Tafinlar® 50 mg
Tafinlar®75 mg

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar ® 50 mg
Tafinlar ® 75 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tafinlar 50 mg hard capsules
Each hard capsule contains dabrafenib mesilate equivalent to 50 mg of dabrafenib.

Tafinlar 75 mg hard capsules
Each hard capsule contains dabrafenib mesilate equivalent to 75 mg of dabrafenib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Tafinlar 50 mg hard capsules
Opaque dark red capsules, with capsule shell imprinted with 'GS TEW' and '50 mg'.

Tafinlar 75 mg hard capsules
Opaque dark pink capsules, with capsule shell imprinted with 'GS LHF' and '75 mg'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

Adjuvant treatment of melanoma

Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Non-small cell lung cancer (NSCLC)

Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

Anaplastic Thyroid Cancer (ATC)

Dabrafenib is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options *[see section 4.2]*.

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

Dabrafenib is indicated, in combination with trametinib, for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options *(see section 4.2)*.

Limitations of use: Dabrafenib is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition (see section 5.1).

BRAF V600E Mutation-Positive Low-Grade Glioma

Dabrafenib is indicated, in combination with trametinib, for the treatment of pediatric patients 6 years of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy *(see section 4.2).*

4.2 Posology and method of administration

Treatment with dabrafenib should be initiated and supervised by a qualified physician experienced in the use of anti-cancer medicinal products.

Before taking dabrafenib, patients must have confirmation of tumour BRAF V600 mutation using a validated test. In ATC, solid tumors and Low-Grade Glioma, confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with dabrafenib and trametinib *(see section 5.1)*.

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF solid tumors. Dabrafenib should therefore not be used in patients with wild type BRAF solid tumors (see sections 4.4 and 5.1).

Posology

The recommended dose of dabrafenib in adult patients, 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, when used in combination with dabrafenib, is 2 mg once daily.

The recommended dose for dabrafenib in pediatric patients who weigh at least 26 kg is based on body weight (Table 1). A recommended dose has not been established in patients who weigh less than 26 kg.

Table 1. Dosing in Pediatric Patients from 6 to 17 Years Old (Weight-Based Dose)*

Body Weight	Recommended Dose
26 to 37 kg	75 mg orally twice daily
38 to 50 kg	100 mg (two 50 mg capsules) orally twice daily
51 kg or greater	150 mg (two 75 mg capsules) orally twice daily

* Refer to the trametinib prescribing information for recommended trametinib dosing information.

Duration of treatment

Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity (see Table 4). In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity. In ATC and Solid Tumors, the recommended duration of treatment is until disease progression or unacceptable toxicity.

The optimal duration of combination therapy in the paediatric LGG population is not defined.

Missed doses

If a dose of dabrafenib is missed, it should not be taken if it is less than 6 hours until the next scheduled dose.

If a dose of trametinib is missed, when dabrafenib is given in combination with trametinib, the dose of trametinib should only be taken if it is more than 12 hours until the next scheduled dose.

Dose modification

Two dabrafenib capsule strengths, 50 mg and 75 mg, are available to effectively manage dose modification requirements.

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Tables 2, 3 and 4).

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see section 4.4).

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level (see section 4.4).

Recommended dose level reductions and recommendations for dose modifications are provided in Tables 2, 3 and 4, respectively.

Table 2. Recommended dose level reductions in adult patients

Dose level	**Dabrafenib dose** Used as monotherapy or in combination with trametinib	**Trametinib dose*** Only when used in combination with dabrafenib
Starting dose	150 mg twice daily	2 mg once daily
1st dose reduction	100 mg twice daily	1.5 mg once daily
2nd dose reduction	75 mg twice daily	1 mg once daily
3rd dose reduction	50 mg twice daily	1 mg once daily

Dose adjustment for dabrafenib below 50 mg twice daily is not recommended, whether used as monotherapy or in combination with trametinib. Dose adjustment for trametinib below 1 mg once daily is not recommended, when used in combination with dabrafenib.
* For dosing instructions for treatment with trametinib monotherapy, see trametinib Prescribing Information, Posology and Method of administration.

Table 3. Recommended Dose Reductions for Dabrafenib for Adverse Reactions in Pediatric Patients (6 to 17 Years Old)

Action	Recommended Dosage *(See table 1)*		
	75 mg orally twice daily	**100 mg (two 50 mg capsules) orally twice daily**	**150 mg (two 75 mg capsules) orally twice daily**
First Dose Reduction	50 mg orally twice daily	75 mg orally twice daily	100 mg (two 50 mg capsules) orally twice daily
Second Dose Reduction	-	50 mg orally twice daily	75 mg orally twice daily
Third Dose Reduction	-	-	50 mg orally twice daily
Subsequent Modification	Permanently discontinue if unable to tolerate dabrafenib 50 mg orally twice daily		

Table 4. Dose modification schedule based on the grade of any adverse reactions (excluding pyrexia)

Grade (CTC-AE)*	**Recommended dabrafenib dose modifications** Used as monotherapy or in combination with trametinib
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.
* The intensity of clinical adverse reactions graded by the Common Terminology Criteria for Adverse Events (CTCAE)	

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The dabrafenib dose should not exceed the recommended dose.

Pyrexia
If a patient's temperature is ≥38ºC, therapy should be interrupted (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and, if necessary, treated in line with local practice (see section 4.4). Dabrafenib, or both dabrafenib and trametinib when used in combination, should be restarted if the patient is symptom-free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level if the pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

If treatment-related toxicities occur when dabrafenib is used in combination with trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued.

Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for uveitis, RAS mutation-positive non-cutaneous malignancies (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions

Uveitis
No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation, and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib (see section 4.4).

RAS mutation-positive non-cutaneous malignancies
The benefits and risks should be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction
If dabrafenib is being used in combination with trametinib and an asymptomatic, absolute decrease of >10% in LVEF compared to baseline occurs, and the ejection fraction is below the institution's lower limit of normal (LLN), please refer to the trametinib Prescribing Information (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib.

Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)
If patients report new visual disturbances such as diminished central vision, blurred vision or loss of vision at any time while on combination therapy with dabrafenib and trametinib, please refer to the trametinib Prescribing Information (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for confirmed cases of RVO or RPED.

Interstitial lung disease (ILD)/Pneumonitis
In patients treated with dabrafenib in combination with trametinib with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations, please refer to the trametinib Prescribing Information (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for cases of ILD or pneumonitis.

Special populations
Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment. There are no clinical data in subjects with severe renal impairment and the potential need for dose adjustment cannot be determined (see section 5.2). Dabrafenib should be used with caution in patients with severe renal impairment when administered as monotherapy or in combination with trametinib.

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in subjects with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined (see section 5.2). Hepatic metabolism and biliary

secretion are the primary routes of elimination of dabrafenib and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure. Dabrafenib should be used with caution in patients with moderate or severe hepatic impairment when administered as monotherapy or in combination with trametinib.

Non-Caucasian patients

Limited safety and efficacy data have been collected on dabrafenib in non-Caucasian patients. The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. No dabrafenib dose adjustment is needed in Asian patients.

Elderly

No adjustment of the initial dose is required in patients >65 years of age.

Paediatric population

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors and LGG
The safety and effectiveness of dabrafenib capsules in combination with trametinib have been established in pediatric patients 6 years of age and older that weigh at least 26 kg with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options; or with LGG with BRAF V600E mutation who require systemic therapy. Use of TAFINLAR in combination with trametinib for these indications is supported by evidence from studies X2101 and G2201 that enrolled 171 patients (1 to < 18 years of age) with BRAF V600 mutation-positive advanced solid tumors, of which 4 (2.3%) patients were 1 to < 2 years of age, 39 (23%) patients were 2 to < 6 years of age, 54 (32%) patients were 6 to < 12 years of age, and 74 (43%) patients were 12 to < 18 years of age *(see sections 4.8, 5.1 and 5.2)*.

The safety and effectiveness of dabrafenib capsules in combination with trametinib have not been established for these indications in pediatric patients less than 6 years old.

The safety and effectiveness of dabrafenib as a single agent in pediatric patients have not been established.

There are no adequate data on the safety and efficacy of combination therapy for long-term paediatric use in LGG.

Studies in juvenile animals have shown adverse effects of dabrafenib which had not been observed in adult animals (see section 5.3).

Method of administration

Tafinlar is for oral use. The capsules are to be swallowed whole with water. They should not be chewed or opened and should not be mixed with food or liquids due to chemical instability of dabrafenib.

It is recommended that the doses of dabrafenib be taken at similar times every day, leaving an interval of approximately 12 hours between doses. When dabrafenib and trametinib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal.

If a patient vomits after taking dabrafenib, the patient should not retake the dose and should take the next scheduled dose.

Please refer to trametinib Prescribing Information for information on method of administration when given in combination with dabrafenib.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When dabrafenib is given in combination with trametinib, the Prescribing Information of trametinib must be consulted prior to intiation of combination treatment. For additional information on warnings and precautions associated with trametinib treatment, please refer to the trametinib Prescribing Information.

BRAF V600 testing

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF solid tumors therefore dabrafenib should not be used in patients with wild-type BRAF solid tumors (see sections 4.2 and 5.1).

Dabrafenib in combination with trametinib in patients with melanoma who have progressed on a BRAF inhibitor

There are limited data in patients taking the combination of dabrafenib with trametinib who have progressed on a prior BRAF inhibitor. These data show that the efficacy of the combination will be lower in these patients (see section 5.1). Therefore, other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

New malignancies

New malignancies, cutaneous and non-cutaneous, can occur when dabrafenib is used as monotherapy or in combination with trametinib.

Cutaneous malignancies

Cutaneous squamous cell carcinoma (cuSCC)

Cases of cuSCC (including keratoacanthoma) have been reported in patients treated with dabrafenib alone and in combination with trametinib (see section 4.8). In the Phase III clinical studies MEK115306 and MEK116513 in patients with unresectable or metastatic melanoma, cuSCC occurred in 10% (22/211) of patients receiving dabrafenib as a monotherapy and in 18% (63/349) of patients receiving vemurafenib as a monotherapy, respectively. Across the pivotal combination therapy studies in melanoma and advanced NSCLC, cuSCC occurred in 2% of patients receiving dabrafenib in combination with trametinib. The median time to diagnosis of the first occurrence of cuSCC in study MEK115306 was 223 days (range 56 to 510 days) in the combination therapy arm and 60 days (range 9 to 653 days) in the dabrafenib monotherapy arm. In the Phase III study BRF115532 (COMBI-AD) in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving dabrafenib in combination with trametinib as compared to 1% (5/432) of patients receiving placebo had developed cuSCC at the time of the primary analysis. During the long-term (up to 10 years) off-treatment follow-up, 2 additional

patients reported cuSCC in each treatment arm. Overall, the median time to onset of the first occurrence of cuSCC in the combination arm of the adjuvant treatment study was approximately 21 weeks and was 34 weeks in the placebo arm.

It is recommended that skin examination be performed prior to initiation of therapy with dabrafenib and monthly throughout treatment and for up to six months after treatment for cuSCC. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and dabrafenib treatment or, if taken in combination, dabrafenib and trametinib should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop.

New primary melanoma

New primary melanomas have been reported in clinical studies in patients treated with dabrafenib. In clinical studies in unresectable or metastatic melanoma, these cases were identified within the first 5 months of dabrafenib as monotherapy. Cases of new primary melanoma can be managed with excision and do not require treatment modification. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous malignancies

In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (MAP kinase) signalling in BRAF wild-type cells with RAS mutations when exposed to BRAF inhibitors. This may lead to increased risk of non-cutaneous malignancies with dabrafenib exposure (see section 4.8) when RAS mutations are present. RAS-associated malignancies have been reported in clinical studies, both with another BRAF inhibitor (chronic myelomonocytic leukaemia and non-cutaneous SCC of the head and neck) as well as with dabrafenib monotherapy (pancreatic adenocarcinoma, bile duct adenocarcinoma) and with dabrafenib in combination with the MEK inhibitor, trametinib (colorectal cancer, pancreatic cancer).

Prior to initiation of treatment patients should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen computerised tomography (CT) scan. During treatment patients should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations are recommended before and at the end of treatment or when considered clinically indicated. Complete blood cell counts and blood chemistry should be performed as clinically indicated.

The benefits and risks should be considered before administering dabrafenib in patients with a prior or concurrent cancer associated with RAS mutations. No dose modification of trametinib is required when taken in combination with dabrafenib.

Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

Haemorrhage

Haemorrhagic events, including major haemorrhagic and fatal haemorrhages, have occurred in patients taking the combination of dabrafenib with trametinib (see section 4.8). Please refer

to the trametinib Prescribing Information (see section 4.4) for additional information.

Visual impairment

In clinical studies ophthalmologic reactions, including uveitis, iridocyclitis and iritis, have been reported in patients treated with dabrafenib as monotherapy and in combination with trametinib. Patients should be routinely monitored for visual signs and symptoms (such as change in vision, photophobia and eye pain) while on therapy.

No dose modifications are required as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

Cases of biocular panuveitis or biocular iridocyclitis suggestive of Vogt-Koyanagi-Harada syndrome have been reported in patients treated with dabrafenib in combination with trametinib. Withhold dabrafenib until resolution of ocular inflammation and consider consulting an ophthalmologist. Systemic corticosteroid treatment may be necessary.

RPED and RVO may occur with dabrafenib in combination with trametinib. Please refer to the trametinib Prescribing Information (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED.

