In the adjuvant treatment of stage III melanoma with *BRAF* V600E/K mutations

EXPLORE 5-YEAR RELAPSE-FREE SURVIVAL DATA FROM TAFINLAR + MEKINIST[1-3]

52% of patients taking TAFINLAR + MEKINIST were relapse free and alive at 5 years vs 36% of patients taking placebo (hazard ratio [HR], 0.51; 95% CI, 0.42-0.61)[3]

- **Median relapse-free survival (RFS) was not reached for TAFINLAR + MEKINIST (95% CI, 47.9-not reached) and was 16.6 months (95% CI, 12.7-22.1) for placebo (HR, 0.51, 95% CI, 0.42-0.61)[3]**
- **Results at 5 years were not prespecified and are observational in nature; as such, there was no prespecified statistical procedure controlling for type 1 error**
- **Primary analysis positive for RFS (HR, 0.47; 95% CI, 0.39-0.58; *P*=.0000000000000153), median follow-up, 2.8 years[1,2,4,5]**

PIVOTAL STUDY DESIGN: COMBI-AD[1-3,4,6]

COMBI-AD was an international, multicenter, randomized, double-blind, placebo-controlled trial that included 870 patients with stage III *BRAF*+ V600E/K melanoma. The primary end point was investigator-assessed 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. Secondary end points were overall survival (OS), distant metastasis-free survival, freedom from relapse, and safety. Patients were randomized (1:1) to receive TAFINLAR® (dabrafenib) capsules 150 mg twice daily with MEKINIST® (trametinib) tablets 2 mg once daily or 2 placebos for up to 1 year. Updated data cutoff date for the 5-year analysis was November 8, 2019.

INDICATION

TAFINLAR in combination with MEKINIST, is indicated for the adjuvant treatment of patients with melanoma with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.

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

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.

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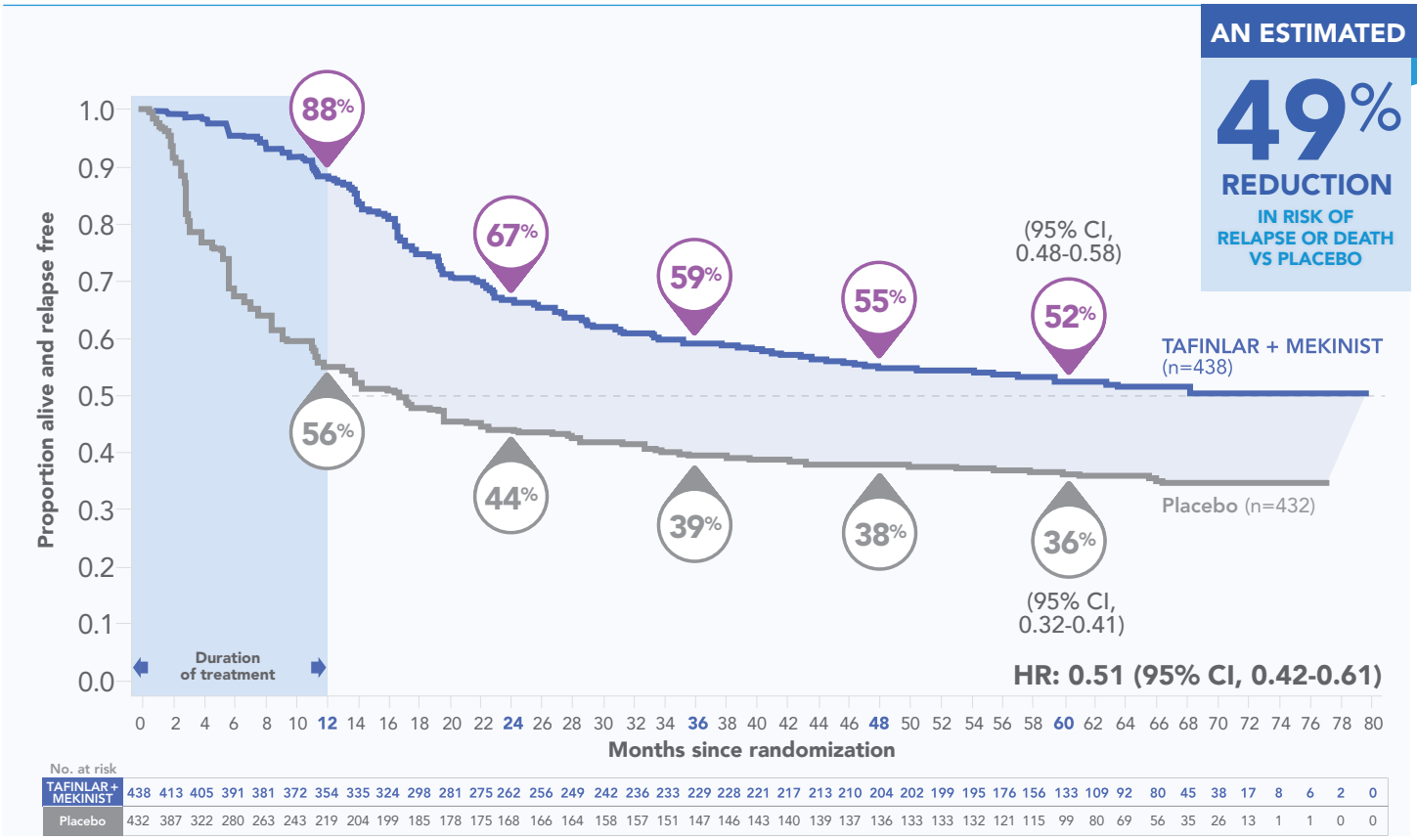
In the adjuvant treatment of patients with stage III *BRAF* V600E/K melanoma

