

# Patients with aggressive form of melanoma lived for more than two years on average when taking Novartis therapies Tafinlar® + Mekinist®

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- Phase III data showed median overall survival of 25.6 months in patients with BRAF+ V600E/K metastatic melanoma who received Tafinlar + Mekinist
- Tafinlar + Mekinist combination also demonstrated significant improvement in health-related quality of life vs vemurafenib monotherapy in this Phase III study
- Metastatic melanoma is a serious, life-threatening skin cancer, and long-term survival rates are low for patients with late-stage disease(1,2)

EAST HANOVER, N.J., Sept. 27, 2015 /PRNewswire/ -- Novartis today announced updated data from the Phase III COMBI-v study showing a significant overall survival benefit for patients with BRAF V600E/K mutation-positive metastatic melanoma when treated with the combination of Tafinlar® (dabrafenib) + Mekinist® (trametinib) compared to vemurafenib monotherapy. The combination also demonstrated significant health-related quality of life improvements in the trial, including overall health, physical and social functioning. Results are being presented at the European Cancer Congress 2015 in Vienna.

"It is remarkable to see so many patients with BRAF V600E/K mutation-positive metastatic melanoma having long term responses and obtaining a significant decrease of the risk of death as compared with vemurafenib monotherapy," said Caroline Robert, MD, PhD, Head of Dermatology, Institute Gustave-Roussy. "This is the second Phase III trial of Tafinlar + Mekinist combination therapy to demonstrate a significant overall survival benefit over BRAF inhibitor monotherapy, further establishing Tafinlar + Mekinist as a standard of care for patients fighting BRAF V600 mutation-positive metastatic melanoma."

The significant overall survival benefit of Tafinlar + Mekinist from COMBI-v is consistent with the results demonstrated by the combination in COMBI-d, another Phase III trial previously reported at the American Society of Clinical Oncology (ASCO) annual meeting earlier this year.

In the COMBI-v study, the combination of Tafinlar + Mekinist achieved a statistically significant overall survival (OS) benefit compared to vemurafenib monotherapy (median for the combination 25.6 months vs 18.0 months; HR 0.66 [95% CI, 0.53-0.81],  $p < 0.001$ ). The rate of OS at two years was 51% for those receiving the Tafinlar + Mekinist combination and 38% for those receiving vemurafenib monotherapy<sup>3</sup>. In addition, the median overall response rate (ORR) was 65.6% in patients receiving the Tafinlar + Mekinist combination compared to 52.8% for those receiving vemurafenib monotherapy. The safety results from this study were consistent with the profile observed to date for the combination; no new safety concerns were observed<sup>3</sup>.

"Helping patients live longer with our targeted combination therapy, Tafinlar and Mekinist, is very gratifying," said Bruno Strigini, President, Novartis Oncology. "This exemplifies our mission to transform cancer care with the ultimate goal of identifying the right treatment for the right patient at the right time."

Metastatic melanoma is the most serious and life-threatening type of skin cancer<sup>1</sup> and only about one in five

patients survives for five years following diagnosis with late-stage disease<sup>2</sup>. There are about 200,000 new cases of melanoma diagnosed worldwide each year<sup>4</sup>, approximately half of which have BRAF mutations<sup>2</sup>. Gene tests can determine whether a tumor has a BRAF mutation, and results can play a key role in prognosis and determining appropriate treatment<sup>2</sup>.

In August 2015, the European Commission approved the combination of Tafinlar + Mekinist for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The European Commission approval applies to all 28 EU member states, plus Iceland, Norway and Liechtenstein. In July 2015, the US Food and Drug Administration (FDA) granted priority review for an application to obtain regular approval of the Tafinlar + Mekinist combination in BRAF V600E/K mutation-positive metastatic melanoma. Since January 2014, the combination of Tafinlar + Mekinist has been approved for use in the US in patients with BRAF V600E/K mutation-positive unresectable or metastatic melanoma as detected by an FDA-approved test. The combination was approved through the FDA's Accelerated Approval program and reviewed under a priority review designation. The approval was contingent on the results of the COMBI-d study, which was designed to evaluate the clinical benefit of the combination in patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation.

#### About the COMBI-v Study

COMBI-v was 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<sup>3</sup>.

