Novartis receives FDA approval of Tafinlar® + Mekinist® for adjuvant treatment of BRAF V600-mutant melanoma

- Tafinlar + Mekinist is the first oral targeted adjuvant combination therapy to demonstrate significant clinical benefit in patients with a BRAF V600 mutation, following complete surgical resection
- Tafinlar + Mekinist significantly reduced the risk of disease recurrence or death compared to placebo by 53%1
- New indication represents a new treatment option for patients in the US with BRAF mutation-positive melanoma at risk of disease recurrence or metastases, and is currently under regulatory review in Europe, Japan, Canada and other countries worldwide

Basel, April 30, 2018 – Novartis announced today that the US Food and Drug Administration (FDA) has approved Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) 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. The FDA granted the combination Breakthrough Therapy Designation for this indication in October 2017 and Priority Review in December 2017.

“Since the initial approval of Tafinlar and Mekinist in metastatic melanoma in 2013, the combination has become an important therapy for many patients carrying a BRAF mutation in both melanoma and lung cancers,” said Liz Barrett, CEO, Novartis Oncology. “Today’s FDA approval is an important milestone for patients who previously had limited treatment options in the adjuvant setting, and reflects our commitment to the ongoing development of this breakthrough treatment.”

The melanoma approval is based on results from COMBI-AD, a Phase III study of 870 patients with Stage III BRAF V600E/K mutation-positive melanoma treated with Tafinlar + Mekinist after complete surgical resection1. Patients received the Tafinlar (150 mg BID) + Mekinist (2 mg QD) combination (n = 438) or matching placebos (n = 432)1. After a median follow-up of 2.8 years, the primary endpoint of relapse-free survival (RFS) was met. Treatment with the combination therapy significantly reduced the risk of disease recurrence or death by 53% as compared to placebo (HR: 0.47 [95% CI: 0.39-0.58]; p<0.001; median not reached with combination therapy vs. 16.6 months with placebo)1. The RFS benefit among the combination arm was observed across all patient subgroups, including disease sub-stage1. Improvements were also observed in key secondary endpoints including overall survival (OS), distant metastasis-free survival (DMFS) and freedom from relapse (FFR)1. These results were published in the New England Journal of Medicine, October 2017.

“The purpose of adjuvant therapy is to improve recurrence-free and overall survival in our patients with melanoma. Adjuvant therapy options are crucial today because more than half of patients have a recurrence after surgery,” said John M. Kirkwood, M.D., Usher Professor of Medicine, Director of Melanoma and Skin Cancer, University of Pittsburgh. “We developed the first adjuvant therapy approved by the FDA 22 years ago, and now we have the first effective
oral targeted therapy combination that prevents relapse among patients with BRAF-mutated melanoma that has spread to lymph nodes."

"Prevention and early detection are important safeguards from melanoma, but that’s only half the picture. Melanoma is an aggressive cancer that can recur, particularly when it shows certain warning signs like increased depth, ulceration, or spread to the lymph nodes," said Sancy Leachman, M.D., Ph.D., Chair of the Department of Dermatology at OHSU School of Medicine. "With proven treatment options for these patients, it is important for dermatologists to assure that appropriate patients are offered adjuvant treatment options – a ‘watch and wait’ approach is no longer the standard of care. Collaborating with a multidisciplinary care team of surgeons, pathologists and oncologists, and determining the right treatment based on the patient's individual circumstances and mutational status is crucial to our patients’ care plans."

Adverse events (AEs) were consistent with other Tafinlar + Mekinist studies, and no new safety signals were reported\(^1\). Of patients treated with the combination, 97% experienced an AE, 41% had grade 3/4 AEs and 26% had AEs leading to treatment discontinuation (vs. 88%, 14%, and 3%, respectively, with placebo)\(^1\).

**About COMBI-AD**
The COMBI-AD study is a randomized, double-blind, placebo-controlled, Phase III study and included a total of 870 patients with Stage III, BRAF V600E/K-mutant melanoma who had undergone prior complete surgical resection, without prior anticancer therapy. Patients were treated for 12 months and stratified based on BRAF mutation (V600E vs. V600K) and stage (IIIA vs. IIIB vs. IIIC, based on American Joint Committee on Cancer Melanoma of the Skin staging, 7th edition).

