatorial strategies will likely be needed to prevent compensatory upregulation of the MAPK and other signaling pathways in *BRAF/NRAS* WT melanoma.

5. Other MEK inhibitors in Melanoma

Binimetinib (MEK162) has shown activity in early phase II study in *NRAS* mutant melanoma with a 20% partial response rate [50]. The combination of cobimetinib with vemurafenib showed prolonged survival in *BRAF*^{V600}-mutated metastatic melanoma although associated with slightly increased risk of toxicity [59]. In a randomized phase II study of 98 patients, selumetinib showed improved progression free survival compared to temozolomide in metastatic uveal melanoma [60]. Other selective MEK inhibitors with preferential affinity for either *BRAF* or *RAS* mutant malignancies are also being developed [61].

6. Adverse Events

6.1 Trametinib monotherapy

In the randomized phase III METRIC study, trametinib was generally well tolerated; with frequent toxicities being skin rash, diarrhea, peripheral edema and fatigue [14]. The adverse events (AE) from trametinib led to dose interruptions in 35% of patients and to dose reductions in 27% of patients. Trametinib was discontinued in 2 patients due to treatment-related cardiac adverse events (less than 1%) [14]. Trametinib monotherapy toxicities are listed in Table 2.

Cutaneous toxicities were the most common side effects (76%) noted with trametinib similar to other MEK inhibitors, primarily including rash in 57% (grade 3/4 in 8%) and acneiform dermatitis in 19% (grade 3 in 1%). Unlike with *BRAF* inhibitors, no cutaneous squamous-cell carcinomas or hyper-proliferative skin lesions were observed with trametinib [14].

Ocular toxicities were rare (all grades 9%); most commonly blurry vision (4%) and central serous retinopathy (grade 3 in <1%). There were no reported retinal-vein occlusions.

Diarrhea (43%) was common and usually mild (grade 2 in 6% and no grade 3 or 4), as was fatigue (all grades 26%; grade 3 in 4%) and peripheral edema (26% and grade 3 in 1%). Hypertension was reported in 15% of patients (grade 3 in 12%). Cardiac adverse events reported were decreased ejection fraction or ventricular dysfunction (7%). Serious grade 3 cardiac-related events occurred in <1% (2 patients) and led to permanent discontinuation of the study drug. Overall, Trametinib appeared to have a favorable impact on patient-reported functional capacity and quality of life as well [62].

6.2 Trametinib and dabrafenib

The combination treatment is reasonably well-tolerated associated with a distinct set of side effects compared to trametinib or dabrafenib monotherapy. The cutaneous toxic effects related to BRAF inhibition from paradoxical MAPK activation were less frequent with concomitant MEK inhibition due to more complete blockade of the MAPK pathway [63]. However, the adverse events related to MEK inhibition such as hypertension, peripheral edema, cardiac and ocular toxicities were relatively more frequent. (Table 3)

Importantly, the incidence of cutaneous toxicity in terms of rash (22–27%), squamous-cell carcinoma (1–7%), or hyperproliferative lesion such as keratocanthoma (4–12%) was significantly less frequent. Also there is a significant delay in onset of cutaneous AEs compared with those on BRAF inhibitor monotherapy [15,18,19].

Pyrexia (51–71%) and chills (30–58%) were more common with combination treatment mainly due to dabrafenib. Due to pyrexia and chills, 58% of patients experienced dose reductions although reescalation was possible in >90% of these [15]. Overall, patients in the combination arm received treatment for longer time compared to dabrafenib alone (11 vs. 6 months) in the phase I/II trial [15]. The clinic-pathological factors associated with onset of pyrexia due to combination of dabrafenib and trametinib were evaluated in a retrospective study and noted no association with age, sex, disease burden, response, and progression-free or overall survival. Steroids were effective in treating these pyrexia episodes and allow dose re-escalation [64].

Ocular and cardiac adverse events were rare (1–2% and 4–9%) rare but notable for grade 3 toxicities such as hypertension (12%), decreased ejection fraction (0–4%) and chorioretinopathy (0–2%). Other common toxicities that were more frequent with combination therapy included fatigue (35–53%), nausea (30–44%), vomiting (29–40%), diarrhea (24–36%), and arthralgia (24–27%).

