Chapter 5
Dabrafenib and Trametinib

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Pharmacological Properties and Early Development

Dabrafenib (GSK2118436) is a reversible, ATP-competitive inhibitor of the *BRAF* V600 kinase. Dabrafenib inhibits BRAF kinases with in vitro IC50 values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively [1]. In preclinical studies, dabrafenib inhibited tumor growth in models of melanoma (A375P) and colorectal cancer (Colo205). Inhibition of the *BRAF* V600E kinase reduces ERK phosphorylation and proliferation of tumor cells through G1-phase cell cycle arrest [2]. In in vivo studies, mice transplanted with human *BRAF* V600E-mutated melanoma (A375P F11) received dabrafenib at doses of 0.1, 1, 10, and 100 mg/kg once daily for 14 days. The inhibition of tumor growth was dose-dependent, with the highest dose inducing complete remission in 50% of mice [3]. In the phase I study BREAK-1, immunohistochemistry was used to analyze the expression of phosphorylated ERK in tissues collected from patients before and during dabrafenib treatment. Compared with baseline, dabrafenib reduced ERK phosphorylation substantially after 1–2 weeks of treatment (median, 83.9%; range, 38.0–93.3%). Similarly, fluorodeoxyglucose-based positron emission tomography (FDG-PET) showed a reduced FDG uptake in 95% of patients after 2 weeks of dabrafenib treatment, with a median reduction in the standardized uptake value (SUVmax) of 60% compared with baseline (range, 19–100%) [4].

Trametinib (GSK1120212, JTP-74057) is an oral, low-molecular-weight, selective inhibitor of the MEK1 and MEK2 kinases. In contrast to *BRAF* mutations, activating *MEK* mutations are very rare in melanoma cells [5]. However, MEK kinases are crucial for the MAPK signaling pathway, because they may be the only

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substrate for both MEK isoforms [6, 7]. In mouse models of colorectal cancer (HT-29 and COLO205) and melanoma (A-375P), trametinib decreased ERK phosphorylation and inhibited the growth of cancer cells carrying the *BRAF*, *NRAS*, and *KRAS* mutations. The inhibition of cell proliferation and G1-phase cell cycle arrest caused apoptosis of tumor cells. The best response to treatment was seen in tumors with *BRAF* mutations. Trametinib given once daily had a long half-life and caused long-term ERK suppression (>24 h). The IC50 values for MEK1 and MEK2 were 0.7–0.9 nmol/l [8, 9]. In a phase I study, the pharmacodynamic properties of trametinib were assessed based on the effects on tumor tissue during treatment (biopsy samples were taken before and 15 days after treatment). At a dose of 2 mg daily, ERK phosphorylation decreased by 30%, Ki-67 phosphorylation decreased by 54%, and p27 phosphorylation increased by 83%. In patients with *BRAF*- and *NRAS*-mutated melanoma, these changes were more pronounced and dose-dependent [10].

By acting on two different kinases (BRAF and MEK), dabrafenib and trametinib jointly block the MAPK signaling pathway. Studies in xenograft models showed that the dabrafenib–trametinib combination inhibited the growth of cancer cells more efficiently than dabrafenib ($p = 0.01$) or trametinib alone ($p = 0.0001$) [11].

Pharmacokinetic Properties of Dabrafenib and Trametinib

Administration of dabrafenib with a meal decreases its bioavailability and delays absorption, with a 51% reduction in the maximum concentration and a 31% reduction in the area under the curve (AUC) compared with the fasting state. Therefore, dabrafenib should be taken ≥1 h before or ≥2 h after a meal. The maximum blood concentration of dabrafenib is reached 2 h after oral ingestion of a single dose, and the mean half-life is 5.2 h. Repeated dosing decreases dabrafenib exposure, which is probably because dabrafenib induces its own metabolism. Age, weight, sex, and race do not significantly affect the pharmacokinetic properties of dabrafenib. Dabrafenib binds highly to plasma proteins (99.7%), mainly albumin. Dabrafenib is metabolized primarily by CYP3A4 and CYP2C8 to hydroxy-dabrafenib, which is then oxidized by CYP3A4 to carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated non-enzymatically to desmethyl dabrafenib. Carboxy-dabrafenib is excreted in the bile and urine. Desmethyl dabrafenib can also be formed in the gut and reabsorbed. Desmethyl dabrafenib is metabolized by CYP3A4 to oxidative metabolites. The terminal half-life for dabrafenib is 8 h, for hydroxy dabrafenib 10 h, and for carboxy dabrafenib and desmethyl dabrafenib 21–22 h. Both hydroxy dabrafenib and desmethyl dabrafenib may contribute to the clinical activity of dabrafenib, but the activity of carboxy dabrafenib is probably insignificant [1, 10]. Dabrafenib is a substrate for and an inducer of CYP3A4, a substrate for CYP2C8, and an inducer of CYP2Cs and CYP2B6. Concomitant use of dabrafenib with drugs that are substrates, inducers, or inhibitors of these metabolic enzymes requires caution because of the risk of serious interactions. Particular caution should be exercised when dabrafenib is used in combination with strong inhibitors of CYP3A4,