Pyrexia

Fever has been reported in clinical studies with dabrafenib as monotherapy and in combination with trametinib (see section 4.8). In 1% of patients in clinical studies with dabrafenib monotherapy, serious non-infectious febrile events were identified (defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency of pre-renal origin in patients with normal baseline renal function) (see section 4.8). The onset of these serious non-infectious febrile events was typically within the first month of dabrafenib as monotherapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

The incidence and severity of pyrexia are increased with combination therapy. In the combination therapy arm of study MEK115306 in patients with unresectable or metastatic melanoma, pyrexia was reported in 57% (119/209) of patients with 7% Grade 3, as compared to the dabrafenib monotherapy arm with 33% (69/211) of patients reporting pyrexia, 2% Grade 3. In the Phase II study BRF113928 in patients with advanced NSCLC the incidence and severity of pyrexia were increased slightly when dabrafenib was used in combination with trametinib (48%, 3% Grade 3) as compared to dabrafenib monotherapy (39%, 2% Grade 3). In the Phase III study BRF115532 in the adjuvant treatment of melanoma, the incidence and severity of pyrexia were higher in the dabrafenib in combination with trametinib arm (67%; 6% Grade 3/4) as compared to the placebo arm (15%; <1% Grade 3).

Dabrafenib administered with Trametinib (Pediatric): In the pooled safety population, pyrexia occurred in 66% of patients.

For patients with unresectable or metastatic melanoma who received dabrafenib in combination with trametinib and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one-third of the patients had 3 or more events.

Therapy (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination) should be interrupted if the patient's temperature is ≥38°C (see section 5.1). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection. Therapy can be restarted once the fever resolves. If fever is associated with other severe signs or symptoms, therapy should be restarted at a reduced dose once fever resolves and as clinically appropriate (see section 4.2).

LVEF reduction/Left ventricular dysfunction

Dabrafenib in combination with trametinib has been reported to decrease LVEF (see section 4.8). Please refer to the trametinib Prescribing Information for additional information (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib.

Renal failure

Renal failure has been identified in <1% of patients treated with dabrafenib alone and in 1% of patients treated with dabrafenib in combination with trametinib. Observed cases were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has been reported (see section 4.8). Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, dabrafenib may need to be interrupted as clinically appropriate. Dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN) therefore caution should be used in this setting (see section 5.2).

Hepatic events

Hepatic adverse events have been reported in clinical studies with dabrafenib in combination with trametinib (see section 4.8). It is recommended that patients receiving treatment with dabrafenib in combination with trametinib have liver function monitored every four weeks for 6 months after treatment initiation with trametinib. Liver monitoring may be continued thereafter as clinically indicated. Please refer to the trametinib Prescribing Information for additional information.

Hypertension

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension (see section 4.8). Please refer to the trametinib Prescribing Information for additional information.

Interstitial lung disease (ILD)/Pneumonitis

Cases of pneumonitis or ILD have been reported in clinical studies with dabrafenib in combination with trametinib. Please refer to the trametinib Prescribing Information section 4.4 for additional information. If dabrafenib is being used in combination with trametinib then therapy with dabrafenib may be continued at the same dose.

Rash

Rash has been observed in about 27% of patients in clinical studies when dabrafenib is used in combination with trametinib (see section 4.8). The majority of these cases were Grade 1 or

2 and did not require any dose interruptions or dose reductions. Please refer to the trametinib Prescribing Information section 4.4 for additional information.

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking dabrafenib in combination with trametinib (see section 4.8). Please refer to the trametinib Prescribing Information section 4.4 for additional information.

Pancreatitis

Pancreatitis has been reported in <1% of patients treated with dabrafenib as monotherapy and in combination with trametinib in unresectable or metastatic melanoma clinical studies and about 4% of patients treated with dabrafenib in combination with trametinib in the NSCLC clinical study. One of the events occurred on the first day of dabrafenib dosing of a metastatic melanoma patient and recurred following re-challenge at a reduced dose. In the adjuvant treatment of melanoma study, pancreatitis was reported in <1% (1/435) of patients receiving dabrafenib in combination with trametinib, and no patients receiving placebo. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when restarting dabrafenib after an episode of pancreatitis.

Deep vein thrombosis /Pulmonary embolism

Pulmonary embolism or deep vein thrombosis can occur when dabrafenib is used in combination with trametinib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care. Permanently discontinue trametinib and dabrafenib for life-threatening pulmonary embolism.

Severe cutaneous adverse reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with dabrafenib/trametinib combination therapy. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be withdrawn.

Gastrointestinal disorders

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking dabrafenib in combination with trametinib (see section 4.8). Please refer to the trametinib Prescribing Information for additional information (see section 4.4).

Sarcoidosis

Cases of sarcoidosis have been reported in patients treated with dabrafenib in combination with trametinib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with dabrafenib and trametinib was maintained. In case of a diagnosis of sarcoidosis, relevant treatment should be considered. It is important not to misinterpret sarcoidosis as disease progression.

Haemophagocytic lymphohistiocytosis

In post-marketing experience, haemophagocytic lymphohistiocytosis (HLH) has been observed in patients treated with dabrafenib in combination with trametinib. Caution should be taken when dabrafenib is administered in combination with trametinib. If HLH is confirmed, administration of dabrafenib and trametinib should be discontinued and treatment for HLH initiated.

Tumour lysis syndrome (TLS)

The occurrence of TLS, which may be fatal, has been associated with the use of dabrafenib in combination with trametinib (see section 4.8). Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine. Patients with risk factors for TLS should be closely monitored and prophylactic hydration should be considered. TLS should be treated promptly, as clinically indicated.

Potentiation of radiation toxicity

Cases of radiation recall and radiation sensitisation have been reported in patients treated with radiation either prior, during or subsequent to treatment with dabrafenib as monotherapy or in combination with trametinib. Most cases were cutaneous in nature, but some cases involved other locations including the spinal cord (see sections 4.5 and 4.8). Dabrafenib should be used with caution when given concomitantly or sequentially with radiation treatment.

Effects of other medicinal products on dabrafenib

Dabrafenib is a substrate of CYP2C8 and CYP3A4. Potent inducers of these enzymes should be avoided when possible as these agents may decrease the efficacy of dabrafenib (see section 4.5).

Effects of dabrafenib on other medicinal products

Dabrafenib is an inducer of metabolising enzymes which may lead to loss of efficacy of many commonly used medicinal products (see examples in section 4.5). A drug utilisation review (DUR) is therefore essential when initiating dabrafenib treatment. Concomitant use of dabrafenib with medicinal products that are sensitive substrates of certain metabolising enzymes or transporters (see section 4.5) should generally be avoided if monitoring for efficacy and dose adjustment is not possible.

Concomitant administration of dabrafenib with warfarin results in decreased warfarin exposure. Caution should be exercised and additional International Normalised Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin and at discontinuation of dabrafenib (see section 4.5).

Concomitant administration of dabrafenib with digoxin may result in decreased digoxin exposure. Caution should be exercised and additional monitoring of digoxin is recommended when digoxin (a transporter substrate) is used concomitantly with dabrafenib and at discontinuation of dabrafenib (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on dabrafenib

Dabrafenib is a substrate for the metabolising enzymes CYP2C8 and CYP3A4, while the active metabolites hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates.

Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are therefore likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with dabrafenib when possible. Dabrafenib should be used with caution if strong inhibitors (e.g. ketoconazole, gemfibrozil, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir) are co-administered with dabrafenib. Co-administration of dabrafenib with potent inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort (*Hypericum perforatum*)) of CYP2C8 or CYP3A4 should be avoided.

Administration of ketoconazole (a CYP3A4 inhibitor) 400 mg once daily, with dabrafenib 75 mg twice daily, resulted in a 71% increase in dabrafenib AUC and a 33% increase in dabrafenib C_{max} relative to administration of dabrafenib 75 mg twice daily alone. Co-administration resulted in increases in hydroxy- and desmethyl-dabrafenib AUC (increases of 82% and 68%, respectively). A decrease of 16% in AUC was noted for carboxy-dabrafenib.

Administration of gemfibrozil (a CYP2C8 inhibitor) 600 mg twice daily, with dabrafenib 75 mg twice daily, resulted in a 47% increase in dabrafenib AUC but did not alter dabrafenib C_{max} relative to administration of dabrafenib 75 mg twice daily alone. Gemfibrozil had no clinically relevant effect on the systemic exposure to dabrafenib metabolites (≤13%).

Administration of rifampin (a CYP3A4/CYP2C8 inducer) 600 mg once daily, with dabrafenib 150 mg twice daily, resulted in a decrease in repeat-dose dabrafenib C_{max} (27%) and AUC (34%). No relevant change in AUC was noted for hydroxy-dabrafenib. There was an increase in AUC of 73% for carboxy-dabrafenib and a decrease in AUC of 30% for desmethyl-dabrafenib.

Co-administration of repeat doses of dabrafenib 150 mg twice daily and the pH-elevating agent rabeprazole 40 mg once daily resulted in a 3% increase in AUC and a 12% decrease in dabrafenib C_{max}. These changes in dabrafenib AUC and C_{max} are considered not clinically meaningful. Medicinal products that alter the pH of the upper gastrointestinal (GI) tract (e.g. proton pump inhibitors, H_2-receptor antagonists, antacids) are not expected to reduce the bioavailability of dabrafenib.

<u>Effect of dabrafenib on other medicinal products</u>

Dabrafenib is an enzyme inducer and increases the synthesis of drug-metabolising enzymes including CYP3A4, CYP2Cs and CYP2B6 and may increase the synthesis of transporters. This results in reduced plasma levels of medicinal products metabolised by these enzymes and may affect some transported medicinal products. The reduction in plasma concentrations can lead to lost or reduced clinical effect of these medicinal products. There is also a risk of increased formation of active metabolites of these medicinal products. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGTs (glucuronide conjugating enzymes). The transport protein P-gp may also be induced as well as other transporters, e.g. MRP-2. Induction of OATP1B1/1B3 and BCRP is not likely based on the observations from a clinical study with rosuvastatin.

In vitro, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4. In a clinical drug interaction study, C_{max} and AUC of oral midazolam (a CYP3A4 substrate) decreased by 47% and 65%, respectively with co-administration of repeat-dose dabrafenib.

Administration of dabrafenib 150 mg twice daily and warfarin resulted in a decrease in AUC of S- and R- warfarin of 37% and 33% respectively, compared to administration of warfarin alone. C_{max} of S- and R-warfarin increased 18% and 19%.

Interactions with many medicinal products eliminated through metabolism or active transport

is expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

The number of affected medicinal products is expected to be large, although the magnitude of the interaction will vary. Groups of medicinal products that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, methadone)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anti-cancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin, see section 4.4)
- Antiepileptics (e.g. carbamazepine, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin, see section 4.4)
- Corticosteroids (e.g. dexamethasone, methylprednisolone)
- HIV antivirals (e.g. amprenavir, atazanavir, darunavir, delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir)
- Hormonal contraceptives (see section 4.6)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressants (e.g. cyclosporin, tacrolimus, sirolimus)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)

Onset of induction is likely to occur after 3 days of repeat dosing with dabrafenib. Upon discontinuation of dabrafenib offset of induction is gradual, concentrations of sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19, UDP glucuronosyl transferase (UGT) and transporter substrates (e.g. P-gp or MRP-2) may increase and patients should be monitored for toxicity and dose of these agents may need to be adjusted.

In vitro, dabrafenib is a mechanism based inhibitor of CYP3A4. Therefore, transient inhibition of CYP3A4 may be observed during the first few days of treatment.

Effects of dabrafenib on substance transport systems

Dabrafenib is an *in vitro* inhibitor of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1), OATP1B3 and BCRP. Following co-administration of a single dose of rosuvastatin (OATP1B1, OATP1B3 and BCRP substrate) with repeat-dose dabrafenib 150 mg twice daily in 16 patients, C_{max} of rosuvastatin increased 2.6-fold whereas the AUC was only minimally changed (7% increase). The increased C_{max} of rosuvastatin is unlikely to have clinical relevance.

Combination with trametinib

Co-administration of repeat dosing of trametinib 2 mg once daily and dabrafenib 150 mg twice daily resulted in no clinically meaningful changes in trametinib or dabrafenib C_{max} and AUC with increases of 16 and 23%, respectively, in dabrafenib C_{max} and AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when trametinib is administered in combination with dabrafenib, a CYP3A4 inducer, using a population pharmacokinetic analysis.

When dabrafenib is used in combination with trametinib refer to the guidance for medicinal

product interactions found in sections 4.4 and 4.5 of dabrafenib and trametinib Prescribing Information.

Effect of food on dabrafenib

Patients should take dabrafenib as monotherapy or in combination with trametinib at least one hour prior to or two hours after a meal due to the effect of food on dabrafenib absorption (see section 5.2).

Radiation treatment

Potentiation of radiation treatment toxicity has been reported in patients receiving dabrafenib as monotherapy or in combination with trametinib (see sections 4.4 and 4.8).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential must use effective methods of contraception during therapy and for at least 2 weeks following discontinuation of dabrafenib and at least 16 weeks following the last dose of trametinib when given in combination with dabrafenib. Dabrafenib may decrease the efficacy of oral or any systemic hormonal contraceptives and an effective alternative method of contraception should be used (see section 4.5).

Pregnancy

There are no data from the use of dabrafenib in pregnant women. Animal studies have shown reproductive toxicity and embryo-foetal developmental toxicities, including teratogenic effects (see section 5.3). Dabrafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. If the patient becomes pregnant while taking dabrafenib, the patient should be informed of the potential hazard to the foetus. Please see trametinib Prescribing Information (see section 4.6) when used in combination with trametinib.

Breast-feeding

It is not known whether dabrafenib is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the breast-feeding child cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue dabrafenib, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data in humans for dabrafenib as monotherapy or in combination with trametinib. Dabrafenib may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals (see section 5.3). Male patients taking dabrafenib as monotherapy or in combination with trametinib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Please see trametinib Prescribing Information (see section 4.6) when used in combination with trametinib.

