Novartis landmark study of Tafinlar® + Mekinist® demonstrates durable survival benefit at five years in patients with BRAF mutation-positive metastatic melanoma

- *Study is longest follow-up to date of a BRAF and MEK inhibitor combination therapy in patients with BRAF V600-mutant metastatic melanoma*¹

- *Study shows stable overall survival and progression-free survival lasting more than five years with consistent tolerability*⁴

- *Initial data from separate Phase II trial of BRAF and MEK inhibitors showed positive results in BRAF V600-mutant melanoma patients with metastatic brain metastases*²

Basel, June 4, 2017 – Novartis today announced results from a Phase II study showing a durable survival benefit for some patients with BRAF V600 mutation-positive metastatic melanoma (MM) when treated with the combination of Tafinlar® (dabrafenib) + Mekinist® (trametinib)¹. The findings from the landmark five-year analysis of the trial, BRF113220, represent the longest follow-up to date of a BRAF and MEK inhibitor combination therapy in this patient population, and were presented today at the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago (Abstract #9505).

A total of 162 patients received either Tafinlar monotherapy (150 mg BID) (n = 54) or the Tafinlar + Mekinist combination (150 mg BID/2 mg OD) (n = 54). After five years, 20 patients (37%) remain in the study, including seven (13%) in the Tafinlar monotherapy arm and 13 (24%) in the combination therapy arm, demonstrating that overall survival (OS) with combination therapy is superior to monotherapy¹. The four- and five-year OS rates with monotherapy were 23% and 21%, respectively. The four- and five-year OS rates with combination therapy were 30% and 28%, respectively, reflecting a stabilization of OS in patients enrolled in the study¹. Progression-free survival (PFS) in the monotherapy arm was consistently 3% whereas PFS at both four and five years was 13%, also demonstrating stabilization¹. Forty-five of 54 patients (83%) in the Tafinlar monotherapy arm included in this updated analysis had crossed over to Tafinlar + Mekinist combination (150 mg BID/2 mg OD); the survival outcomes in these crossover patients continued to be followed under the Tafinlar arm.

“These recent results from the longest follow-up of a BRAF and MEK inhibitor targeted study show that a significant cohort of patients with metastatic melanoma positive for the BRAF V600 mutation can achieve long-term survival with Tafinlar + Mekinist combination therapy,” said lead investigator Jeff Weber, MD, PhD, Deputy Director, Laura and Isaac Perlmutter Cancer Center, Co-Director, Melanoma Program & Head of Experimental Therapeutics NYU Langone Medical Center. “This combination of targeted therapy should be considered by physicians when making treatment decisions.”

Adverse events were consistent with other Tafinlar + Mekinist studies, and additional follow-up revealed no new safety signals¹.
“These data demonstrate the long-term benefit of Tafinlar in combination with Mekinist for certain patients living with metastatic melanoma,” said Vas Narasimhan, Global Head Drug Development and Chief Medical Officer, Novartis. “We are gratified to see these data showing that patients can benefit long-term from Tafinlar + Mekinist, and we look forward to evaluating additional Phase III long-term survival data.”

Additionally, Novartis presented results from a Phase II study showing a positive, statistically significant intracranial response for patients with BRAF V600 mutation-positive metastatic melanoma (MM) when treated with the combination of Tafinlar + Mekinist (Abstract #9506). The findings from the 30-month trial, COMBI-MB, represent the first report of a Phase II trial evaluating a BRAF and MEK inhibitor combination therapy in patients with BRAF V600-mutant melanoma brain metastases (MBM).

The COMBI-MB study evaluated Tafinlar + Mekinist in 125 patients enrolled in four cohorts. In Cohort A (patients who were BRAF V600E mutation-positive, had asymptomatic MBM and no local prior treatment), investigator-assessed intracranial response rate (IRR) was 58% (95% CI: 46, 69). Extracranial response rate (ERR) was 55% (95% CI: 43, 67) and overall response rate (ORR) was 58% (95% CI: 46, 69). Median PFS was 5.6 months (95% CI: 5.3, 7.4). Six-month OS was 79%; with 31 patients (41%) still in follow-up. Preliminary median OS was 10.8 months (95% CI: 8.7, 19.6).