7. Conclusions:

Trametinib extends progression-free and overall survival in patients with advanced malignant melanoma. The combination of trametinib with dabrafenib delays the onset of resistance and results in higher response rates, prolonged PFS and OS compared to BRAF inhibitors alone. Due to more complete abrogation of MAPK pathway, the incidence of

cutaneous toxicities is reduced as well. Recent randomized phase III studies have established this combination as the standard first-line targeted therapy options for patients with *BRAF*^{V600} mutant melanoma. Based on the preclinical and preliminary clinical evidence, currently trametinib is being explored in other subsets of melanoma and other malignancies as well.

Improved understanding of predictive biomarkers of response and resistance are needed to identify appropriate patients most likely to benefit from MEK inhibitor based regimens. Furthermore, rational therapy partners have been identified and are being evaluated in ongoing clinical trials. The most effective approach is still being elucidated but trametinib will likely play a major role in future targeted strategies.

8. Expert Opinion

Trametinib is the first FDA approved MEK inhibitor for the treatment of *BRAF*^{V600} mutant metastatic melanoma as single agent and in combination with dabrafenib. We rarely use trametinib monotherapy except in the rare patient that cannot tolerate combination therapy or BRAF inhibitor monotherapy. The combination of dabrafenib with trametinib, conversely, has demonstrated superior clinical outcomes compared to BRAF inhibitor monotherapy. This regimen has now emerged as the standard of care first-line treatment for patients with *BRAF*-mutant metastatic melanoma. Both the combination of BRAF and MEK inhibitors along with immune therapies has revolutionized the treatment of malignant melanoma with significant tumor responses and prolonged disease remissions.

Trametinib has not been directly compared with other MEK inhibitors but certain MEK inhibitors reportedly have preferential activity for specific tumor types. While trametinib and cobimetinib seem to have more activity in BRAF mutant melanomas, binimetinib has shown more promising activity in *NRAS* mutant melanoma. Other MEK inhibitors such as GDC-0623 and CH4987655 may have better efficacy in RAS mutant tumors by blocking feedback activation of MEK by *BRAF* wild type tumors [61,65]. Likewise, in a randomized phase II study of 98 patients, selumetinib showed improved progression free survival compared to temozolomide in metastatic uveal melanoma; the efficacy of trametinib in this setting is still being elucidated.

Unlike *BRAF*^{V600} mutant melanoma, targeted treatment options for non-*BRAF* mutant melanoma including those with *NRAS* mutations, atypical *BRAF* alterations, and deletions of *NFI* are limited. Preclinical and early clinical trials suggest sensitivity of trametinib to atypical *BRAF* mutations (non-V600) and *NRAS* mutant melanoma. Currently early phase I/II trials of trametinib in combination with AKT or CDK4/6 inhibitors in *BRAF* wild type metastatic melanoma are ongoing. A detailed list of ongoing clinical trials of trametinib in melanoma are listed in Table 4 below.

Furthermore, role of trametinib in the treatment of other *RAS/RAF* mutated non-melanomatous malignancies such as pancreatic cancer, NSCLC, colon cancer and acute leukemia are being explored. *BRAF* mutations were noted in 15% of cholangiocarcinoma patients and MEK inhibitors have never been explored in these tumors but Loaiza-Bonilla

and colleagues reported a patient with refractory cholangiocarcinoma with excellent response with combination therapy with trametinib and dabrafenib [66].

When discussing melanoma therapies, the rapid and promising developments in immunotherapy cannot be ignored. While combined BRAF/MEK regimens have induced higher response rates, their use is limited to *BRAF* mutant melanoma. However, the immune based therapies including immune checkpoint inhibitors, anti-PD-1/PD-L1 (programmed death-1/ligand) receptor antibodies have shown efficacy irrespective of the underlying oncogenic driver mutation. Although, anti-PD-1 has demonstrated relatively lower response rates (25–40%), they have a very tolerable side effect profile, and more importantly, have induced sustained long-term responses. Currently ipilimumab, pembrolizumab, and nivolumab are FDA approved immune therapies for the treatment of metastatic melanoma. In addition, in a phase I study of 53 patients, the combination of ipilimumab with nivolumab resulted in rapid durable tumor regressions (80% or more) irrespective of *BRAF* mutations status in around 40% of patients but severe grade 3 or 4 adverse events were noted in 62% of patients [67].