The primary endpoint was RFS. Secondary endpoints included OS, DMFS, FFR and safety.

AEs were consistent with other Tafinlar + Mekinist studies, and no new safety signals were reported\(^1\).

**About Melanoma**
There are nearly 200,000 new diagnoses of melanoma (Stages 0-IV) worldwide each year, approximately half of which have BRAF mutations. Biomarker tests can determine whether a tumor has a BRAF mutation\(^2,3\).

Some patients who receive surgical treatment for melanoma may have a high risk of recurrence because melanoma cells can remain in the body after surgery; almost half (44%) of patients receiving placebo per the COMBI-AD study had a recurrence of disease within the first year\(^1,4\). Adjuvant therapy is additional treatment given after surgical resection, and may be recommended for patients with high-risk melanoma to help reduce the risk of melanoma returning\(^4\).

**About Tafinlar and Mekinist**
In the EU, Tafinlar in combination with Mekinist is approved for the treatment of patients with a BRAF V600 mutation in metastatic melanoma and non-small cell lung cancer (NSCLC).

In the US, Tafinlar in combination with Mekinist is approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or K mutations, as detected by an FDA-approved test, and for the adjuvant treatment of melanoma with BRAF V600E or K mutations and involvement of lymph node(s) following complete resection. Tafinlar + Mekinist is also approved for BRAF V600E mutation-positive NSCLC.

Tafinlar and Mekinist are also indicated in more than 60 countries worldwide, including the US and EU, as single agents to treat patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Indications vary by country and not all indications are available in every country. The safety and efficacy profile of Tafinlar and Mekinist have not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that Tafinlar and Mekinist will become commercially available for additional indications anywhere else in the world.

**Tafinlar + Mekinist Combination Important Safety Information**

Tafinlar + Mekinist combination may cause serious side effects.

Tafinlar in combination with Mekinist should only be used to treat patients with a change (mutation) in the BRAF gene; therefore, doctors should test their patients before treatment, as patients without a BRAF mutation and with a RAS mutation can be at risk of increased cell proliferation in the presence of a BRAF inhibitor.

Doctors should also consider other treatment options for their patients if they had been previously treated with a BRAF inhibitor as single agent, as the limited data available have shown that the efficacy of Tafinlar + Mekinist is lower in these patients.

When Tafinlar is used in combination with Mekinist, or when Tafinlar is administered as monotherapy, it can cause new cancers (both skin cancer and non-skin cancer). Patients should be advised to contact their doctor immediately for any new lesions, changes to existing lesions on their skin, or signs and symptoms of other malignancies.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause severe bleeding, and in some cases can lead to death. Patients should be advised to call their healthcare provider and get medical help right away if they have headaches, dizziness, or feel weak, cough up blood or blood clots, vomit blood or their vomit looks like "coffee grounds," have red or black stools that look like tar, or any unusual signs of bleeding.

Tafinlar in combination with Mekinist, or either drug alone, can cause severe eye problems that can lead to blindness. Patients should be advised to call their healthcare provider right away if they get these symptoms of eye problems: blurred vision, loss of vision, or other vision changes, seeing color dots, halo (seeing blurred outline around objects), eye pain, swelling, or redness.

Tafinlar in combination with Mekinist, or Tafinlar alone, can cause fever which may be serious. When taking Tafinlar in combination with Mekinist, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever. Patients should be advised to call their healthcare provider right away if they get a fever above 38.5°C (101.3°F) while taking Tafinlar.

Tafinlar in combination with Mekinist, or Mekinist alone, can affect how well the heart pumps blood. A patient's heart function should be checked before and during treatment. Patients should be advised to call their healthcare provider right away if they have any of the following signs and symptoms of a heart problem: feeling like their heart is pounding or racing, shortness of breath, swelling of their ankles and feet, or feeling lightheaded.

