For patients with *MET*ex14 and *BRAF* V600E in mNSCLC,

TREATMENT AND TESTING GUIDELINES

MET ex14

TABRECTA® (capmatinib) tablets 150 mg · 200 mg

BRAF V600E

Tafinlar® (dabrafenib) 50 mg, 75 mg capsules + Mekinist® (trametinib) 0.5 mg, 2 mg tablets

BRAF, v-raf murine sarcoma viral oncogene homolog B1; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping; mNSCLC, metastatic non-small cell lung cancer.

Indication

TABRECTA® (capmatinib) tablets is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information

Interstitial Lung Disease (ILD)/Pneumonitis. ILD/pneumonitis, which can be fatal, occurred in patients treated with TABRECTA. ILD/pneumonitis occurred in 4.5% of patients treated with TABRECTA in the GEOMETRY mono-1 study, with 1.8% of patients experiencing grade 3 ILD/pneumonitis and 1 patient experiencing death (0.3%). Eight patients (2.4%) discontinued TABRECTA due to ILD/pneumonitis.

Please see additional Important Safety Information throughout and on page 6.

Please click here for full Prescribing Information for TABRECTA.

Indication

TAFINLAR® (dabrafenib) capsules, in combination with MEKINIST® (trametinib) tablets, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with *BRAF* V600E mutation as detected by an FDA-approved test.

Limitation of Use: TAFINLAR is not indicated for the treatment of patients with wild-type *BRAF* NSCLC.

Important Safety Information

New Primary Malignancies.

Cutaneous Malignancies

Across clinical trials of TAFINLAR administered with MEKINIST (“the combination”), the incidence of cutaneous squamous cell carcinomas (cuSCCs), including keratoacanthomas, occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and <1% of patients, respectively.

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

Please see additional Important Safety Information throughout and on pages 7-8.

Please click here for full Prescribing Information for TAFINLAR and click here for full Prescribing Information for MEKINIST.

TABRECTA: the first FDA-approved treatment for *MET*ex14 in mNSCLC

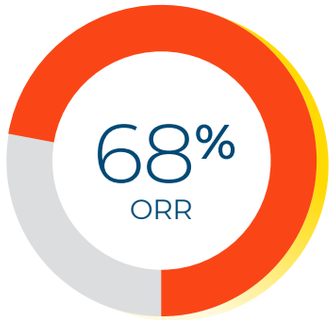
*MET*ex14 is an oncogenic driver in mNSCLC[1]

- In the United States, ~4,000-5,000 patients have mutations leading to *MET*ex14 in mNSCLC[2,3]*

Start strong with TABRECTA

Delivered a nearly 70% ORR in **treatment-naive patients** (n=28)[4,5]

POWERFUL RESPONSES



95% CI, 48-84
- CR, 1 (4%)
- PR, 18 (64%)

SUSTAINED RESPONSES

95% CI, 5.5-25.3
n=19

Durable responses that lasted more than 1 year

Percentage of patients with responses at ≥12 months was 47%

Efficacious and sustained responses in previously treated patients (n=69)[4,5]

- **41%** achieved an overall response (95% CI, 29-53; CR, 0 [0%] + PR, 28 [41%])
- **9.7-month mDOR** (95% CI, 5.5-13.0; n=28)
  - Percentage of patients with responses at ≥12 months was 32%

Highlights of Important Safety Information

- TABRECTA® (capmatinib) tablets has Warnings and Precautions for interstitial lung disease (ILD/pneumonitis), hepatotoxicity, risk of photosensitivity, and embryo-fetal toxicity
- The most common adverse reactions (all grades, incidence ≥20%) were peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite

Trial design[4,5]

TABRECTA was studied in GEOMETRY mono-1, a multicenter, nonrandomized, open-label, multicohort study of patients with EGFR wild-type, ALK-negative, metastatic NSCLC. Patients with *MET*ex14 (n=97) comprised 2 cohorts: treatment naive (n=28) and treated previously with 1 or 2 prior lines of therapy (n=69). Patients received TABRECTA 400 mg twice daily. Treatment was continued until disease progression, drug intolerance, or investigator-led discontinuation. Evaluable patients were defined as those who completed at least 6 cycles of treatment (18 weeks) or discontinued treatment earlier. The major efficacy outcome was overall response rate, and duration of response was an additional efficacy outcome as determined by a blinded independent review committee (BIRC) according to RECIST 1.1.