Combination strategies of immune therapy and targeted therapy are being explored aiming for deeper and durable responses [68]. The overall impact of MEK inhibition on immune response is not well defined due to conflicting preclinical data. One study suggests MEK inhibitors inhibit T cell function and suppress PD-L1 expression [69] and another implicates negative impact of MEK inhibition on the immune system through reduced cytokine production and impaired T cell and dendritic function [70].

Appropriate sequencing or combination of these targeted and immune agents in the treatment of *BRAF* mutant melanoma remains elusive. In a phase I study of combination of ipilimumab with BRAF inhibitor vemurafenib resulted in severe hepatotoxicity leading to early closure of the study [71]. The combination of ipilimumab with combined dabrafenib and trametinib also had severe toxicities although so far dabrafenib and ipilimumab appears tolerable [72]. Currently combinations of anti PD-1/PDL-1 with trametinib +/- dabrafenib are ongoing. In the future, rationally selected newer combinational strategies will be pursued (Table 4).

In summary, trametinib in combination with dabrafenib has been a remarkable advancement in the treatment of *BRAF* mutant melanoma and has future potential in other non-*BRAF* mutant melanomas as well. With the recent dramatic change in the treatment landscape of metastatic melanoma, the future use of trametinib may be undermined amidst future development of other MEK inhibitors and immune therapies. Better understanding of the molecular mechanisms of resistance via aberrantly activated signaling pathways will facilitate rational development of future combinational therapies.

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Drug Summary Box

Drug name	Trametinib
Phase	III
Indication	<i>BRAF</i> ^{V600} mutant metastatic melanoma
Pharmacology	Inhibitor of MEK 1 and 2, resulting in growth factor-mediated inhibition of cell signalling and proliferation
Route of administration	Oral
Chemical structure	N-(3-(3-cyclopropyl-5-(2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl acetamide
Pivotal trial(s)	Phase I [15, 26, 32], Phase II [15, 47], Phase III [14, 18, 19]

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Table 1:

Clinical Trials of Trametinib in melanoma

Trial	Phase	Target	Drug	Study population		PFS	RR	Remarks
Infante et.al [26]	I	MEK	Trametinib	Advanced solid tumors N=206	Pancreatic (n=26) Colorectal (n=28) NSCLC (n=30) Melanoma (n=97) Others (n=25)	-	10%	MTD =3 mg daily RP2D = 2mg daily
Falchook et.al [32]	I	MEK	Trametinib	Metastatic Melanoma N=97	BRAF mutant (n=36) BRAFi naïve (n= 30) Prior BRAFi (n=6) BRAF wild (n=39) BRAF unknown (n=6) NRAS mutant (n=7) Uveal melanoma (n=16)	5.7 NA 2 NA NA 1.8	40% NA 10% 0% 0% 0%	Concurrent BRAFV600 WT/NRAS WT (n=20) had a trend of higher RR (20%) than BRAFV600WT/ NRAS-mutant patients
Kim et.al [47]	II	MEK	Trametinib	BRAF mutant Metastatic N=97	BRAFi therapy (n= 40) BRAFi naïve (n=57)	1.8 4	0% 25%	stable disease =28% stable disease =51%
Flaherty et.al [14]	III	MEK	Trametinib vs. Chemo	BRAF mutant Metastatic N=322	Trametinib (n= 214) Chemotherapy (n= 108)	4.8 1.5	22% 8%	6 month OS = 81% vs, 67% stable disease = 56% vs. 31%
Flaherty et.al [15]	I/II	BRAF MEK	Dabrafenib/ Trametinib	BRAF V600 mutant Metastatic N=162	DT 150/2 (n =54) DT 150/1 (n=54) D150 (n=54)	9.4 9.2 5.8	76% 50% 54%	
Long et.al [18]	III	BRAF MEK	Dabrafenib/ Trametinib vs. Dabrafenib	BRAF V600E/K N=423	DT (n=211) D (n=212)	9.3 8.8	67% 55%	
Robert et.al [19]	III	BRAF MEK	Dabrafenib/ Trametinib vs. Vemurafenib	BRAF V600E/K N=604	DT (n=352) V (n=352)	11.4 7.3	64% 51%	12 month OS 72% vs. 67%