4.7 Effects on ability to drive and use machines

Dabrafenib has minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of dabrafenib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should be made aware of the potential for fatigue and eye problems to affect these activities.

4.8 Undesirable effects

Summary of the safety profile

The safety of dabrafenib monotherapy is based on the integrated safety population from five clinical studies, BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680, which included 578 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with dabrafenib 150 mg twice daily. The most common adverse reactions (incidence ≥15%) reported with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting.

The safety of dabrafenib in combination with trametinib has been evaluated in the integrated safety population of 1 188 adult patients with BRAF V600 mutant unresectable or metastatic melanoma, Stage III BRAF V600 mutant melanoma following complete resection (adjuvant treatment), advanced NSCLC and advanced DTC treated with dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The mean treatment duration was 16 months (see section 5.1).

The most common adverse reactions (incidence ≥20%) for dabrafenib in combination with trametinib were: pyrexia, fatigue, nausea, rash, chills, diarrhoea, headache, arthralgia, vomiting, cough, haemorrhage and peripheral oedema.

The safety of dabrafenib when administered with trametinib was also evaluated in a multi-cohort, multi-center, non-randomized, open-label study in adult patients with cancers with the BRAF V600E mutation (Study BRF117019). A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 were enrolled in specific solid tumor cohorts, and 65 in other malignancies *(see section 5.1)*. Patients received dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity.

Among these 206 patients, 103 (50%) were exposed to dabrafenib for ≥ 1 year and 101 (49%) were exposed to trametinib for ≥ 1 year. The median age was 60 years (range: 18 to 89); 56% were male; 79% were White; and 34% had baseline ECOG performance status of 0 and 60% had ECOG performance status of 1.

The adverse reaction profile among all patients in study BRF117019 was similar to that observed in other approved indications.

Tabulated list of adverse reactions

Adverse reactions associated with dabrafenib obtained from clinical studies and post-marketing surveillance are tabulated below for dabrafenib monotherapy (Table 5) and dabrafenib in combination with trametinib (Table 6). Adverse reactions are listed below by MedDRA system organ class and ranked by frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the

available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5. Adverse reactions with dabrafenib monotherapy

System organ class	Frequency (all grades)	Adverse reactions
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Very common	Papilloma
	Common	Cutaneous squamous cell carcinoma
		Seborrhoeic keratosis
		Acrochordon (skin tags)
		Basal cell carcinoma
	Uncommon	New primary melanoma
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
	Common	Peripheral neuropathy (including sensory and motor neuropathy)
Eye disorders	Uncommon	Uveitis
Respiratory, thoracic and mediastinal disorders	Very common	Cough
Gastrointestinal disorders	Very common	Nausea
		Vomiting
		Diarrhoea
	Common	Constipation
	Uncommon	Pancreatitis
Skin and subcutaneous tissue disorders	Very common	Hyperkeratosis
		Alopecia
		Rash
		Palmar –plantar erythrodysaesthesia syndrome
	Common	Dry skin
		Pruritus
		Actinic keratosis
		Skin lesion
		Erythema
		Photosensitivity
	Uncommon	Acute febrile neutrophilic dermatosis
		Panniculitis
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
Renal and urinary disorders	Uncommon	Renal failure, acute kidney injury
		Nephritis

General disorders and administration site conditions	Very common	Pyrexia
		Fatigue
		Chills
		Asthenia
	Common	Influenza-like illness
Injury, poisoning and procedural complications	Common	Potentiation of radiation toxicity

Table 6. Adverse reactions with dabrafenib in combination with trametinib

System organ class	Frequency (all grades)	Adverse reactions
Infections and infestations	Very common	Nasopharyngitis
		Urinary tract infection
	Common	Cellulitis
		Folliculitis
		Paronychia
		Rash pustular
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma[a]
		Papilloma[b]
		Seborrhoeic keratosis
	Uncommon	New primary melanoma[c]
		Acrochordon (skin tags)
Blood and lymphatic system disorders	Very Common	Neutropenia
		Anaemia
	Common	Thrombocytopenia
		Leukopenia
Immune system disorders	Uncommon	Hypersensitivity[d]
		Sarcoidosis
	Rare	Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia
	Not known	Tumour lysis syndrome
Nervous system disorders	Very common	Headache
		Dizziness
	Common	Peripheral neuropathy (including sensory and motor neuropathy)
Eye disorders	Common	Vision blurred
		Visual impairment
		Uveitis[e]
	Uncommon	Chorioretinopathy
		Retinal detachment
		Periorbital oedema
Cardiac disorders	Common	Ejection fraction decreased
		Bradycardia
	Uncommon	Cardiac failure
		Left ventricular dysfunction
		Atrioventricular block[f]

	Not known	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage[g]
	Common	Hypotension
		Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Pneumonitis
		Dyspnoea
	Rare	Interstitial lung disease
Gastrointestinal disorders	Very common	Abdominal pain[h]
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Gastrointestinal perforation
		Pancreatitis
		Colitis
Skin and subcutaneous tissue disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema[i]
		Dermatitis acneiform
	Common	Dermatitis exfoliative generalised[i]
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Skin fissures
		Photosensitivity
	Uncommon	Acute febrile neutrophilic dermatosis
	Not known	Stevens-Johnson syndrome
		Drug reaction with eosinophilia and systemic symptoms
		Tattoo-associated skin reactions
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms[j]
	Uncommon	Rhabdomyolysis
Renal and urinary disorders	Common	Renal failure, acute kidney injury
	Rare	Nephritis
General disorders and administration site	Very common	Fatigue
		Chills

conditions		Asthenia
		Oedema peripheral
		Pyrexia
		Influenza-like illness
	Common	Mucosal inflammation
		Face oedema
Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
		Blood creatine phosphokinase increased
Injury, poisoning and procedural complications	Common	Potentiation of radiation toxicity

[a] Cutaneous squamous cell carcinoma (cu SCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma
[b] Papilloma, skin papilloma
[c] Malignant melanoma, and superficial spreading melanoma stage unspecified
[d] Includes drug hypersensitivity
[e] Includes cases of biocular panuveitis or biocular iridocyclitis suggestive of Vogt-Koyanagi-Harada syndrome
[f] Atrioventricular block, atrioventricular block first degree, atrioventricular block second degree
[g] Bleeding from various sites, including intracranial bleeding and fatal bleeding
[h] Includes abdominal pain upper and abdominal pain lower
[i] Includes skin exfoliation
[j] Muscle spasms, musculoskeletal stiffness

Description of selected adverse reactions

Cutaneous squamous cell carcinoma

For dabrafenib monotherapy in study MEK115306, cutaneous squamous cell carcinomas (including those classified as keratoacanthoma or mixed keratoacanthoma subtype) occurred in 10% of patients and approximately 70% of the events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. Across the pivotal combination therapy studies in melanoma and NSCLC, 2% of patients developed cuSCC and the events occurred later than with dabrafenib monotherapy with a median time to onset of 18-31 weeks. All patients receiving dabrafenib as monotherapy or in combination with trametinib who developed cuSCC continued on treatment without dose modification.

New primary melanoma

New primary melanomas have been reported in clinical studies with dabrafenib as monotherapy and in combination with trametinib in melanoma studies. Cases were managed with excision and did not require treatment modification (see section 4.4). No new primary melanoma was reported from the Phase II NSCLC study (BRF113928).

Non-cutaneous malignancy

Activation of MAP kinase signalling in BRAF wild-type cells which are exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations (see section 4.4). Non-cutaneous malignancies were reported in 1% (6/586) of patients in the integrated safety population of dabrafenib monotherapy, and <1% of patients in the pivotal combination therapy studies in melanoma and NSCLC. In the Phase III study BRF115532 (COMBI-AD) in the adjuvant treatment of melanoma, 1% (5/435) of patients

receiving dabrafenib in combination with trametinib as compared to <1% (3/432) of patients receiving placebo developed non-cutaneous malignancies. During the long-term (up to 10 years) off-treatment follow-up, 9 additional patients reported non-cutaneous malignancies in the combination arm and 4 in in the placebo arm. Cases of RAS-driven malignancies have been seen with dabrafenib as monotherapy and in combination with trametinib. Patients should be monitored as clinically appropriate.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking dabrafenib in combination with trametinib. Please refer to the trametinib Prescribing Information.

LVEF reduction/Left ventricular dysfunction

Decreased LVEF has been reported in 8% of patients in the integrated safety population of dabrafenib in combination with trametinib. Most cases were asymptomatic and reversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical studies with dabrafenib. Dabrafenib in combination with trametinib should be used with caution in patients with conditions that could impair left ventricular function. Please refer to the trametinib Prescribing Information.

Pyrexia

Fever has been reported in clinical studies with dabrafenib as monotherapy and in combination with trametinib; the incidence and severity of pyrexia are increased with the combination therapy (see section 4.4). For patients who received dabrafenib in combination with trametinib and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one-third of the patients had 3 or more events. In 1% of patients receiving dabrafenib as monotherapy in the integrated safety population, serious non-infectious febrile events were identified as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency or pre-renal origin in subjects with normal baseline renal function. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care (see sections 4.2 and 4.4).

Hepatic events

Hepatic adverse events have been reported in clinical studies with dabrafenib in combination with trametinib. Please refer to the trametinib Prescribing Information.

Hypertension

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate.

Arthralgia

Arthralgia was reported very commonly in the integrated safety populations of dabrafenib monotherapy (28%) and dabrafenib in combination with trametinib (25%) although these were mainly Grade 1 and 2 in severity with Grade 3 occurring uncommonly (<1%) and no Grade 4 occurrences being reported.

Hypophosphataemia

Hypophosphataemia has been reported commonly in the integrated safety population of dabrafenib monotherapy (7%) and of dabrafenib in combination with trametinib (4%). It should be noted that approximately half of these occurrences were Grade 3 in severity.

Pancreatitis

Pancreatitis has been reported in dabrafenib monotherapy and in combination with trametinib. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis (see section 4.4).

Renal failure

Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon; however, dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN). Caution should be used in this setting (see section 4.4).

Special populations

Paediatric

Pediatric Safety Pool

The pediatric pooled safety population reflects exposure to weight-based dabrafenib orally, twice daily administered in combination with trametinib in 166 pediatric patients across two trials: a multi-center, open-label, multi cohort study in pediatric patients with BRAF V600E mutation-positive glioma requiring systemic therapy (Study G2201; n=123) and a multi-center, open-label, multiple cohort study in pediatric patients with refractory or recurrent solid tumors with MAPK pathway activation (Study X2101; n=43) (see section 5.1). Among 166 patients who received dabrafenib administered with trametinib, 84% were exposed for 6 months or longer and 70% were exposed for greater than one year. The most common (> 20%) adverse reactions were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%) and dermatitis acneiform (23%). The most common (> 2%) Grade 3 or 4 laboratory abnormalities were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and increased aspartate aminotransferase (3.1%).

BRAF V600E Mutation-Positive Solid Tumors in Pediatric Patients

Study CTMT212X2101 (X2101)

The safety of dabrafenib when administered with trametinib was evaluated in Study X2101, a multi-center, open-label, multi-cohort study in pediatric patients (n=48) with refractory or recurrent solid tumors *(see section 5.1).* The median duration of exposure to dabrafenib in Parts C (dose escalation) and D (cohort expansion) was 20.8 and 24.9 months, respectively. The median duration of exposure to trametinib in Parts C and D was 20.8 and 24.4 months, respectively. The median age of pediatric patients who received dabrafenib with trametinib was 9 years (range: 1 to 17).

Serious adverse reactions occurred in 46% of patients who received dabrafenib in combination with trametinib. Serious adverse reactions in > 5% of patients included pyrexia

(25%) and decreased ejection fraction (6%). Permanent treatment discontinuation due to an adverse reaction occurred in 21% of patients. Adverse reactions which resulted in permanent treatment discontinuation in > 3% of patients included increased ALT (6%), increased AST (4.2%) and decreased ejection fraction (4.2%). Dose interruptions due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dose interruption in > 5% of patients included pyrexia (56%), vomiting (19%), neutropenia (13%), rash (13%), decreased ejection fraction (6%), and uveitis (6%). Dose reductions due to an adverse reaction occurred in 25% of patients. Adverse reactions which required dose reductions in > 5% of patients included pyrexia (13%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, are listed in Table 7 and Table 8.

Table 7 summarizes the adverse reactions in Study X2101.

Table 7. Adverse Reactions (≥20%) in Pediatric Patients Treated With Dabrafenib Plus Trametinib in Study X2101[a]

Adverse Reactions	Dabrafenib plus Trametinib (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
General		
Pyrexia	75	17
Fatigue[b]	48	0
Skin and subcutaneous tissue		
Rash[c]	73	2.1
Dry skin	48	0
Dermatitis acneiform[d]	40	0
Gastrointestinal		
Vomiting	52	4.2
Diarrhea	42	2.1
Abdominal pain[e]	33	4.2
Nausea	33	2.1
Constipation	23	0
Respiratory system		
Cough	44	0
Nervous system		
Headache	35	0
Vascular		
Hemorrhage[f]	33	0
Infections and infestations		
Paronychia	23	0

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, asthenia and malaise.
[c] Includes rash, rash maculo-papular, rash erythematous, rash papular, rash pustular, and rash macular.
[d] Includes dermatitis acneiform and acne.
[e] Includes abdominal pain and abdominal pain upper.
[f] Includes epistaxis, hematuria, contusion, hematoma, petechiae, rectal hemorrhage, and red blood cell count decreased.

Clinically relevant adverse reactions for TAFINLAR in Study X2101 observed in less than 20% of patients (N=48) who received TAFINLAR in combination with trametinib were: atrioventricular block (2.1%).