glucuronidation, and/or transport proteins (e.g., ketoconazole, nefazodone, clarithromycin, ritonavir, itraconazole, voriconazole, posaconazole). Conversely, concomitant use of dabrafenib with strong inducers of CYP3A4 or CYP2C8 (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's wort) may result in incomplete exposure to dabrafenib. Dabrafenib is excreted as metabolites in feces (71%) and urine (23%). The clearance of dabrafenib is unchanged in patients with mild to moderate renal or hepatic impairment. In severe renal or hepatic impairment, caution should be exercised because dabrafenib has not been tested in these patients [1].

Trametinib is rapidly absorbed in the gastrointestinal tract following oral ingestion. Taking trametinib with a meal decreases its bioavailability and delays absorption, with a 70% reduction in the maximum concentration and a 10% reduction in the AUC compared with the fasting state. After ingestion of a single dose, the maximum blood concentration of trametinib is reached after 1.5 h, and the mean half-life is 5.3 days. Repeated dosing of trametinib leads to accumulation. The mean accumulation ratio for repeated dosing of 2 mg/day is 5.97. Trametinib binds highly to human plasma proteins (97.4%). Trametinib is metabolized mainly by deacetylation, deacetylation with monooxygenation, or in combination with glucuronidation. Oxidation by the CYP3A4 isoenzymes is considered a minor metabolic pathway. Therefore, trametinib has a low risk of drug interactions. However, because biliary metabolism and excretion are the major routes of elimination, trametinib should be used with caution in patients with moderate or severe hepatic impairment. In patients with mild or moderate renal impairment, trametinib clearance remains unchanged [10, 12, 13].

The use of dabrafenib in combination with trametinib did not significantly affect the pharmacokinetics of either drug [1].

Phase I Trials

The phase I study assessing the safety, tolerability, and recommended phase II dose of dabrafenib included 184 patients with incurable solid tumors (156 with metastatic melanoma) [4]. The maximum tolerated dose (MTD) was not reached, and doses up to 300 mg twice daily were well tolerated. Based on these findings, the recommended dose for phase II studies was 150 mg twice daily. Of 36 patients with *BRAF* V600-mutated advanced melanoma who received dabrafenib at a dose of 150 mg twice daily, 18 (50%) achieved a confirmed partial response (PR) or complete response (CR). The median response duration was 6.2 months [95% confidence interval (CI): 4.2–7.7 months]; the median progression-free survival (PFS) was 5.5 months. Of 10 patients with previously untreated brain melanoma metastases, 9 had tumor regression.

The open-label, first-in-human, dose-escalation, phase I study MEK111054 assessed the safety, pharmacokinetics, and pharmacodynamics of trametinib in patients with solid tumors or lymphomas [12]. The dose of 2.0 mg once daily was

selected for further evaluation. Only patients with melanoma were included in this evaluation. Of 36 patients with BRAF-mutated advanced melanoma, 30 had not previously received a BRAF inhibitor. In this subgroup, 2 patients achieved a CR and 10 achieved a PR (confirmed response rate, 33%). The median PFS in this subgroup was 5.7 months (95% CI: 4.0–7.4 months). Of 6 patients with prior BRAF inhibitor treatment, 1 had an unconfirmed PR. Of 39 patients with non-BRAF-mutated melanoma, 4 had a confirmed PR (10%).

Activity and Efficacy

The efficacy of dabrafenib in patients with BRAF-mutated metastatic melanoma was assessed in phase II and phase III studies (BRF113710 [BREAK-2], BRF113683 [BREAK-3], BRF113929 [BREAK-MB]) [14–16]. In the phase II trial, 45 patients (59%) with *BRAF* V600E mutations and 2 patients (13%) with V600K mutations achieved a confirmed response. The median PFS was 6.3 months for patients with V600E mutations and 4.5 months for those with V600K mutations; the median overall survival (OS) was 13.1 months and 12.9 months, respectively [14]. Dabrafenib has been approved for the treatment of patients with BRAF-mutated metastatic melanoma based on the results of the randomized phase III trial BREAK-3 that compared the efficacy of dabrafenib and dacarbazine. The study included 250 previously untreated patients who were randomized in a 3:1 ratio to dabrafenib (150 mg twice daily) or dacarbazine (1000 mg/m^2 intravenously every 3 weeks) [17]. The complete or partial response rate was 50% in the dabrafenib arm and 6% in the dacarbazine arm. The PFS hazard ratio was 0.37 (95% CI: 0.23, 0.57), with the median PFS 6.9 months in the dabrafenib arm and 2.7 months in the dacarbazine arm. The median OS was 18.2 months and 15.6 months, respectively. However, the OS in the dacarbazine arm was confounded because patients with disease progression could cross-over to dabrafenib [15, 18].