PFS- progression free survival (in months); RR- response rates; NSCLC- Non small cell lung cancer; MTD-Maximum Tolerated Dose; RP2D- Recommended phase 2 dose; WT- wild type; BRAFi – BRAF inhibitor; n- number of patients; OS- overall survival

Table 2:

Adverse events with Trametinib monotherapy:

Adverse Event	Frequency of toxicity (%) –All grade (grade 3 and 4)		
	Infante et.al [26]	Falchook et.al [32]	Kim et.al [47]
Rash/Dermatitis Acneiform	80 (8)	92 (8)/85 (8)	75 (9)
Diarrhea	42 (<1)	42 (0)	52 (4)
Fatigue	33 (4)	35 (4)	26 (2)
Peripheral edema	29 (<1)	35 (0)	29 (3)
Nausea	28 (0)	21 (0)	30 (0)
Vomiting	17 (1)	8 (0)	18 (0)
Pruritis	14 (0)	15 (0)	27 (1)
Dry skin	18 (0)	-	22 (0)
Decreased appetite	10 (<1)	-	11 (1)
Ocular toxicity	15 (<1)	-	-
Mucosal inflammation	7 (0)	4 (0)	-
Constipation	5 (0)	-	14 (0)
Decreased Ejection fraction	8 (0)	-	-
Periorbital edema	5 (0)	-	-
Thrombocytopenia	5 (<1)	-	-
Dry mouth	5 (0)	-	11 (0)
Dry skin	-	31 (0)	-

Table 3:

Adverse events with combination therapy with Trametinib

Adverse event	Trametinib+ Dabrafenib		
	Frequency of toxicity (%) –All grade (grade 3)		
	Robert et.al [19]	Long et.al [18]	Flaherty et.al [15]
Pyrexia	53 (4)	51 (6)	71 (5)
Fatigue	-	35 (2)	53 (4)
Headache	-	30 (<1)	29 (0)
Nausea	35 (<1)	30 (0)	44 (2)
Chills	31 (1)	30 (0)	58 (2)
Arthralgia	24 (1)	24 (<1)	27 (0)
Diarrhea	32 (1)	24 (1)	36 (2)
Rash	22 (1)	23 (0)	27 (0)
Hypertension	-	22 (4)	9 (2)
Vomiting	29 (1)	20 (1)	40 (2)
Cough	-	16 (0)	29 (0)
Peripheral edema	-	14 (<1)	29 (0)
Pain in a limb	-	14 (1)	
Decreased appetite	-	11 (<1)	22 (0)
Abdominal pain	-	11 (1)	-
Elevated ALT	-	11 (2)	-
Elevated AST	-	11 (3)	-
Elevated Alkaline phosphatase	-		9 (0)
Constipation	-	11 (<1)	22 (0)
Myalgia	-	11 (<1)	22 (2)
Asthenia	-	10 (<1)	-
Dizziness	-	10 (0)	-
Nasopharyngitis	-	10 (0)	-
Back pain	-	9 (1)	-
Dry skin	-	9 (0)	-
Pruritis	-	8 (0)	-
Alopecia	6 (0)	7 (0)	5 (0)
Hand foot syndrome	4 (0)	5 (0)	-
Hyperkeratosis	4 (0)	3 (0)	9 (0)
Skin papilloma	2 (0)	1 (0)	4 (0)
Night sweats	-	-	24 (0)
Cutaneous SCC	1 (1)	2 (2)	7 (5)
Decreased EF	8 (4)	4 (<1)	9 (0)
Chorioretinopathy	1 (0)	<1 (0)	2 (2)
Decreased Vision		2 (0)	-

Adverse event	Trametinib+ Dabrafenib		
	Frequency of toxicity (%) –All grade (grade 3)		
	Robert et.al [19]	Long et.al [18]	Flaherty et.al [15]
Dermatitis Acneiform	6 (0)	8 (0)	-
Photosensitivity	4 (0)	-	-

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Table 4:

Ongoing combination phase III trials*

Trial	Type	Setting	Drug	Phase	Target	Status	Remarks
Combination trials of Trametinib and Dabrafenib							
	BRAF V600	Stage IIC	Dabrafenib (D) Trametinib (T)	II	BRAF MEK	Recruiting	Neoadjuvant
COMBL-NEO	BRAF V600E/K	Stage III or Oligo-metastatic resectable stage IV	Dabrafenib Trametinib	II	BRAF MEK	Recruiting	Neoadjuvant Adjuvant
COMBL-AD	BRAF V600E/K	Stage IIIA (LN>1mm) Stage IIIB, C Recurrent stage I/II	Dabrafenib Trametinib	III	BRAF MEK	Completed accrual	Adjuvant study in high risk patients
	BRAF V600E/K	Recurrent Unresectable Stage IV	Dabrafenib Trametinib/ AT13387	I	BRAF MEK Hsp90	Recruiting	BRAF inhibitor resistant
	BRAF V600 E/D/K/R	Brain metastases	Dabrafenib Trametinib	II	BRAF MEK	Recruiting	To evaluate the intracranial response rate
	BRAF V600 E/K	Unresectable Stage III/IV	Dabrafenib Trametinib	II	BRAF MEK	Recruiting	First line treatment in Acral Lentiginous Melanoma
	BRAF V600E/K	Recurrent Unresectable Stage III/IV	DT day 1-56 DT day 1-7, 29-56	II	BRAF MEK	Recruiting	Compare intermittent dosing and continuous dosing of combination
Combination trials of Trametinib and Dabrafenib with Immune therapy							
	BRAF V600E/K	Unresectable Stage III/IV	Dabrafenib Trametinib Ipilimumab (ipi)	I	BRAF MEK T cell	Recruiting	
	BRAF V600	Unresectable Stage III/Stage IV	Ipilimumab+DT Ipilimumab+D Ipilimumab+T Ipilimumab	I	BRAF MEK T cell	Recruiting	
	BRAF wild and mutant	Unresectable Stage III/IV	Pembrolizumab+DT Pembrolizumab+D Pembrolizumab+T DT alone	I/II	BRAF MEK T cell	Recruiting	No prior immune therapy allowed
Combination trials of Trametinib and Dabrafenib with other drugs							
	BRAF V600E	Unresectable Stage IIC/IV	Dabrafenib Trametinib Metformin	I/II	BRAF MEK	Recruiting	First line treatment

Trial	Type	Setting	Drug	Phase	Target	Status	Remarks
	BRAF V600E	Stage IV	Dabrafenib Trametinib Hydroxychloroquine	I/II	BRAF MEK Autophagy	Recruiting	
	BRAFV600E/K	Recurrent Unresectable or Stage IV	Dabrafenib Trametinib AT13387	I	BRAF MEK Hsp90	Recruiting	BRAF inhibitor resistant
Combination trials of Trametinib with other targeted therapies							
	Uveal melanoma	Stage IV	Trametinib T+ GSK2141795	I	MEK AKT	Recruiting	First line systemic treatment
	BRAF Wild	Unresectable Stage III/IV	Trametinib GSK2141795	II	MEK AKT	Recruiting	
	Non BRAF mutant	Advanced solid tumors	Trametinib Palbociclib	I	MEK CDK4/6	Recruiting	Excluded BRAF mutation+
	BRAF Wild	Unresectable Stage III/IV	Trametinib Digoxin	I	MEK	Recruiting	
	BRAFV600E/K	Stage IIIC Stage IV	Dabrafenib Trametinib DNE3	I/II	BRAF MEK PI3K-AKT	Terminated	Due to safety concerns with DNE3
	BRAF nonV600	Recurrent Stage IIIB/C/IV	Trametinib	II	MEK	Recruiting	Allowed prior immunotherapy or chemotherapy but no inhibitors to MAPK pathway
	BRAFV600E/K	Recurrent Stage IIIB/C/IV	DT->Ipi+Nivolumab Ipi+Nivolumab->DT	III	BRAF MEK T cell	Not open yet	
	BRAF wild/mutant	Unresectable Stage III/ IV	Trametinib+ Nab-paclitaxel	I	MEK	Not open yet	No more than one line of prior chemotherapy allowed

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