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MEDIA & INVESTOR RELEASE

Novartis Tafinlar® + Mekinist® demonstrates long-term, relapse-free survival benefit for high-risk, stage III melanoma patients in study published in NEJM

- *COMBI-AD is first trial to demonstrate 5-year relapse-free survival with targeted therapy as adjuvant treatment in high-risk patients with stage III BRAF-mutated melanoma*[1]

- *Adjuvant treatment with standard-of-care targeted therapy Tafinlar + Mekinist reduced the risk of relapse or death by 49% compared to placebo*[1]

- *Updated data show Tafinlar + Mekinist improved distant metastasis-free survival, a secondary endpoint*[1]

Basel, September 16, 2020 — Novartis announced previously reported data from the Phase III COMBI-AD study were published today in *The New England Journal of Medicine.* The study shows more than half of high-risk patients with resected, stage III BRAF V600-mutated melanoma treated with Tafinlar® (dabrafenib) + Mekinist® (trametinib) were alive and relapse-free at 5 years[1]. Research suggests the majority of relapses in high-risk stage III melanoma generally occur within 5 years[1,2].

“Findings published today offer confidence that treatment with dabrafenib and trametinib following surgery provides a durable, long-term relapse-free survival benefit for those at high risk of cancer recurrence,” said Prof. Reinhard Dummer, M.D., Vice Chairman of the Department of Dermatology, University Hospital of Zurich. “These findings add to the growing body of evidence demonstrating the clinical value of dabrafenib and trametinib in the adjuvant setting.”

Results showed 52% of patients (95% CI, 48-58%) treated with Tafinlar + Mekinist were alive and relapse-free at 5 years compared to 36% of patients (95% CI, 32-41%) who received placebo. Median relapse-free survival (RFS) was not reached in the Tafinlar + Mekinist arm (95% CI, 47.9 months-NR) compared to 16.6 months (95% CI, 12.7-22.1 months) in the placebo arm. Treatment with Tafinlar + Mekinist reduced the risk of relapse or death by 49% compared to placebo (hazard ratio, HR, 0.51 [95% CI, 0.42-0.61])[1]. These findings were presented at the 2020 ASCO Virtual Scientific Program.

A subgroup analysis showed a generally similar RFS benefit across all substages, as assessed by AJCC-7 criteria. The five-year distant metastasis-free survival (DMFS) rate, a secondary endpoint, was 65% (95% CI, 61-71%) in patients treated with Tafinlar + Mekinist compared to 54% (95% CI, 49-60%) in patients who received placebo. COMBI-AD is ongoing to assess the secondary endpoint of overall survival (OS); the OS analysis at the first interim analysis showed a 3-year OS rate of 86% in the Tafinlar + Mekinist arm compared to 77% in the placebo arm. Overall survival results favored the combination therapy with Tafinlar +

Mekinist over placebo, but the prespecified interim significance threshold of P = 0.000019 was not met.

“Reaching the five year mark without relapse is a profound moment for a patient living with high-risk, stage III melanoma,” said Jeff Legos, Ph.D., MBA, Senior Vice President, Head of Oncology Drug Development, Novartis Oncology. “Tafinlar + Mekinist has helped patients and clinicians reimagine what is possible for patients living with advanced melanoma. We are proud of the deep and durable benefit demonstrated in COMBI-AD and remain grateful to the patients, investigators and their families who participated in this clinical trial.”

During the extended follow-up, all patients had completed therapy. There was no clinically meaningful difference between the Tafinlar + Mekinist and placebo arms in the rate or severity of serious adverse events reported during the follow-up period.

More than 285,000 cases of melanoma are diagnosed every year globally and about half of these have a BRAF mutation[3,4]. Patients who receive surgical treatment for stage III melanoma may have a risk of recurrence because melanoma cells may remain in the body after surgery[5].

About the COMBI-AD Study
COMBI-AD is a pivotal Phase III study evaluating Tafinlar (dabrafenib) + Mekinist (trametinib) in patients with stage III, BRAF V600E/K-mutant melanoma without prior anticancer therapy. It is the longest follow-up, at 60 months, and largest dataset to date of patients with stage III melanoma receiving targeted therapy for adjuvant treatment[1,6].

It is a two-arm, randomized, double-blind Phase III study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of melanoma after surgical resection. Patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk [stage IIIa (lymph node metastasis >1 mm), IIIb or IIIc as per AJCC 7th edition] cutaneous melanoma were screened for eligibility. Subjects were randomized to receive either dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) combination therapy or two placebos for up to one year. The primary end point is recurrence-free survival, and secondary endpoints include overall survival, distant metastasis-free survival, freedom from relapse analysis and safety[1,7].

About Tafinlar + Mekinist Combination
Tafinlar and Mekinist are prescription medicines that can be used in combination to treat people with a type of skin cancer called melanoma:

- That has spread to other parts of the body (metastatic) or cannot be removed by surgery (unresectable), and
- That has a certain type of abnormal "*BRAF*" (V600E or V600K mutation-positive) gene

Tafinlar and Mekinist are prescription medicines that can be used in combination to help prevent melanoma that has a certain type of abnormal "*BRAF*" gene from coming back after the cancer has been removed by surgery.

Tafinlar and Mekinist are prescription medications that can be used in combination to treat a type of lung cancer called non-small cell lung cancer (NSCLC) that has spread to other parts of the body (metastatic NSCLC), and that has a certain type of abnormal "*BRAF* V600E" gene.

Tafinlar and Mekinist are prescription medications that can be used in combination to treat a type of thyroid cancer called anaplastic thyroid cancer (ATC):

- That has spread to other parts of the body and you have no satisfactory treatment options, and
- That has a certain type of abnormal "*BRAF*" gene

Tafinlar, in combination with Mekinist, should not be used to treat people with wild-type *BRAF* melanoma. Mekinist should not be used to treat people who already have received a *BRAF* inhibitor for treatment of their melanoma and it did not work or is no longer working.

Your health care provider will perform a test to make sure that Tafinlar and Mekinist , in combination, are right for you.

It is not known if Tafinlar and Mekinist are safe and effective in children.

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 any skin changes, including 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, may need to be treated in a hospital, or lead to death. Patients should be advised to call their

health care provider if they get any of the following symptoms: blisters or peeling of skin, mouth sores, blisters on the lips or around the mouth or eyes, high fever or flu-like symptoms, and/or enlarged lymph nodes.

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 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.

Men (including those who have had a vasectomy) should use condoms during sexual intercourse during treatment with Tafinlar and Mekinist and for at least 4 months after the last dose of Tafinlar and Mekinist. For women of reproductive potential, Tafinlar and Mekinist, in combination, may harm your unborn baby. Use effective birth control (contraception) during treatment with Tafinlar and Mekinist in combination, and for 4 months after stopping treatment with Tafinlar and Mekinist. The most common side effects for patients with metastatic melanoma are: pyrexia, nausea, rash, chills, diarrhea, headache, vomiting, hypertension, arthralgia, peripheral edema, and cough. The most common side effects for patients with stage III melanoma receiving the combination as adjuvant therapy are: pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia. The most common side effects for patients with NSCLC: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea.

Please see full Prescribing Information for Tafinlar at https://www.novartis.us/sites/www.novartis.us/files/tafinlar.pdf and Mekinist at https://www.novartis.us/sites/www.novartis.us/files/mekinist.pdf.

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containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 109,000 people of more than 140 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

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