FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

RAFINLAR 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 Warnings and Precautions (5) and Clinical Pharmacology (11.1)]*.

1.2 Adjuvant treatment of melanoma

RAFINLAR 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.

1.3 BRAF V600E Mutation-Positive Metastatic NSCLC

RAFINLAR is indicated, in combination with trametinib, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation. *[see Dosage and Administration (2.1)]*.

1.4 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

RAFINLAR 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 Dosage and Administration (2.1)]*.

1.5 Limitations of Use

- RAFINLAR is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition *[see Clinical Pharmacology (11.1)]*.
- RAFINLAR is not indicated for treatment of patients with wild-type BRAF solid tumors *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Melanoma

- Treatment with RAFINLAR should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.
- Before taking RAFINLAR, patients must have confirmation of tumor BRAF V600 mutation using a validated test.
- The efficacy and safety of RAFINLAR have not been established in patients with wild-type BRAF melanoma. RAFINLAR should therefore not be used in patients with wild-type BRAF melanoma *[see Warnings and Precautions (5) and Clinical Pharmacology (11.1)]*.

NSCLC

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with RAFINLAR and trametinib *[see Clinical Studies (13.4)]*.

Solid Tumors

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with RAFINLAR and trametinib *[see Clinical Studies (13.5)]*.

2.2 Recommended Dosage

Adult Patients

The recommended dosage for RAFINLAR capsules in adult patients, either used as monotherapy or in combination with trametinib, is 150 mg (two 75mg capsules) twice daily (corresponding to a total daily dose of 300mg) *[see Dosage and Administration (2.3)]*. The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily.

Pediatric Patients (*for Solid Tumors only)*

The recommended dosage for RAFINLAR capsules in pediatric patients who weigh at least 26 kg is based on body weight (Table 1) *[see Dosage and Administration (2.3)]*. A recommended dosage of RAFINLAR capsules has not been established in patients who weigh less than 26 kg.

Table 1. Recommended Dosage for RAFINLAR Capsules in Pediatric Patients (Weight-based)

Body Weight	Recommended Dosage
26 to 37 kg	75 mg orally twice daily
38 to 50 kg	100 mg orally twice daily
51 kg or greater	150 mg orally twice daily

Duration of Treatment

- The recommended duration of treatment for patients with unresectable or metastatic melanoma, solid tumors or metastatic NSCLC is until disease progression or unacceptable toxicity.
- In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.

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

2.3 Administration

- Take RAFINLAR at the same time each day, approximately 12 hours apart.
- Take RAFINLAR at least 1 hour before or 2 hours after a meal *[see Clinical Pharmacology (11.3)]*.
- Do not take a missed dose of RAFINLAR within 6 hours of the next dose of RAFINLAR.
- If vomiting occurs after RAFINLAR administration, do not take an additional dose. Take the next dose at its scheduled time.
- Do not open, crush, or break RAFINLAR capsules.

2.4 Dosage Modifications for Adverse Reactions

Dose reductions for adverse reactions associated with RAFINLAR are presented in Tables 2 and 3.

Table 2. Recommended Dosage Reductions for RAFINLAR Capsules for Adverse Reactions

Recommended Dosage	75 mg orally twice daily	100 mg orally twice daily	150 mg orally twice daily
First dose reduction	50 mg orally twice daily	75 mg orally twice daily	100 mg orally twice daily
Second dose reduction	N/A	50 mg orally twice daily	75 mg orally twice daily
Third dose reduction	N/A	N/A	50 mg orally twice daily

Subsequent modification	Permanently discontinue if unable to tolerate RAFINLAR capsules 50 mg orally twice daily.

Table 3. Recommended Dosage Modifications for RAFINLAR for Adverse Reactions

Severity of Adverse Reaction[a]	Dosage Modification for RAFINLAR[b]
New Primary Malignancies [see Warnings and Precautions (5.1)]	
Non-Cutaneous RAS Mutation-positive Malignancies	Permanently discontinue RAFINLAR.
Cardiomyopathy [see Warnings and Precautions (5.4)]	
• Symptomatic cardiomyopathy • Absolute decrease in left ventricular ejection fraction (LVEF) of greater than 20% from baseline that is below the institutional lower limit of normal (LLN)	Withhold RAFINLAR until LVEF improves to at least the institutional LLN and absolute decrease to less than or equal to 10% compared to baseline, then resume RAFINLAR at same dose.
Uveitis [see Warnings and Precautions (5.5)]	
• Uveitis, including iritis and iridocyclitis	For mild or moderate uveitis that does not respond to ocular therapy, or for severe uveitis, withhold RAFINLAR for up to 6 weeks. • If improved to Grade 0-1, then resume RAFINLAR at same or lower dose. • If not improved, permanently discontinue RAFINLAR.
Febrile Reactions [see Warnings and Precautions (5.6)]	
• Fever of 100.4°F to 104°F (or first symptoms in case of recurrence)	Withhold RAFINLAR until fever resolves, then resume RAFINLAR at same or lower dose.
• Fever higher than 104°F • Fever complicated by rigors, hypotension, dehydration, or renal failure	• Withhold RAFINLAR until febrile reactions resolve for at least 24 hours, then resume RAFINLAR at lower dose. Or • Permanently discontinue RAFINLAR.
Skin Toxicities [see Warnings and Precautions (5.7)]	
• Intolerable Grade 2 • Grade 3 or 4	Withhold RAFINLAR for up to 3 weeks. • If improved, resume RAFINLAR at lower dose. • If not improved, permanently discontinue RAFINLAR.
• Severe cutaneous adverse reactions (SCARs)	Permanently discontinue RAFINLAR.
Other Adverse Reactions[c], including Hemorrhage [see Warnings and Precautions (5.3)]	
• Intolerable Grade 2 • Any Grade 3	Withhold RAFINLAR. • If improved to Grade 0-1, resume RAFINLAR at lower dose. • If not improved, permanently discontinue RAFINLAR.
• First occurrence of any Grade 4	• Withhold RAFINLAR until improves to Grade 0-1, then resume at lower dose. Or • Permanently discontinue RAFINLAR.
• Recurrent Grade 4	Permanently discontinue RAFINLAR.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
[b] See Tables 2 for recommended dose reductions of RAFINLAR.
[c] Dose modifications are not recommended for RAFINLAR when administered with trametinib for the following adverse reactions of trametinib: retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), interstitial lung disease/pneumonitis, and uncomplicated venous thromboembolism. Dose modification of RAFINLAR is not required for new primary cutaneous malignancies.

Refer to the trametinib prescribing information for dose modifications for adverse reactions associated with trametinib.

3 DOSAGE FORMS AND STRENGTHS

RAFINLAR Capsules:

- 50 mg: Dark red capsule imprinted with 'GS TEW' and '50 mg'.
- 75 mg: Dark pink capsule imprinted with 'GS LHF' and '75 mg'.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

Cutaneous Malignancies

RAFINLAR Monotherapy (Adult): In the pooled safety population *[see Adverse Reactions (6.1)],* cutaneous squamous cell carcinomas (cuSCC), and keratoacanthomas occurred in 11% and 4% of patients, respectively. Basal cell carcinoma and new primary melanoma occurred in 4% and 1% of patients, respectively.

RAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, the incidence of cuSCC (including keratoacanthomas) occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and < 1% of patients, respectively.

RAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, new primary melanoma occurred in < 1% of patients.

Perform dermatologic evaluations prior to initiation of RAFINLAR, every 2 months while on therapy, and for up to 6 months following discontinuation of RAFINLAR.

Non-Cutaneous Malignancies

Based on its mechanism of action, RAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*.

In the pooled adult safety populations of RAFINLAR monotherapy and RAFINLAR administered with trametinib *[see Adverse Reactions (6.1)]*, non-cutaneous malignancies occurred in 1% of patients.

Monitor patients receiving RAFINLAR for signs or symptoms of non-cutaneous malignancies. Permanently discontinue RAFINLAR for RAS mutation-positive non-cutaneous malignancies *[see Dosage and Administration (2.4)]*.

5.2 Tumor Promotion in BRAF Wild-Type Tumors

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation status prior to initiation of RAFINLAR as a single agent or in combination with trametinib *[see Indications and Usage (1.4), Dosage and Administration (2.1)]*.

5.3 Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur when RAFINLAR is administered with trametinib. Fatal cases have been reported.

RAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, hemorrhagic events occurred in 17% of patients; gastrointestinal hemorrhage occurred in 3% of patients; intracranial hemorrhage occurred in 0.6% of patients; fatal hemorrhage occurred in 0.5% of patients. The fatal events were cerebral hemorrhage and brainstem hemorrhage.

RAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, hemorrhagic events occurred in 25% of patients; the most common type of bleeding was epistaxis (16%). Serious events of bleeding occurred in 3.6% of patients and included gastrointestinal hemorrhage (1.2%), cerebral hemorrhage (0.6%) uterine hemorrhage (0.6%), post-procedural hemorrhage (0.6%), and epistaxis (0.6%).

Permanently discontinue RAFINLAR for all Grade 4 hemorrhagic events and for any Grade 3 hemorrhagic events that do not improve. Withhold RAFINLAR for Grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

5.4 Cardiomyopathy

RAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and below the institutional lower limit of normal (LLN), occurred in 6% of patients. Development of cardiomyopathy resulted in dose interruption or discontinuation of RAFINLAR in 3% and < 1% of patients, respectively. Cardiomyopathy resolved in 45 of 50 patients who received RAFINLAR administered with trametinib.

RAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, cardiomyopathy, defined as a decrease in LVEF ≥ 10% from baseline and below the institutional LLN, occurred in 9% of patients.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of RAFINLAR in combination with trametinib, one month after initiation, and then at 2- to 3-month intervals while on treatment. Withhold RAFINLAR for symptomatic cardiomyopathy or an absolute decrease in LVEF of greater than 20% from baseline that is below the institutional LLN. Resume RAFINLAR at the same dose level upon recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease to less than or equal to 10% compared to baseline *[see Dosage and Administration (2.4)]*.

5.5 Uveitis

RAFINLAR Monotherapy (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, uveitis occurred in 1% of patients.

RAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)],* uveitis occurred in 2% of patients.

Cases of biocular panuveitis or biocular iridocyclitis have been reported in the post-marketing setting.

RAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, uveitis occurred in 1.2% of patients.

Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (e.g., change in vision, photophobia, eye pain). If iritis is diagnosed, administer ocular therapy and continue RAFINLAR without dose modification. If severe uveitis (i.e., iridocyclitis) or if mild or moderate uveitis does not respond to ocular therapy, withhold RAFINLAR and treat as clinically indicated. Resume RAFINLAR at the same or lower dose if improves to Grade 0 or 1. Permanently discontinue RAFINLAR for persistent Grade 2 or greater uveitis of > 6 weeks *[see Dosage and Administration (2.4)]*.

5.6 Serious Febrile Reactions

Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur with RAFINLAR.

The incidence and severity of pyrexia are increased when RAFINLAR is administered with trametinib compared with RAFINLAR as a single agent *[see Adverse Reactions (6.1)]*.

RAFINLAR Monotherapy (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, fever (serious and non-serious) occurred in 30% of patients. Approximately 13% of these patients experienced 3 or more discrete episodes. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills occurred in 6% of patients.

RAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, fever occurred in 58% of patients. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration or renal failure occurred in 5% of patients. Fever was complicated by hypotension in 4%, dehydration in 3%, syncope in 2%, renal failure in 1%, and severe chills/rigors in < 1% of patients.

RAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population *[see Adverse Reactions (6.1)],* pyrexia occurred in 66% of patients.

Withhold RAFINLAR when used as monotherapy, and both RAFINLAR and trametinib when used in combination, if the patient's temperature is ≥ 100.4°F. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia *[see Adverse Reactions (6.1)]*. Fever may be complicated by hypotension, rigors or chills, dehydration, or renal failure. Evaluate for signs and symptoms of infection and monitor serum creatinine and other evidence of renal function during and following severe pyrexia. If appropriate, RAFINLAR, or both RAFINLAR and trametinib when used in combination, may be restarted if the patient has recovered from the febrile reaction for at least 24 hours, either at the same or lower dose *[see Dosage and Administration (2.4)]*. Administer antipyretics as secondary prophylaxis when resuming RAFINLAR if patient had a prior episode of severe febrile reaction or fever associated with complications. Administer corticosteroids (e.g., prednisone 10 mg daily) for at least 5 days for second or subsequent pyrexia if temperature does not return to baseline within 3 days of onset of pyrexia, or for pyrexia associated with complications, such as dehydration, hypotension, renal failure, or severe chills/rigors, and there is no evidence of active infection.

5.7 Serious Skin Toxicities

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with RAFINLAR administered with trametinib *[see Adverse Reactions (6.2)]*.

RAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, other serious skin toxicity occurred in < 1% of patients.

RAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, serious adverse events of skin and subcutaneous tissue disorders occurred in 1.8% of patients.

Monitor for new or worsening serious skin reactions. Permanently discontinue RAFINLAR for SCARs *[see Dosage and Administration (2.4)]*. For other skin toxicities, withhold RAFINLAR for intolerable or severe skin toxicity. Resume RAFINLAR at a lower dose in patients with improvement or recovery from skin toxicity within 3 weeks. Permanently discontinue RAFINLAR if skin toxicity has not improved within 3 weeks *[see Dosage and Administration (2.4)]*.

5.8 Hyperglycemia

RAFINLAR Monotherapy (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, 14% of patients with a history of diabetes that received RAFINLAR required more intensive hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia occurred in 3% of patients.

RAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, 15% of patients with a history of diabetes who had received RAFINLAR with trametinib required more intensive hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia occurred in 2% of patients.

RAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, Grade 3 and Grade 4 hyperglycemia events occurred in < 1% of patients.

Monitor serum glucose levels upon initiation and as clinically appropriate when RAFINLAR is administered in patients with preexisting diabetes or hyperglycemia. Initiate or optimize anti-hyperglycemic medications as clinically indicated.

5.9 Glucose-6-Phosphate Dehydrogenase Deficiency

RAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking RAFINLAR.

5.10 Risks Associated with Combination Treatment

RAFINLAR is indicated for use in combination with trametinib. Review the prescribing information for trametinib for information on the serious risks of trametinib prior to initiation of RAFINLAR with trametinib.

5.11 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) has been observed in the post-marketing setting when RAFINLAR was administered with trametinib. If HLH is suspected, interrupt treatment. If HLH is confirmed, discontinue treatment and initiate appropriate management of HLH.

5.12 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, RAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended adult clinical dose. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to use effective non-hormonal contraception, since RAFINLAR can render hormonal contraceptives ineffective, during treatment with RAFINLAR and for 2 weeks after the last dose *[see Drug Interactions (7.2), Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Tumor Promotion in BRAF Wild-Type Tumors *[see Warnings and Precautions (5.2)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*
- Cardiomyopathy *[see Warnings and Precautions (5.4)]*
- Uveitis *[see Warnings and Precautions (5.5)]*
- Serious Febrile Reactions *[see Warnings and Precautions (5.6)]*
- Serious Skin Toxicities *[see Warnings and Precautions (5.7)]*
- Hyperglycemia *[see Warnings and Precautions (5.8)]*
- Glucose-6-Phosphate Dehydrogenase Deficiency *[see Warnings and Precautions (5.9)]*
- Hemophagocytic Lymphohistiocytosis *[see Warnings and Precautions (5.11)]*

There are additional adverse reactions associated with trametinib. Refer to the trametinib prescribing information for additional information.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Safety Pools

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to RAFINLAR 150 mg orally, twice daily as a single agent in 586 patients with various solid tumors, including BRAF V600 mutation-positive unresectable or metastatic melanoma, enrolled in BREAK-2, BREAK-3, BREAK-MB, BRF113220, and BRF112680. Among these 586 patients who received RAFINLAR as a single agent, 46% were exposed for 6 months or longer and 15% were exposed for greater than one year.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to RAFINLAR 150 mg orally, twice daily, administered in combination with trametinib 2 mg orally, once daily, in 1087 patients enrolled in COMBI-d, COMBI-v, COMBI-AD, and BRF113928 with unresectable or metastatic melanoma, adjuvant melanoma, or NSCLC. Among these 1087 patients who received RAFINLAR administered with trametinib, 70% were exposed for 6 months or longer and 21% were exposed for greater than one year.

Pediatric Safety Pool

The pediatric pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to weight-based RAFINLAR 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, multi-cohort study in pediatric patients with refractory or recurrent solid tumors with MAPK pathway activation (Study X2101; n = 43) *[see Clinical Studies (13.5)]*. Among 166 patients who received RAFINLAR 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%).

Unresectable or Metastatic BRAF V600E or V600K Mutation-Positive Melanoma

RAFINLAR as a Single Agent

The safety of RAFINLAR was evaluated in BREAK-3, a multi-center, international, open-label, randomized (3:1), controlled trial that allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive RAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n = 63) *[see Clinical Studies (13.1)]*. The trial excluded patients with abnormal LVEF or cardiac valve morphology (≥ Grade 2), corrected QT interval ≥ 480 milliseconds on electrocardiogram, or a known history of G6PD deficiency. The median duration on treatment was 4.9 months for patients treated with RAFINLAR and 2.8 months for dacarbazine-treated patients. The population exposed to RAFINLAR was 60% male, 99% White, and had a median age of 53 years.

The most common adverse reactions (≥ 20%) in patients treated with RAFINLAR were, in order of decreasing frequency: hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome (PPES).

The incidence of adverse events resulting in permanent discontinuation of study medication in the BREAK-3 study was 3% for patients treated with RAFINLAR and 3% for patients treated with dacarbazine. The most frequent (≥ 2%) adverse reactions leading to dose reduction of RAFINLAR were pyrexia (9%), PPES (3%), chills

(3%), fatigue (2%), and headache (2%). Table 4 and Table 5 present adverse reactions and laboratory abnormalities, respectively, of RAFINLAR as a single agent in the BREAK-3 study.

Table 4. Select Adverse Reactions Occurring in ≥ 10% (All Grades) or ≥ 2% (Grades 3 or 4) of Patients Treated with RAFINLAR in the BREAK-3 Study[a]

Adverse Reactions	RAFINLAR N = 187		Dacarbazine N = 59	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
Skin and subcutaneous tissue				
Hyperkeratosis	37	1	0	0
Alopecia	22	NA	2	NA
Palmar-plantar erythrodysesthesia syndrome	20	2	2	0
Rash	17	0	0	0
Nervous system				
Headache	32	0	8	0
General				
Pyrexia	28	3	10	0
Musculoskeletal and connective tissue				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	0	0
Neoplasms				
Papilloma[c]	27	0	2	0
cuSCC[d]	7	4	0	0
Respiratory system				
Cough	12	0	5	0
Gastrointestinal				
Constipation	11	2	14	0
Infections and infestations				
Nasopharyngitis	10	0	3	0

Abbreviations: cuSCC, cutaneous squamous cell carcinoma, includes squamous cell carcinoma of the skin and keratoacanthoma; NA, not applicable.

[a] Adverse reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of toxicity.

[b] Grade 4 adverse reactions limited to hyperkeratosis (n = 1) and constipation (n = 1).

[c] Includes skin papilloma and papilloma.

[d] Cases of cuSCC were required to be reported as Grade 3 per protocol.

Table 5. Laboratory Abnormalities Worsening from Baseline Occurring at a Higher Incidence in Patients Treated with RAFINLAR in the BREAK-3 Study [Between-Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grades 3 or 4)][a]

Laboratory Abnormality	RAFINLAR N = 187		Dacarbazine N = 59	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycemia	50	6	43	0
Hypophosphatemia	37	6[b]	14	2
Increased alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

[a] Adverse reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of toxicity.
[b] Grade 4 laboratory abnormality limited to hypophosphatemia (n = 1).

Other clinically important adverse reactions for RAFINLAR in a pool of RAFINLAR monotherapy clinical studies observed in less than 10% of patients who received RAFINLAR were:

Gastrointestinal: Pancreatitis

Immune System: Hypersensitivity manifesting as bullous rash

Nervous System: Peripheral neuropathy

Renal and Urinary: Interstitial nephritis

Skin and Subcutaneous Tissue: Photosensitivity

RAFINLAR with Trametinib

The safety of RAFINLAR when administered with trametinib was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600E or V600K mutation-positive melanoma who received RAFINLAR in two trials, the COMBI-d study (n = 209), a multi-center, double-blind, randomized (1:1), active-controlled trial and the COMBI-v study (n = 350), a multi-center, open-label, randomized (1:1), active-controlled trial. In both trials, patients received RAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. Both trials excluded patients with abnormal LVEF, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED), QTcB interval ≥ 480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases, or known history of G6PD deficiency *[see Clinical Studies (13.2)]*.