Tafinlar in combination with Mekinist, or Tafinlar alone, can cause abnormal kidney function or inflammation of the kidney. Abnormal kidney function may happen more often for patients with fever or too much fluid loss. Patients should be advised to call their healthcare provider right away if they have a fever above 38.5°C (101.3°F), decreased urine, fatigue, loss of appetite or discomfort in lower abdomen or back. Tafinlar has not been studied in patients with renal insufficiency (defined as creatinine > 1.5 x ULN) therefore caution should be used in this setting.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause abnormal liver function. A patient may feel tired, lose appetite, yellow skin, dark urine colour, or discomfort in abdomen.
The liver function abnormality needs to be assessed by laboratory test of the blood. Patients should consult their healthcare provider if they have such experience. Administration of Tafinlar or Mekinist should be done with caution in patients with moderate to severe hepatic impairment.

Elevations in blood pressure have been reported in association with Mekinist in combination with Tafinlar, or with Mekinist alone, in patients with or without pre-existing hypertension. Patients should be advised to monitor blood pressure during treatment with Mekinist and control potential hypertension by standard therapy, as appropriate.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause inflammation of the lung tissue. Patients should notify their doctor if they experience any new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Rash is a common side effect of Tafinlar in combination with Mekinist, or with Mekinist alone. Tafinlar in combination with Mekinist, or Mekinist alone, can also cause other skin reactions which can be severe, and may need to be treated in a hospital. Patients should be advised to call their healthcare provider if they get any of the following symptoms: skin rash that bothers them or does not go away, acne, redness, swelling, peeling, or tenderness of hands or feet, skin redness.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause muscle breakdown, a condition called Rhabdomyolysis. Patients experiencing muscle pain, tenderness, weakness or a swelling of their muscles should contact their healthcare provider immediately.

Tafinlar in combination with Mekinist, or Tafinlar alone, can uncommonly cause an inflammation of the pancreas (pancreatitis). Patients should be promptly investigated if they experience unexplained abdominal pain and closely monitored if they re-start Tafinlar after a prior episode of pancreatitis.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause blood clots in the arms or legs, which can travel to the lungs and can lead to death. Patients should be advised to get medical help right away if they have the following symptoms: chest pain, sudden shortness of breath or trouble breathing, pain in their legs with or without swelling, swelling in their arms or legs, or a cool or pale arm or leg.

Mekinist in combination with Tafinlar, or Mekinist alone, may increase the risk of developing holes in the stomach or intestine (gastrointestinal perforation). Treatment with Mekinist alone or in combination with Tafinlar should be used with caution in patients with risk factors for gastrointestinal perforation, including concomitant use of medications with a recognized risk of gastrointestinal perforation.

Tafinlar and Mekinist both can cause harm to an unborn baby when taken by a pregnant woman. Tafinlar can also render hormonal contraceptives ineffective.

The most common side effects of Tafinlar + Mekinist combination include fever, nausea, diarrhea, fatigue, chills, headache, vomiting, joint pain, high blood pressure, rash and cough. The incidence and severity of fever is increased when Mekinist is used in combination with Tafinlar.

Patients should tell their doctor of any side effect that bothers them or does not go away. These are not all of the possible side effects of Tafinlar + Mekinist combination. For more information, patients should ask their doctor or pharmacist.

Patients should take Tafinlar + Mekinist combination exactly as their health care provider tells them. Patients should not change their dose or stop taking Tafinlar + Mekinist combination unless their health care provider advises them to. Mekinist should be taken only once daily (either in the morning or evening, at the same time as Tafinlar). The first and second doses of
Tafinlar should be taken approximately 12 hours apart. Patients should take Tafinlar + Mekinist at least 1 hour before or 2 hours after a meal. Do not take a missed dose of Tafinlar within 6 hours of the next dose of Tafinlar. Do not open, crush, or break Tafinlar capsules. Do not take a missed dose of Mekinist within 12 hours of the next dose of Mekinist.

Please see full Prescribing Information for Tafinlar and Mekinist.

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