ALK, anaplastic lymphoma kinase; CR, complete response; EGFR, epidermal growth factor receptor; mDOR, median duration of response; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

*This calculation is based on a 3% prevalence rate and mNSCLC-specific incidence and recurrence data from Kantar Health.

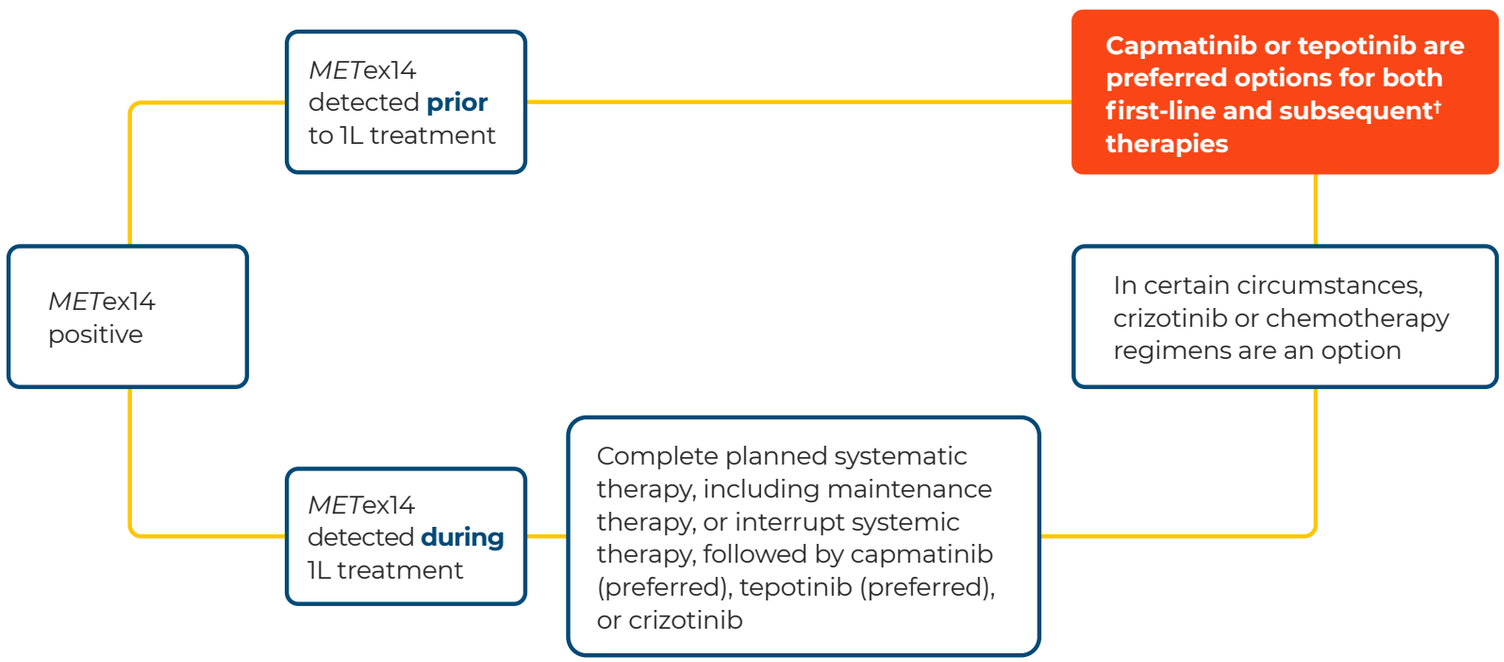
Important Safety Information

Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever). Immediately withhold TABRECTA in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified.

Please see additional Important Safety Information throughout and on page 6.
Please click here for full Prescribing Information for TABRECTA.

TABRECTA® (capmatinib) tablets 150 mg · 200 mg

Capmatinib (TABRECTA® tablets) is a preferred option of the National Comprehensive Cancer Network® (NCCN®) for patients with *MET*ex14-positive mNSCLC[4,6]*



*See the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for detailed recommendations, including other options.
†If *MET*ex14-mutation inhibitors were not previously given.

Note: All recommendations are category 2A unless otherwise indicated.
NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Recommendations may not reflect the FDA-approved use for all therapies.

