Novartis’ Tafinlar® (dabrafenib) + Mekinist® (trametinib) demonstrate superior overall survival benefit in advanced melanoma patients at three-year follow up

- Latest data confirm an estimated 45% of patients who received Tafinlar® + Mekinist® combination therapy are alive versus 31% of patients on BRAF monotherapy.
- Second trial to confirm three-year landmark overall survival data for the combination.
- Advanced melanoma is a serious, life-threatening skin cancer, with typically low rates of survival for patients with late-stage disease.

Basel, October 8, 2016 – Novartis today announced data from the Phase III COMBI-v study demonstrating an overall survival (OS) and a progression-free survival benefit for patients with BRAF V600 mutation-positive advanced melanoma when treated first-line with the combination of Tafinlar® (dabrafenib) + Mekinist® (trametinib) compared to vemurafenib monotherapy. The results of this study, which was conducted in 704 patients, are being presented at the European Society for Medical Oncology (ESMO) 2016 Congress in Copenhagen.

“The three-year overall survival follow-up data from COMBI-v is remarkable because it is the second Phase III study this year to demonstrate a significant long-term survival benefit for BRAF mutation-positive melanoma patients treated with Tafinlar + Mekinist combination therapy compared to BRAF inhibitor monotherapy,” said Caroline Robert, MD, PhD, Head of Dermatology, Institute Gustave-Roussy. “The results of this trial continue to reinforce Tafinlar + Mekinist as a standard of care and sets a new benchmark for treating patients with BRAF V600 mutation-positive advanced melanoma.”

Results from the COMBI-v study found the estimated three-year survival rate to be 45% of patients receiving the combination of Tafinlar + Mekinist (95% CI, 39.1%-49.8%) compared with 31% of patients who received vemurafenib monotherapy (95% CI, 26.1%-36.4%)1. There were 34 patients who crossed over from the vemurafenib monotherapy arm to the combination arm after the combination demonstrated a significant OS benefit in a prior analysis1. Additionally, the estimated three-year progression-free survival rate was 24% (95% CI, 19.4%-28.8%) for the combination arm and 10% (95% CI, 5.9%-14.5%) for the vemurafenib monotherapy arm1.

“We are pleased to see the continued benefit of Tafinlar + Mekinist targeted combination therapy beyond three-years in another study,” said Alessandro Riva, MD, Global Head, Oncology Development & Medical Affairs. “As we’ve come to understand, this combination of targeted inhibitors has demonstrated an unprecedented ability to block the known resistance pathways and extend overall survival for BRAF mutation-positive patients. These results underscore our commitment to advancing the practice of precision oncology and extending patients’ lives through treatment options that target the root cause of their cancer.”

At three years of follow up, the combination of Tafinlar + Mekinist continued to demonstrate a benefit on the measures of duration of response (DoR) and overall response rate (ORR), in line with results seen at the two-year follow up analysis1.

The safety results were consistent with the profile observed to date for the combination and consistent with the profile observed for vemurafenib monotherapy; no new safety concerns were observed.
About the COMBI-v Study
COMBI-v is a two-arm, open-label, Phase III study comparing the combination of Tafinlar + Mekinist with vemurafenib monotherapy in patients with BRAF V600E/K mutation-positive unresectable or metastatic melanoma. The primary endpoint of this study was OS. The Independent Data Monitoring Committee (IDMC) stopped the trial early based on efficacy results observed in the Tafinlar + Mekinist study arm as part of a planned interim analysis¹.

About Melanoma
Advanced melanoma is the most serious and life-threatening type of skin cancer and is associated with low survival rates²,³. Only about 20% of people will survive for at least five years following a diagnosis with late-stage disease². There are about 200,000 new cases of melanoma diagnosed worldwide each year⁴, approximately half of which have BRAF mutations, a key target in the treatment of metastatic melanoma²,⁵. Gene tests can determine whether a tumor has a BRAF mutation²,⁶.

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 40 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 in combination with Mekinist combination may cause serious side effects.

Tafinlar in combination with Mekinist should only be used to treat melanoma 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 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 38.5oC (101.3oF) 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 38.5oC (101.3oF), 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, alone or in combination with Tafinlar, 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 recognised 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, tiredness, nausea, headache, chills, diarrhea, rash, joint pain, high blood pressure, vomiting 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.*

**Disclaimer**

The foregoing release contains forward-looking statements that can be identified by words such as “to confirm,” “continue,” “commitment,” “being investigated,” “ongoing,” “yet,” or similar terms, or by express or implied discussions regarding potential marketing approvals or new indications or labeling for Tafinlar and Mekinist, either in combination or as single agents, or regarding potential future revenues from Tafinlar and Mekinist, either in combination or as single agents. 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 and Mekinist, either in combination or as single agents, 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 in combination or as single agents, will be submitted or approved for sale in any additional markets, or at any particular time. Nor can there be any guarantee that Tafinlar and Mekinist, either in combination or as single agents, will be commercially successful in the future. In particular, management’s expectations regarding Tafinlar and Mekinist, in combination and as single agents, could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected 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 pressures; unexpected 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, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.

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References
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