Table 8 summarizes the laboratory abnormalities in Study X2101.

Table 8. Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Pediatric Patients Treated With Dabrafenib Plus Trametinib in Study X2101

Laboratory Abnormality	Dabrafenib plus Trametinib[a]	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Hyperglycemia	65	2.2
Hypoalbuminemia	48	2.1
Hypocalcemia	40	2.1
Decreased phosphate	38	0
Decreased magnesium	33	2.1
Hypernatremia	27	0
Hypokalemia	21	2.1
Hepatic		
Increased AST	55	4.2
Increased ALT	40	6
Increased alkaline phosphatase	28	6
Increased total bilirubin	21	2.1
Hematology		
Decreased hemoglobin	60	6
Decreased neutrophils	49	28

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] The denominator used to calculate the rate varied from 39 to 48 based on the number of patients with a baseline value and at least one post-treatment value.

BRAF V600E Mutation-Positive Low-Grade Glioma in Pediatric Patients

Study CDRB436G2201 (G2201)

The safety of dabrafenib in combination with trametinib was evaluated in pediatric patients 1 to < 18 years of age in Study G2201. Patients with low-grade glioma (LGG) who required first systemic therapy were randomized (2:1) to dabrafenib plus trametinib (n=73) or carboplatin plus vincristine (n=33). Nine patients crossed over from the carboplatin plus vincristine arm to the dabrafenib and trametinib arm. Pediatric patients received weight based dabrafenib orally twice daily administered in combination with trametinib until disease progression or intolerable toxicity. Patients in the control arm received carboplatin and vincristine at doses of 175 mg/m^2 and 1.5 mg/m^2, respectively in 10-week induction course followed by eight 6-week cycles of maintenance therapy or until disease progression or intolerable toxicity. Among patients with low-grade glioma who were randomized to dabrafenib plus trametinib (n = 73), 95% were exposed for 6 months or longer and 71% were exposed for greater than one year.

The median age of these patients was 10 years (range: 1 to 17); 60% female; 75% White, 7% Asian, 2.7% Black or African American, 4% other race and 11% where race was unknown or not reported.

Serious adverse reactions occurred in 40% of these patients. Serious adverse reactions in > 3% of patients included pyrexia (14%) and vomiting (4%).

Permanent discontinuation of dabrafenib due to an adverse reaction occurred in 4% of patients. Adverse reactions which resulted in permanent discontinuation of dabrafenib included chills, fatigue, pyrexia, weight increased, and headache.

Dosage interruptions of dabrafenib due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (53%).

Dose reductions of dabrafenib due to an adverse reaction occurred in 48% of patients. Adverse reactions which required dose reductions in > 2% of patients included rash (2.7%).The most common (≥ 15%) adverse reactions were pyrexia (68%), rash (51%), headache (47%), vomiting (34%), musculoskeletal pain (34%), fatigue (33%), diarrhea (29%), dry skin (26%), nausea (25%), hemorrhage (25%), abdominal pain (25%), dermatitis acneiform (22%), dizziness (15%), upper respiratory tract infection (15%), and weight increased (15%).

The most common (≥ 20%) laboratory abnormalities that worsened from baseline were leukopenia (59%), increased alkaline phosphatase (55%), anemia (46%), decreased neutrophils (44%), increased AST (37%), decreased magnesium (34%), increased magnesium (32%), decreased platelets (30%), increased ALT (29%), and increased lymphocytes (24%).

Table 9 summarizes the adverse reactions in Study G2201.

Table 9. Adverse Reactions (≥ 15%) in Pediatric LGG Patients Who Received Dabrafenib in Combination with Trametinib in Study G2201[a]

Adverse Reactions	**Dabrafenib plus Trametinib N=73**		**Carboplatin plus Vincristine N=33**	
	All grades (%)	**Grade ≥ 3 (%)**	**All grades (%)**	**Grade ≥ 3 (%)**
Gastrointestinal				
Vomiting	34	1	48	3
Diarrhea[b]	29	0	18	6
Nausea	25	0	45	0
Abdominal Pain[c]	25	0	24	0
Constipation	12	0	36	0
Stomatitis[d]	10	0	18	0
General				
Pyrexia[e]	68	8	18	3
Fatigue[f]	33	0	39	0
Nervous system				
Headache[g]	47	1	33	3
Dizziness[h]	15	0	9	3
Peripheral Neuropathy[i]	7	0	45	6
Vascular				
Hemorrhage[j]	25	0	12	0
Skin and subcutaneous tissue				
Rash[k]	51	2.7	18	3
Dry skin	26	0	3	0
Dermatitis acneiform[l]	22	0	0	0
Alopecia	3	0	24	0
Musculoskeletal And Connective Tissue				
Musculoskeletal Pain[m]	34	0	30	0
Pain in jaw	1.4	0	18	0
Metabolism And Nutrition				
Decreased Appetite	5	0	24	0
Respiratory, Thoracic And Mediastinal				

Adverse Reactions	Dabrafenib plus Trametinib N=73		Carboplatin plus Vincristine N=33	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Oropharyngeal Pain	11	0	18	0
Psychiatric				
Anxiety	1.4	0	15	3
Immune System				
Hypersensitivity	0	0	15	3
Infections and infestations				
Upper Respiratory Tract Infection	15	0	6	0
Injury, Poisoning And Procedural Complications				
Infusion-Related Reaction	0	0	15	3
Investigations				
Weight Increased	15	7	0	0

[a] NCI CTCAE version 4.03.
[b] Includes diarrhea, colitis, enterocolitis, and enteritis.
[c] Includes abdominal pain and upper abdominal pain.
[d] Includes stomatitis, cheilitis, mouth ulceration, aphthous ulcer, and glossitis.
[e] Includes pyrexia and body temperature increased.
[f] Includes fatigue and asthenia.
[g] Includes headache and migraine with aura.
[h] Includes dizziness and vertigo.
[i] Includes peripheral neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia, neuralgia, hypoaesthesia, and peripheral sensory neuropathy.
[j] Includes epistaxis, post-procedural hemorrhage, hematuria, upper gastrointestinal hemorrhage, and hemorrhage intracranial.
[k] Includes rash, rash macular, rash maculo-papular, rash pustular, rash papular, rash erythematous, eczema, erythema multiforme, dermatitis, dermatitis exfoliative, skin exfoliation, palmar-plantar erythrodysaesthesia syndrome, and dermatitis bullous.
[l] Includes dermatitis acneiform, acne, and acne pustular.
[m] Includes back pain, myalgia, pain in extremity, arthralgia, bone pain, non-cardiac chest pain, neck pain, and musculoskeletal stiffness.

Table 10 summarizes the laboratory abnormalities in Study G2201.

Table 10. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Pediatric LGG Patients Who Received Dabrafenib in Combination with Trametinib in Study G2201[a]

Laboratory Abnormality	Dabrafenib plus Trametinib N=73		Carboplatin plus Vincristine N=33	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hepatic				
Increased alkaline phosphatase	55	0	13	0
Increased AST	37	1.4	55	0
Increased ALT	29	3	61	9
Chemistry				
Decreased magnesium	34	4.1	76	6
Increased magnesium	32	0	24	3
Increased potassium	15	4.2	21	6
Decreased calcium	14	4.1	22	9
Decreased potassium	8	1.4	70	0
Decreased phosphate	7	2.7	33	3
Decreased sodium	5	1.4	27	6
Increased serum fasting glucose	0	0	44	0
Hematology				
Decreased leukocytes	59	0	91	18
Decreased hemoglobin	46	0	94	36
Decreased neutrophils	44	17	84	75
Decreased platelets	30	0	73	18
Increased lymphocytes	24	0	13	3.1
Decreased lymphocytes	16	1.4	56	6

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] The denominator used to calculate the rate varied from 70 to 73 in D + T arm and 9 to 33 in C + V arm based on the number of patients with a baseline value and at least one post-treatment value.

Elderly

Of the total number of patients in the integrated safety population of dabrafenib monotherapy (n=578), 22% were 65 years of age and older, and 6% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had adverse reactions that led to study drug dose reductions (22% versus 12%) or interruptions (39% versus 27%). In addition, older patients experienced more serious adverse reactions compared to younger patients (41% versus 22%). No overall differences in efficacy were observed between these subjects and younger subjects.

In the integrated safety population of dabrafenib in combination with trametinib (n=1188), 27% of patients were 65 years of age and older and 6% were 75 years of age and older. The proportion of patients experiencing AEs was similar in those aged <65 years and those aged ≥65 years in all clinical studies. Patients ≥65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years.

Of the 26 patients with ATC who received dabrafenib in Study BRF117019, 77% were aged 65 years and older, and 31% were aged 75 years and older (see section 5.1). This study in

ATC did not include sufficient numbers of younger adults to determine whether they respond differently compared to geriatric patients.

Dabrafenib in combination with trametinib in patients with brain metastases

The safety and efficacy of the combination of dabrafenib and trametinib have been evaluated in a multi-cohort, open-label, Phase II study in patients with BRAF V600 mutant melanoma with brain metastases. The safety profile observed in these patients appears to be consistent with the integrated safety profile of the combination.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
(https://sideeffects.health.gov.il/)
And to Novartis using the following email address: safetydesk.israel@novartis.com

4.9 Overdose

There is no specific treatment for an overdose of dabrafenib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, B-Raf serine-threonine kinase (BRAF) inhibitors, ATC code: L01EC02

Mechanism of action

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma. The most commonly observed BRAF mutation is V600E, which accounts for approximately 90% of the BRAF mutations that are seen in melanoma.

Preclinical data generated in biochemical assays demonstrated that dabrafenib inhibits BRAF kinases with activating codon 600 mutations (Table 11).

Table 11. Kinase inhibitory activity of dabrafenib against RAF kinases

Kinase	Inhibitory concentration 50 (nM)
BRAF V600E	0.65
BRAF V600K	0.50
BRAF V600D	1.8
BRAF WT	3.2
CRAF WT	5.0

Dabrafenib demonstrated suppression of a downstream pharmacodynamic biomarker (phosphorylated ERK) and inhibited cell growth of BRAF V600 mutant melanoma cell lines, *in vitro* and in animal models.

In subjects with BRAF V600 mutation-positive melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

In the setting of BRAF-mutant colorectal cancer, induction of EGFR-mediated MAPK pathway re-activation has been identified as a mechanism of intrinsic resistance to BRAF inhibitors *(see section 4.1).*

Combination with trametinib

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway.

Thus, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and RAF, and therefore the combination provides concomitant inhibition of the pathway. The combination of dabrafenib with trametinib has shown anti-tumour activity in BRAF V600 mutation-positive melanoma cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation-positive melanoma xenografts.

Determination of BRAF mutation status

Before taking dabrafenib or combination with trametinib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. In the Phase II and III clinical studies in melanoma, screening for eligibility required central testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with an investigational use only assay (IUO). The IUO is an allele-specific polymerase chain reaction (PCR) assay performed on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue. The assay was specifically designed to differentiate between the V600E and V600K mutations. Only subjects with BRAF V600E or V600K mutation-positive tumours were eligible for study participation.

Subsequently, all patient samples were re-tested using the bioMerieux (bMx) THxID BRAF validated assay, which has CE marking. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical studies with retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity. Of the specimens from the non-clinical and clinical studies (n=876) that were mutation-positive by the THxID BRAF assay and subsequently were sequenced using the reference method, the specificity of the assay was 94%.

Clinical efficacy and safety

Unresectable or metastatic melanoma

- *Dabrafenib in combination with trametinib*

Treatment-naïve patients
The efficacy and safety of the recommended dose of trametinib (2 mg once daily) in combination with dabrafenib (150 mg twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two

Phase III studies and one supportive Phase I/II study.

MEK115306 (COMBI-d):
MEK115306 was a Phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was progression-free survival (PFS), with a key secondary endpoint of overall survival (OS). Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 423 subjects were randomised 1:1 to either combination (N=211) or dabrafenib (N=212). Most subjects were Caucasian (>99%) and male (53%), with a median age of 56 years (28% were ≥65 years). The majority of subjects had Stage IVM1c disease (67%). Most subjects had LDH ≤ULN (65%), Eastern Cooperative Oncology Group (ECOG) performance status of 0 (72%), and visceral disease (73%) at baseline. The majority of subjects had a BRAF V600E mutation (85%). Subjects with brain metastases were not included in the study.

