Novartis Phase III study demonstrates adjuvant Tafinlar® + Mekinist® reduced the risk of disease recurrence by 53% in patients with resected BRAF V600 mutation-positive melanoma

- The three-year relapse-free survival (RFS) rate for patients treated with the combination was 58%, compared to 39% with placebo

- Consistent improvement in RFS observed across all pre-specified subgroups, including patients with stage III A, B and C melanoma

- Study demonstrated clinically meaningful improvements in secondary endpoints, including overall survival (OS), distant metastasis-free survival (DMFS) and freedom from relapse (FFR)

- First adjuvant targeted therapy combination to demonstrate a clinical benefit in patients with a BRAF V600 mutation

- Results from COMBI-AD presented at the European Society for Medical Oncology annual congress and simultaneously published in the New England Journal of Medicine

Basel, September 11, 2017 – Novartis today announced results from a Phase III study of 870 patients with stage III BRAF V600E/K mutation-positive melanoma after complete surgical resection treated with the combination of Tafinlar® (dabrafenib) + Mekinist® (trametinib). Findings from the COMBI-AD study, which met its primary endpoint, found a statistically significant 53% reduction in the risk of death or recurrence in patients treated with the BRAF and MEK inhibitor combination therapy versus placebo (HR [hazard ratio]: 0.47 [95% CI (confidence interval): 0.39-0.58]; median not reached vs. 16.6 months, respectively; p<0.001), with no new safety signals reported. Results of the study will be presented during the Presidential Symposium today at the European Society for Medical Oncology Congress (ESMO) in Madrid (Abstract #LBA6), and were simultaneously published in the New England Journal of Medicine.

“The efficacy and tolerability of Tafinlar in combination with Mekinist seen in this study represent an important step forward in the treatment of stage III BRAF V600E/K mutation-positive melanoma,” said lead investigator Axel Hauschild, MD, PhD, Professor of Dermatology, University Hospital Schleswig-Holstein, in Kiel, Germany. “These unprecedented results confirm a targeted therapy combination has the potential to transform the standard of care in the melanoma adjuvant setting.”

“While surgery is a curative option for most patients with localized melanoma, there is a need for improved standard of care therapies for patients – especially for stage III disease, which carries a higher risk of relapse and death following resection,” said Vas Narasimhan, Global Head Drug Development and Chief Medical Officer, Novartis. “The COMBI-AD data results address a significant unmet need in patients with stage III melanoma. We look forward to discussing the results with regulatory authorities worldwide.”
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) and Mekinist (2 mg QD) combination (n = 438) or matching placebos (n = 432)\(^1\). After a median follow-up of 2.8 years, the primary endpoint was met in that 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 reached vs. 16.6 months, respectively; p<0.001)\(^1\). 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: 58% vs. 39%)\(^1\). 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 where the combination demonstrated a clinically meaningful benefit include DMFS (HR: 0.51 [95% CI: 0.40-0.65]), and FFR (HR: 0.47 [95% CI: 0.39-0.57])\(^1\).

Adverse events (AEs) were consistent with other Tafinlar + Mekinist studies, and no new safety signals were reported\(^1\). Of patients treated with the combination, 97% experienced an AE; 41% had grade 3/4 AEs and 26% had AEs leading to treatment discontinuation (vs. 88%, 14% and 3%, respectively, with placebo)\(^1\).

In a separate study, Novartis presented Phase II results from BRF113928, showing efficacy for patients with BRAF V600E-mutant metastatic non-small cell lung cancer (NSCLC) without prior systemic therapy for metastatic disease when treated with the combination of Tafinlar + Mekinist (Abstract #LBA51)\(^2\). Among the 36 treatment-naïve patients receiving 150 mg of Tafinlar twice daily and 2 mg of Mekinist once daily, the overall response rate (ORR) was 64% (95% CI: 46%-79%). After a median follow-up of 15.9 months, median duration of response (DoR) was 10.4 months (95% CI: 8.3-17.9 months), and median progression-free survival (PFS) was 10.9 months (95% CI: 7.0-16.6 months)\(^2\). Median OS was 24.6 months (95% CI: 12.3 months-not estimable), two-year OS rate was 51% (95% CI: 33-67%)\(^3\). These study results were simultaneously published in *The Lancet Oncology*\(^4\).