Among these 559 patients, 199 (36%) were exposed to RAFINLAR for > 6 months to 12 months while 185 (33%) were exposed to RAFINLAR for ≥ 1 year. The median age was 55 years (range: 18 to 91), 57% were male, 98% were White, 72% had baseline ECOG performance status of 0 and 28% had ECOG performance status of 1, 64% had M1c disease, 35% had elevated lactate dehydrogenase (LDH) at baseline, and 0.5% had a history of brain metastases.

The most common adverse reactions (≥ 20%) for RAFINLAR in patients who received RAFINLAR plus trametinib in the COMBI-d and COMBI-v studies were: pyrexia, rash, chills, headache, arthralgia, and cough.

The demographics and baseline tumor characteristics of patients enrolled in the COMBI-d study are summarized in Clinical Studies *[see Clinical Studies (13.2)]*. Patients who received RAFINLAR plus trametinib had a median duration of exposure of 11 months (range: 3 days to 30 months) to RAFINLAR. Among the 209 patients who received RAFINLAR plus trametinib, 26% were exposed to RAFINLAR for > 6 months to 12 months while 46% were exposed to RAFINLAR for > 1 year.

In the COMBI-d study, adverse reactions leading to discontinuation of RAFINLAR occurred in 11% of patients who received RAFINLAR plus trametinib; the most frequent was pyrexia (1.9%). Adverse reactions leading to dose reductions of RAFINLAR occurred in 26% of patients who received RAFINLAR plus trametinib; the most frequent were pyrexia (14%), neutropenia (1.9%), rash (1.9%), and chills (1.9%). Adverse reactions leading to dose interruptions of RAFINLAR occurred in 56% of patients who received RAFINLAR plus trametinib; the most frequent were pyrexia (35%), chills (11%), vomiting (7%), nausea (5%), and decreased ejection fraction (5%).

Table 6 and Table 7 present adverse reactions and laboratory abnormalities, respectively, observed in the COMBI-d study.

Table 6. Select Adverse Reactions Occurring in ≥ 10% (All Grades) of Patients Treated with RAFINLAR Administered with Trametinib in the COMBI-d Study[a]

Adverse Reactions	Pooled RAFINLAR plus Trametinib N = 559		COMBI-d Study			
			RAFINLAR plus Trametinib N = 209		RAFINLAR N = 211	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Skin and subcutaneous tissue						
Rash[c]	32	1.1	42	0	27	1.4
Dry skin	10	0	12	0	16	0
Nervous system						
Headache	30	0.9	33	0.5	30	1.4
Dizziness	11	0.2	14	0	7	0
Musculoskeletal and connective tissue						
Arthralgia	25	0.9	26	0.9	31	0
Myalgia	15	0.2	13	0.5	13	0
Respiratory system						
Cough	20	0	21	0	21	0
Gastrointestinal						
Constipation	13	0.2	13	0.5	10	0
Infections and infestations						
Nasopharyngitis	12	0	12	0	10	0

[a] NCI CTCAE version 4.0.
[b] Grade 4 adverse reactions limited to headache (n = 1).
[c] Includes rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, rash maculo-papular, and rash follicular.

Other clinically important adverse reactions for RAFINLAR across the COMBI-d and COMBI-v studies (N = 559) observed in less than 10% of patients who received RAFINLAR administered with trametinib were:

Cardiac: Atrioventricular block, bundle branch block

Gastrointestinal: Colitis, gastrointestinal perforation, pancreatitis

Immune System: Sarcoidosis

Nervous System: Peripheral neuropathy, Guillain-Barré syndrome

Skin and Subcutaneous Tissue: Panniculitis, photosensitivity

Table 7. Select Laboratory Abnormalities Worsening from Baseline Occurring at ≥ 10% (All Grades) of Patients Who Received RAFINLAR with Trametinib in the COMBI-d Study

Laboratory Abnormalities	Pooled RAFINLAR plus Trametinib N = 559[a]		COMBI-d Study			
			RAFINLAR plus Trametinib N = 209[b]		RAFINLAR N = 211[b]	
	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypophosphatemia	38	6	38	3.8	35	7
Hyponatremia	25	8	24	6	14	2.9
Hepatic						
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5

[a] For these laboratory tests, the denominator is 556.
[b] For these laboratory tests, the denominator is 208 for the combination arm, 208-209 for the RAFINLAR arm.
[c] Grade 4 adverse reactions limited to hyperglycemia (n = 4), hyponatremia and hypophosphatemia (each n = 1) in the pooled combination arm; hyperglycemia (n = 1) in the COMBI-d study combination arm; hypophosphatemia (n = 1) in the RAFINLAR arm.

Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

The safety of RAFINLAR when administered with trametinib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study *[see Clinical Studies (13.3)]*. Patients received RAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily for 12 months. The trial excluded patients with abnormal LVEF; history of acute coronary syndromes, coronary angioplasty, or stenting within 6 months; Class II or greater congestive heart failure; QTc interval ≥ 480 msec; treatment refractory hypertension; uncontrolled arrhythmias; or history of RVO.

Patients who received RAFINLAR in combination with trametinib had a median duration of exposure of 11 months (range: 0 to 12) to RAFINLAR. Among the 435 patients receiving RAFINLAR in combination with trametinib, 71% were exposed to RAFINLAR for > 6 months. The median age of patients who received RAFINLAR administered with trametinib was 50 years (range: 18 to 89), 56% were male, 99% were White, 92% had baseline ECOG performance status of 0, and 8% had baseline ECOG performance status of 1.

The most common adverse reactions (≥ 20%) in patients who received RAFINLAR administered with trametinib were: pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia.

Adverse reactions resulting in discontinuation, dose reduction, or dose interruption of RAFINLAR occurred in 25%, 35%, and 66% of patients, respectively; the most frequent for each were pyrexia and chills.

Table 8 summarizes the adverse reactions that occurred in at least 20% of patients who received RAFINLAR administered with trametinib.

Table 8. Adverse Reactions Occurring in ≥ 20% of Patients in the COMBI-AD Study[a]

Adverse Reactions	RAFINLAR plus Trametinib N = 435		Placebo N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General				
Pyrexia[b]	63	5	11	< 1
Fatigue[c]	59	5	37	< 1
Chills	37	1	4	0
Gastrointestinal				
Nausea	40	< 1	20	0
Diarrhea	33	< 1	15	< 1
Vomiting	28	< 1	10	0
Nervous system				
Headache[d]	39	1	24	0
Skin and subcutaneous tissue				
Rash[e]	37	< 1	16	< 1
Musculoskeletal and connective tissue				
Arthralgia	28	< 1	14	0
Myalgia[f]	20	< 1	14	0

[a] NCI CTCAE version 4.0.
[b] Includes pyrexia and hyperpyrexia.
[c] Includes fatigue, asthenia, and malaise.
[d] Includes headache and tension headache.
[e] Includes rash, rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.
[f] Includes myalgia, musculoskeletal pain, and musculoskeletal chest pain.

Other clinically important adverse reactions for RAFINLAR in the COMBI-AD study observed in less than 20% of patients who received RAFINLAR administered with trametinib were: blurred vision (6%), decreased ejection fraction (5%), peripheral neuropathy (2.5%), rhabdomyolysis (< 1%), atrioventricular block (< 1%), Guillain-Barré syndrome (< 1%), and sarcoidosis (< 1%).

The laboratory abnormalities are summarized in Table 9.

Table 9. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the COMBI-AD Study

Laboratory Abnormality	RAFINLAR plus Trametinib[a] N = 435		Placebo[a] N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Chemistry				
Hyperglycemia	63	3	47	2
Hypophosphatemia	42	7	10	< 1
Hypoalbuminemia	25	< 1	< 1	0
Hepatic				
Increased AST	57	6	11	< 1
Increased ALT	48	5	18	< 1
Increased blood alkaline phosphatase	38	1	6	< 1
Hematology				
Neutropenia	47	6	12	< 1
Lymphopenia	26	5	6	< 1
Anemia	25	< 1	6	< 1

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] The incidence is based on the number of patients who had both a baseline and at least one on-study laboratory measurement: RAFINLAR plus Trametinib (range: 429 to 431) and placebo arm (range: 426 to 428).

Trial COMBI-aPlus (Pyrexia Management Study)

COMBI-aPlus evaluated the impact of pyrexia-related outcomes of a revised pyrexia management algorithm in patients who received dabrafenib administered with trametinib in the adjuvant treatment of BRAF V600 mutation-positive melanoma after complete resection. The pyrexia management algorithm interrupted both dabrafenib and trametinib when patient's temperature is ≥100.4°F.

Grade 3-4 pyrexia occurred in 4.3% of patients, hospitalizations due to pyrexia occurred in 5.1% of patients, pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) occurred in 2.2% of patients, and treatment discontinuation due to pyrexia occurred in 2.5% of patients.

Metastatic, BRAF V600E Mutation-Positive Non-Small Cell Lung Cancer

The safety of RAFINLAR when administered with trametinib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multi-center, multi-cohort, non-randomized, open-label trial (Study BRF113928). Patients received RAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. The trial excluded patients with abnormal LVEF, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure, QTc interval ≥ 480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases, history of interstitial lung disease or pneumonitis, or history or current RVO *[see Clinical Studies (13.4)]*.

Among these 93 patients, 53 (57%) were exposed to RAFINLAR and trametinib for > 6 months and 27 (29%) were exposed to RAFINLAR and trametinib for ≥ 1 year. The median age was 65 years (range: 41 to 91); 46% were male; 85% were White; 32% had baseline ECOG performance status of 0 and 61% had ECOG performance status of 1; 98% had non-squamous histology; and 12% were current smokers, 60% were former smokers, and 28% had never smoked.

The most common adverse reactions (≥ 20%) in these 93 patients were: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea.

Adverse reactions leading to discontinuation of RAFINLAR occurred in 18% of patients; the most frequent were pyrexia (2.2%), decreased ejection fraction (2.2%), and respiratory distress (2.2%). Adverse reactions leading to dose reductions of RAFINLAR occurred in 35% of patients; the most frequent were pyrexia (10%), diarrhea (4.3%), nausea (4.3%), vomiting (4.3%), and neutropenia (3.2%). Adverse reactions leading to dose interruptions of RAFINLAR occurred in 62% of patients; the most frequent were pyrexia (27%), vomiting (11%), neutropenia (8%), and chills (6%).