Important Safety Information (continued)

Hepatotoxicity. Hepatotoxicity occurred in patients treated with TABRECTA. Increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in 13% of patients treated with TABRECTA in GEOMETRY mono-1. Grade 3 or 4 increased ALT/AST occurred in 6% of patients. Three patients (0.9%) discontinued TABRECTA due to increased ALT/AST.

Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of TABRECTA, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Based on the severity of the adverse reaction, withhold, reduce dose, or permanently discontinue TABRECTA.

Please see additional Important Safety Information throughout and on page 6.
Please click here for full Prescribing Information for TABRECTA.

TABRECTA® (capmatinib) tablets 150 mg · 200 mg

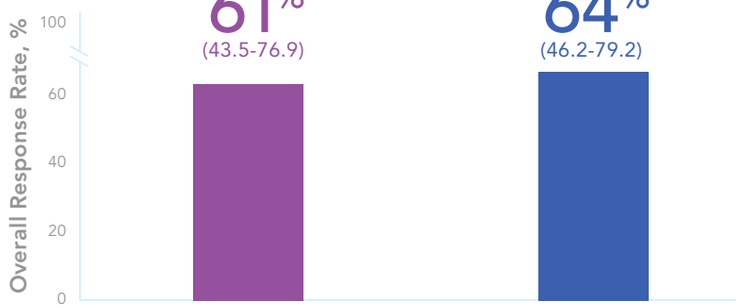
TAFINLAR + MEKINIST: THE FIRST AND ONLY TARGETED THERAPY PROVEN TO TREAT PATIENTS WITH BRAF V600E METASTATIC NSCLC[7,8]

BRAF V600E is an oncogenic driver in metastatic NSCLC[9]

- In the United States, approximately 2% of patients with metastatic NSCLC may have *BRAF* V600E mutation, amounting to approximately 2000-3000 patients per year[3,10,11]*

Proven response rates for TAFINLAR® (dabrafenib) capsules + MEKINIST® (trametinib) tablets in first-line patients (n=36)

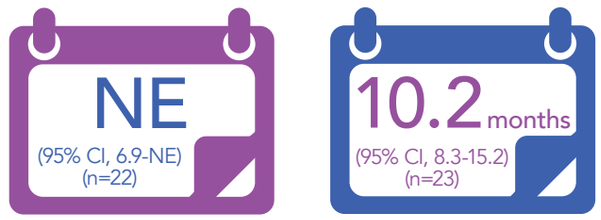
ORR



As assessed by IRC
CR, 3%; PR, 58%
August 2016 Data Cutoff[12-14]

As assessed by the investigator
CR, 6%; PR, 58%
June 2019 Data Cutoff (Interim Analysis†)[15]

MEDIAN DOR



As assessed by IRC
Responders with DOR
≥6 months: 59%
August 2016 Data Cutoff[12-14]

As assessed by the investigator
June 2019 Data Cutoff (Interim Analysis†)[15]

Previously treated patients (n=57)[12,13]

Based on independent review (August 2016 data cutoff):

- **ORR: 63%** (95% CI, 49-76) (CR, 4%; PR, 60%)
- **mDOR: 12.6 months** (95% CI, 5.8-NE) (n=36)
  – Responders with DOR ≥6 months: 64%

Highlights of Important Safety Information

- TAFINLAR, in combination with MEKINIST, can cause serious side effects including new primary malignancies, tumor promotion in *BRAF* wild-type tumors, hemorrhage, colitis and gastrointestinal perforation, venous thromboembolism, cardiomyopathy, ocular toxicities, interstitial lung disease, serious febrile reactions, serious skin toxicity, hyperglycemia, hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency, and embryo-fetal toxicity
- In the NSCLC clinical trial, the most commonly occurring adverse reactions (≥20%) in patients receiving the combination were pyrexia (55%), fatigue (51%), nausea (45%), vomiting (33%), diarrhea (32%), dry skin (31%), decreased appetite (29%), edema (28%), rash (28%), chills (23%), hemorrhage (23%), cough (22%), and dyspnea (20%)

Trial design[12-14]

TAFINLAR, in combination with MEKINIST, was studied in BRF113928, a multicenter, nonrandomized, open-label, activity-estimating, multicohort study of patients with confirmed *BRAF* V600E metastatic NSCLC, who had 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 Cohort B (n=57) were treated previously with 1 to 3 prior lines of therapy, while patients enrolled in Cohort C (n=36) were treatment naive. Patients in Cohorts B and C received TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily. The major efficacy outcomes were ORR, per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) as assessed by an IRC, and DOR.