Findings from the study demonstrated clinically meaningful antitumor activity in patients who had not received prior systemic therapy and in patients who had received at least one platinum-based chemotherapy for their metastatic NSCLC, supporting recent approvals by the European Commission (EC) and US Food and Drug Administration (FDA).

The most common AEs (incidence >20%) were pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough and dyspnea.

Additional poster and oral presentations related to the investigational use of Tafinlar and Mekinist in melanoma were also presented at the meeting, including:

- **Phase II Study of Neoadjuvant Dabrafenib + Trametinib (D+T) for Resectable Stage IIIb/C BRAF V600-Mutant Melanoma** [Abstract #1220PD]
- **Five-year Efficacy and Safety Update From METRIC: Trametinib vs. Chemotherapy in Patients with BRAF V600E/K–Mutant Advanced or Metastatic Melanoma** [Abstract #1226PD]
- **A Phase III Randomized, Double-Blind, Placebo-Controlled Study Comparing the Combination of PDR001 + Dabrafenib + Trametinib vs. Placebo + Dabrafenib + Trametinib in Treatment-Naïve Patients with Unresectable or Metastatic BRAF V600-Mutant Melanoma** (COMBI-i) [Abstract #1259TiP]
- **KEYNOTE-022 Update: Phase I Study of First-Line Pembrolizumab (pembro) Plus Dabrafenib (D) and Trametinib (T) for BRAF-Mutant Advanced Melanoma** [Abstract #1216O]
- **A Phase II, Randomized, Open Label Study of Neoadjuvant Pembrolizumab with/without Dabrafenib and Trametinib (D+T) in BRAF V600-Mutant Resectable Stage IIIb/C/D Melanoma (NeoTrio Trial)** [Abstract #1256TiP]
Dabrafenib and Trametinib Combination in Real Life Patients Including Brain Metastases: French Experience within MelBase [Abstract #1255P]

About COMBI-AD
The COMBI-AD study is a randomized, double-blind, placebo-controlled, Phase III study and included a total of 870 patients with stage III, BRAF V600E/K-mutant melanoma who had undergone prior complete surgical resection. Patients were treated for 12 months and stratified based on BRAF mutation (V600E vs. V600K) and stage (IIIA vs. IIIB vs. IIIC).

The primary endpoint was RFS. Secondary endpoints included OS, DMFS, FFR, and safety.

About Melanoma
There are about 200,000 new cases of melanoma diagnosed worldwide each year, approximately half of which have BRAF mutations. Gene tests can determine whether a tumor has a BRAF mutation\(^5,6\). Patients who receive surgical treatment for melanoma may have a high risk of recurrence because melanoma cells can remain in the body after surgery\(^7\). Adjuvant therapy may be recommended for patients with high-risk melanoma to help reduce the risk of melanoma returning\(^7\).

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.

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 + Mekinist combination may cause serious side effects.

Tafinlar in combination with Mekinist should only be used to treat patients with a change (mutation) in the BRAF gene; therefore, doctors should test their patients before treatment, as patients without a BRAF mutation and with a RAS mutation can be at risk of increased cell proliferation in the presence of a BRAF inhibitor.

Doctors should also consider other treatment options for their patients if they had been previously treated with a BRAF inhibitor as single agent, as the limited data available have shown that the efficacy of Tafinlar + Mekinist is lower in these patients.

When Tafinlar is used in combination with Mekinist, or when Tafinlar is administered as monotherapy, it can cause new cancers (both skin cancer and non-skin cancer). Patients should be advised to contact their doctor immediately for any new lesions, changes to existing lesions on their skin, or signs and symptoms of other malignancies.
Tafinlar in combination with Mekinist, or Mekinist alone, can cause severe bleeding, and in some cases can lead to death. Patients should be advised to call their healthcare 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," have red or black stools that look like tar, or any unusual signs of bleeding.