Adverse events across cohorts (any, 98%; grade 3/4, 48%) were consistent with prior Tafinlar + Mekinist studies; 10% of patients (8% in cohort A) discontinued due to adverse events.

Results of the COMBI-MB study were simultaneously published in the June issue of The Lancet Oncology, available online on Sunday, June 4, at 10:00 AM.

Additional poster and oral presentations related to the investigational use of Tafinlar and Mekinist were also presented at the meeting, including an updated five year landmark analysis of Phase II (BREAK-2) and Phase III (BREAK-3) studies evaluating Tafinlar monotherapy in patients with BRAF V600-mutant melanoma, and studies in BRAF V600E-mutated advanced thyroid cancer (ATC) and non-small cell lung cancer (NSCLC).

About BRF113220
The BRF113220 study is an open-label, Phase II trial. Patients with BRAF V600-mutant MM were randomly assigned to receive Tafinlar monotherapy (150 mg BID), Tafinlar + Mekinist (150 mg BID/1 mg OD), or Tafinlar + Mekinist (150 mg BID/2 mg OD). Patients who progressed on Tafinlar alone could cross over to the Tafinlar + Mekinist 150/2 arm. Patient disposition, patient demographics, and four- and five-year efficacy and safety were analyzed for the Tafinlar monotherapy and Tafinlar + Mekinist (approved 150/2 dose) arms.

About COMBI-MB
The COMBI-MB study is an open-label, Phase II trial and included four patient cohorts based on mutation status, MBM symptoms and history of treatment: (A) BRAF V600E, asymptomatic MBM, and no prior local therapy (76 patients); (B) BRAF V600E, asymptomatic MBM, and prior local therapy (16 patients); (C) BRAF V600D/K/R, asymptomatic MBM, with or without prior local therapy (16 patients); and (D) BRAF V600D/E/K/R, symptomatic MBM, with or without prior local therapy (17 patients).

The primary endpoint was intracranial response (IR) in cohort A patients. Secondary endpoints included IR in cohorts B, C, and D; intracranial disease control; extracranial response (ER); overall response (OR); duration of IR, ER, and OR; PFS; OS; and safety.
About Melanoma
Metastatic melanoma is the most serious and life-threatening type of skin cancer and is associated with low survival rates. Only about 20% of people will survive for at least five years following a diagnosis with late-stage disease. There are about 200,000 new cases of melanoma diagnosed worldwide each year, approximately half of which have BRAF mutations, a key target in the treatment of metastatic melanoma. Gene tests can determine whether a tumor has a BRAF mutation.

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, Australia, Canada and other countries.

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 non-small cell lung cancer (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 indication.

Tafinlar and Mekinist are also indicated in more than 50 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 for Metastatic Melanoma
TAFINLAR and MEKINIST, in combination, may cause serious side effects such as the risk of new cancers, including both skin cancer and non-skin cancer. Patients should be advised to contact their doctor 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, and can lead to death. Patients should be advised to call their health care 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,” or have red or black stools that look like tar.

MEKINIST, alone or in combination with TAFINLAR, can cause inflammation of the colon and bleeding in the stomach or intestines that can lead to death. Patients should report to their health care provider immediately if they have diarrhea, stomach or abdominal pain, 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 more 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 is a common side effect of TAFINLAR in combination with MEKINIST. TAFINLAR, in combination with MEKINIST, can also cause other skin reactions. In some cases these rashes and other skin reactions can be severe, 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 G6PD 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, or dizziness.

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

Please see full prescribing information for TAFINLAR and MEKINIST at https://www.hcp.novartis.com/products/tafinlar-mekinist/advanced-metastatic-melanoma.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "should," "can," "look forward," "later this year," "investigational," "will," "being investigated," "ongoing," "yet," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Tafinlar + Mekinist, or regarding potential future revenues from Tafinlar and Mekinist, both as single agents and in combination with the other. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or
more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Tafinlar + Mekinist will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Tafinlar and Mekinist, either as single agents or in combination with the other will be commercially successful in the future. In particular, management’s expectations regarding Tafinlar and Mekinist, both as single agents and in combination with the other could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; the company’s ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing and reimbursement pressures; safety, quality or manufacturing issues, 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.

About Novartis

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 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 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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