Table 10 and Table 11 present adverse reactions and laboratory abnormalities, respectively, of RAFINLAR administered with trametinib in Study BRF113928.

Table 10. Adverse Reactions Occurring in ≥ 20% (All Grades) of Patients Treated with RAFINLAR Administered with Trametinib in Study BRF113928[a]

Adverse Reactions	RAFINLAR plus Trametinib N = 93	
	All Grades (%)	Grades 3 and 4 (%)
General		
Pyrexia	55	5
Fatigue[b]	51	5
Edema[c]	28	0
Chills	23	1.1
Gastrointestinal		
Nausea	45	0
Vomiting	33	3.2
Diarrhea	32	2.2
Decreased appetite	29	0
Skin and subcutaneous tissue		
Dry skin	31	1.1
Rash[d]	28	3.2
Vascular		
Hemorrhage[e]	23	3.2
Respiratory system		
Cough	22	0
Dyspnea	20	5

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, malaise, and asthenia.
[c] Includes peripheral edema, edema, and generalized edema.
[d] Includes rash, rash generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.
[e] Includes hemoptysis, hematoma, epistaxis, purpura, hematuria, subarachnoid hemorrhage, gastric hemorrhage, urinary bladder hemorrhage, contusion, hematochezia, injection site hemorrhage, pulmonary hemorrhage, and retroperitoneal hemorrhage.

Other clinically important adverse reactions for RAFINLAR in Study BRF113928 observed in less than 20% of patients who received RAFINLAR administered with trametinib were:

Cardiac: Atrioventricular block

Gastrointestinal: Pancreatitis

Nervous System: Peripheral neuropathy

Renal and Urinary: Tubulointerstitial nephritis

Table 11. Treatment-Emergent Laboratory Abnormalities Occurring in ≥ 20% (All Grades) of Patients Who Received RAFINLAR with Trametinib in Study BRF113928

Laboratory Abnormality	RAFINLAR plus Trametinib N = 93	
	All Grades (%)	Grades 3 and 4 (%)
Chemistry[a]		
Hyperglycemia	71	9
Hyponatremia	57	17
Hypophosphatemia	36	7
Increased creatinine	21	1.1
Hepatic[a]		
Increased blood alkaline phosphatase	64	0
Increased AST	61	4.4
Increased ALT	32	6
Hematology[b]		
Leukopenia	48	8
Anemia	46	10
Neutropenia	44	8
Lymphopenia	42	14

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] For these laboratory tests, the denominator is 90.
[b] For these laboratory tests, the denominator is 91.

Advanced BRAF V600E Mutation-Positive Tumors

Study BRF117019

The safety of RAFINLAR when administered with trametinib was 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 Clinical Studies (13.5)]*. Patients received RAFINLAR 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 RAFINLAR 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.

Serious adverse reactions occurred in 45% of patients who received RAFINLAR in combination with trametinib. Serious adverse reactions in > 5% of patients included pyrexia (11%) and pneumonia (6%). Fatal adverse reactions occurred in 3.9% of patients who received RAFINLAR in combination with trametinib. Fatal adverse reactions that occurred in > 1% of patients included sepsis (1.9%).

Permanent treatment discontinuation due to an adverse reaction occurred in 13% of patients. Adverse reactions which resulted in permanent treatment discontinuation in > 1% of patients included nausea (1.5%).

Dosage interruptions due to an adverse reaction occurred in 55% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (22%), chills (9%), fatigue (6%), neutropenia (6%), and nausea (5%).

Dose reductions due to an adverse reaction occurred in 44% of patients. Adverse reactions which required dose reductions in > 5% of patients included pyrexia (18%), chills (8%), and fatigue (6%).

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, are listed in Table 12 and Table 13.

Table 12 summarizes the adverse reactions in Study BRF117019.

Table 12. Adverse Reactions (≥ 20%) in Adult Patients Treated with RAFINLAR Plus Trametinib in Study BRF117019

Adverse Reactions	RAFINLAR plus Trametinib[a] (N = 206)	
	All Grades (%)	Grade 3 or 4 (%)
General		
Pyrexia	55	4.9
Fatigue[b]	50	5
Chills	30	0.5
Peripheral edema[c]	22	0
Gastrointestinal		
Nausea	40	1.5
Constipation	27	0
Vomiting	27	1.5
Diarrhea	26	2.9
Skin and subcutaneous tissue		
Rash[d]	40	2.4
Nervous system		
Headache	30	1.5
Vascular		
Hemorrhage[e]	29	4.4
Respiratory system		
Cough[f]	29	0
Musculoskeletal and connective tissue		
Myalgia[g]	24	0.5
Arthralgia	23	0.5

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, asthenia, and malaise.
[c] Includes peripheral edema and peripheral swelling.
[d] Includes rash, rash maculo-papular, rash erythematous, rash pustular, and rash papular.
[e] Includes epistaxis, hematuria, contusion, hematoma, hemoptysis, conjunctival hemorrhage, hematochezia, rectal hemorrhage, hemorrhoidal hemorrhage, melena, purpura, eye contusion, eye hemorrhage, gastric hemorrhage, gingival bleeding, hematemesis, hemorrhage intracranial, hemorrhagic stroke, hemothorax, increased tendency to bruise, large intestinal hemorrhage, mouth hemorrhage, petechiae, pharyngeal hemorrhage, prothrombin time prolonged, pulmonary hematoma, retinal hemorrhage, vaginal hemorrhage, and vitreous hemorrhage.
[f] Includes cough and productive cough.
[g] Includes myalgia, musculoskeletal chest pain, and musculoskeletal pain.

Clinically relevant adverse reactions for RAFINLAR in Study BRF117019 observed in less than 20% of patients who received RAFINLAR in combination with trametinib were: peripheral neuropathy (9%), decreased ejection fraction (8%), atrioventricular block (2.9%), uveitis (1.9%), hypersensitivity (1.9%), and Guillain-Barré syndrome (< 1%).

Table 13 summarizes the laboratory abnormalities in Study BRF117019.

Table 13. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Adult Patients Treated with RAFINLAR Plus Trametinib in Study BRF117019

Laboratory Abnormality	RAFINLAR plus Trametinib[a]	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Hyperglycemia	61	8
Decreased sodium	35	10
Decreased magnesium	24	0
Increased creatinine	21	1.5
Hepatic		
Increased alkaline phosphatase	51	5
Increased AST	51	4.6
Increased ALT	39	3
Hematology		
Decreased hemoglobin	44	9

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] The denominator used to calculate the rate varied from 199 to 202 based on the number of patients with a baseline value and at least one post-treatment value.

BRAF V600E Mutation-Positive Solid Tumors in Pediatric Patients

Study CTMT212X2101 (X2101)

The safety of RAFINLAR 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 Clinical Studies (13.5)]*. The median duration of exposure to RAFINLAR 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 RAFINLAR with trametinib was 9 years (range: 1 to 17).

Serious adverse reactions occurred in 46% of patients who received RAFINLAR 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%). Dosage interruptions due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage 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 14 and Table 15.

Table 14 summarizes the adverse reactions in Study X2101.

Table 14. Adverse Reactions (≥ 20%) in Pediatric Patients Treated with RAFINLAR Plus Trametinib in Study X2101[a]

Adverse Reactions	RAFINLAR plus Trametinib[a] (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 RAFINLAR in Study X2101 observed in less than 20% of patients (N=48) who received RAFINLAR in combination with trametinib were: atrioventricular block (2.1%).

Table 15 summarizes the laboratory abnormalities in Study X2101.

Table 15. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Pediatric Patients Treated with RAFINLAR Plus Trametinib in Study X2101

Laboratory Abnormality	RAFINLAR 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of RAFINLAR in combination with trametinib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac: Atrioventricular block complete

Immune System: Hemophagocytic lymphohistiocytosis (HLH) *[see Warnings and Precautions (5.11)]*

Skin and Subcutaneous Tissue: SCAR (including DRESS and SJS) *[see Warnings and Precautions (5.7)]*

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on RAFINLAR

Strong inhibitors of CYP3A4 or CYP2C8 may increase the concentration of dabrafenib *[see Clinical Pharmacology (11.3)]*. Substitution of strong inhibitors of CYP3A4 or CYP2C8 is recommended during treatment with RAFINLAR. If concomitant use of strong inhibitors of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors.

7.2 Effects of RAFINLAR on Other Drugs

Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/CYP1A2 substrate) *[see Clinical Pharmacology (11.3)]*. Monitor international normalized ratio (INR) levels more frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib. Coadministration of RAFINLAR with other substrates of these enzymes, including dexamethasone or hormonal contraceptives, can result in decreased concentrations and loss of efficacy *[see Use in Specific Populations (8.1, 8.3)]*. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies and its mechanism of action *[see Clinical Pharmacology (11.1)]*, RAFINLAR can cause fetal harm when administered to a pregnant woman. There is insufficient data in pregnant women exposed to RAFINLAR to assess the risks. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended adult clinical dose of 150 mg twice daily *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a combined female fertility and embryo-fetal development study in rats conducted during the period of organogenesis, developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape at a dabrafenib dose of 300 mg/kg/day [approximately three times the human exposure at the recommended adult dose based on area under the curve (AUC)]. At doses of 20 mg/kg/day or greater (equivalent to the human exposure at the recommended adult dose based on AUC), rats demonstrated delays in skeletal development and reduced fetal body weight.

8.2 Lactation

Risk Summary

There are no data on the presence of dabrafenib in human milk, or the effects of dabrafenib on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with RAFINLAR and for 2 weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating RAFINLAR.

Contraception

Based on data from animal studies and its mechanism of action, RAFINLAR can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Females

Advise female patients of reproductive potential to use effective contraception during treatment with RAFINLAR and for 2 weeks after the last dose. Counsel patients to use a non-hormonal method of contraception since RAFINLAR can render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

To avoid potential drug exposure to pregnant partners and female partners of reproductive potential, advise male patients (including those who have had vasectomies) with female partners of reproductive potential to use condoms during treatment with RAFINLAR and for 2 weeks after the last dose.

Infertility

Females

Advise female patients of reproductive potential that RAFINLAR may impair fertility. A reduction in fertility was observed in female rats at dose exposures equivalent to the human exposure at the recommended adult dose. A reduction in the number of corpora lutea was noted in pregnant rats at dose exposures approximately three times the human exposure at the recommended adult dose *[see Nonclinical Toxicology (12.1)]*.