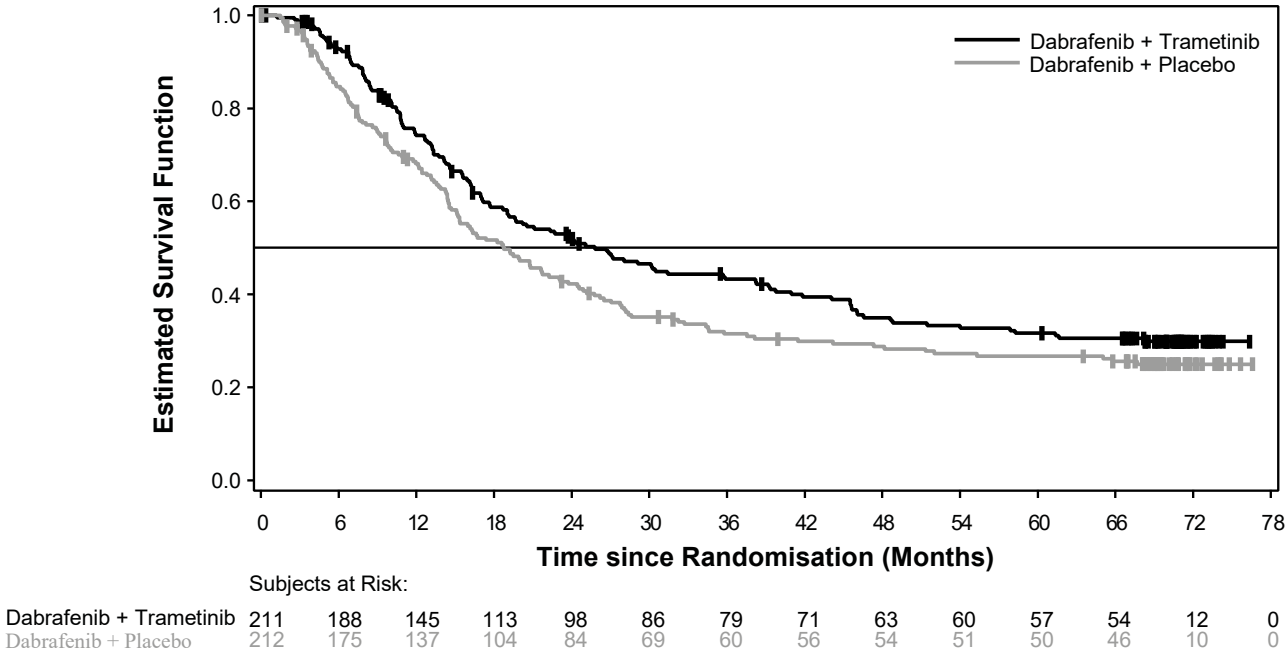
Median OS and estimated 1-year, 2-year 3-year, 4 year and 5-year survival rates are presented in Table 12. From an OS analysis at 5 years, the median OS for the combination arm was approximately 7 months longer than for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5-year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy (Table 12, Figure 1). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 1). The 5-year overall survival rate was 40% (95% CI: 31.2, 48.4) in the combination arm versus 33% (95% CI: 25.0, 41.0) in the dabrafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 8.4, 26.0) in the combination arm versus 14% (95% CI: 6.8, 23.1) in the dabrafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 12. Overall Survival results for Study MEK115306 (COMBI-d)

	OS analysis (data cut-off: 12-Jan-2015)		**5-year OS analysis (data cut-off: 10-Dec-2018)**	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
Number of patients				
Died (event), n (%)	99 (47)	123 (58)	135 (64)	151 (71)
Estimates of OS (months)				
Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.80 (0.63, 1.01)	
p-value	0.011		NA	
Overall survival estimate, % (95% CI)	**Dabrafenib + Trametinib (n=211)**		**Dabrafenib + Placebo (n=212)**	
At 1 year	74 (66.8, 79.0)		68 (60.8, 73.5)	
At 2 years	52 (44.7, 58.6)		42 (35.4, 48.9)	
At 3 years	43 (36.2, 50.1)		31 (25.1, 37.9)	
At 4 years	35 (28.2, 41.8)		29 (22.7, 35.2)	

At 5 years	32 (25.1, 38.3)	27 (20.7, 33.0)
NR = Not reached, NA = Not applicable		

Figure 1 Kaplan-Meier overall survival curves for Study MEK115306 (ITT population)



Improvements for the primary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to dabrafenib monotherapy. Improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to dabrafenib monotherapy (Table 13).

Table 13. Efficacy results for Study MEK115306 (COMBI-d)

	Primary analysis (data cut-off: 26-Aug-2013)		Updated analysis (data cut-off: 12-Jan-2015)		5-year analysis (data cut-off: 10-Dec-2018)	
Endpoint	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
PFS[a]						
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)	160 (76)	166 (78)
Median PFS (months) (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	10.2 (8.1, 12.8)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)		0.73 (0.59, 0.91)	
P value	0.035		<0.001 [f]		NA	
ORR[b] % (95% CI)	67 (59.9, 73.0)	51 (44.5, 58.4)	69 (61.8,74.8)	53 (46.3, 60.2)	69 (62.5, 75.4)	54 (46.8, 60.6)
ORR difference (95% CI)	15[e] (5.9, 24.5)		15[e] (6.0, 24.5)		NA	
P value	0.0015		0.0014[f]		NA	
DoR[c] **(months)** Median (95% CI)	9.2[d] (7.4, NR)	10.2[d] (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1, 13.8)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

[a] – Progression-free survival (investigator assessed)
[b] – Overall Response Rate = Complete Response + Partial Response
[c] – Duration of response
[d] - At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing
[e] – ORR difference calculated based on the ORR result not rounded
[f] – Updated analysis was not pre-planned and the p-value was not adjusted for multiple testing
NR = Not reached
NA = Not applicable

MEK116513 (COMBI-v):
Study MEK116513 was a 2-arm, randomised, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was OS with a key secondary endpoint of PFS. Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 704 subjects were randomised 1:1 to either combination or vemurafenib. Most subjects were Caucasian (>96%) and male (55%), with a median age of 55 years (24% were ≥65 years). The majority of subjects had Stage IV M1c disease (61% overall). Most subjects had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at Baseline. Overall, 54% of subjects had <3 disease sites at baseline. The majority of subjects had BRAF V600E mutation-positive melanoma (89%). Subjects with brain metastases were not included in the study.

Median OS and estimated 1-year, 2-year, 3-year, 4-year and 5-year survival rates are presented in Table 14. From an OS analysis at 5 years, the median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.0 months versus 17.8 months) with 5-year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 14, Figure 2). The Kaplan-Meier OS curve

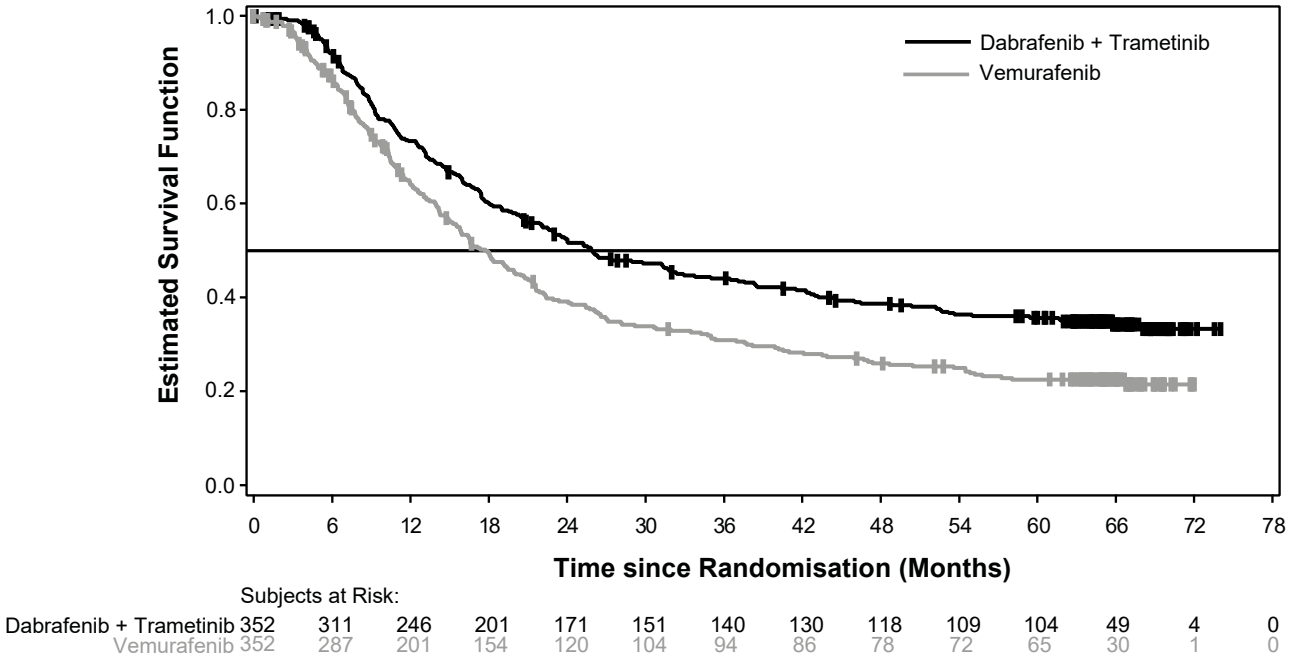
appears to stabilise from 3 to 5 years (see Figure 2). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 14. Overall Survival results for Study MEK116513 (COMBI-v)

	OS analysis (data cut-off: 13-Mar-2015)		**5-year OS analysis (data cut-off: 08-Oct-2018)**	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Number of patients				
Died (event), n (%)	155 (44)	194 (55)	216 (61)	246 (70)
Estimates of OS (months)				
Median (95% CI)	25.6 (22.6, NR)	18.0 (15.6, 20.7)	26.0 (22.1, 33.8)	17.8 (15.6, 20.7)
Adjusted hazard ratio (95% CI)	0.66 (0.53, 0.81)		0.70 (0.58, 0.84)	
p-value	<0.001		NA	
Overall survival estimate, % (95% CI)	**Dabrafenib + Trametinib (n=352)**		**Vemurafenib (n=352)**	
At 1 year	72 (67, 77)		65 (59, 70)	
At 2 years	53 (47.1, 57.8)		39 (33.8, 44.5)	
At 3 years	44 (38.8, 49.4)		31 (25.9, 36.2)	
At 4 years	39 (33.4, 44.0)		26 (21.3, 31.0)	
At 5 years	36 (30.5, 40.9)		23 (18.1, 27.4)	

NR = Not reached, NA = Not applicable

Figure 2 **Kaplan-Meier overall survival curves for Study MEK116513**



Improvements for the secondary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to vemurafenib monotherapy. Improvements were also observed for ORR. and a longer DoR was observed in the combination arm compared to vemurafenib monotherapy (Table 15).

Table 15. Efficacy results for Study MEK116513 (COMBI-v)

	Primary analysis (Data cut-off: 17-Apr-2014)		5-year analysis (Data cut-off: 08-Oct-2018)	
Endpoint	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
PFS[a]				
Progressive disease or death, n (%)	166 (47)	217 (62)	257 (73)	259 (74)
Median PFS (months) (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)	12.1 (9.7, 14.7)	7.3 (6.0, 8.1)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)		0.62 (0.52, 0.74)	
P value	<0.001		NA	
ORR[b] %(95% CI)	64 (59.1, 69.4)	51 (46.1, 56.8)	67 (62.2, 72.2)	53 (47.2, 57.9)
ORR difference (95% CI)	13 (5.7, 20.2)		NA	
P value	0.0005		NA	
DoR[c] (months) Median (95% CI)	13.8[d] (11.0, NR)	7.5 [d] (7.3, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

a – Progression-free survival (investigator assessed)
b – Overall Response Rate = Complete Response + Partial Response
c – Duration of response
d – At the time of the reporting the majority (59% of dabrafenib+trametinib and 42% of vemurafenib) of investigator-assessed responses were still ongoing
NR = Not reached
NA = Not applicable

Prior BRAF inhibitor therapy
There are limited data in patients taking the combination of dabrafenib with trametinib who have progressed on a prior BRAF inhibitor.

Part B of study BRF113220 included a cohort of 26 patients that had progressed on a BRAF inhibitor. The trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination demonstrated limited clinical activity in patients who had progressed on a BRAF inhibitor. The investigator-assessed confirmed response rate was 15% (95% CI: 4.4, 34.9) and the median PFS was 3.6 months (95% CI: 1.9, 5.2). Similar results were seen in the 45 patients who crossed over from dabrafenib monotherapy to the trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination in Part C of this study. In these patients a 13% (95 CI: 5.0, 27.0) confirmed response rate was observed with a median PFS of 3.6 months (95% CI: 2, 4).

Patients with brain metastases
The efficacy and safety of dabrafenib in combination with trametinib in patients with BRAF mutation-positive melanoma that has metastasised to the brain was studied in a non-randomised, open-label, multicentre, Phase II study (COMBI-MB study). A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with BRAF V600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort B: patients with BRAF V600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or1.
- Cohort C: patients with BRAF V600D/K/R mutant melanoma with asymptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort D: patients with BRAF V600D/E/K/R mutant melanoma with symptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1 or 2.

The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Intracranial response assessed by the investigator in Cohorts B, C and D were secondary endpoints of the study. Due to small sample size reflected by wide 95% CIs, the results in Cohorts B, C, and D should be interpreted with caution. Efficacy results are summarised in Table 16.

Table 16. Efficacy data by investigator assessment from COMBI-MB study

	All treated patients population				
Endpoints/ assessment		**Cohort A N=76**	**Cohort B N=16**	**Cohort C N=16**	**Cohort D N=17**
Intracranial response rate, % (95% CI)					
		59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	59% (32.9, 81.6)
Duration of intracranial response, median, months (95% CI)					
		6.5 (4.9, 8.6)	7.3 (3.6, 12.6)	8.3 (1.3, 15.0)	4.5 (2.8, 5.9)
Overall response rate, % (95% CI)					
		59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	65% (38.3, 85.8)
Progression-free survival, median, months (95% CI)					
		5.7 (5.3, 7.3)	7.2 (4.7, 14.6)	3.7 (1.7, 6.5)	5.5 (3.7, 11.6)
Overall survival, median, months (95% CI)					
		10.8 (8.7, 17.9)	24.3 (7.9, NR)	10.1 (4.6, 17.6)	11.5 (6.8, 22.4)
CI = Confidence Interval, NR = Not reached					

- *Dabrafenib monotherapy*

The efficacy of dabrafenib in the treatment of adult patients with BRAF V600 mutation-

positive unresectable or metastatic melanoma has been evaluated in 3 clinical studies (BRF113683 [BREAK-3], BRF113929 [BREAK-MB], and BRF113710 [BREAK-2]) including patients with BRAF V600E and/or V600K mutations.