ALK, anaplastic lymphoma kinase; CR, complete response; DOR, duration of response; *EGFR*, epidermal growth factor receptor; IRC, independent review committee; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.
*This calculation is based on a 2% prevalence rate and metastatic NSCLC–specific incidence and recurrence data from Kantar Health.
†At the time of the June 2019 data cutoff, 7 of 36 patients in the first-line population (Cohort C) and 4 of 57 patients in the second-line plus population (Cohort B) were still in follow-up. Results are subject to change pending longer trial follow-up.

Important Safety Information (continued)

Noncutaneous Malignancies

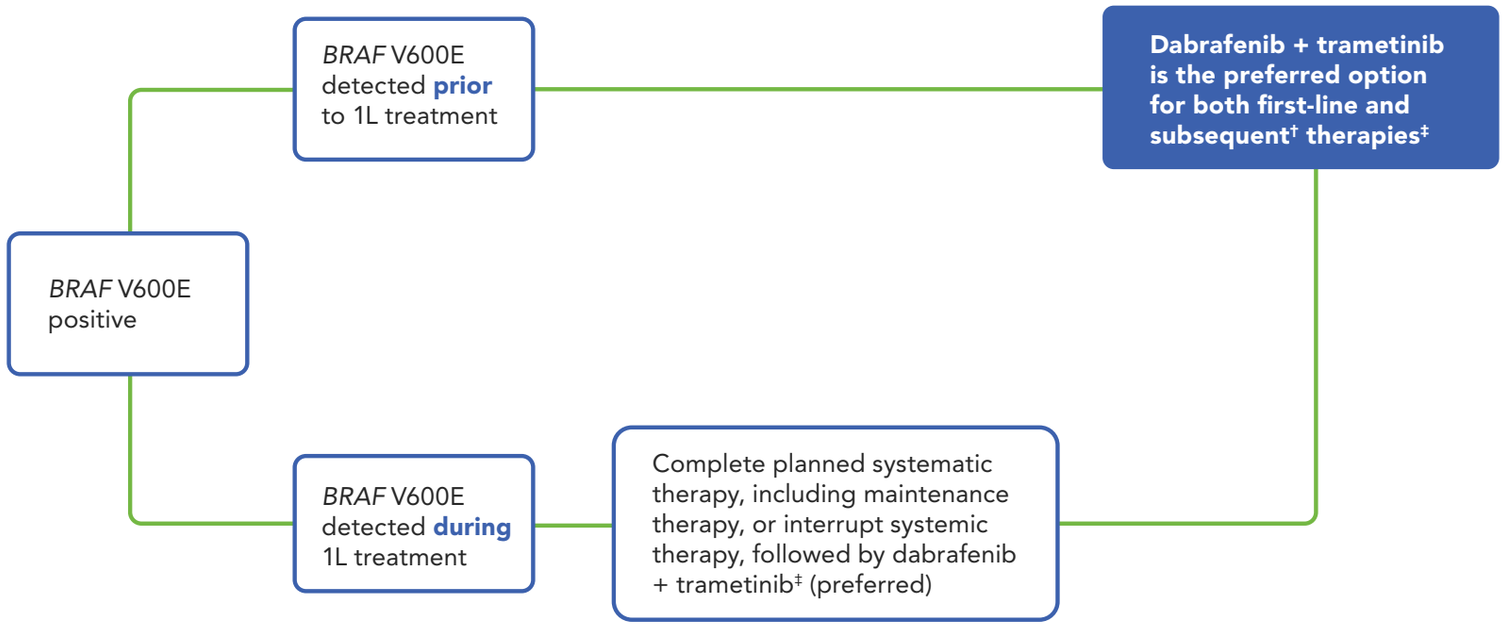
Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of monomeric G protein (RAS) through mutation or other mechanisms. Across clinical trials of TAFINLAR monotherapy and the combination, noncutaneous malignancies occurred in 1% of patients.