Tafinlar in combination with Mekinist, or either drug alone, can cause severe eye problems that can lead to blindness. Patients should be advised to call their healthcare provider right away if they get these symptoms of eye problems: 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, or Tafinlar alone, can cause fever which may be serious. When taking Tafinlar in combination with Mekinist, fever may happen more often or may be more severe. 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 healthcare provider right away if they get a fever above 38.5°C (101.3°F) while taking Tafinlar.

Tafinlar in combination with Mekinist, or Mekinist alone, can affect how well the heart pumps blood. A patient's heart function should be checked before and during treatment. Patients should be advised to call their healthcare 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, or Tafinlar alone, can cause abnormal kidney function or inflammation of the kidney. Abnormal kidney function may happen more often for patients with fever or too much fluid loss. Patients should be advised to call their healthcare provider right away if they have a fever above 38.5°C (101.3°F), decreased urine, fatigue, loss of appetite or discomfort in lower abdomen or back. Tafinlar has not been studied in patients with renal insufficiency (defined as creatinine > 1.5 x ULN) therefore caution should be used in this setting.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause abnormal liver function. A patient may feel tired, lose appetite, yellow skin, dark urine colour, or discomfort in abdomen. The liver function abnormality needs to be assessed by laboratory test of the blood. Patients should consult their healthcare provider if they have such experience. Administration of Tafinlar or Mekinist should be done with caution in patients with moderate to severe hepatic impairment.

Elevations in blood pressure have been reported in association with Mekinist in combination with Tafinlar, or with Mekinist alone, in patients with or without pre-existing hypertension. Patients should be advised to monitor blood pressure during treatment with Mekinist and control potential hypertension by standard therapy, as appropriate.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause inflammation of the lung tissue. Patients should notify their doctor if they experience any new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Rash is a common side effect of Tafinlar in combination with Mekinist, or with Mekinist alone. Tafinlar in combination with Mekinist, or Mekinist alone, can also cause other skin reactions which can be severe, and may need to be treated in a hospital. Patients should be advised to call their healthcare 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, skin redness.
Tafinlar in combination with Mekinist, or Mekinist alone, can cause muscle breakdown, a condition called Rhabdomyolysis. Patients experiencing muscle pain, tenderness, weakness or a swelling of their muscles should contact their healthcare provider immediately.

Tafinlar in combination with Mekinist, or Tafinlar alone, can uncommonly cause an inflammation of the pancreas (pancreatitis). Patients should be promptly investigated if they experience unexplained abdominal pain and closely monitored if they re-start Tafinlar after a prior episode of pancreatitis.

Tafinlar in combination with Mekinist, or Mekinist alone, 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.

Mekinist in combination with Tafinlar, or Mekinist alone, may increase the risk of developing holes in the stomach or intestine (gastrointestinal perforation). Treatment with Mekinist alone or in combination with Tafinlar should be used with caution in patients with risk factors for gastrointestinal perforation, including concomitant use of medications with a recognized risk of gastrointestinal perforation.

Tafinlar and Mekinist both can cause harm to an unborn baby when taken by a pregnant woman. Tafinlar can also render hormonal contraceptives ineffective.

The most common side effects of Tafinlar + Mekinist combination include fever, nausea, diarrhea, fatigue, chills, headache, vomiting, joint pain, high blood pressure, rash and cough. The incidence and severity of fever is increased when Mekinist is used in combination with Tafinlar.

Patients should tell their doctor of any side effect that bothers them or does not go away. These are not all of the possible side effects of Tafinlar + Mekinist combination. For more information, patients should ask their doctor or pharmacist.

Patients should take Tafinlar + Mekinist combination exactly as their health care provider tells them. Patients should not change their dose or stop taking Tafinlar + Mekinist combination unless their health care provider advises them to. Mekinist should be taken only once daily (either in the morning or evening, at the same time as Tafinlar). The first and second doses of Tafinlar should be taken approximately 12 hours apart. Patients should take Tafinlar + Mekinist at least 1 hour before or 2 hours after a meal. Do not take a missed dose of Tafinlar within 6 hours of the next dose of Tafinlar. Do not open, crush, or break Tafinlar capsules. Do not take a missed dose of Mekinist within 12 hours of the next dose of Mekinist.

Please see full Prescribing Information for Tafinlar and Mekinist.

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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 119,000 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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