In monotherapy, trametinib is less effective than dabrafenib for *BRAF*-mutated metastatic melanoma. The phase II study MEK113583 assessed the objective response rate, safety, and pharmacokinetics of trametinib at a dose of 2.0 mg once daily in patients with advanced BRAF-mutated melanoma after failure of prior BRAF inhibitor therapy (group A, $n = 40$) or without prior BRAF inhibition (group B, $n = 57$). In group A ($n = 40$), the clinical activity of trametinib was low: 11 patients (28%) had stable disease (SD), and the median PFS was 1.8 months. In group B, 1 patient (2%) achieved a CR, 13 (23%) achieved a PR, and 29 (51%) had SD (confirmed response rate, 25%); the median PFS was 4.0 months. Trametinib activity was observed in patients with *BRAF* V600E mutations but also in those with rarer mutations (*BRAF* K601E, *BRAF* V600R) [19]. In the randomized, phase III study METRIC (MEK114267), the efficacy of trametinib was compared with chemotherapy (dacarbazine or paclitaxel) in 322 patients with *BRAF* V600E/K-mutated unresectable or metastatic melanoma [20]. Patients were randomized in a 2:1 ratio to trametinib (2 mg once daily) or first-line or second-line chemotherapy (no prior

treatment with BRAF or MEK inhibitors or ipilimumab). A cross-over from the chemotherapy arm to the trametinib arm was allowed after confirmation of disease progression. The median PFS was 4.8 months in the trametinib arm and 1.5 months in the chemotherapy arm (HR for disease progression or death in the trametinib arm at baseline was 0.45; 95% CI: 0.33–0.63, $p < 0.001$). After 6 months, the OS rate was 81% in the trametinib arm and 67% in the chemotherapy arm, despite the cross-over (HR for death was 0.54; 95% CI: 0.32–0.92; $p = 0.01$). The objective response rate was 22% for the trametinib arm and 8% for the chemotherapy arm ($p = 0.001$). These results led to the approval of trametinib monotherapy for *BRAF* V600E- or V600K-mutated unresectable or metastatic melanoma [20].

Combined therapy with dabrafenib and trametinib improved treatment outcomes in patients with *BRAF*-mutated melanoma. A phase I/II study assessed the safety, pharmacokinetics, and efficacy of the dabrafenib–trametinib combination in 247 patients with BRAF-mutated advanced melanoma. Part C of this study compared the efficacy of dabrafenib monotherapy with the dabrafenib–trametinib combination. The objective response rate was higher in patients receiving dabrafenib (300 mg/day) and trametinib (2 mg/day) than in patients receiving dabrafenib monotherapy (76% vs. 54%, $p = 0.03$). The median PFS was 9.4 months for the combined treatment and 5.8 months for dabrafenib monotherapy (HR 0.39; 95% CI: 0.25–0.62; $p < 0.001$) [21]. In that study, OS was 30% at 4 years and 28% at 5 years of follow-up [22].

The efficacy of the dabrafenib–trametinib combination as a first-line treatment was assessed in two phase III studies: COMBI-d ($n = 423$) and COMBI-v ($n = 704$). In the COMBI-d study, patients who received dabrafenib monotherapy served as the control arm. The response rate was 69% for the dabrafenib–trametinib combination and 53% for dabrafenib monotherapy ($p = 0.0014$). The median PFS was 11 months for the dabrafenib–trametinib combination and 8.8 months for dabrafenib monotherapy (HR 0.67; 95% CI: 0.53–0.84, $p = 0.0004$); the median OS was 25.1 months and 18.7 months, respectively (HR 0.71, 95% CI: 0.55–0.92; $p = 0.01$) [23]. In addition, compared with dabrafenib monotherapy, the dabrafenib–trametinib combination improved the health-related quality of life and reduced pain [24]. In the phase III COMBI-v study, patients in the control arm received vemurafenib monotherapy. The objective response rate was 64% in the dabrafenib–trametinib combination arm and 51% in the vemurafenib arm ($p < 0.001$) [25]. The dabrafenib–trametinib combination improved OS significantly compared with vemurafenib monotherapy (26.1 vs. 17.8 months; HR = 0.68; 95% CI: 0.56–0.83). The median PFS in the dabrafenib–trametinib arm was 12.1 months and 7.3 months in the vemurafenib arm (HR = 0.61, 95% CI 0.51–0.73) [26].