Included in these clinical studies were in total 402 subjects with BRAF V600E and 49 subjects with BRAF V600K mutation. Patients with melanoma driven by BRAF mutations other than V600E were excluded from the confirmatory study and with respect to patients with the V600K mutation in single arm clinical studies the activity appears lower than in V600E tumours.

No data is available in patients with melanoma harbouring BRAF V600 mutations others than V600E and V600K. Efficacy of dabrafenib in subjects previously treated with a protein kinase inhibitor has not been investigated.

Previously untreated patients (results from the Phase III study [BREAK-3])
The efficacy and safety of dabrafenib were evaluated in a Phase III randomised, open-label study [BREAK 3] comparing dabrafenib to dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation-positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Patients with melanoma driven by BRAF mutations other than V600E were excluded.

The primary objective for this study was to evaluate the efficacy of dabrafenib compared to DTIC with respect to PFS per investigator assessment. Patients on the DTIC arm were allowed to cross over to dabrafenib after independent radiographic confirmation of initial progression. Baseline characteristics were balanced between treatment groups. Sixty percent of patients were male and 99.6% were Caucasian; the median age was 52 years with 21% of patients being ≥65 years, 98.4% had ECOG status of 0 or 1, and 97% of patients had metastatic disease.

At the pre-specified analysis with a 19 December 2011 data cut, a significant improvement in the primary endpoint of PFS (HR = 0.30; 95% Cl 0.18, 0.51; p < 0.0001) was achieved. Efficacy results from the primary analysis and a post-hoc analysis with 6-months additional follow up are summarised in Table 17. OS data from a further post-hoc analysis based on a 18 December 2012 data cut are shown in Figure 3.

Table 17. Efficacy in previously untreated patients (BREAK-3 Study, 25 June 2012)

	Data as of December 19, 2011		**Data as of June 25, 2012**	
	Dabrafenib N=187	**DTIC N=63**	**Dabrafenib N=187**	**DTIC N=63**
Progression-free survival				
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)	6.9 (5.2,9.0)	2.7 (1.5,3.2)
HR (95% CI)	0.30 (0.18, 0.51) P < 0.0001		0.37 (0.24, 0.58) P < 0.0001	
Overall response[a]				
% (95% CI)	53 (45.5, 60.3)	19 (10.2, 30.9)	59 (51.4, 66.0)	24 (14, 36.2)
Duration of response				
Median, months (95% CI)	N=99 5.6 (4.8, NR)	N=12 NR (5.0, NR)	N=110 8.0 (6.6, 11.5)	N=15 7.6 (5.0, 9.7)

Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; NR: not reached
[a] Defined as confirmed complete + partial response.

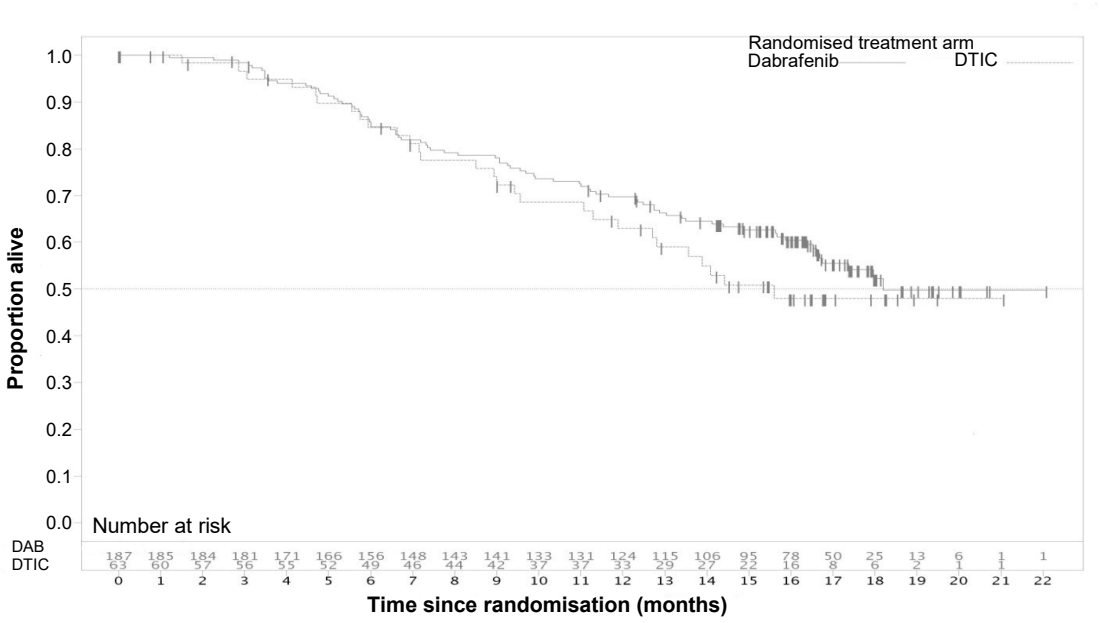
As of 25 June 2012 cut-off, thirty five subjects (55.6%) of the 63 randomised to DTIC had crossed over to dabrafenib and 63% of subjects randomised to dabrafenib and 79% of subjects randomised to DTIC had progressed or died. Median PFS after cross-over was 4.4 months.

Table 18. Survival data from the primary analysis and post-hoc analyses

Cut-off date	Treatment	Number of deaths (%)	Hazard ratio (95% CI)
December 19, 2011	DTIC	9 (14%)	0.61 (0.25, 1.48) [(a)]
	dabrafenib	21 (11%)	
June 25, 2012	DTIC	21 (33%)	0.75 (0.44, 1.29) [(a)]
	dabrafenib	55 (29%)	
December 18, 2012	DTIC	28 (44%)	0.76 (0.48, 1.21) [(a)]
	dabrafenib	78 (42%)	
[(a)] Patients were not censored at the time of cross-over			

OS data from a further post-hoc analysis based on the 18 December 2012 data cut demonstrated a 12-month OS rate of 63% and 70% for DTIC and dabrafenib treatments, respectively.

Figure 3 Kaplan-Meier curves of overall survival (BREAK-3) (18 December 2012)



Patients with brain metastases (results from the Phase II study (BREAK-MB)
BREAK-MB was a multicentre, open-label, two-cohort, Phase II study designed to evaluate the intracranial response of dabrafenib in subjects with histologically confirmed (Stage IV) BRAF mutation-positive (V600E or V600K) melanoma metastatic to the brain. Subjects were enrolled into Cohort A (subjects with no prior local therapy for brain metastasis) or Cohort B (subjects who received prior local therapy for brain metastasis).

The primary endpoint of the study was overall intracranial response rate (OIRR) in the V600E patient population, as assessed by investigators. The confirmed OIRR and other efficacy results per investigator assessment are presented in Table 19.

Table 19. Efficacy data in patients with brain metastases (BREAK-MB Study)

	All Treated Subjects Population			
	BRAF V600E (Primary)		BRAF V600K	
	Cohort A N=74	Cohort B N=65	Cohort A N=15	Cohort B N=18
Overall intracranial response rate,% (95% CI)[a]				
	39% (28.0, 51.2) P < 0.001[b]	31% (19.9, 43.4) P < 0.001[b]	7% (0.2, 31.9)	22% (6.4, 47.6)
Duration of intracranial response, median, months (95% CI)				
	N=29 4.6 (2.8, NR)	N=20 6.5 (4.6, 6.5)	N=1 2.9 (NR, NR)	N=4 3.8 (NR, NR)
Overall response,% (95% CI)[a]				
	38% (26.8, 49.9)	31% (19.9, 43.4)	0 (0, 21.8)	28% (9.7, 53.5)
Duration of response, median, months (95% CI)				
	N=28 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=5 3.1 (2.8, NR)
Progression-free survival, median, months (95% CI)				
	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
Overall survival, median, months (95% CI)				
Median, months	7.6 (5.9, NR)	7.2 (5.9, NR)	3.7 (1.6, 5.2)	5.0 (3.5, NR)

Abbreviations: CI: confidence interval; NR: not reached; NA: not applicable
[a] Confirmed response.
[b] This study was designed to support or reject the null hypothesis of OIRR ≤10% (based on historical results) in favour of the alternative hypothesis of OIRR ≥30% in BRAF V600E mutation-positive subjects.

Patients who were previously untreated or failed at least one prior systemic therapy (results from the Phase II [BREAK-2])
BRF113710 (BREAK-2) was a multicentre, single-arm study that enrolled 92 subjects with metastatic melanoma (Stage IV) with confirmed BRAF V600E or V600K mutation-positive melanoma.

The investigator assessed confirmed response rate in patients with BRAF V600E metastatic melanoma (n=76) was 59% (95% CI: 48.2, 70.3) and the median DoR was 5.2 months (95% CI: 3.9, not calculable) based on a median follow-up time of 6.5 months. In patients with BRAF V600K mutation-positive metastatic melanoma (n=16) the response rate was 13% (95% CI: 0.0, 28.7) with a median DoR of 5.3 months (95% CI: 3.7, 6.8). Although limited by the low number of patients, median OS appeared consistent with data in patients with BRAF V600E mutation-positive tumours.

Adjuvant treatment of Stage III melanoma

BRF115532 (COMBI-AD)
The efficacy and safety of dabrafenib in combination with trametinib were studied in a Phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with Stage III (Stage IIIA [lymph node metastasis >1 mm], IIIB, or IIIC) cutaneous melanoma with a BRAF V600 E/K mutation, following complete resection.

Patients were randomised 1:1 to receive either combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily) or two placebos for a period of 12 months. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks

prior to randomisation. Any prior systemic anti-cancer treatment, including radiotherapy, was not allowed. Patients with a history of prior malignancy, if disease-free for at least 5 years, were eligible. Patients presenting with malignancies with confirmed activating RAS mutations were not eligible. Patients were stratified by BRAF mutation status (V600E versus V600K) and stage of disease prior to surgery using the American Joint Committee on Cancer (AJCC) 7th edition Melanoma Staging System (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumour size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomisation to disease recurrence or death from any cause. Radiological tumour assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint), freedom from relapse (FFR) and distant metastasis-free survival (DMFS).

A total of 870 patients were randomised to the combination therapy (n=438) and placebo (n=432) arms. Most patients were Caucasian (99%) and male (55%), with a median age of 51 years (18% were ≥65 years). The study included patients with all sub-stages of Stage III disease prior to resection; 18% of these patients had lymph node involvement only identifiable by microscope and no primary tumour ulceration. The majority of patients had a BRAF V600E mutation (91%).

The median duration of follow-up at the time of the primary analysis was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

Results for the primary analysis of RFS are presented in Table 20. The study showed a statistically significant difference for the primary outcome of investigator-assessed RFS between treatment arms, with a median RFS of 16.6 months for the placebo arm and not yet reached for the combination arm (HR: 0.47; 95% confidence interval: (0.39, 0.58); $p=1.53\times10^{-14}$). The observed RFS benefit was consistently demonstrated across subgroups of patients including age, sex and race. Results were also consistent across stratification factors for disease stage and BRAF V600 mutation type.

Table 20. Investigator-assessed RFS results for Study BRF115532 (COMBI-AD primary analysis)

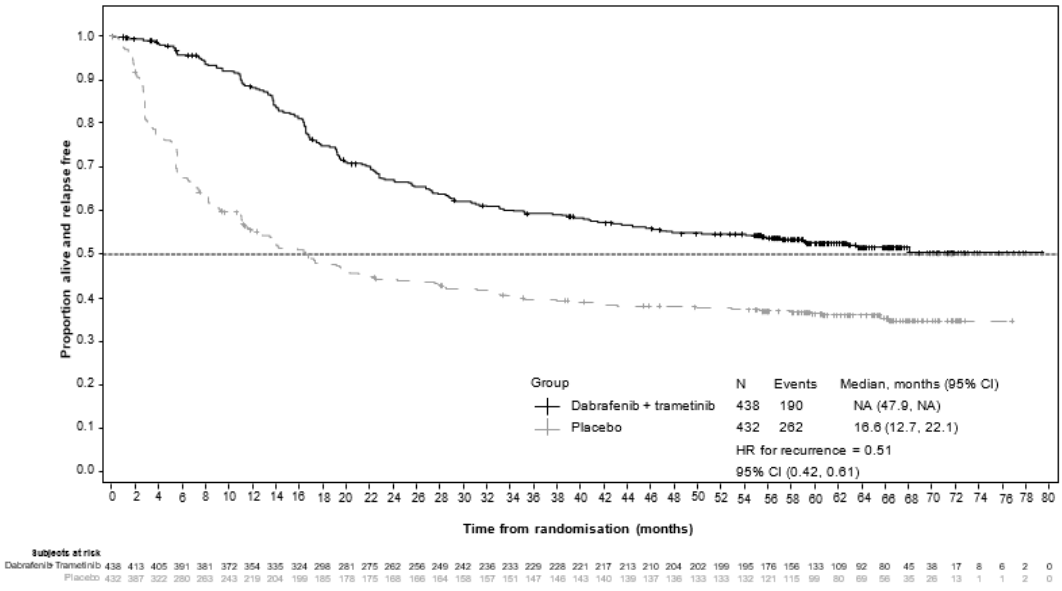
RFS parameter	Dabrafenib + Trametinib N=438	Placebo N=432
Number of events, n (%)	166 (38%)	248 (57%)
Recurrence	163 (37%)	247 (57%)
Relapsed with distant metastasis	103 (24%)	133 (31%)
Death	3 (<1%)	1 (<1%)
Median (months)	NE	16.6
(95% CI)	(44.5, NE)	(12.7, 22.1)
Hazard ratio[1]	0.47	
(95% CI)	(0.39, 0.58)	
p-value[2]	1.53×10^{-14}	
1-year rate (95% CI)	0.88 (0.85, 0.91)	0.56 (0.51, 0.61)
2-year rate (95% CI)	0.67 (0.63, 0.72)	0.44 (0.40, 0.49)
3-year rate (95% CI)	0.58 (0.54, 0.64)	0.39 (0.35, 0.44)

[1] Hazard ratio is obtained from the stratified Pike model.
[2] P-value is obtained from the two-sided stratified log-rank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K)
NE = not estimable

Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an

estimated HR of 0.51 (95% CI: 0.42, 0.61) (Figure 4). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared to 36% (95% CI: 32, 41) in the placebo arm.

