European Commission approves Novartis combination therapy Tafinlar® + Mekinist® for adjuvant treatment of BRAF V600 mutation-positive melanoma

- Approval based on COMBI-AD study demonstrating greater than 50% reduction in risk of disease recurrence or death in stage III melanoma patients
- More than 50% of stage III melanoma patients are likely to recur to stage IV during their lifetime
- EC approval marks third indication in Europe for leading BRAF/MEK inhibitor combination Tafinlar + Mekinist

Basel, August 29, 2018 – Novartis announced today that the European Commission (EC) has approved Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) for the adjuvant treatment of stage III patients with BRAF V600 mutation-positive melanoma after complete surgical resection. This approval is the third for Tafinlar in combination with Mekinist in Europe across a variety of tumor types identified with a high level of BRAF mutation. It also demonstrates Novartis leadership in BRAF+ targeted therapy, and to date, more than 60,000 patients worldwide have been treated with the combination therapy across four indications.

“Novartis’ deep therapeutic knowledge and our ability to apply novel approaches to the development of new medicines has resulted again in a new treatment advance for melanoma patients,” said Liz Barrett, CEO, Novartis Oncology. “The European approval of the Tafinlar and Mekinist combination illustrates Novartis’ continued efforts to reimagine cancer by providing a highly effective, targeted therapy for earlier-stage melanoma patients.”

The approval is based on results from the Phase III COMBI-AD global study, which enrolled more than 870 patients with stage III, BRAF V600E/K-mutant melanoma without prior anticaner therapy, and who were randomized within 12 weeks of complete surgical resection. Patients received the Tafinlar (150 mg BID) + Mekinist (2 mg QD) combination (n = 438) or matching placebos (n = 432). In the primary analysis, and after a median follow-up of 2.8 years, the primary endpoint was met, with the combination therapy significantly reducing the risk of disease recurrence or death by 53% vs. placebo. Based on updated data, with an additional 10 months of follow-up compared to the primary analysis (minimum follow-up of 40 months), treatment with the combination therapy reduced the risk of recurrence or death by 51% vs. placebo. Additionally, the relapse free survival (RFS) benefit among the combination arm was observed across all patient subgroups, including stage III A, B and C. The combination treatment group also saw an improvement in a key secondary endpoint of overall survival³.

The BRAF gene belongs to a class of genes known as oncogenes and provides instructions for making a protein that helps transmit chemical signals from outside the cell to the cell's nucleus. This protein is part of a signaling pathway known as the RAS/MAPK pathway, which controls several important cell functions. Specifically, the RAS/MAPK pathway regulates the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement (migration) and the self-destruction of cells
Chemical signaling through this pathway is essential for normal development before birth. When mutated, oncogenes have the potential to cause normal cells to become cancerous. During cancer treatment, targeted therapies may inhibit the mutation from occurring, thus slowing the growth of the cancer tumor.

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

The Committee for Medical Products for Human Use of the European Medicines Agency adopted a positive opinion recommending the approval of Tafinlar + Mekinist in July, and the combination was approved by the US Food and Drug Administration for the adjuvant treatment of melanoma in April 2018.

About COMBI-AD
The COMBI-AD study evaluated Tafinlar + Mekinist among patients with stage III, BRAF V600E/K-mutant melanoma without prior anticancer therapy, randomized within 12 weeks of complete surgical resection. Patients received the Tafinlar (150 mg BID) + Mekinist (2 mg QD) combination (n = 438) or matching placebos (n = 432). In the initial primary analysis, and after a median follow-up of 2.8 years, the primary endpoint was met in that the combination therapy significantly reduced the risk of disease recurrence or death by 53% vs. placebo (HR: 0.47 [95% CI: 0.39-0.58]; median not yet reached vs. 16.6 months, respectively; p<0.001). Based on updated data with minimum follow-up of 10 months (a minimum follow up of 40 months), the RFS benefit was maintained with an estimated reduction in the risk of disease recurrence or death by 51% vs placebo (HR: 0.49 [95% CI: (0.40-0.59)]. The relapse-free survival benefit among the combination arm was observed across all patient subgroups, including stage III A, B and C. The estimated one-year, two-year, and three-year RFS were consistently higher than placebo (one year: 88% vs. 56%; two year: 67% vs. 44%; three year: 59% vs. 40%).

