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MEDIA & INVESTOR RELEASE

Novartis announces long-term, relapse-free survival benefit for high-risk, stage III melanoma patients treated with Tafinlar® + Mekinist® following surgery

- *More than half of patients with BRAF-mutated advanced melanoma taking Tafinlar + Mekinist were alive and free of a relapse at 5-years*[1]

- *Study conclusions are drawn from the largest dataset and longest follow-up to date of patients with BRAF-mutated melanoma treated with targeted therapy following the surgical removal of their cancer*[1,2]

- *Data are from the five-year follow-up of the COMBI-AD trial presented at the ASCO20 Virtual Scientific Program*[1]

Basel, May 29, 2020 — Novartis announced today updated results from the landmark COMBI-AD clinical trial, demonstrating that treatment with Tafinlar® (dabrafenib) and Mekinist® (trametinib) following the surgical removal of melanoma offers a long-term and durable relapse-free survival (RFS) benefit to high-risk patients diagnosed with stage III, BRAF-mutation positive melanoma[1]. Researchers reported that 52% (95% CI, 48%-58%) of patients treated with adjuvant Tafinlar + Mekinist were alive and relapse-free at five years[1]. Among patients in the study's placebo arm 36% (95% CI, 32%-41%) were alive and relapse-free at the time of this analysis, generally consistent with typical melanoma relapse-free survival rates seen among patients with resected stage III disease without treatment[1,3-5]. Consistent RFS benefit was observed across all AJCC 7 stage III subgroups[1,6].

Median RFS, or the length of time when 50% of patients are still alive and relapse-free, was not yet reached at the 5-year data cut-off for patients on Tafinlar + Mekinist treatment, suggesting long-term benefit of targeted therapy in the adjuvant (post-surgical) setting (NR; 95% CI, 47.9 mo-NR)[1]. Median RFS was 16.6 months for patients taking a placebo (95% CI, 12.7-22.1 mo)[1]. 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].

"Our goal as clinicians is to give our stage III patients the best chance for relapse-free survival," said Prof. Axel Hauschild, MD, Professor of Dermatology, University Hospital Schleswig-Holstein, Germany. "Results from COMBI-AD show that adjuvant treatment with Tafinlar + Mekinist after surgical resection gives melanoma patients the chance for long-term relapse-free survival. Five years is a clinically and emotionally significant milestone for patients. Recurrent BRAF+ melanoma, once spread to other organs, can be more dangerous and difficult to treat. The durable, long-term results seen among patients in the COMBI-AD trial clearly point to the important role targeted therapy plays in the adjuvant setting."

The COMBI-AD study results are drawn from a prospective analysis of 870 patients with BRAF V600-mutated melanoma treated with Tafinlar + Mekinist after their surgery[1]. This study represents the largest collection of data and longest follow-up to date in this patient population treated with targeted therapy[2]. The findings were presented at the ASCO20 Virtual Scientific Program (Abstract #10001)[1].

“The five-year survival mark is an important and predictive milestone for people with melanoma and the doctors who care for them,” said John Tsai, MD, Head of Global Drug Development and Chief Medical Officer, Novartis. “We see an almost 50% risk reduction in melanoma relapse or death in the COMBI-AD data announced today, and we believe patients will find this information helpful in choosing a treatment after surgery. We thank the patients and their families who participated in this long-term clinical trial. Their participation and commitment is helping the community learn how a BRAF-targeted therapy can reimagine outcomes for patients with resectable stage III melanoma.”

Visit https://www.virtualcongress.novartis.com/ASCO20 for the latest information from Novartis, including our commitment to the Oncology community, and access to our ASCO20 Virtual Scientific Program data presentations (for registered participants).

About the COMBI-AD Study[1,2,6,7]
COMBI-AD is a pivotal Phase III study evaluating Tafinlar (dabrafenib) + Mekinist (trametinib) among 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.

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] 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.

Melanoma staging assessed based on AJCC guidelines version 7.

During the five-year follow-up, updated safety analyses were not performed because no patients remained on therapy during the extended follow-up period.

About Melanoma
There are more than 285,000 new diagnoses of melanoma (Stages 0-IV) worldwide each year, approximately half of which have a BRAF mutation[8,9]. Genetic tests can determine whether a tumor has a BRAF mutation[10].

One way melanoma is staged is by how far it has metastasized[11]. In stage III melanoma, tumors have spread to the regional lymph nodes, presenting a higher risk of recurrence or metastases[11]. Patients who receive surgical treatment for stage III melanoma may have a high risk of recurrence because melanoma cells may remain in the body after surgery[12]. Generally the majority of relapses in stage III melanoma occur within 5 years[13]. Patients should ask their doctor if they are at risk for melanoma returning[12].

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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About Novartis

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