Monitor patients receiving the combination for signs or symptoms of noncutaneous malignancies. Permanently discontinue TAFINLAR for RAS-mutation–positive noncutaneous malignancies. No dose modification is required for MEKINIST in patients who develop noncutaneous malignancies.

Please see additional Important Safety Information throughout and on pages 7-8.
Please click here for full Prescribing Information for TAFINLAR and click here for full Prescribing Information for MEKINIST.

Tafinlar® (dabrafenib) 50 mg, 75 mg capsules + Mekinist® (trametinib) 0.5 mg, 2 mg tablets

Dabrafenib + trametinib (TAFINLAR® capsules + MEKINIST® tablets) IS THE PREFERRED OPTION OF THE NCCN FOR PATIENTS WITH BRAF *V600E-POSITIVE METASTATIC NSCLC*[6,12,13]*



*See the NCCN Guidelines for detailed recommendations, including other options.
†If *BRAF* V600E-mutation inhibitors were not previously given.
‡Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated.

Note: All recommendations are category 2A unless otherwise indicated.
NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TAFINLAR monotherapy is not indicated for the treatment of *BRAF* V600E in mNSCLC.
Recommendations may not reflect the FDA-approved use for all therapies.

Important Safety Information (continued)

Tumor Promotion in *BRAF* Wild-type Tumors. In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (MAPK) signaling and increased cell proliferation in *BRAF* wild-type cells that are exposed to *BRAF* inhibitors. Confirm evidence of *BRAF* V600E or V600K mutation status prior to initiation of therapy.

Hemorrhage. Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with the combination. Fatal cases have been reported.

Please see additional Important Safety Information throughout and on pages 7-8.
Please click here for full Prescribing Information for TAFINLAR and click here for full Prescribing Information for MEKINIST.

Tafinlar® (dabrafenib) 50 mg, 75 mg capsules + Mekinist® (trametinib) 0.5 mg, 2 mg tablets

Important Safety Information for TABRECTA® (capmatinib) tablets

Interstitial Lung Disease (ILD)/Pneumonitis. ILD/pneumonitis, which can be fatal, occurred in patients treated with TABRECTA. ILD/pneumonitis occurred in 4.5% of patients treated with TABRECTA in the GEOMETRY mono-1 study, with 1.8% of patients experiencing grade 3 ILD/pneumonitis and 1 patient experiencing death (0.3%). Eight patients (2.4%) discontinued TABRECTA due to ILD/pneumonitis.

Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever). Immediately withhold TABRECTA in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified.

Hepatotoxicity. Hepatotoxicity occurred in patients treated with TABRECTA. Increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in 13% of patients treated with TABRECTA in GEOMETRY mono-1. Grade 3 or 4 increased ALT/AST occurred in 6% of patients. Three patients (0.9%) discontinued TABRECTA due to increased ALT/AST.

Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of TABRECTA, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Based on the severity of the adverse reaction, withhold, reduce dose, or permanently discontinue TABRECTA.

Risk of Photosensitivity. Based on findings from animal studies, there is a potential risk of photosensitivity reactions with TABRECTA. In GEOMETRY mono-1, it was recommended that patients use precautionary measures against ultraviolet exposure, such as use of sunscreen or protective clothing, during treatment with TABRECTA. Advise patients to limit direct ultraviolet exposure during treatment with TABRECTA.

Embryo-Fetal Toxicity. Based on findings from animal studies and its mechanism of action, TABRECTA can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TABRECTA and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TABRECTA and for 1 week after the last dose.

Most Common Adverse Reactions. The most common adverse reactions (≥20%) were peripheral edema (52%), nausea (44%), fatigue (32%), vomiting (28%), dyspnea (24%), and decreased appetite (21%). The most common grade 3 adverse reactions (≥2%) were peripheral edema (9%), fatigue (8%), dyspnea (7%), nausea (2.7%), vomiting (2.4%), and noncardiac chest pain (2.1%). Grade 4 dyspnea was reported in 0.6% of patients.

Clinically Relevant Adverse Reactions. Clinically relevant adverse reactions observed in <10% of patients were pruritus (allergic and generalized), ILD/pneumonitis, cellulitis, acute kidney injury (including renal failure), urticaria, and acute pancreatitis.