Males

Advise male patients of the potential risk for impaired spermatogenesis which may be irreversible. Effects on spermatogenesis have been observed in animals treated with dabrafenib at dose exposures up to three times the human exposure at the recommended adult dose *[see Nonclinical Toxicology (12.1)]*.

8.4 Pediatric Use

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

The safety and effectiveness of RAFINLAR in combination with trametinib have been established in 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. Use of RAFINLAR 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 Adverse Reactions (6.1), Clinical Pharmacology (11.3), Clinical Studies (13.5)]*.

The safety and effectiveness of RAFINLAR in combination with trametinib have not been established for these indications in pediatric patients < 6 years old.

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

Juvenile Animal Toxicity Data

In a repeat-dose toxicity study in juvenile rats, an increased incidence of kidney cysts and tubular deposits were noted at doses as low as 0.2 times the human exposure at the recommended adult dose based on AUC. Additionally, forestomach hyperplasia, decreased bone length, and early vaginal opening were noted at doses as low as 0.8 times the human exposure at the recommended adult dose based on AUC.

8.5 Geriatric Use

Of the 586 patients with various solid tumors who received single agent RAFINLAR, 22% were aged 65 years and older. Of the 187 patients with melanoma who received single-agent RAFINLAR in the BREAK-3 study, 21% were aged 65 years or older *[see Clinical Studies (13.1)]*. No overall differences in the effectiveness or safety of RAFINLAR were observed between geriatric patients as compared to younger adults in the BREAK-3 study.

Of the 994 patients with melanoma who received RAFINLAR plus trametinib in the COMBI-d, COMBI-v, and COMBI-AD studies *[see Clinical Studies (13.2, 13.3)]*, 21% were aged 65 years and older and 5% were aged 75 years and older. No overall differences in the effectiveness of RAFINLAR plus trametinib were observed in geriatric patients as compared to younger adults across these melanoma studies. The incidences of peripheral edema (26% vs. 12%) and anorexia (21% vs. 9%) were increased in geriatric patients as compared to younger adults in these studies.

Of the 171 patients with NSCLC who received RAFINLAR in Study BRF113928, there were insufficient numbers of geriatric patients to determine whether they respond differently from younger adults *[see Clinical Studies (13.4)]*.

8.6 Hepatic Impairment

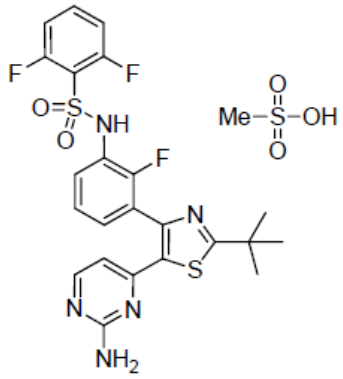
Dose adjustment is not recommended for patients with mild (bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or bilirubin > 1x to 1.5x ULN and any AST) hepatic impairment. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, patients with moderate (bilirubin > 1.5x to 3x ULN and any AST) to severe (bilirubin > 3x to 10x ULN and any AST) hepatic impairment may have increased exposure. An appropriate dosage has not been established for patients with moderate to severe hepatic impairment *[see Clinical Pharmacology (11.3)]*.

9 OVERDOSAGE

There is no information on overdosage of RAFINLAR. Since dabrafenib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with RAFINLAR.

10 DESCRIPTION

Dabrafenib mesylate is a kinase inhibitor. The chemical name for dabrafenib mesylate is N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt. It has the molecular formula $C_{23}H_{20}F_3N_5O_2S_2 \bullet CH_4O_3S$ and a molecular weight of 615.68 g/mol. Dabrafenib mesylate has the following chemical structure:



Dabrafenib mesylate is a white to slightly colored solid with three pK_as: 6.6, 2.2, and -1.5. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

RAFINLAR (dabrafenib) capsules for oral use are supplied as 50 mg and 75 mg capsules for oral administration. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg of dabrafenib free base. Each 75 mg capsule contains 88.88 mg dabrafenib mesylate equivalent to 75 mg of dabrafenib free base. The inactive ingredients of RAFINLAR capsules are colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose. Capsule shells contain hypromellose, red iron oxide (E172), and titanium dioxide (E171).

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC_{50} values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC_{50} values of 3.2 and 5.0 nM, respectively, and other kinases, such as SIK1, NEK11, and LIMK1 at higher concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth *[see Indications and Usage (1)]*. Dabrafenib inhibits cell growth of various BRAF V600 mutation-positive tumors in vitro and in vivo.

Dabrafenib and trametinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Use of dabrafenib and trametinib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation-positive tumor xenografts compared with either drug alone.

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 Indications and Usage (1.5)]*.

11.2 Pharmacodynamics

Cardiac Electrophysiology

The potential effect of RAFINLAR on QT interval was assessed in a dedicated multiple-dose study in 32 patients with BRAF V600 mutation-positive tumors. No large changes in the mean QT interval (i.e., > 20 ms) were detected with dabrafenib 300 mg administered twice daily (two times the recommended dosage).

In clinical trials, QTc (heart rate-corrected QT) prolongation to ≥ 500 ms occurred in 0.8% of 264 patients who received RAFINLAR with trametinib and in 1.5% of patients who received RAFINLAR as a single agent. The QTc was increased > 60 ms from baseline in 3.8% of patients who received RAFINLAR with trametinib and 3% of patients treated with RAFINLAR as a single agent.

11.3 Pharmacokinetics

Following administration of RAFINLAR capsules, dabrafenib C_{max} and AUC increased in a dose-proportional manner across the dose range of 12 mg (0.08 times the approved recommended adult dose) to 300 mg (2 times the approved recommended adult dose), but the increase was less than dose-proportional after steady state twice-daily dosing. After twice-daily dosing, the mean accumulation ratio was 0.7, and the intersubject variability (CV%) of AUC at steady-state was 38%.

Absorption

The median time to achieve peak plasma concentration (T_{max}) is 2 hours. Mean absolute bioavailability of RAFINLAR capsules is 95%.

Effect of Food

Following administration of RAFINLAR capsules, a high-fat meal (approximately 1000 calories, 58-75 grams fat, 58 grams carbohydrates, and 33 grams protein) decreased C_{max} by 51%, decreased AUC by 31%, and delayed median T_{max} by 3.6 hours as compared with the fasted state.

Distribution

Dabrafenib is 99.7% bound to human plasma proteins. The apparent volume of distribution (V_c/F) is 70.3 L.

Elimination

The mean terminal half-life is 8 hours. Hydroxy-dabrafenib terminal half-life (10 hours) parallels that of dabrafenib while the carboxy- and desmethyl-dabrafenib metabolites exhibit longer half-lives (21 to 22 hours). The apparent clearance of dabrafenib is 17 L/h after a single dose and 34 L/h after twice-daily dosing for 2 weeks.

Metabolism

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib. Hydroxy-dabrafenib is further oxidized via CYP3A4 to form carboxy-dabrafenib and subsequently excreted in bile and urine. Carboxy-dabrafenib is decarboxylated to form desmethyl-dabrafenib; desmethyl-dabrafenib may be reabsorbed from the gut. Desmethyl-dabrafenib is further metabolized by CYP3A4 to oxidative metabolites. Mean metabolite-to-parent AUC ratios following repeat-dose administration are 0.9, 11, and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on systemic exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib.

Excretion

Fecal excretion is the major route of elimination accounting for 71% of radioactive dose while urinary excretion accounted for 23% of total radioactivity as metabolites only.

Specific Populations

Age (18 to 93 years), sex, weight (36 to 170 kg), and renal impairment (eGFR 15 to 89 mL/min/1.73 m^2) have no clinically relevant effect on the pharmacokinetics of dabrafenib.

Pediatric Patients

The pharmacokinetics of dabrafenib in glioma and other solid tumors were evaluated in 243 patients aged 1 to < 18 years following a single dose or multiple doses. Pharmacokinetic parameters in patients aged 1 to < 18 years

are within range of values previously observed in adults given the same dose based on weight. Weight (6 to 156 kg) had a statistically significant effect on dabrafenib oral clearance in this population.

Patients with Hepatic Impairment

Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1x to 1.5x ULN and any AST) has no effect on systemic exposure to dabrafenib and its metabolites. No data are available in patients with moderate (bilirubin > 1.5x to 3x ULN and any AST) or severe (bilirubin > 3x to 10x ULN and any AST) hepatic impairment.

Drug Interaction Studies

Effect of Trametinib on Dabrafenib: Coadministration of RAFINLAR 75 mg twice daily with trametinib 2 mg daily resulted in a 23% increase in AUC of dabrafenib, a 33% increase in AUC of desmethyl-dabrafenib, and no change in AUC of hydroxy-dabrafenib as compared with administration of dabrafenib.

Effect of Strong Inhibitors of CYP3A4 or CYP2C8 on Dabrafenib: Coadministration of RAFINLAR 75 mg twice daily and ketoconazole (a strong CYP3A4 inhibitor) for 4 days increased dabrafenib AUC by 71%, hydroxy-dabrafenib AUC by 82%, and desmethyl-dabrafenib AUC by 68%.

Coadministration of RAFINLAR 75 mg twice daily and gemfibrozil (a strong CYP2C8 inhibitor) for 4 days increased dabrafenib AUC by 47%, with no change in the AUC of dabrafenib metabolites.

Effect of Strong Inducers of CYP3A4 or Moderate Inducers of CYP2C8 on Dabrafenib: Coadministration of RAFINLAR 150 mg twice daily and rifampin (a strong CYP3A4 and moderate CYP2C8 inducer) for 10 days decreased dabrafenib AUC by 34% and desmethyl-dabrafenib AUC by 30%, and had no effect on hydroxy-dabrafenib AUC.

Effect of Acid Reducing Agents on Dabrafenib: Coadministration of RAFINLAR 150 mg twice daily and rabeprazole for 4 days did not result in clinically relevant changes in exposures to dabrafenib and its metabolites.

Effect of Dabrafenib on CYP Substrates: Coadministration of RAFINLAR 150 mg twice daily for 15 days and a single dose of midazolam (a CYP3A4 substrate) decreased midazolam AUC by 65%. Coadministration of RAFINLAR 150 mg twice daily for 15 days and a single dose of warfarin decreased the AUC of S-warfarin (a CYP2C9 substrate) by 37% and the AUC of R-warfarin (CYP3A4/CYP1A2 substrate) by 33%.