About Melanoma
There are about 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.

Melanoma is staged by how far it has metastasized. In stage III melanoma, tumors have spread to the regional lymph nodes, presenting a higher risk of recurrence or metastases. Patients who receive surgical treatment for Stage III 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. 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.

About Tafinlar + Mekinist Combination
Combination use of Tafinlar + Mekinist in patients with unresectable or metastatic melanoma who have a BRAF V600 mutation is approved in the US, EU, Japan, Australia, Canada and other countries.
The combination of Tafinlar + Mekinist is also approved for the treatment of metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation in the US and advanced NSCLC with a BRAF V600 mutation in the EU.

Tafinlar and Mekinist target different kinases within the serine/threonine kinase family – BRAF and MEK1/2, respectively – in the RAS/RAF/MEK/ERK pathway, which is implicated in NSCLC and melanoma, among other cancers. When Tafinlar is used with Mekinist, the combination has been shown to slow tumor growth more than either drug alone. The combination of Tafinlar + Mekinist is currently being investigated in an ongoing clinical trial program across a range of tumor types conducted in study centers worldwide.

The safety and efficacy profile of the Tafinlar + Mekinist combination has not yet been established outside of the approved indications.

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.

**Tafinlar + Mekinist Combination Important Safety Information**

Tafinlar and Mekinist, in combination, may cause serious side effects such as the risk of new cancers, including both skin cancer and nonskin cancer. Patients should be advised to contact their health care provider immediately for a new wart, skin sore, or bump that bleeds or does not heal, or a change in the size or color of a mole.

When Tafinlar is used in combination with Mekinist, it can cause serious bleeding problems, especially in the brain or stomach, that can lead to death. Patients should be advised to call their health care provider and get medical help right away if they have any signs of bleeding, including headaches, dizziness, or feel weak, cough up blood or blood clots, vomit blood or their vomit looks like “coffee grounds,” or red or black stools that look like tar.

Mekinist, alone or in combination with Tafinlar, can cause inflammation of the intestines or tears in the stomach or intestines that can lead to death. Patients should report to their health care provider immediately if they have any of the following symptoms: bleeding, diarrhea (loose stools) or more bowel movements than usual, stomach-area (abdomen) pain or tenderness, fever, or nausea.

Tafinlar, in combination with Mekinist, 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.

The combination of Tafinlar and Mekinist can cause heart problems, including heart failure. A patient’s heart function should be checked before and during treatment. Patients should be advised to call their health care 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, can cause severe eye problems that can lead to blindness. Patients should be advised to call their health care provider right away if they get: 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, can cause lung or breathing problems. Patients should be advised to tell their health care provider if they have new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Fever is common during treatment with Tafinlar in combination with Mekinist, but may also be serious. 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 health care provider right away if they get a fever.

Rash and other skin reactions are common side effects of Tafinlar in combination with Mekinist. In some cases these rashes and other skin reactions can be severe or serious, and may need to be treated in a hospital. Patients should be advised to call their health care 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, or skin redness.

Some people may develop high blood sugar or worsening diabetes during treatment with Tafinlar in combination with Mekinist. For patients who are diabetic, their health care provider should check their blood sugar levels closely during treatment. Their diabetes medicine may need to be changed. Patients should be advised to tell their health care provider if they have increased thirst, urinate more often than normal, or produce an increased amount of urine.

Tafinlar, in combination with Mekinist, may cause healthy red blood cells to break down too early in people with glucose-6-phosphate dehydrogenase deficiency. This may lead to a type of anemia called hemolytic anemia, where the body does not have enough healthy red blood cells. Patients should be advised to tell their health care provider if they have yellow skin (jaundice), weakness or dizziness, or shortness of breath.

Tafinlar, in combination with Mekinist, can cause new or worsening high blood pressure (hypertension). A patient’s blood pressure should be checked during treatment. Patients should be advised to tell their health care provider if they develop high blood pressure, their blood pressure worsens, or if they have severe headache, lightheadedness, blurry vision, or dizziness.

The most common side effects of Tafinlar, in combination with Mekinist, include fever, rash, nausea, fatigue, headache, chills, diarrhea, vomiting, high blood pressure (hypertension), joint aches, muscle aches, swelling of the face, arms, or legs, and cough.

Please see full Prescribing Information for Tafinlar and Mekinist.

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Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 125,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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