The pooled analysis of data from these two studies was published in 2019. In total, 563 patients received dabrafenib with trametinib; the median follow-up was 22 months. The rates of 4-year and 5-year PFS in patients receiving dabrafenib with trametinib were 21% (95% CI: 17–24) and 19% (95% CI: 15–22), respectively. The OS rate was 37% (95% CI: 33–42) after 4 years and 34% (95% CI: 30–38) after 5 years. A CR was observed in 109 patients (19%), which was associated with an improvement in long-term results: the 5-year OS rate in this group was 71% (95%

Table 5.1 Results of phase III studies of dabrafenib and trametinib in monotherapy or in combination for advanced melanoma

	BREAK-3 [15]	METRIC [20]	COMBI-d [28]		COMBI-v [25, 26]	
Drug	Dabrafenib	Trametinib	Dabrafenib	Dabrafenib + trametinib	Vemurafenib	Dabrafenib + trametinib
Objective response rate (ORR), %	50	22	53	69	51	64
Median progression-free survival (PFS), months	6.9.	4.8	8.8	11	7.3	11.1
Median overall survival (OS), months	15	15.6	18.7	25.1	17.8	25.9
3-year overall survival rate, %	24	–	32	44	31	45

– not reported

CI 62–79). Multivariate analyses showed that male sex, ECOG performance status 1, lactate dehydrogenase (LDH) level above the upper limit of normal, and metastases to three or more organs were unfavorable factors for PFS and OS [27].

The phase III trials of dabrafenib and trametinib are summarized in Table 5.1.

The example of dramatic response to dabrafenib–trametinib in a patient with metastatic melanoma treated in Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland is shown in Fig. 5.1.

Efficacy of Dabrafenib Combined with Trametinib in Patients with Brain Melanoma Metastases

Melanoma patients with brain metastases have a poor prognosis. The efficacy of targeted therapy in these patients has been proven in several prospective clinical trials. The first clinical trials among patients with brain melanoma metastases assessed the efficacy of BRAF inhibitors as monotherapy. The largest study to date, in 172 patients with asymptomatic brain metastases, assessed the efficacy of dabrafenib (phase II BREAK-MB study). The intracranial response rate was 39.2% for patients without prior local treatment and 30.8% for patients with disease progression after local treatment. The median overall survival in both cohorts was approximately 31 weeks [16]. A combined inhibition of BRAF and MEK, with dabrafenib plus trametinib, improved outcomes when compared with dabrafenib monotherapy in advanced melanoma without brain metastases. The only prospective clinical trial evaluating the activity of this combination in patients with brain metastases was the phase II trial COMBI-MB [29]. This study enrolled 125 patients with ECOG

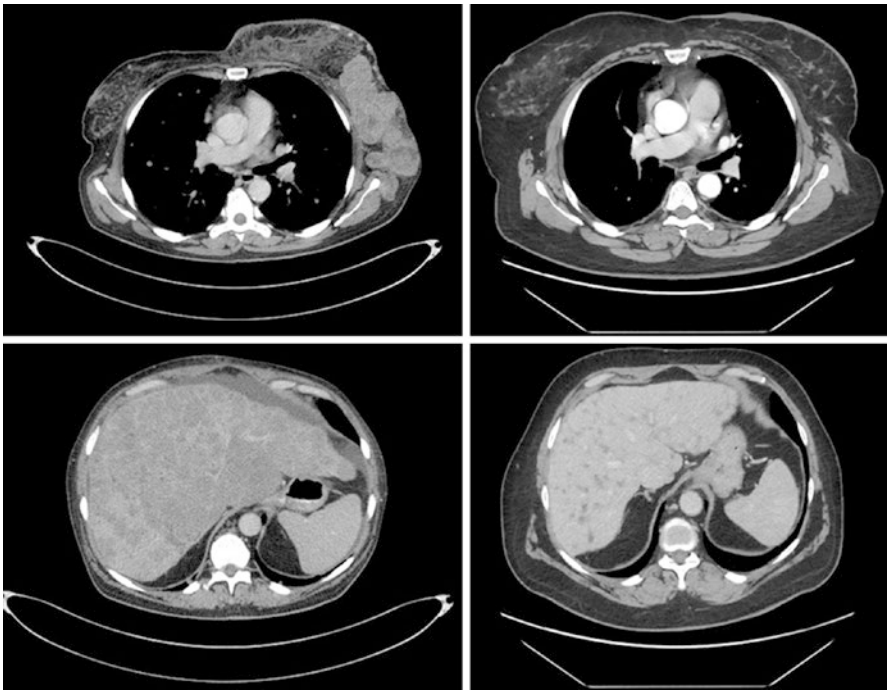

Fig. 5.1 Computed tomography findings before (left) and after 6 months (right) of treatment with dabrafenib and trametinib in a patient with metastatic melanoma