In vitro data demonstrate that dabrafenib is an inducer of CYP3A4 and CYP2B6 via activation of the pregnane X receptor (PXR) and constitutive androstane receptor (CAR) nuclear receptors. Dabrafenib may also induce CYP2C enzymes via the same mechanism.

Effect of Transporters on Dabrafenib: Dabrafenib and its metabolites, hydroxyl-dabrafenib and desmethyl-dabrafenib, are substrates of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) but are not substrates of organic cation transporter (OCT1) or organic anion transporting polypeptide (OATP1A2, OATP1B1, OATP1B3, OATP2B1) in vitro.

Effect of Dabrafenib on Transporters: Coadministration of RAFINLAR 150 mg twice daily with a single dose of rosuvastatin (a sensitive OATP1B1 and OATP1B3 substrate) increased rosuvastatin C_{max} by 2.6-fold but did not change its AUC.

Dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib, are inhibitors of organic anion transporter (OAT1 and OAT3) in vitro. Dabrafenib and desmethyl-dabrafenib are inhibitors of OCT2 and BCRP in vitro.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with dabrafenib have not been conducted. RAFINLAR increased the risk of cuSCCs in patients in clinical trials.

Dabrafenib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay and was not clastogenic in an in vivo rat bone marrow micronucleus test.

In a combined female fertility and embryo-fetal development study in rats, a reduction in fertility was noted at doses greater than or equal to 20 mg/kg/day (equivalent to the human exposure at the recommended adult dose based on AUC). A reduction in the number of ovarian corpora lutea was noted in pregnant females at 300 mg/kg/day (which is approximately three times the human exposure at the recommended adult dose 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 at doses equivalent to and three times the human exposure at the recommended adult dose based on AUC, respectively.

12.2 Animal Toxicology and/or Pharmacology

Adverse cardiovascular effects were noted in dogs at dabrafenib doses of 50 mg/kg/day (approximately five times the human exposure at the recommended adult dose based on AUC) or greater, when administered for up to 4 weeks. Adverse effects consisted of coronary arterial degeneration/necrosis and hemorrhage, as well as cardiac atrioventricular valve hypertrophy/hemorrhage.

13 CLINICAL STUDIES

13.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – RAFINLAR as a Single Agent

BREAK-3 Study

The safety and efficacy of RAFINLAR as a single agent were evaluated in an international, multi-center, randomized (3:1), open-label, active-controlled trial (the BREAK-3 study; NCT01227889) conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. Patients were randomized to receive RAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n = 63). Randomization was stratified by disease stage at baseline [unresectable Stage III (regional nodal or in-transit metastases), M1a (distant skin, subcutaneous, or nodal metastases), or M1b (lung metastases) versus M1c melanoma (all other visceral metastases or elevated serum LDH)]. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. In addition, an independent radiology review committee (IRRC) assessed the following efficacy outcome measures in pre-specified supportive analyses: PFS, confirmed overall response rate (ORR), and duration of response (DoR).

The median age of patients in the BREAK-3 study was 52 years. The majority of the trial population was male (60%), White (99%), had an ECOG performance status of 0 (67%), had M1c disease (66%), and had normal LDH (62%). All patients had tumor tissue with mutations in BRAF V600E as determined by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were tested.

The median durations of follow-up prior to initiation of alternative treatment in patients randomized to receive RAFINLAR was 5.1 months and in the dacarbazine arm was 3.5 months. Twenty-eight (44%) patients crossed over from the dacarbazine arm at the time of disease progression to receive RAFINLAR.

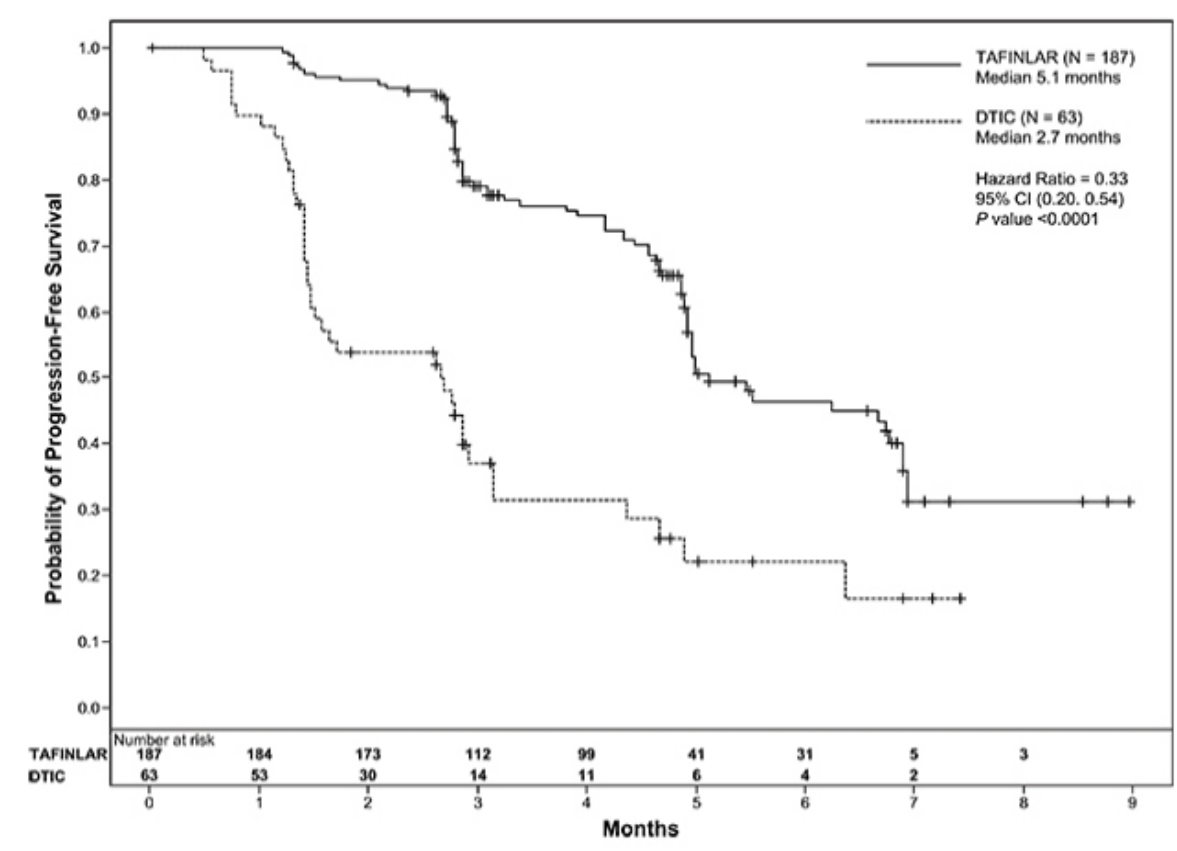
The BREAK-3 study demonstrated a statistically significant increase in PFS in the patients treated with RAFINLAR. Table 16 and Figure 1 summarize the PFS results.

Table 16. Investigator-Assessed Progression-Free Survival and Confirmed Overall Response Results in the BREAK-3 Study

Investigator-Assessed Endpoints	**RAFINLAR N = 187**	**Dacarbazine N = 63**
Progression-Free Survival		
Number of events (%)	78 (42%)	41 (65%)
Progressive disease	76	41
Death	2	0
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR[a] (95% CI)	0.33 (0.20, 0.54)	
P value[b]	< 0.0001	
Confirmed Tumor Responses		
Overall response rate (95% CI)	52% (44%, 59%)	17% (9%, 29%)
Complete response, n (%)	6 (3%)	0
Partial response, n (%)	91 (48%)	11 (17%)
Duration of response		
Median DoR, months (95% CI)	5.6 (5.4, NR)	NR (5.0, NR)

Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; NR, not reached.
[a] Pike estimator, stratified by disease state.
[b] Stratified log-rank test.

Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival in the BREAK-3 Study



In supportive analyses based on IRRC assessment and in an exploratory subgroup analysis of patients with retrospectively confirmed V600E mutation-positive melanoma, the PFS results were consistent with those of the primary efficacy analysis.

BREAK-MB Study

The activity of RAFINLAR for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in a single-arm, open-label, two-cohort multi-center trial (the BREAK-MB study; NCT01266967). All patients received RAFINLAR 150 mg twice daily. Patients in Cohort A (n = 74) had received no prior local therapy for brain metastases, while patients in Cohort B (n = 65) had received at least one local therapy for brain metastases, including, but not limited to, surgical resection, whole brain radiotherapy, or stereotactic radiosurgery, such as gamma knife, linear-accelerated-based radiosurgery, or charged particles. In addition, patients in Cohort B were required to have evidence of disease progression in a previously treated lesion or an untreated lesion. Additional eligibility criteria were at least one measurable lesion of 0.5 cm or greater in largest diameter on contrast-enhanced MRI, stable or decreasing corticosteroid dose, and no more than two prior systemic regimens for treatment of metastatic disease. The major efficacy outcome measure was estimation of the overall intracranial response rate (OIRR) in each cohort.

The median age of patients in Cohort A was 50 years, 72% were male, 100% were White, 59% had a pre-treatment ECOG performance status of 0, and 57% had elevated LDH at baseline. The median age of patients in Cohort B was 51 years, 63% were male, 98% were White, 66% had a pre-treatment ECOG performance status of 0, and 54% had elevated LDH at baseline. The intracranial response rate as determined by an independent radiology review committee, masked to investigator response assessments, was 18% (95% CI: 10%, 28%) in Cohort A and 18% (95% CI: 10%, 30%) in Cohort B. The median duration of intracranial response was 4.6 months in both cohorts.

13.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma – RAFINLAR With Trametinib

COMBI-d Study and COMBI-v Study

The safety and efficacy of RAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01584648) and one open-label trial (the COMBI-v study; NCT01597908).

The COMBI-d study compared RAFINLAR plus trametinib to RAFINLAR plus placebo as first-line therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive RAFINLAR 150 mg twice daily plus trametinib 2 mg once daily or RAFINLAR 150 mg twice daily plus matching placebo. Randomization was stratified by LDH level (> ULN vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR).

The COMBI-v study compared RAFINLAR and trametinib to vemurafenib as first-line treatment therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive RAFINLAR 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily. Randomization was stratified by lactate dehydrogenase (LDH) level (> ULN vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS and ORR as assessed by investigator per RECIST v1.1.