THE FIRST AND ONLY APPROVED TARGETED THERAPY THAT DEMONSTRATES 5-YEAR RFS[1-3,7-11]

RFS in the COMBI-AD study (as of November 8, 2019 cutoff)[3,6]



- Median duration of follow-up for updated analysis was 60 months in the TAFINLAR + MEKINIST treatment arm and 58 months for placebo[3]
- First tumor assessment was performed at 3 months[5]
- Median RFS was not reached for TAFINLAR + MEKINIST (95% CI, 47.9-not reached) and was 16.6 months (95% CI, 12.7-22.1) for placebo (HR 0.51, 95% CI, 0.42-0.61)[3]

PRIMARY ANALYSIS POSITIVE FOR RFS, WITH HR OF 0.47 (95% CI, 0.39-0.58), *P*=.0000000000000153 (MEDIAN FOLLOW-UP: 2.8 YEARS)[1,2,4,5]

- Results at 12, 24, 36, 48, and 60 months were not prespecified and are observational in nature; as such there was no prespecified statistical procedure controlling for type 1 error

IMPORTANT SAFETY INFORMATION (continued)

Cutaneous Malignancies (continued)

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.

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OFFER TREATMENT WITH AN ESTABLISHED SAFETY PROFILE

Adverse Reactions Occurring in ≥20% of Patients (as of June 30, 2017 data cutoff)

In COMBI-AD[1,2,a]

Adverse reactions	TAFINLAR + MEKINIST (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				
Rash[e]	37	<1	16	<1
Musculoskeletal				
Arthralgia	28	<1	14	0
Myalgia[f]	20	<1	14	0

[a]National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. [b]Includes pyrexia and hyperpyrexia. [c]Includes fatigue, asthenia, and malaise. [d]Includes headache and tension headache. [e]Includes rash, rash maculopapular, 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.

- 26% of patients discontinued TAFINLAR® (dabrafenib) capsules and MEKINIST® (trametinib) tablets due to an adverse reaction (AR), vs 3% with placebo[6]
  - 72% completed the scheduled 12-month treatment regimen (66% had dose interruptions and 38% had dose reductions due to adverse reactions)[5]
- The most common cause of discontinuation in the treatment arm was pyrexia (9%)[5]
- During the 5-year follow-up, updated safety analyses were not performed because no patients remained on therapy during the extended follow-up period

IMPORTANT SAFETY INFORMATION (continued)

New Primary Malignancies (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.

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GIVE PATIENTS A PATH FOR INDIVIDUALIZED TREATMENT SUPPORT

Encourage your patients to find out if they are eligible to enroll in the Novartis Oncology Universal Co-pay Program by visiting CoPay.NovartisOncology.com or calling 1-877-577-7756.

IMPORTANT SAFETY INFORMATION (continued)

Noncutaneous Malignancies (continued)

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 tablets 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® (dabrafenib) capsules 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® (trametinib) tablets 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.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

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® (trametinib) tablets, 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® (dabrafenib) capsules 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.

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

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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® (dabrafenib) capsules for temperature of ≥101.3°F or fever complicated by hypotension, rigors or chills, dehydration, or renal failure, and evaluate for signs and symptoms of infection. Withhold MEKINIST® (trametinib) tablets for a temperature of >104°F or fever complicated by hypotension, rigors or chills, dehydration, or renal failure, and evaluate for signs and symptoms of infection. Monitor serum creatinine and other evidence of renal function during and following severe pyrexia. Upon resolution, resume at same or 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® (dabrafenib) capsules and/or MEKINIST® (trametinib) tablets 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 COMBI-AD study, the most common adverse reactions (≥20%) for the combination were pyrexia (63%), fatigue (59%), nausea (40%), headache (39%), rash (37%), chills (37%), diarrhea (33%), vomiting (28%), arthralgia (28%), and myalgia (20%). The most common grade 3 or 4 adverse reactions (≥2%) for the combination were pyrexia (5%) and fatigue (5%).

Other Clinically Important Adverse Reactions. In the COMBI-AD study, other clinically important adverse reactions observed in <20% of patients receiving the combination were blurred vision (6%), decreased ejection fraction (5%), and rhabdomyolysis (<1%).

Laboratory Abnormalities. In the COMBI-AD study, treatment-emergent laboratory abnormalities occurring in ≥20% of patients receiving the combination were hyperglycemia (63%), increased aspartate aminotransferase (AST) (57%), increased alanine aminotransferase (ALT) (48%), neutropenia (47%), hypophosphatemia (42%), increased blood alkaline phosphatase (38%), lymphopenia (26%), anemia (25%), and hypoalbuminemia (25%).

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References: 1. Tafinlar [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020. **2.** Mekinist [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020. **3.** Data on file. FIR Documentation. BRF115532/DRB436F2301. Novartis Pharmaceuticals Corp; February 19, 2019. **4.** Hauschild A, Dummer R, Schadendorf D, et al. *J Clin Oncol.* 2018. doi:10.1200/JCO.18.01219. **5.** Data on file. Clinical study report. BRF115532/DRB436F2301. Novartis Pharmaceuticals Corp; October 12, 2017. **6.** Long GV, Hauschild A, Santinami M, et al. *N Engl J Med.* 2017;377(19):1813-1823. **7.** Zelboraf [prescribing information]. South San Francisco, CA: Genentech Inc; 2017. **8.** Cotellic [prescribing information]. South San Francisco, CA: Genentech Inc; 2018. **9.** Braftovi [prescribing information]. Boulder, CO: Array BioPharma Inc; 2018. **10.** Mektovi [prescribing information]. Boulder, CO: Array BioPharma Inc; 2018. **11.** Maio M, Lewis K, Demidov L, et al. *Lancet Oncol.* 2018;19:510-520.

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