performance status 0–2, with or without prior local treatment for brain metastases. Intracranial response rates of 56–59% were observed regardless of prior local treatment or symptomatic metastases. The responses were most prolonged in patients with asymptomatic brain metastases. However, the median duration of response was significantly shorter than that observed in phase III clinical trials that did not include patients with brain metastases (approximately 6 months vs. 12–14 months) [24, 30, 31]. Symptomatic brain metastases were associated with a particularly poor prognosis (median OS 3–4 months). Nevertheless, the COMBI-MB study showed that the dabrafenib–trametinib combination is effective in patients with melanoma brain metastases. The main advantage of targeted therapy in these patients is a rapid improvement of the general condition.

Stereotactic radiation therapy is often used in patients with melanoma brain metastases. Data on the effects of combining BRAF inhibitors with radiation therapy are contradictory. On one hand, in vitro studies suggest that BRAF inhibitors could sensitize melanoma cells to radiation therapy [32]. On the other hand, this radiosensitizing effect may worsen adverse effects. There is no conclusive evidence that combining targeted therapy with radiation therapy increases the risks for neurotoxicity, brain hemorrhage, or radiation necrosis [33–35]. Molecularly targeted therapy combined with brain radiosurgery has fewer adverse effects than when combined with standard radiation therapy. Skin toxicity is the most common adverse effect of standard radiation therapy (more severe with vemurafenib) [28, 36].

Currently, it is recommended to discontinue BRAF or MEK inhibitors 1 day before and 1 day after stereotactic radiosurgery used to treat brain metastases [33].

The Effects of the Dabrafenib–Trametinib Combination in Patients Previously Treated with BRAF Inhibitors

In a prospective, phase II study in patients with melanoma and documented disease progression on BRAF inhibitors (with or without trametinib) and immunotherapy, a combination of dabrafenib and trametinib was started ≥12 weeks after the last targeted therapy. Partial remission was seen in 8 out of 25 patients (32%), and stable disease in 10 (40%); the median PFS was 4.9 months [37]. The efficacy of BRAF/MEK inhibitors rechallenge in clinical practice was confirmed in several retrospective studies: the response rates to BRAF/MEK inhibitors ranged from 27% to 43%, and the median PFS was 5–5.9 months [38–40].

Dabrafenib and Trametinib as Adjuvant Treatment

The efficacy of the dabrafenib–trametinib combination as adjuvant treatment was assessed in the randomized, phase III clinical trial COMBI-AD (n = 870). In this study, patients received adjuvant treatment with dabrafenib (300 mg/day) plus trametinib (2 mg/day) for 1 year after surgical treatment of BRAF-mutated, stage III melanoma (stage IIIA with metastases of >1 mm, IIIB, IIIC according to American Joint Committee on Cancer staging system ed. 7); placebo was used in the control arm. The dabrafenib–trametinib combination improved relapse-free survival (RFS) in all patient subgroups (HR [95% CI]: IIIA, 0.61 [0.35–1.07]; IIIB, 0.50 [0.37–0.67; IIIC], 0.48 [0.36–0.64]). The 4-year and 5-year RFS rates were 55% (95% CI, 50–60%) and 52% (95% CI, 48–58%) in the combination arm, and 38% (95% CI, 34–43%) and 36% (95% CI, 32–41%) in the placebo arm. The median distant metastasis-free survival (DMFS) was not reached, but the 5-year DMFS rate was higher in the dabrafenib plus trametinib arm than in the placebo arm (65% vs. 54%; HR, 0.55 [95% CI, 0.44–0.70]) [41, 42].

Toxicity Profile

Skin Toxicity

Dabrafenib causes various cutaneous side effects, which occur due to different mechanisms: inflammatory reactions, proliferation of squamous cells or melanocytes, and hypersensitivity reactions. As they occur frequently during dabrafenib