Laboratory Abnormalities. Select laboratory abnormalities (≥20%) worsening from baseline in patients who received TABRECTA were decreased albumin (68%), increased creatinine (62%), decreased lymphocytes (44%), increased ALT (37%), increased alkaline phosphatase (32%), increased amylase (31%), increased gamma-glutamyltransferase (29%), increased lipase (26%), increased AST (25%), decreased hemoglobin (24%), decreased leukocytes (23%), decreased sodium (23%), decreased phosphate (23%), increased potassium (23%), and decreased glucose (21%).

Please click here for full Prescribing Information for TABRECTA.

TABRECTA® (capmatinib) tablets 150 mg · 200 mg

Important Safety Information for TAFINLAR® (dabrafenib) capsules and MEKINIST® (trametinib) tablets

New Primary Malignancies.

Cutaneous Malignancies

Across clinical trials of TAFINLAR administered with MEKINIST ("the combination"), the incidence of cutaneous squamous cell carcinomas (cuSCCs), including keratoacanthomas, occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and <1% of patients, respectively.

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

Noncutaneous Malignancies

Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of monomeric G protein (RAS) through mutation or other mechanisms. Across clinical trials of TAFINLAR monotherapy and the combination, noncutaneous malignancies occurred in 1% of patients.

Monitor patients receiving the combination for signs or symptoms of noncutaneous malignancies. Permanently discontinue TAFINLAR for RAS-mutation–positive noncutaneous malignancies. No dose modification is required for MEKINIST in patients who develop noncutaneous malignancies.

Tumor Promotion in *BRAF* Wild-type Tumors. In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (MAPK) signaling and increased cell proliferation in *BRAF* wild-type cells that are exposed to *BRAF* inhibitors. Confirm evidence of *BRAF* V600E or V600K mutation status prior to initiation of therapy.

Hemorrhage. Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with the combination. Fatal cases have been reported.

Across clinical trials of the combination, hemorrhagic events occurred in 17% of patients. Gastrointestinal hemorrhage occurred in 3% of patients who received the combination. Intracranial hemorrhage occurred in 0.6% of patients who received the combination. Fatal hemorrhage occurred in 0.5% of patients who received the combination. The fatal events were cerebral hemorrhage and brainstem hemorrhage.

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

Colitis and Gastrointestinal Perforation. Colitis and gastrointestinal perforation, including fatal outcomes, can occur. Across clinical trials of the combination, colitis occurred in <1% of patients and gastrointestinal perforation occurred in <1% of patients. Monitor patients closely for colitis and gastrointestinal perforations.

Venous Thromboembolic Events. Across clinical trials of the combination, deep vein thrombosis (DVT) and pulmonary embolism (PE) occurred in 2% of patients.

Advise patients to immediately seek medical care if they develop symptoms of DVT or PE, such as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue MEKINIST for life-threatening PE. Withhold MEKINIST for uncomplicated DVT and PE for up to 3 weeks; if improved, MEKINIST may be resumed at a lower dose level.

Cardiomyopathy. Cardiomyopathy, including cardiac failure, can occur. Across clinical trials of the combination, 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 TAFINLAR in 3% and <1% of patients, respectively, and in 3% and <1% of patients receiving MEKINIST, respectively. Cardiomyopathy resolved in 45 of 50 patients who received the combination.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of the combination, 1 month after initiation, and then at 2- to 3-month intervals while on treatment. Withhold TAFINLAR for symptomatic cardiomyopathy or asymptomatic left ventricular dysfunction of >20% from baseline that is below institutional LLN. Resume TAFINLAR at the same dose level upon recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease ≤10% compared to baseline. For an asymptomatic absolute decrease in LVEF of 10% or greater from baseline that is below the LLN, withhold MEKINIST for up to 4 weeks. If improved to normal LVEF value, resume at a lower dose. If no improvement to normal LVEF value within 4 weeks, permanently discontinue MEKINIST. For symptomatic cardiomyopathy or an absolute decrease in LVEF of >20% from baseline that is below LLN, permanently discontinue MEKINIST.

Ocular Toxicities.

Retinal Vein Occlusion (RVO): There were no cases of RVO across clinical trials of the combination. RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Urgently (within 24 hours) perform ophthalmologic evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue MEKINIST in patients with documented RVO.

Retinal Pigment Epithelial Detachment (RPED): RPED can occur. Retinal detachments may be bilateral and multifocal, occurring in the central macular region of the retina or elsewhere in the retina. In clinical trials, routine monitoring of patients to detect asymptomatic RPED was not conducted; therefore, the true incidence of this finding is unknown.