Figure 4 Kaplan-Meier RFS curves for Study BRF115532 (ITT population, updated results)



At the time of the final OS analysis, the median duration of follow-up was 8.3 years in the combination arm and 6.9 years in the placebo arm. The observed difference in OS was not statistically significant (HR: 0.80; 95% CI: 0.62, 1.01) with 125 events (29%) in the combination arm and 136 events (31%) in the placebo arm. Estimated 5-year OS rates were 79% in the combination arm and 70% in the placebo arm, and estimated 10-year OS rates were 66% in the combination arm and 63% in the placebo arm.

Non-small cell lung cancer

Study BRF113928
The efficacy and safety of dabrafenib in combination with trametinib was studied in a Phase II, three-cohort, multicentre, non-randomised and open-label study in which patients with stage IV BRAF V600E mutant NSCLC were enrolled. The primary endpoint was ORR using the (RECIST 1.1) assessed by the investigator. Secondary endpoints included DoR, PFS, OS, safety and population pharmacokinetics. ORR, DoR and PFS were also assessed by an Independent Review Committee (IRC) as a sensitivity analysis.

Cohorts were enrolled sequentially:
- Cohort A: Monotherapy (dabrafenib 150 mg twice daily), 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease.
- Cohort B: Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 59 patients enrolled. 57 patients had 1-3 lines of previous systemic treatment for their metastatic disease. 2 patients had no previous systemic treatment and were included in the analysis for patients enrolled in Cohort C.
- Cohort C: Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 34 patients. All patients received study medicinal product as first-line treatment for metastatic disease.

Among the total of 93 patients who were enrolled in the combination therapy cohorts B and C, most patients were Caucasian (>90%), and similar female versus male (54% versus 46%),

with a median age of 64 years in second line or higher patients and 68 years in the first line patients. Most patients (94%) enrolled in the combination therapy treated cohorts had an ECOG performance status of 0 or 1. 26 (28%) had never smoked. The majority of patients had a non-squamous histology. In the previously treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

At the time of the primary analysis, the primary endpoint of investigator-assessed ORR in the first line population was 61.1% (95% CI, 43.5%, 76.9%) and in the previously treated population was 66.7% (95% CI, 52.9%, 78.6%). These met the statistical significance to reject the null hypothesis that the ORR of dabrafenib in combination with trametinib for this NSCLC population was less than or equal to 30%. The ORR results assessed by IRC were consistent with the investigator assessment. The efficacy of the combination with trametinib was superior when indirectly compared to dabrafenib monotherapy in Cohort A. The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 21 .

Table 21. Summary of efficacy in the combination treatment cohorts based on investigator and independent radiology review

Endpoint	Analysis	Combination 1st line N=36[1]	Combination 2nd line plus N=57[1]
Overall confirmed response n (%) (95% CI)	By Investigator By IRC	23 (63.9%) (46.2, 79.2) 23 (63.9%) (46.2, 79.2)	39 (68.4%) (54.8, 80.1)36 (63.2%) (49.3, 75.6)
Median DoR Months (95% CI)	By Investigator By IRC	10.2 (8.3, 15.2)15.2 (7.8, 23.5)	9.8 (6.9, 18.3)12.6 (5.8, 26.2)
Median PFS Months (95% CI)	By Investigator By IRC	10.8 (7.0, 14.5)14.6 (7.0, 22.1)	10.2 (6.9, 16.7)8.6 (5.2, 16.8)
Median OS Months (95% CI)	-	17.3 (12.3, 40.2)	18.2 (14.3, 28.6)
[1] Data cut-off: 7 January 2021			

Other studies - pyrexia management analysis
Study CPDR001F2301 (COMBI-i) and Study CDRB436F2410 (COMBI-Aplus)
Pyrexia is observed in patients treated with dabrafenib and trametinib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia (fever ≥38.5°C). In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-Aplus, N=552), interruption of both medicinal products when patient's temperature is ≥38°C (COMBI-Aplus), or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia) was advised. In COMBI-i and COMBI-Aplus there was a lower incidence of grade 3/4 pyrexia, complicated pyrexia, hospitalisation due to serious pyrexia adverse events of special interest (AESIs), the time spent in pyrexia AESIs, and permanent discontinuations from both medicinal products due to pyrexia AESIs (the latter in the adjuvant setting only) compared to COMBI-d, COMBI-v and COMBI-AD. The COMBI-Aplus study met its primary endpoint with a composite rate of 8.0% (95% CI: 5.9, 10.6) for grade 3/4 pyrexia, hospitalisation due to

pyrexia, or permanent treatment discontinuation due to pyrexia compared to 20.0% (95% CI: 16.3, 24.1) for the historical control (COMBI-AD).

Anaplastic Thyroid Cancer (ATC)

The safety and efficacy of dabrafenib administered with trametinib was evaluated in an activity-estimating, nine-cohort, multi-center, non-randomized, open-label trial (Study BRF117019; NCT02034110) in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. Trial BRF117019 excluded patients who could not swallow or retain the medication; who received prior treatment with BRAF or MEK inhibitors; with symptomatic or untreated CNS metastases; or who had airway obstruction. Patients received dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The major efficacy outcome measure was overall response rate (ORR) per RECIST v1.1 as assessed by independent review committee (IRC) and duration of response (DoR).

Thirty-six patients were enrolled and were evaluable for response in the ATC cohort. The median age was 71 years (range 47 to 85); 44% were male, 50% White, 44% Asian; and 94% had ECOG performance status of 0 or 1. Prior anti-cancer treatments included surgery and external beam radiotherapy (83% each), and systemic therapy (67%).

Efficacy results are summarized in Table 22.

Table 22. Efficacy Results in the ATC Cohort Based on Independent Review of Study BRF117019

ATC Cohort Population	**N= 36**
Overall Response Rate	
ORR (95% CI)	53% (35.5%, 69.6%)
Complete Response	6%
Partial Response	47%
Duration of Response	n = 19
Median DoR, months (95% CI)	13.6 (3.8, NE)
% with DoR ≥6 months	68%
% with DoR ≥ 12 months	53%

Abbreviations: ATC, anaplastic thyroid cancer; CI, confidence interval; DoR, duration of response; NE, not estimable; ORR, overall response rate.

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

The safety and efficacy of dabrafenib in combination with trametinib for the treatment of BRAF V600E mutation-positive unresectable or metastatic solid tumors were evaluated in Trials BRF117019, NCI-MATCH, and CTMT212X2101, and supported by results in COMBI-d, COMBI-v, and BRF113928. In adult studies, patients received dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The major efficacy outcome measures were ORR per RECIST v1.1, RANO [HGG] or modified RANO [LGG] criteria and duration of response (DoR).

BRF117019 Study and NCI-MATCH Study

Study BRF117019 (NCT02034110) is a multi-cohort, multi-center, non-randomized, open-label trial in adult patients with selected tumors with the BRAF V600E mutation, including high-grade glioma (HGG) (n = 45), biliary tract cancer (BTC) (n = 43), low-grade glioma (LGG) (n = 13), adenocarcinoma of small intestine (ASI) (n = 3), gastrointestinal stromal tumor (GIST) (n = 1), and anaplastic thyroid cancer. Patients were enrolled based on local

assessments of BRAF V600E mutation status; a central laboratory confirmed the BRAF V600E mutation in 93 of 105 patients.

Arm H (EAY131-H) of the NCI-MATCH study (NCT02465060) is a single-arm, open-label study that enrolled patients with a BRAF V600E mutation. Patients with melanoma, thyroid cancer, or CRC were excluded. BRAF V600E mutation status for enrollment was determined either by central or local laboratory test. The study included adult patients with solid tumors including gastrointestinal tumors (n = 14), lung tumors (n = 7), gynecologic or peritoneal tumors (n = 6), CNS tumors (n = 4), and ameloblastoma of mandible (n = 1).

Among the 131 patients enrolled in BRF117019 and NCI-MATCH with the tumor types shown in Table 23, the baseline characteristics were: median age of 51 years with 20% age 65 or older; 56% female; 85% White, 9% Asian, 3% Black, 3% Other; and 37% ECOG PS of 0, 56% ECOG PS of 1, and 6% ECOG PS of 2. Of the 131 patients, 90% received prior systemic therapy.

Efficacy results in patients with solid tumors are summarized in Table 23.

Table 23. Efficacy Results Based on Independent Review in Studies BRF117019 and NCI-MATCH Arm H

Tumor Type[a]	N	Objective Response Rate (ORR)		Duration of Response (DoR)
		%	95% CI	Range (months)
Biliary tract cancer[b]	48	46	(31, 61)	1.8[d], 40[d]
High-grade glioma[c]	48	33	(20, 48)	3.9, 44
Glioblastoma	32	25	(12, 43)	3.9, 27
Anaplastic pleomorphic xanthoastrocytoma	6	67	(22, 96)	6, 43
Anaplastic astrocytoma	5	20	(0.5, 72)	15
Astroblastoma	2	100	(16, 100)	15, 23[d]
Undifferentiated	1	PR	(2.5, 100)	6
Anaplastic ganglioglioma	1	0	NA	NA
Anaplastic oligodendroglioma	1	0	NA	NA
Low-grade glioma	14	50	(23, 77)	6, 29[d]
Astrocytoma	4	50	(7, 93)	7, 23
Ganglioglioma	4	50	(7, 93)	6, 13
Pleomorphic xanthoastrocytoma	2	50	(1.3, 99)	6
Pilocytic astrocytoma	2	0	NA	NA
Choroid plexus papilloma	1	PR	(2.5, 100)	29[d]
Gangliocytoma/Ganglioglioma	1	PR	(2.5, 100)	18[d]
Low-grade serous ovarian carcinoma	5	80	(28, 100)	12, 42[d]
Adenocarcinoma small intestine	4	50	(7, 93)	7, 8
Adenocarcinoma pancreas	3	0	NA	NA
Mixed ductal / adenoneuroendocrine carcinoma	2	0	NA	NA

Neuroendocrine carcinoma of colon	2	0	NA	NA
Ameloblastoma of mandible	1	PR	(2.5, 100)	30
Combined small cell-squamous carcinoma of lung	1	PR	(2.5, 100)	5
Mucinous-papillary serous adenocarcinoma of peritoneum	1	PR	(2.5, 100)	8
Adenocarcinoma of anus	1	0	NA	NA
Gastrointestinal stromal tumor	1	0	NA	NA

Abbreviations: NA, not applicable; PR, partial response.

[a] Excludes NSCLC (n=6) and ATC (n=36) (previously approved tumor types for dabrafenib in combination with trametinib).

[b] Median DoR 9.8 months (95% CI: 5.3, 20.4).

[c] Median DoR 13.6 months (95% CI: 5.5, 26.7).

[d] Denotes a right-censored DoR.

CTMT212X2101 (X2101) Study

Study X2101 (NCT02124772) was a multi-center, open-label, multi-cohort study in pediatric patients with refractory or recurrent solid tumors. Part C was a dose escalation of dabrafenib in combination with trametinib in patients with a BRAF V600E mutation. Part D was a cohort expansion phase of dabrafenib in combination with trametinib in patients with LGG with a BRAF V600E mutation. The major efficacy outcome measure was ORR as assessed by independent review committee per RANO criteria.

The efficacy of dabrafenib in combination with trametinib was evaluated in 48 pediatric patients, including 34 patients with LGG and 2 patients with HGG.

For patients with BRAF V600E mutation positive LGG and HGG in Parts C and D, the median age was 10 years (range: 1-17); 50% were male, 75% White, 8% Asian, 3% Black; and 58% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (83%), external beam radiotherapy (2.8%), and systemic therapy (92%). The ORR was 25% (95% CI: 12%, 42%). For the 9 patients who responded, DoR was ≥6 months for 78% of patients, and ≥24 months for 44% of patients.

CDRB436G2201 (G2201) Study – High-Grade Glioma Cohort

Study G2201 (NCT02684058) was a multi-center, randomized, open-label, Phase II study of dabrafenib and trametinib in chemotherapy-naïve pediatric patients with BRAF V600E mutant low-grade glioma (LGG) and patients with relapsed or progressive BRAF V600E mutant HGG. Patients with HGG were enrolled in a singlearm cohort. The major efficacy outcome measure for the HGG cohort was ORR as assessed by independent review committee per RANO 2010 criteria.

The efficacy of dabrafenib in combination with trametinib was evaluated in 41 pediatric patients with relapsed or progressive HGG.

For patients with BRAF V600E mutant HGG enrolled in the HGG cohort, the median age was 13 years (range: 2 to 17); 56% were female, 61% White, 27% Asian, 2.4% Black and 37% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (98%), radiotherapy (90%), and chemotherapy (81%). The ORR was 56% (95% CI: 40, 72). The median DoR was not reached (95% CI: 9.2, NE). For the 23 patients who responded in the HGG cohort, DoR was ≥ 6 months for 78% of patients, ≥ 12 months for 48% of patients, and ≥ 24 months for 22% of patients.