therapy, patients should be under careful dermatologic surveillance [11, 15, 21, 43, 44]. The most common cutaneous side effects of dabrafenib include hyperkeratosis, papillomas, alopecia, and the hand-foot skin syndrome. Phototoxic reactions, common with vemurafenib [45, 46], are rare during dabrafenib treatment. Cutaneous warts, palmar-plantar erythrodysesthesia, and grade 2 or higher cutaneous squamous cell carcinoma (cuSCC)/keratoacanthoma (KA) are found in <20% of patients. Usually, squamous cell carcinoma of the skin is well-differentiated, does not metastasize, and requires surgical removal only. The oncogenesis of cuSCC during dabrafenib treatment is multifactorial, with *RAS* mutations and paradoxical MAPK signaling being implicated [47]. Proliferation of keratinocytes, which leads to skin changes, might be caused by an activation of signaling through *CRAF* dimerization that results from both an inhibition of unmutated *BRAF* and a secondary *BRAF* transactivation [48, 49]. Because dabrafenib has lower specificity toward unmutated *BRAF* and *CRAF*, paradoxical activation of RAF dimers is less likely during dabrafenib treatment, which may explain lower skin toxicity compared with vemurafenib. Anforth et al. showed that dabrafenib-induced cuSCC develops mainly in sites where cuSCC/KA does not usually arise spontaneously (on the arm, thorax, and/or thigh). A *RAS* mutation may occur in as many as half of the cases of cuSCC or papillary hyperkeratotic lesions induced by dabrafenib [50]. Another cutaneous side effect of dabrafenib is panniculitis. Painful, erythematous, subcutaneous nodules are located mainly on the limbs and may be accompanied by fever, pain, and joint swelling [51] (Table 5.2).

Table 5.2 The most common adverse events related to dabrafenib in phase II and III studies

	BREAK-2 [14]		BREAK-3 [15]	
	Grade 3/4	Total	Grade 3/4	Total
Adverse event	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Any event	33 (36)	86 (93)	58 (28)	100 (53)
Arthralgia	1 (1)	30 (33)	2 (1)	36 (19)
Hyperkeratosis	1 (1)	25 (27)	3 (1.5)	67 (36)
Pyrexia	0	22(24)	5 (3)	30 (16)
Asthenia	1 (1)	20 (22)	2 (1)	33 (18)
Headache	2 (2)	19 (21)	0	34 (18)
Nausea	1 (1)	18 (20)	0	26 (14)
Skin papilloma	0	14 (15)	0	42 (22)
Vomiting	1 (1)	14 (15)		
Decreased appetite	1 (1)	12 (13)		
Hair loss	0	11 (12)	1 (<1)	50 (27)
Chills	0	11 (12)		
Diarrhea	1 (1)	10 (11)		
cuSCC/KA	8 (9)	10 (11)	14 (7)	18 (10)
Pruritus	0	9 (10)		
Palmar-plantar hyperkeratosis			4 (2)	36 (19)
Rash			0	56 (30)

cuSCC cutaneous squamous cell carcinoma, *KA keratoacanthoma*

Table 5.3 The most common adverse events related to trametinib in phase III METRIC study [20]

Adverse events	Any grade	Grade 2	Grade 3
($n = 211$)	n (%)	n (%)	n (%)
Rash	121 (57)	40 (19)	16(8)
Diarrhea	91 (43)	13 (6)	0
Fatigue	54 (26)	11 (5)	8 (4)
Peripheral edema	54 (26)	8 (4)	2 (1)
Dermatitis acneiform	40 (19)	20 (9)	2 (1)
Nausea	38 (18)	5 (2)	2 (1)
Alopecia	36 (17)	3 (1)	1 (<1)
Hypertension	32 (15)	6 (3)	26 (12)
Constipation	30 (14)	3 (1)	0
Vomiting	27 (13)	3 (1)	2 (1)

The skin toxicity profile of MEK inhibitors differs from that of dabrafenib. No secondary skin neoplasms were found during treatment with trametinib [20]. The rash that appears during trametinib treatment is maculo-pustular, and it is different from the hyperkeratotic and maculopapular changes observed during dabrafenib treatment. An acne-like eruption, which resembles the lesions caused by epidermal growth factor inhibitors, such as cetuximab, is also associated with trametinib treatment. These eruptions usually occur on the face, chest, and back, possibly due to the greater number of sweat glands in these areas; treatment usually includes topical antibiotics [52] (Table 5.3).

The addition of trametinib to dabrafenib reduced the percentage of typical skin complications seen with dabrafenib, that is, cuSCC/KA, cutaneous warts, and hyperkeratotic lesions [21]. This reduction is related to the inhibition of paradoxical activation of signal transduction in the MAPK pathway via CRAF by the MEK inhibitor [11, 21]. The acne-like lesions characteristic of trametinib monotherapy are also less frequent. Overall, the skin complications of the dabrafenib–trametinib combination are usually mild and manageable, and they do not require dose reduction or treatment discontinuation.