In the COMBI-d study, 423 patients were randomized to RAFINLAR plus trametinib (n = 211) or RAFINLAR plus placebo (n = 212). The median age was 56 years (range: 22 to 89), 53% were male, > 99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIC, 66% had M1c disease, 65% had normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations

as determined by centralized testing with the FDA-approved companion diagnostic test; 85% with BRAF V600E mutation positive melanoma and 15% with BRAF V600K mutation positive melanoma.

In the COMBI-v study, 704 patients were randomized to RAFINLAR plus trametinib (n = 352) or single-agent vemurafenib (n = 352). The median age was 55 years (range: 18 to 91), 96% were White, 55% were male, 6% had Stage IIIC, 61% had M1c disease, 67% had normal LDH, 70% had ECOG performance status of 0, 89% had BRAF V600E mutation-positive melanoma, and one patient had a history of brain metastases.

The COMBI-d and COMBI-v studies demonstrated statistically significant improvements in OS and PFS. Table 17 and Figures 2 and 3 summarize the efficacy results.

Table 17. Efficacy Results in Patients with BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma[a]

Endpoint	COMBI-d Study		COMBI-v Study	
	RAFINLAR plus Trametinib N = 211	**RAFINLAR plus Placebo N = 212**	**RAFINLAR plus Trametinib N = 352**	**Vemurafenib N = 352**
Overall Survival				
Number of deaths (%)	99 (47%)	123 (58%)	100 (28%)	122 (35%)
Median, months (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.1)	NR (18.3, NR)	17.2 (16.4, NR)
HR (95% CI)	0.71 (0.55, 0.92)		0.69 (0.53, 0.89)	
P value (log-rank test)	0.01		0.005[a]	
Progression-Free Survival[b]				
Number of events (%)	102 (48%)	109 (51%)	166 (47%)	217 (62%)
Median, months (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)
HR (95% CI)	0.75 (0.57, 0.99)		0.56 (0.46, 0.69)	
P value (log-rank test)	0.035		< 0.001	
Overall Response Rate[b]				
ORR (95% CI)	66% (60%, 73%)	51% (44%, 58%)	64% (59%, 69%)	51% (46%, 56%)
P value	< 0.001		< 0.001	
Complete response	10%	8%	13%	8%
Partial response	56%	42%	51%	43%
Median DoR, months (95% CI)	9.2 (7.4, NR)	10.2 (7.5, NR)	13.8 (11.0, NR)	7.5 (7.3, 9.3)

Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; NR, not reached; ORR, overall response rate.
[a] *P*-value is comparing with the allocated alpha of 0.021 for the interim analysis based on 77% information.
[b] PFS and ORR were assessed by investigator.

Figure 2. Kaplan-Meier Curves for Overall Survival in the COMBI-d Study

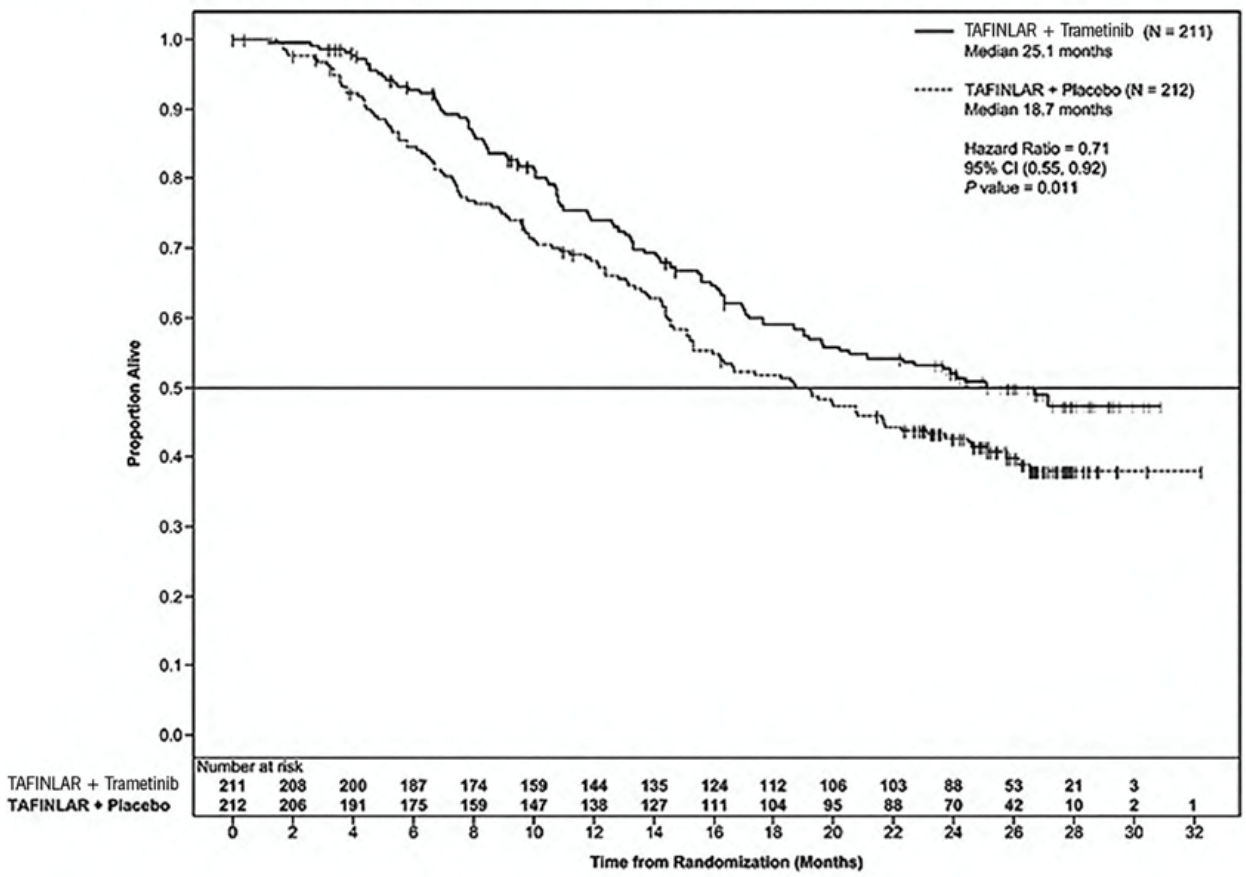
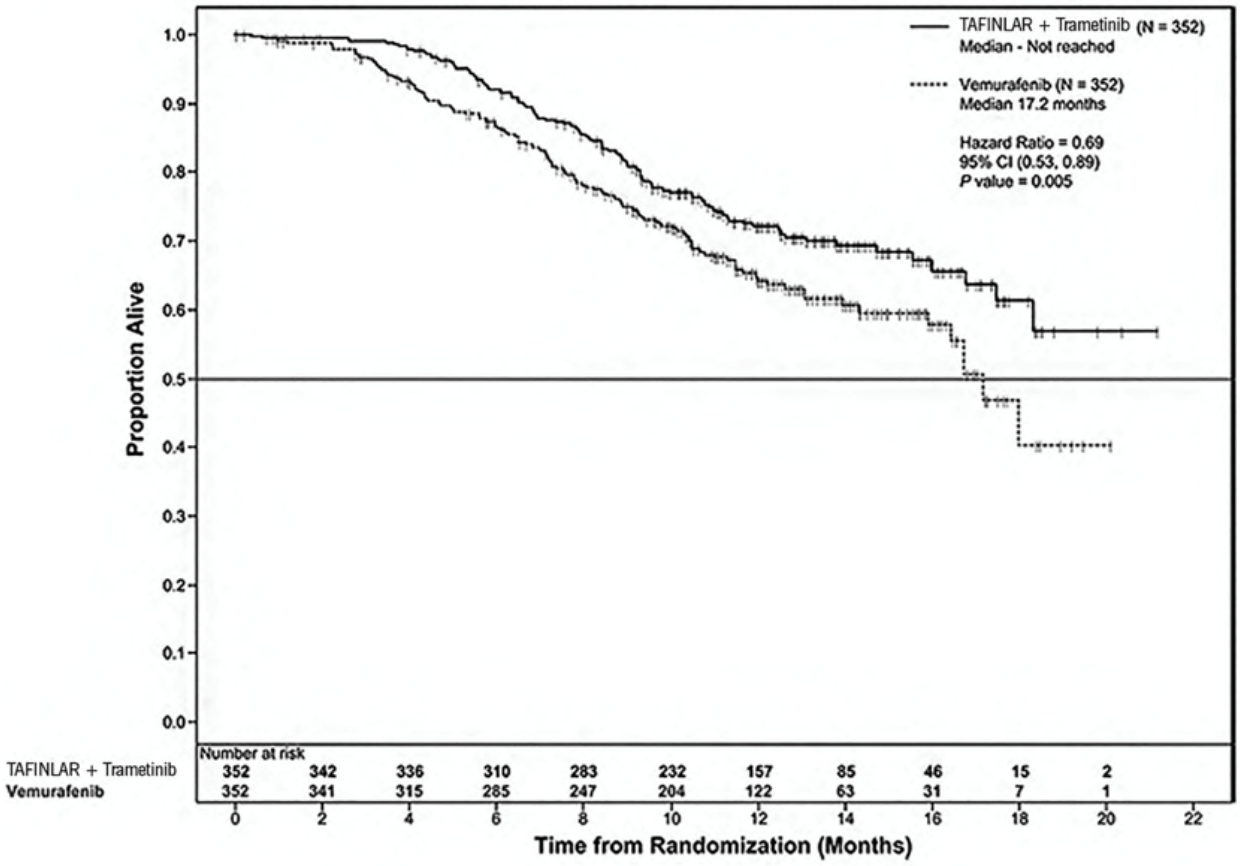


Figure 3. Kaplan-Meier Curves for Overall Survival in the COMBI-v Study



COMBI-MB Study

The activity of RAFINLAR with trametinib for the treatment of BRAF V600E or V600K mutation-positive melanoma, metastatic to the brain, was evaluated in a non-randomized, open-label, multi-center, multi-cohort trial (the COMBI-MB study; NCT02039947). Eligible patients were required to have at least one measurable intracranial lesion and to have no leptomeningeal disease, parenchymal brain metastasis greater than 4 cm in diameter, ocular melanoma, or primary mucosal melanoma. Patients received RAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was intracranial response rate, defined as the percentage of patients with a confirmed intracranial response per RECIST v1.1, modified to allow up to five intracranial target lesions at least 5 mm in diameter, as assessed by independent review.