Perform ophthalmologic evaluation periodically, and at any time a patient reports visual disturbances. Withhold MEKINIST if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmologic evaluation within 3 weeks, resume MEKINIST at the same or a reduced dose. If no improvement after 3 weeks, resume at a reduced dose or permanently discontinue MEKINIST.

Tafinlar® (dabrafenib) 50 mg, 75 mg capsules + Mekinist® (trametinib) 0.5 mg, 2 mg tablets

Important Safety Information for TAFINLAR® (dabrafenib) capsules and MEKINIST® (trametinib) tablets (continued)

Uveitis: Uveitis occurred in 2% of patients treated with the combination across trials. Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops.

Monitor patients for visual signs and symptoms of uveitis (eg, change in vision, photophobia, and eye pain). If iritis is diagnosed, administer ocular therapy and continue TAFINLAR without dose modification. If severe uveitis (ie, iridocyclitis) or if mild or moderate uveitis does not respond to ocular therapy, withhold TAFINLAR and treat as clinically indicated. Resume TAFINLAR at the same or lower dose if uveitis improves to grade 0 or 1. Permanently discontinue TAFINLAR for persistent grade 2 or greater uveitis of >6 weeks.

Interstitial Lung Disease (ILD)/Pneumonitis. Across clinical trials of the combination, interstitial lung disease or pneumonitis occurred in 1% of patients.

Withhold MEKINIST in patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue MEKINIST for patients diagnosed with treatment-related ILD or pneumonitis.

Serious Febrile Reactions. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur. The incidence and severity of pyrexia are increased when TAFINLAR is administered with MEKINIST.

Across clinical trials of the combination, 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.

Withhold TAFINLAR and MEKINIST for temperature of ≥100.4°F. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. 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. Upon 24 hours after resolution, if appropriate, resume both TAFINLAR and MEKINIST at the same or a lower dose. Administer antipyretics as secondary prophylaxis when resuming TAFINLAR and/or MEKINIST if the patient had a prior episode of severe febrile reaction or fever associated with complications. Administer corticosteroids (eg, 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 hypotension, severe rigors or chills, dehydration, or renal failure, and there is no evidence of active infection.

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 the combination. Across clinical trials of the combination, other serious skin toxicity occurred in <1% of patients.

Monitor for new or worsening serious skin reactions. Permanently discontinue the combination for SCARs. For other skin toxicities, withhold TAFINLAR and/or MEKINIST for intolerable or severe skin toxicity. Resume TAFINLAR and/or MEKINIST at a lower dose in patients with improvement or recovery from skin toxicity within 3 weeks. Permanently discontinue TAFINLAR and/or MEKINIST if skin toxicity has not improved within 3 weeks.

Hyperglycemia. Across clinical trials of the combination, 15% of patients with a history of diabetes required more intensive hypoglycemic therapy. Grade 3 and grade 4 hyperglycemia occurred in 2% of patients.

Monitor serum glucose levels upon initiation and as clinically appropriate in patients with preexisting diabetes or hyperglycemia. Initiate or optimize antihyperglycemic medications as clinically indicated.

Glucose-6-Phosphate Dehydrogenase Deficiency. TAFINLAR, 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 TAFINLAR.

Embryo-fetal Toxicity. TAFINLAR and MEKINIST can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use effective nonhormonal contraception during treatment, and for 4 months after treatment.

Most Common Adverse Reactions. In the NSCLC clinical trial, the most commonly occurring adverse reactions (≥20%) in patients receiving the combination were pyrexia (55%), fatigue (51%), nausea (45%), vomiting (33%), diarrhea (32%), dry skin (31%), decreased appetite (29%), edema (28%), rash (28%), chills (23%), hemorrhage (23%), cough (22%), and dyspnea (20%). The most common grade 3 or 4 adverse reactions (incidence ≥2%) were pyrexia (5%), fatigue (5%), dyspnea (5%), hemorrhage (3.2%), rash (3.2%), vomiting (3.2%), and diarrhea (2.2%).

Other Clinically Important Adverse Reactions. The other clinically important adverse reactions observed in ≤10% of patients with NSCLC receiving the combination were pancreatitis and tubulointerstitial nephritis.