Pyrexia

Fever is a very common complication of the dabrafenib–trametinib combination (51–63%) [23, 25, 41]. It occurs more often than with dabrafenib alone (16–24%) [14, 15] (Table 5.4). The pathophysiological mechanism of fever is unclear, but it is not related to treatment efficacy. Fever usually starts within the first 4 weeks of treatment. In half of the patients, it is recurrent: 1 in 5 patients has ≥4 episodes of fever [53]. Fever may be associated with severe chills, dehydration, and hypotension,

Table 5.4 Incidence of the most common adverse events related to dabrafenib–trametinib therapy in phase III trials (COMBI-v and COMBI-d)

	COMBI-v [25]				COMBI-d [23]			
	Dabrafenib + trametinib		Vemurafenib		Dabrafenib + trametinib		Dabrafenib	
	(*n* = 350)		(*n* = 349)		(*n* = 209)		(*n* = 211)	
Adverse events	Any grade *n* (%)	Grade 3 *n* (%)	Any grade *n* (%)	Grade 3 *n* (%)	Any grade *n* (%)	Grade 3 *n* (%)	Any grade *n* (%)	Grade 3 *n* (%)
Total	343 (98)	167 (48)	345 (99)	198 (57)	199 (95)	66 (32)	203 (96)	72 (34)
Fever	184 (53)	15 (4)	73 (21)	2(<1)	107 (51)	12 (6)	59 (28)	4 (2)
Nausea	121 (35)	1(<1)	125 (36)	2(<1)	63 (30)	0	54 (26)	3 (1)
Diarrhea	112 (32)	4 (1)	131 (38)	1(<1)	51 (24)	1(<1)	30 (14)	2(<1)
Chills	110 (31)	3(<1)	27 (8)	0	62 (30)	0	33 (16)	0
Fatigue	101 (29)	4 (1)	115 (33)	6 (2)	74 (35)	4 (2)	74 (35)	2(<1)
Headache	101 (29)	3(<1)	77 (22)	2(<1)	63 (30)	1(<1)	62 (29)	3 (1)
Vomiting	101 (29)	4 (1)	53 (15)	3(<1)	42 (20)	2(<1)	29 (14)	1(<1)
Hypertension	92 (26)	48 (14)	84 (24)	32 (9)	46 (22)	8 (4)	29 (14)	10 (5)
Arthralgia	84 (24)	3(<1)	178 (51)	15 (4)	51 (24)	1(<1)	8 (27)	0
Rash	76 (22)	4 (1)	149 (43)	30 (9)	48 (23)	0	46 (22)	2(<1)
Pruritus	30 (9)	0	75 (21)	3(<1)				
Alopecia	20 (6)	0	137 (39)	1(<1)	15 (7)	0	55 (26)	0
Hyperkeratosis	15 (4)	0	86 (25)	2(<1)	7 (3)	0	68 (32)	1(<1)
Skin papilloma	6 (2)	0	80 (23)	2(<1)	3 (1)	0	45 (21)	0
cuSCC/KA	5 (1)		63 (18)		5 (2)		20 (9)	

cuSCC cutaneous squamous cell carcinoma, *KA* keratoacanthoma

which in some cases may lead to acute renal failure. An infectious cause of fever should always be ruled out. When fever occurs, treatment should be interrupted. Fever can be treated with paracetamol or nonsteroidal anti-inflammatory drugs [54]. Steroid prophylaxis is sometimes used in patients with frequent relapses [55].

Arthralgia and Myalgia

Arthralgia is associated with dabrafenib. It can be seen in one or more joints. During dabrafenib monotherapy, joint pain occurs in 23–35% of patients, but in dabrafenib–trametinib combination it is less frequent (16–28%) [14, 15]. Joint pain is rarely ≥grade 3 (about 1%). Usually, joint pain is managed with standard analgesics, and it does not warrant treatment discontinuation or dose adjustment.

Myalgia occurs in 19% of patients treated with dabrafenib plus trametinib [25]. Similar to joint pain, myalgia is usually mild and disappears with analgesics.

Gastrointestinal Toxicity

The most common gastrointestinal complications of dabrafenib include nausea (14–26%), diarrhea (11–14%), and vomiting (14–15%) [14, 15, 23]. The incidence of gastrointestinal complications with trametinib monotherapy is similar. In the METRIC study, diarrhea was observed in 43% of patients, nausea in 18%, and vomiting in 13% of patients [20]. Compared with dabrafenib monotherapy, the dabrafenib–trametinib combination causes a two-fold increase in the incidence of diarrhea (18–34% vs. 9–14%); nausea (30–40%) and vomiting (20–28%) are also more common [23] (Table 5.3). Gastrointestinal complications occur most frequently at the beginning of treatment, usually within the first 2 months; they are most often grade 1 or 2. Symptomatic treatment (oral rehydration, loperamide, electrolyte supplementation) is sufficient for good symptom control. Other causes of diarrhea, such as bacterial, viral, or parasitic infections, should be ruled out.