The COMBI-MB study enrolled 121 patients with a BRAF V600E (85%) or V600K (15%) mutation. The median age was 54 years (range: 23 to 84), 58% were male, 100% were White, 8% were from the United States, 65% had normal LDH at baseline, and 97% had an ECOG performance status of 0 or 1. Intracranial metastases were asymptomatic in 87% and symptomatic in 13% of patients, 22% received prior local therapy for brain metastases, and 87% also had extracranial metastases.

The intracranial response rate was 50% (95% CI: 41, 60), with a complete response rate of 4.1% and a partial response rate of 46%. The median duration of intracranial response was 6.4 months (range: 1 to 31). Of the patients with an intracranial response, 9% had stable or progressive disease as their best overall response.

13.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

The efficacy of RAFINLAR administered with trametinib was evaluated in an international, multi-center, randomized, double-blind, placebo-controlled trial (COMBI AD; NCT01682083) that enrolled patients with Stage III melanoma with BRAF V600E or V600K mutations and pathologic involvement of regional lymph node(s). Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable in-transit metastases, distant metastatic disease, or prior systemic anti-cancer treatment, including radiotherapy. Patients were randomized (1:1) to receive RAFINLAR 150 mg twice daily and trametinib 2 mg once daily or two placebos for up to 1 year. Randomization was stratified by BRAF mutation status (V600E or V600K). The major efficacy outcome measure was relapse-free survival (RFS), defined as the time from randomization to disease recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first as assessed by the investigator. Patients underwent imaging for tumor recurrence every 3 months for the first two years and every 6 months thereafter.

In COMBI-AD, a total of 870 patients were randomized: 438 to RAFINLAR in combination with trametinib and 432 to placebo. Median age was 51 years (range: 18 to 89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIA (18%), Stage IIIB (41%), Stage IIIC (40%), stage unknown (1%); BRAF V600E mutation (91%), BRAF V600K mutation (9%); macroscopic lymph nodes (65%); and tumor ulceration (41%).

The median duration of follow-up at the time of the primary analysis was 2.8 years.

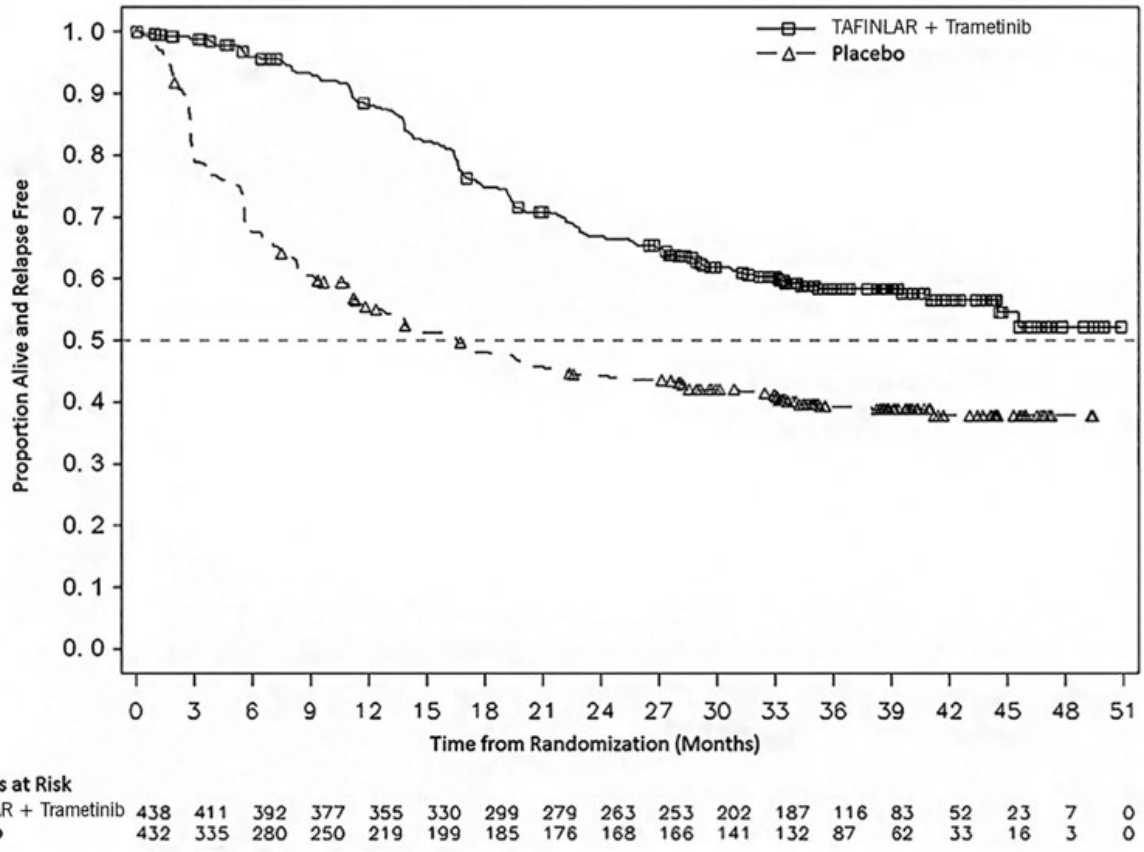
COMBI-AD showed a statistically significant improvement in RFS in patients randomized to RAFINLAR in combination with trametinib compared to those randomized to placebo. Efficacy results are presented in Table 18 and Figure 4.

Table 18. Efficacy Results in COMBI-AD in the Adjuvant Treatment of Melanoma

Investigator-Assessed Endpoint	RAFINLAR plus Trametinib N = 438	Placebo N = 432
Relapse-Free Survival		
Number of events (%)	166 (38)	248 (57)
Median, months (95% CI)	NE (44.5, NE)	16.6 (12.7, 22.1)
HR (95% CI)[a]	0.47 (0.39, 0.58)	
P value[b]	< 0.0001	

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable.
[a] Pike estimator obtained from the stratified log-rank test.
[b] Log-rank test stratified by disease stage (IIIA vs. IIIB vs. IIIC) and BRAF V600 mutation type (V600E vs. V600K).

Figure 4. Kaplan-Meier Curves for Investigator-Assessed Relapse-Free Survival in COMBI-AD in the Adjuvant Treatment of Melanoma



The median duration of follow-up at the time of the final overall survival analysis was 8.0 years. The estimated hazard ratio for overall survival was 0.80 (95% CI: 0.62, 1.01; p = 0.063) with 125 events (29%) in the combination arm and 136 events (31%) in the placebo arm. Median overall survival was not estimable in both arms.

13.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety and efficacy of RAFINLAR alone or administered with trametinib were evaluated in a multi-center, three-cohort, non-randomized, activity-estimating, open-label trial (Study BRF113928, NCT01336634). Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK-inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). Patients enrolled in Cohorts A and B were required to have received at least one previous platinum-based chemotherapy regimen for NSCLC with demonstrated disease progression but no more than three prior systemic regimens. Patients enrolled in Cohort C could not have received prior systemic therapy for metastatic NSCLC. Patients in Cohort A received RAFINLAR 150 mg twice daily. Patients in Cohorts B and C received RAFINLAR 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).

There were a total of 171 patients enrolled which included 78 patients enrolled in Cohort A, 57 patients enrolled in Cohort B, and 36 patients enrolled in Cohort C. The characteristics of the study population were: a median age of 66 years, 48% male; 81% White, 14% Asian, 3% Black, and 2% Hispanic; 60% former smokers, 32% never smokers, and 8% current smokers; 27% had ECOG performance status (PS) of 0, 63% had ECOG PS of 1, and 11% had ECOG PS of 2; 99% had metastatic disease of which 6% had brain metastasis at baseline and 14% had

liver metastasis at baseline; 11% had systemic anti-cancer therapy in the adjuvant setting and 58% of the 135 previously treated patients had only one line of prior systemic therapy for metastatic disease; 98% had non-squamous histology.

Efficacy results are summarized in Table 19.

Table 19. Efficacy Results Based on Independent Review in Study BRF113928

Treatment	**RAFINLAR**	**RAFINLAR + Trametinib**	
Population	**Previously Treated N = 78**	**Previously Treated N = 57**	**Treatment Naïve N = 36**
Overall Response Rate[a]			
ORR (95% CI)	27% (18%, 38%)	61% (48%, 74%)	61% (44%, 77%)
Complete response	1%	5%	8%
Partial response	26%	56%	53%
Duration of Response[a]	n = 21	n = 35	n = 22
Median DoR, months (95% CI)	18.0 (4.2, 40.1)	9.0 (5.8, 26.2)	15.2 (7.8, 23.5)

Abbreviations: CI, confidence interval; DoR, duration of response; ORR, overall response rate.
[a] Represents final analysis results (cutoff date of 24 Feb 2021) for the primary analysis responder cohorts.

In a subgroup analysis of patients with retrospectively, centrally confirmed BRAF V600E mutation-positive NSCLC, the ORR results were similar to those presented in Table 18.

13.5 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

The safety and efficacy of RAFINLAR 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 *[see Clinical Studies (13.2)]*, and BRF113928 *[see Clinical Studies (13.4)]*. In adult studies, patients received RAFINLAR 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 *[see Clinical Studies (14.5)]*. 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 17, 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 20.

Table 20. Efficacy Results Based on Independent Review in Studies BRF117019 and NCI-MATCH Arm H

Tumor Type[a]	N	Objective Response Rate		Duration of Response
		%	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)
[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 RAFINLAR in combination with trametinib in patients with a BRAF V600E mutation. Part D was a cohort expansion phase of RAFINLAR 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 RAFINLAR 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 to 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 single-arm 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 RAFINLAR 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.

14 HOW SUPPLIED/STORAGE AND HANDLING

RAFINLAR Capsules:

50 mg capsules: Dark red capsule imprinted with ‘GS TEW’ and ‘50 mg’ available in bottles of 120 with child-resistant closures. Each bottle contains a silica gel desiccant.

75 mg capsules: Dark pink capsule imprinted with ‘GS LHF’ and ‘75 mg’ available in bottles of 120 with child-resistant closures. Each bottle contains a silica gel desiccant.

Do not store above 30°C.

Store in the original container.

Do not remove bottle with the desiccant

Storage information might differ in some countries.

Rafinlar must be kept out of the reach and sight of children.

15 PRODUCT REGISTRATION HOLDER

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