Laboratory Abnormalities. In the NSCLC clinical trial, the most common treatment-emergent laboratory abnormalities occurring at ≥20% of patients receiving the combination were hyperglycemia (71%), increased blood alkaline phosphatase (64%), increased aspartate aminotransferase (AST) (61%), hyponatremia (57%), leukopenia (48%), anemia (46%), neutropenia (44%), lymphopenia (42%), hypophosphatemia (36%), increased alanine aminotransferase (ALT) (32%), and creatinine (21%). The most common grade 3 or 4 laboratory abnormalities (incidence ≥10%) were hyponatremia (17%), lymphopenia (14%), and anemia (10%).

Please click here for full Prescribing Information for TAFINLAR and click here for full Prescribing Information for MEKINIST.

Tafinlar® (dabrafenib) 50 mg, 75 mg capsules + Mekinist® (trametinib) 0.5 mg, 2 mg tablets

BROAD MOLECULAR PROFILING IS A KEY STEP IN INFORMING CARE FOR PATIENTS WITH mNSCLC[6*†]

If feasible, clinicians should obtain biomarker test results in eligible patients at diagnosis of mNSCLC, prior to administering a first-line therapy[6,16†]

Guidelines recommend broad molecular profiling[6,17-19]:

- ✓ to identify driver variants that may have an available targeted therapy
- ✓ to help ensure the most appropriate treatment for patients

A broad, panel-based approach, most typically next-generation sequencing (NGS), is recommended[6,17,19]

- Broad molecular profiling should be done as part of biomarker testing using a validated test
- At a minimum, NCCN recommends molecular testing for the following genetic variants: *EGFR* mutations, *BRAF* mutations, *MET*ex14 mutations, *KRAS* mutations, *RET* rearrangements, *ALK* fusions, *NTRK1/2/3* fusions, and *ROS1* fusions

*It is recommended at this time that, when feasible, molecular testing be performed via a broad, panel-based approach, most typically next-generation sequencing (NGS).
†The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories.

References: 1. Smyth EC, Sclafani F, Cunningham D. *Onco Targets Ther.* 2014;7:1001-1014. **2.** Vuong HG, Ho ATN, Altibi AMA, Nakazawa T, Katoh R, Kondo T. *Lung Cancer.* 2018;123:76-82. **3.** Data on file. Novartis Calculation. Kantar Health. my.khapps.com. **4.** Tabrecta [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2022. **5.** Data on file. CINC280A2201. Novartis Pharmaceuticals Corp; 2019. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed December 7, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** Roviello G, D'Angelo A, Sirico M, Pittacolo M, Conter FU, Sobhani N. Advances in anti-BRAF therapies for lung cancer. *Invest New Drugs.* 2021;39(3):879-890. **8.** US Food and Drug Administration. FDA grants regular approval to dabrafenib and trametinib in combination for metastatic NSCLC with BRAF V600E mutation. June 22, 2017. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-dabrafenib-and-trametinib-combination-metastatic-nsclc-braf-v600e. Accessed April 21, 2021. **9.** Wan PTC, Garnett MJ, Roe SM, et al. *Cell.* 2004;116(6):855-867. **10.** Brustugun OT, Khattak AM, Trømborg AK, et al. *Lung Cancer.* 2014;84(1):36-38. **11.** Marchetti A, Felicioni L, Malatesta S, et al. *J Clin Oncol.* 2011;29(26):3574-3579. **12.** Tafinlar [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021. **13.** Mekinist [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021. **14.** Data on file. CDRB436E2201 Interim clinical study report. Novartis Pharmaceuticals Corp; 2017. **15.** Data on file. CDRB436E2201 Interim clinical study report. Novartis Pharmaceuticals Corp; 2020. **16.** Leighl NB, Rekhtman N, Biermann WA, et al. *J Clin Oncol.* 2014;32(32):3673-3679. **17.** Lindeman NI, Cagle PT, Aisner DL, et al. *J Mol Diagn.* 2018;20(2):129-159. **18.** Kalemkerian GP, Narula N, Kennedy EB, et al. *J Clin Oncol.* 2018;36(9):911-919. **19.** Planchard D, Popat S, Kerr K, et al. *Ann Oncol.* 2018;29(suppl 4):iv192-iv237.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

2/22

117254-1