Cardiovascular Events

Overall, the dabrafenib–trametinib combination is associated with a higher risk of cardiac complications than dabrafenib monotherapy. The most common cardiac complications are arterial hypertension and reduced left ventricular ejection fraction (LVEF). Pulmonary embolism and QTc prolongation are less frequent.

In clinical trials, hypertension was observed in 11–26% of patients who received dabrafenib and trametinib, in 14% of patients who received dabrafenib, and in 5% of those who received trametinib [20, 23, 31, 56]. Two pathophysiological mechanisms of hypertension during treatment with BRAF or MEK inhibitors have been described. One mechanism is dysregulation of the renin–angiotensin system due to the inhibition of BRAF and MEK signaling. The other mechanism is a reduced production and bioavailability of nitric oxide (NO). The inhibition of the MAPK pathway disturbs the vascular endothelial growth factor signaling pathway, which regulates NO synthesis. Reduced production or bioavailability of NO causes vasoconstriction, leukocyte adhesion to the endothelium, increased platelet aggregation, thrombus formation, and increased vascular smooth muscle cell proliferation [57, 58]. These effects, in turn, can cause pulmonary embolism and myocardial infarction.

MEK inhibition can reduce LVEF. Reduced LVEF was observed in 4–8% of patients who received dabrafenib and trametinib, 2% of patients who received dabrafenib, and 7% of those who received trametinib [14, 15, 20, 23, 25]. Mincu et al. showed that patients younger than 55 years of age have a higher risk of LVEF reduction [56]. The pathogenesis of LVEF reduction during treatment with BRAF and MEK inhibitors is not fully understood. The MAPK signaling pathway could be cardioprotective. Inhibition of this pathway can lead to hypertrophy, apoptosis, and myocyte remodeling [56, 59]. LVEF reduction of grade 3 or greater is rare: it occurs

in 1% of patients who receive dabrafenib plus trametinib. Heart failure or LVEF reduction by >20% from baseline warrants discontinuation of dabrafenib [56]. In most cases, this complication is reversible.

QTc prolongation is rarely seen with dabrafenib treatment. The addition of trametinib to dabrafenib did not affect the incidence of this complication. Dabrafenib should not be used in patients with unregulated electrolyte disturbances (including magnesium concentrations), long QT syndrome, or taking drugs that prolong the QT interval. During treatment with dabrafenib, it is necessary to monitor the electrocardiogram and electrolytes [56, 60].

Eye Complications

Serous neurosensory detachment (SND) is the most common ocular side effect. It has been associated with the use of trametinib. The incidence of SND is difficult to estimate due to the asymptomatic course in some patients. In clinical trials with BRAF and MEK inhibitors (vemurafenib + cobimetinib, encorafenib + binimetinib) in which optical coherence tomography (OCT) was performed routinely, the incidence was 8–13% [61, 62].

Unlike central serous retinopathy, lesions in SND are usually binocular, multifocal, and symmetrical. SND is often asymptomatic. In some patients, it causes reduced visual acuity, color vision disorders, or photophobia. Trametinib treatment should be interrupted in patients with SND. In most patients, SND resolves without permanent sequelae [63].

Uveitis and conjunctivitis are ocular side effects of dabrafenib. Usually, treatment with topical steroids is sufficient. In most patients, it is mild and does not require treatment modification.

Retinal vein occlusion (<1%) is a very rare but serious complication of BRAF and MEK inhibitors. Treatment with dabrafenib and trametinib should be discontinued in patients with retinal vein occlusion [1, 13, 58].

Summary of Approval and Regulatory Indications

Dabrafenib (Tafinlar®) as monotherapy or in combination with trametinib (Mekinist®) is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF V600* mutation. Trametinib may be also used in monotherapy in this indication. Dabrafenib in combination with trametinib is also approved for the adjuvant treatment of patients with stage III melanoma with *BRAF V600* mutations following complete resection.

Additionally, beyond melanoma combination of dabrafenib and trametinib is approved for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600 mutation and for therapy of patients with locally

advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600 mutation and with no satisfactory locoregional treatment options (the latter is FDA label only). The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily.

The recommended dose of dabrafenib, either used as monotherapy or in combination with trametinib, is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, either used as monotherapy or in combination with dabrafenib, is 2 mg once daily. Two dabrafenib capsule strengths, 50 mg and 75 mg, and two trametinib capsule strengths, 2 mg and 0.5 mg, are available for management of dose modification requirements. The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation.

Trametinib may be used as monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. This indication seems justified when BRAF inhibitor is contraindicated and there are no options of immunotherapy. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy. Treatment with BRAF and MEK inhibitors should be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.

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