Results from the COMBI-v study showed that the combination of Tafinlar + Mekinist achieved a statistically significant OS benefit compared to vemurafenib monotherapy (median for the combination 25.6 months vs 18.0 months; HR 0.66 [95% CI, 0.53-0.81],  $p < 0.001$ ). A statistically significant reduction of 34% in the risk of death among patients receiving combination therapy was observed in the study. The analysis reported median progression free survival (PFS) of 12.6 months, ORR of 65.6%, and median duration of response (DoR) of 13.8 months for the Tafinlar + Mekinist combination arm compared to PFS of 7.3 months, ORR of 52.8%, and median DoR of 8.5 months for the vemurafenib monotherapy arm. The most frequent adverse events in the Tafinlar + Mekinist combination arm ( $\geq 30\%$ ) were pyrexia, nausea, diarrhea, and chills. More patients had AEs leading to dose modifications in the combination arm compared to the vemurafenib monotherapy arm. For the combination group compared to the vemurafenib group, there was a lower incidence of rash, 22% ( $n=76$ ) vs 43% ( $n=149$ ); photosensitivity reaction, 4% ( $n=13$ ) vs 22% ( $n=78$ ); hand-foot syndrome, 4% ( $n=14$ ) vs 25% ( $n=87$ ); skin papillomas, 2% ( $n=6$ ) vs 23% ( $n=80$ ); squamous-cell carcinomas and keratoacanthomas, 1% ( $n=5$ ) vs 18% ( $n=63$ ); and hyperkeratosis, 4% ( $n=15$ ) vs 25% ( $n=86$ ). Adverse events occurring more frequently in the combination arm compared with the vemurafenib monotherapy arm included pyrexia, 53% ( $n=184$ ) vs 21% ( $n=73$ ), respectively, and bleeding events, 18% ( $n=62$ ) vs 7% ( $n=25$ ), respectively. Discontinuation of treatment due to adverse events was similar between the treatment groups: 13% ( $n=44$ ) for the combination group compared to 12% ( $n=41$ ) for the monotherapy group<sup>3</sup>.

Results from an analysis of the COMBI-v study of the patients' health-related quality of life showed statistically significant and clinically meaningful improvements among those receiving the combination of Tafinlar + Mekinist, compared to those receiving vemurafenib monotherapy. Overall health, physical and social functioning, and specific symptoms such as pain, insomnia, and loss of appetite were all improved in the group receiving combination therapy<sup>5</sup>.

#### About Tafinlar + Mekinist Combination

Combination use of Tafinlar + Mekinist in patients with unresectable or metastatic melanoma who have a BRAF V600E/K mutation is approved in the US. In addition, combination use of Tafinlar + Mekinist in patients

with unresectable or metastatic melanoma who have a BRAF V600 mutation is approved in the EU, Australia, Canada and additional 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 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.

In 2015, as part of its purchase of oncology products from GlaxoSmithKline, Novartis obtained the worldwide exclusive rights granted by Japan Tobacco Inc. (JT) to develop, manufacture, and commercialize trametinib. JT retains co-promotion rights in Japan.

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 35 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 + Mekinist combination may cause serious side effects, such as:

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.

Before taking Tafinlar in combination with Mekinist, doctors should test their patients for BRAF wild-type melanoma, as patients without BRAF mutation and with RAS mutation can be at risk of increased cell proliferation in the presence of a BRAF inhibitor.

When Tafinlar is used in combination with Mekinist, it can increase the incidence and severity of 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, 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.

Tafinlar in combination with 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 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 alone, or in combination with Mekinist, 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.

Patients should notify their doctor if they experience any new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Tafinlar alone or in combination with Mekinist 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 degrees C (101.3 degrees F) while taking Tafinlar.

Rash is a common side effect of Tafinlar alone, or when used in combination with Mekinist. Tafinlar alone, or 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 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.

Some people may develop high blood sugar or worsening diabetes during treatment with Tafinlar, alone or in combination with Mekinist. For patients who are diabetic, their healthcare 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 healthcare provider if they have any of the following symptoms of severe high blood sugar: increased thirst or urinating more often than normal, or urinating an increased amount of urine.

Tafinlar 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 healthcare provider if they have any of the following signs or symptoms of anemia or breakdown of red blood cells: yellow skin (jaundice), weakness or dizziness, or shortness of breath.

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, tiredness, rash, chills, diarrhea, headache, vomiting, hypertension, joint pain, peripheral edema 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 dose 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 "mission," "goal," "being investigated," "ongoing," "yet," or similar terms, or by express or implied discussions regarding

potential marketing approvals or new indications or labeling for the combination of Tafinlar plus Mekinist, 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 the combination of Tafinlar plus Mekinist will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that the combination of Tafinlar plus Mekinist 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, either in combination or 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 issues; unexpected manufacturing or quality 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.

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Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which 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 2014, the Group achieved net sales of USD 58.0 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 120,000 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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