BRAF V600E Mutation-Positive Low-Grade Glioma

CDRB436G2201 (G2201) Study – Low-Grade Glioma Cohort

The safety and efficacy of dabrafenib in combination with trametinib for the treatment of BRAF V600E mutation-positive low-grade glioma (LGG) in pediatric patients aged 1 to < 18 years of age were evaluated in the multi-center, open-label trial (Study CDRB436G2201; NCT02684058). Patients with LGG (WHO grades 1 and 2) who required first systemic therapy were randomized in a 2:1 ratio to dabrafenib plus trametinib (D + T) or carboplatin plus vincristine (C + V).

BRAF mutation status was identified prospectively via a local assessment or a central laboratory test. In addition, retrospective testing of available tumor samples by the central laboratory was performed to evaluate BRAF V600E mutation status.

Patients received age- and weight-based dosing of dabrafenib and trametinib until loss of clinical benefit or until unacceptable toxicity. Carboplatin and vincristine were dosed based on body surface area at doses 175 mg/m^2 and 1.5 mg/m^2 (0.05 mg/kg for patients < 12 kg), respectively, as one 10-week induction course followed by eight 6-week cycles of maintenance therapy.

The major efficacy outcome measure was overall response rate (ORR) by independent review based on RANO LGG (2017) criteria. Additional efficacy outcome measures were progression free survival and overall survival. The primary analysis was performed when all patients had completed at least 32 weeks of therapy.

In the LGG cohort, 110 patients were randomized to D + T (n=73) or C + V (n=37). Median age was 9.5 years (range: 1 to 17); 60% were female. Study G2201 showed a statistically significant improvement in ORR and PFS in LGG patients randomized to D + T compared to those randomized to C + V. Efficacy results are shown in Table 24.

Table 24. Efficacy Results Based on Independent Review in Study G2201 (LGG cohort)

	dabrafenib plus Trametinib N=73	Carboplatin plus Vincristine N=37
Overall Response Rate		
ORR% (95% CI)[a]	46.6 (34.8, 58.6)	10.8 (3.0, 25.4)
P-value	< 0.001	
Complete response (CR), n (%)	2 (2.7)	1 (2.7)
Partial response (PR), n (%)	32 (44)	3 (8)
Duration of Response		
Median (95% CI)[b], months	23.7 (14.5, NE)	NE (6.6, NE)
% with observed DoR ≥ 12 months	56	50
% with observed DoR ≥ 24 months	15	25
Progression-Free Survival		
Median (95% CI)[b], months	20.1 (12.8, NE)	7.4 (3.6, 11.8)
Hazard ratio (95% CI)[c]	0.31 (0.17, 0.55)	
P-value	< 0.001	

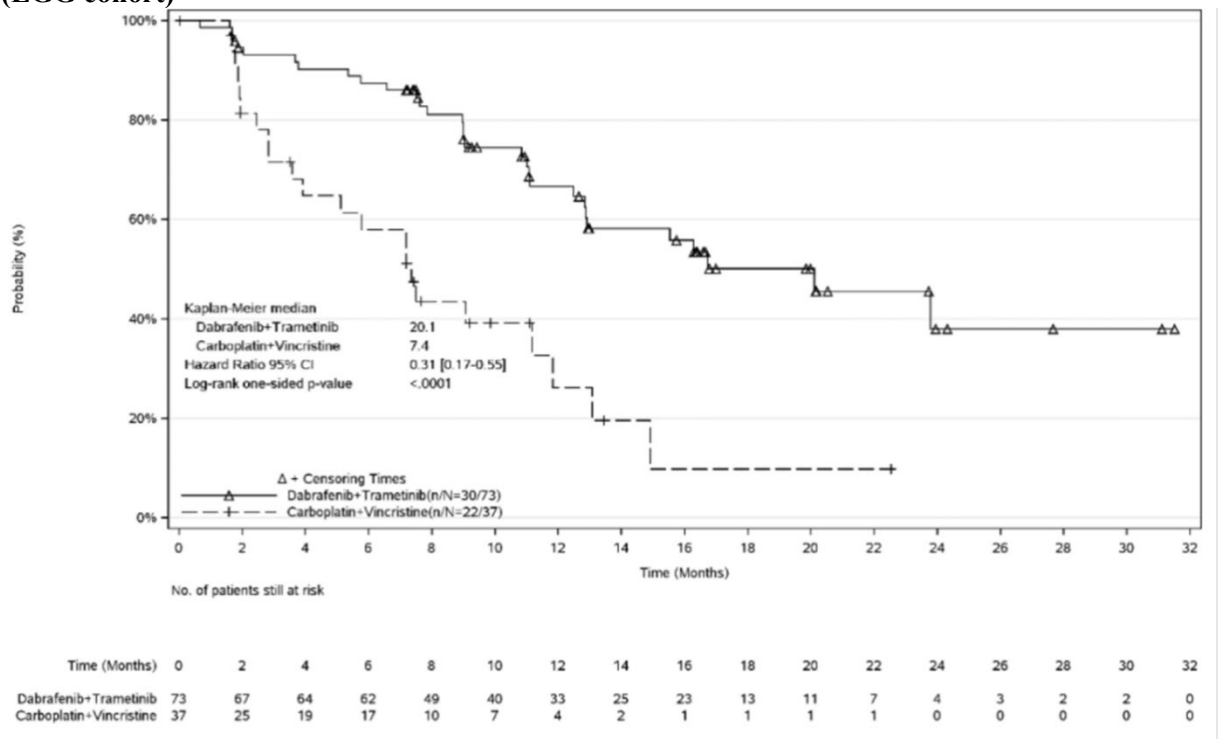
Abbreviations: CI, confidence interval; DoR, duration of response; NE, not estimable; ORR, overall response rate.

[a] Based on Clopper-Pearson exact confidence interval.

[b] Based on Kaplan-Meier method.

[c] Based on proportional hazards model.

Figure 5. Kaplan-Meier Curves for Progression-Free Survival in Study G2201 (LGG cohort)



At the time of the interim analysis of overall survival (OS), conducted when all patients had completed at least 32 weeks of treatment or had discontinued earlier, there was one death on the C+V arm. The OS results at interim analysis did not reach statistical significance.

QT prolongation

Worst-case QTc prolongation of >60 millisecond (msec) was observed in 3% of dabrafenib-treated subjects (one >500 msec in the integrated safety population). In the Phase III study MEK115306 no patients treated with trametinib in combination with dabrafenib had worst-case QTcB prolongation to >500 msec; QTcB was increased more than 60 msec from baseline in 1% (3/209) of patients. In the Phase III study MEK116513 four patients (1%) treated with trametinib in combination with dabrafenib had a QTcB Grade 3 increase (>500 msec). Two of these patients had a QTcB Grade 3 increase (>500 msec) that was also an increase >60 msec from baseline.

The potential effect of dabrafenib on QT prolongation was assessed in a dedicated multiple dose QT study. A supratherapeutic dose of 300 mg dabrafenib twice daily was administered in 32 subjects with BRAF V600 mutation-positive tumours. No clinically relevant effect of dabrafenib or its metabolites on the QTc interval was observed.

5.2 Pharmacokinetic properties

Absorption

Dabrafenib is absorbed orally with median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral dabrafenib is 95% (90% CI: 81, 110%). Dabrafenib exposure (C_{max} and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice daily dosing. A decrease in exposure was observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios was 0.73. Following administration of 150 mg twice daily, geometric mean C_{max}, AUC(0-τ) and predose concentration (Cτ) were 1478 ng/ml, 4341 ng*hr/ml and 26 ng/ml, respectively.

Administration of dabrafenib with food reduced the bioavailability (C_{max} and AUC decreased by 51% and 31% respectively) and delayed absorption of dabrafenib capsules when compared to the fasted state.

Distribution

Dabrafenib binds to human plasma protein and is 99.7% bound. The steady-state volume of distribution following intravenous microdose administration is 46 L.

Biotransformation

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidised via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib may also be formed in the gut and reabsorbed. Desmethyl-dabrafenib is metabolised by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hrs while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21-22 hours). Mean metabolite-to-parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based

on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib while the activity of carboxy-dabrafenib is not likely to be significant.

Medicinal product interactions

Effects of other medicinal products on dabrafenib
Dabrafenib is a substrate of human P-glycoprotein (P-gp) and human BCRP *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination and the risk for clinically relevant drug-drug interactions with inhibitors of P-gp or BCRP is low. Neither dabrafenib nor its 3 main metabolites were demonstrated to be inhibitors of P-gp *in vitro*.

Effects of dabrafenib on other medicinial products
Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporter (OAT) 1 and OAT3 *in vitro* and dabrafenib and its desmethyl metabolite were found to be inhibitors of organic cation transporter 2 (OCT2) *in vitro,* the risk of a drug-drug interaction at these transporters is minimal based on clinical exposure of dabrafenib and its metabolites .

Elimination

Terminal half-life of dabrafenib following an intravenous single microdose is 2.6 hours. Dabrafenib terminal half-life after a single oral dose is 8 hours due to absorption-limited elimination after oral administration (flip-flop pharmacokinetics). IV plasma clearance is 12 l/hr.

After an oral dose, the major route of elimination of dabrafenib is metabolism, mediated via CYP3A4 and CYP2C8. Dabrafenib related material is excreted primarily in faeces, with 71% of an oral dose recovered in faeces; 23% of the dose was recovered in urine in the form of metabolites only.

Special patient populations

Hepatic impairment

A population pharmacokinetic analysis indicates that mildly elevated bilirubin and/or AST levels (based on National Cancer Institute [NCI] classification) do not significantly affect dabrafenib oral clearance. In addition, mild hepatic impairment as defined by bilirubin and AST did not have a significant effect on dabrafenib metabolite plasma concentrations. No data are available in patients with moderate to severe hepatic impairment. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, administration of dabrafenib should be undertaken with caution in patients with moderate to severe hepatic impairment (see section 4.2).

Renal impairment

A population pharmacokinetic analysis suggests that mild renal impairment does not affect oral clearance of dabrafenib. Although data in moderate renal impairment are limited these data may indicate no clinically relevant effect. No data are available in subjects with severe renal impairment (see section 4.2).

Elderly

Based on the population pharmacokinetic analysis, age had no significant effect on dabrafenib

pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and desmethyl-dabrafenib plasma concentrations with a 40% greater exposure in subjects ≥75 years of age, relative to subjects <75 years old.

Body weight and gender

Based on the population pharmacokinetic analysis, gender and weight were found to influence dabrafenib oral clearance; weight also impacted oral volume of distribution and distributional clearance. These pharmacokinetic differences were not considered clinically relevant in adult patients.

Pediatric Patients

The pharmacokinetics of dabrafenib were evaluated in 109 pediatric patients after single or repeat weight-adjusted dosing. The pharmacokinetic exposures of dabrafenib at the recommended weight-adjusted dosage in pediatric patients were within range of those observed in adults.

Race

The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. There are insufficient data to evaluate the potential effect of other races on dabrafenib pharmacokinetics.

5.3 Preclinical safety data

Carcinogenicity studies with dabrafenib have not been conducted. Dabrafenib was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

In combined female fertility, early embryonic and embryo-foetal development studies in rats numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on oestrous cycle, mating or fertility indices. Developmental toxicity including embryo-lethality and ventricular septal defects and variation in thymic shape were seen at 300 mg/kg/day, and delayed skeletal development and reduced foetal body weight at ≥20 mg/kg/day (≥0.5 times human clinical exposure based on AUC).

Male fertility studies with dabrafenib have not been conducted. However, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period (see section 4.6).

Cardiovascular effects, including coronary arterial degeneration/necrosis and/or haemorrhage, cardiac atrioventricular valve hypertrophy/haemorrhage and atrial fibrovascular proliferation were seen in dogs (≥2 times human clinical exposure based on AUC). Focal arterial/perivascular inflammation in various tissues was observed in mice and an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) was observed in rats (≥0.5 and 0.6 times human clinical exposure for rats and mice, respectively). Hepatic effects, including hepatocellular necrosis and inflammation, were observed in mice (≥0.6 times human clinical exposure). Bronchoalveolar inflammation of the lungs was observed in several dogs at ≥20 mg/kg/day (≥9 times human clinical exposure based on AUC) and was associated with shallow and/or laboured breathing.

Reversible haematological effects have been observed in dogs and rats given dabrafenib. In studies of up to 13 weeks, decreases in reticulocyte counts and/or red cell mass were observed in dogs and rats (≥10 and 1.4 times human clinical exposure, respectively).

In juvenile toxicity studies in rats, effects on growth (shorter long bone length), renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations) and testicular toxicity (degeneration and tubular dilation) were observed (≥0.2 times human clinical exposure based on AUC).

Dabrafenib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and *in vivo* at doses ≥100 mg/kg (>44 times human clinical exposure based on C_{max}) in an oral phototoxicity study in hairless mice.

Combination with trametinib

In a study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks, signs of gastrointestinal toxicity and decreased lymphoid cellularity of the thymus were observed at lower exposures than in dogs given trametinib alone. Otherwise, similar toxicities were observed as in comparable monotherapy studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Microcrystalline cellulose
Magnesium stearate
Colloidal silicone dioxide

Capsule shell
Red iron oxide (E172)
Titanium dioxide (E171)
Hypromellose (E464)

Printing ink:

Shellac (E904)
Black iron oxide (E172)
Butyl Alcohol
Isopropyl Alcohol
Propylene glycol (E1520)
Ammonium Hydroxide (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Opaque white high-density polyethylene (HDPE) bottle with polypropylene child resistant screw cap and a silica gel desiccant.

Each bottle contains 28 capsules.

7. REGISTRATION HOLDER AND IMPORTER AND ITS ADDRESS

Novartis Israel Ltd.
P.O.B 9240, Tel Aviv-Yafo, 6109102.

8. REGISTRATION NUMBER

Tafinlar 50 mg: 151 42 33976
Tafinlar 75 mg: 151 43 33977

Revised in August 2026.