Novartis COMBI-AD study of Tafinlar® + Mekinist® continues to demonstrate relapse free survival benefit in patients with BRAF V600-mutant stage III melanoma

- Extended follow up results confirm leading BRAF/MEK inhibitor combination Tafinlar + Mekinist continues to show relapse free survival benefit
- Cure rate modeling which estimates fraction of patients who may not relapse was 54% with adjuvant Tafinlar + Mekinist compared to 37% with placebo
- Updated COMBI-AD data results simultaneously published in Journal of Clinical Oncology

Basel, October 22, 2018 – Novartis announced today a new data analysis of COMBI-AD, a phase III multi-center study evaluating Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) in stage III adjuvant resected BRAF V600-mutant melanoma. With extended study follow up, Tafinlar in combination with Mekinist continued to show more than 50% risk reduction in relapse free survival (RFS) versus placebo in patients with resected BRAF V600-mutant stage III melanoma. The updated COMBI-AD data was also used to generate a statistical cure-rate model that estimated the fraction of patients who may not relapse. The cure rate was 54% (95% CI, 49%-59%) in the Tafinlar + Mekinist arm compared to 37% (95% CI, 32%-42%) in the placebo arm. These data were presented at the European Society of Medical Oncology in Munich, Germany (Abstract #LBA43) today and simultaneously published in The Journal of Clinical Oncology.

A separate biomarker analysis was conducted to identify predictors of clinical outcome and treatment response. These analyses showed that subgroups of patients at a higher risk of relapse could be defined based on specific immune gene expression signatures (GES) and tumor mutation burden (TMB). Exploratory analysis of RFS in the treatment vs. placebo arms in all TMB/immune GES subgroups suggested that specific subgroups may have a greater RFS benefit, but the predictive value of TMB and immune GES warrants further validation in a prospective study.

“In addition to confirming prior relapse free survival results in the adjuvant setting, this biomarker analysis of COMBI-AD provides important information about the prognostic and potentially predictive value of TMB and immune gene expression signatures in resected BRAF V600-mutant melanoma patients,” said Georgina Long, BSc., PhD, MBBS, FRACP, Medical Oncologist, Melanoma Institute Australia, The University of Sydney.

In the phase III COMBI-AD global study, at median follow-ups of 44 months (Tafinlar + Mekinist) and 42 months (placebo), the three-and four-year RFS rates were 59% ([95% CI, 0.55-0.64]) and 54% ([95% CI, 0.49-0.59]) in the Tafinlar + Mekinist arm and 40% ([95% CI, 0.35-0.45]) and 38% ([95% CI, 0.34-0.44]) in the placebo arm, respectively (HR, 0.49 [95% CI, 0.40-0.59]). RFS was also analyzed by subgroups defined by baseline disease stage by the American Joint Committee on Cancer 7th and 8th editions and included nodal metastatic burden, and ulceration status. A cure rate model estimated that the fraction of patients who
may not relapse was 54% (95% CI, 49%-59%) in the Tafinlar + Mekinist arm compared with 37% (95% CI, 32%-42%) in the placebo arm. The fraction of patients remaining relapse free long term was estimated using a Weibull mixture cure-rate model. No updated safety analysis was performed as all patients have completed treatment at the time of the updated RFS analysis.

“The data generated from the COMBI-AD study have the ability to transform treatment decisions for patients with BRAF V600 melanoma,” said Samit Hirawat, MD, Head, Novartis Oncology Global Drug Development. “Not only do the results from the extended analysis continue to provide confirmation of the long-term benefit with adjuvant Tafinlar and Mekinist, but the comprehensive biomarker analysis of the largest adjuvant dataset to date highlight important prognostic information to identify patients at higher risk of relapse.”

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 (apoptosis). 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.

About COMBI-AD
The COMBI-AD study evaluated Tafinlar + Mekinist among patients with stage III, BRAF V600-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). The combination treatment group also saw an improvement in a key secondary endpoint of OS (HR: 0.57 [95% CI: 0.42-0.79] p=0.0006, which did not cross the predefined interim analysis boundary of p=0.000019 to claim statistical significance).

Other secondary endpoints in the initial primary analysis where the combination demonstrated a clinically meaningful benefit included distant metastasis-free survival (DMFS) (HR: 0.51 [95% CI: 0.40-0.65]), and freedom from relapse (FFR) (HR: 0.47 [95% CI: 0.39-0.57]). In a separate analysis, Tafinlar + Mekinist also demonstrated benefit regardless of baseline factors, including disease stage, nodal metastatic burden, and ulceration. 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).

Based on updated data with median follow up of 44 months (Tafinlar + Mekinist) and 42 months (matching placebo), the 3- and 4-year relapse-survival benefit maintained at 59% (95% CI, 55%-64%) and 54% (95% CI, 49%-59%) in the dabrafenib plus trametinib arm and 40% (95% CI, 35%-45%) and 38% (95% CI, 34%-44%) in the placebo arm, respectively (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, three-year, and four-year RFS were consistently higher than placebo (one year: 88% vs. 56%; two year: 67% vs. 44%; three year: 59% vs. 40%; four year: 54% vs. 38%). The combination treatment group also saw an improvement in the secondary endpoint of distant metastasis-free survival (DMFS) (HR: 0.53 [95% CI: 0.42-0.67]). No new safety analysis was performed.
About Melanoma
There are about 280,000 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
Tafinlar + 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 melanoma and NSCLC, among other cancers. When Tafinlar is used with Mekinist, the combination has been shown to slow tumor growth more than either drug alone.

Tafinlar + Mekinist have been investigated for the treatment of a variety of cancers as part of an ongoing clinical trial program. Tafinlar + Mekinist are approved in more than 60 countries, for uses including:

- as monotherapy and in combination for the treatment of subjects with unresectable or metastatic melanoma with a BRAFV600 mutation
- in combination for the adjuvant treatment of patients with Stage III melanoma with a BRAFV600 mutation, following complete resection
- in combination for the treatment of patients with advanced NSCLC with a BRAFV600 mutation
- in combination for the treatment of patients with locally advanced or metastatic ATC with a BRAFV600 mutation

Approved indications vary worldwide. Please refer to local labeling for indication language in a particular country.

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 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, 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.

Disclaimer
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About Novartis

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 1 billion people globally and we are finding innovative ways to expand access to our latest treatments. About 125,000 people of more than 140 nationalities work at Novartis around the world. Find out more at www.novartis.com.

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