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Combination of Novartis drugs Tafinlar® and Mekinist® shows significant survival benefit in patients with metastatic melanoma

- *Final analysis of COMBI-d confirms overall survival benefit of combination therapy in patients with BRAF V600E/K mutation-positive metastatic melanoma*
- *Tafinlar and Mekinist in combination achieved a median overall survival of 25.1 months compared to 18.7 months for Tafinlar monotherapy in this Phase III study*
- *Three-year data from Phase I-II study reinforce long-term overall survival benefit of combination therapy*

Basel, May 31, 2015 – Novartis today announced data from the Phase III COMBI-d study showing a significant survival benefit for patients with BRAF V600E/K mutation-positive metastatic melanoma when treated with the combination of Tafinlar® (dabrafenib) and Mekinist® (trametinib) compared to Tafinlar monotherapy alone. This is the first combination of BRAF/MEK inhibitors to demonstrate a statistically significant overall survival benefit for this patient population in two Phase III studies. Results are being presented today at the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago.

“This final analysis from COMBI-d confirms prior results showing a statistically significant improvement in overall survival among patients with BRAF V600E/K mutation-positive metastatic melanoma receiving the combination of dabrafenib and trametinib compared to dabrafenib monotherapy,” said Georgina Long, B.Sc., Ph.D., M.B.B.S., F.R.A.C.P., medical oncologist, Melanoma Institute Australia, The University of Sydney. “These findings further reinforce the rationale for the treatment of metastatic melanoma with this combination.”

The final analysis included the 423 patients enrolled in COMBI-d and showed that the combination of Tafinlar and Mekinist achieved a statistically significant overall survival (OS) benefit compared to Tafinlar monotherapy (median of 25.1 months vs 18.7 months)[1]. The analysis for the combination also showed median progression-free survival (PFS) of 11.0 months, overall response rate (ORR) of 69%, and median duration of response (DoR) of 12.9 months[1]. The safety results were consistent with the profile observed to date for the combination and consistent with the profile observed for Tafinlar monotherapy; no new safety concerns were observed[1]. The most common adverse events (≥20%) in the combination arm were pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, joint pain (arthralgia), hypertension, vomiting, cough and peripheral edema[1].

“We are very pleased to have entered into a new disease area with the acquisition of two medicines that are making a positive impact on the lives of people with this serious form of skin cancer,” said Bruno Strigini, President, Novartis Oncology. “These COMBI-d data prove that these medicines can significantly extend the lives of people with BRAF V600E/K mutation-positive melanoma, and we are proud to be part of the progress in this disease.”

In addition to results from the COMBI-d study, long-term data from a Phase I-II study showed a three-year OS rate of 38% (95% CI, 25%, 51%) after treatment with the combination of Tafinlar and Mekinist in all patients with BRAF V600 E/K mutation-positive metastatic melanoma. Safety results from this study were consistent with those observed in other trials evaluating the combination.

Other data being presented at the meeting, including oral presentations related to the investigational use of dabrafenib and trametinib, include studies in BRAF V600E-mutated metastatic colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and other rare cancers.

The results from the COMBI-d study are also being published online in *The Lancet* on May 31.

About the COMBI-d Study
COMBI-d is a pivotal Phase III randomized, double-blinded study (NCT01584648) comparing the combination of the BRAF inhibitor, Tafinlar, and the MEK inhibitor, Mekinist, to single agent therapy with Tafinlar and placebo in patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The study randomized 423 patients from investigative sites in Australia, Europe and North and South America. The primary endpoint of this study was investigator-assessed PFS. Secondary endpoints included OS, ORR, DoR, and safety. There was no crossover between treatment arms.

The final OS analysis showed that the combination of Tafinlar and Mekinist achieved a statistically significant OS benefit compared to Tafinlar monotherapy (median of 25.1 months vs 18.7 months; Hazard Ratio [HR] 0.71 [95% Confidence Interval (CI), 0.55-0.92], p=0.011). A 33% reduction in the risk of progression or death was demonstrated with the combination therapy compared to monotherapy (median PFS of 11.0 months in the 211 patients receiving combination therapy vs 8.8 months in the 212 patients receiving monotherapy; HR 0.67 [95% CI, 0.53-0.84], p<0.001). The combination achieved ORR of 69% compared to 53% for monotherapy [difference=15% (95% CI, 6.0%-24.5%), p=0.001]. The median DoR for the 144 responders receiving combination therapy was 12.9 months [95% CI, 9.4-19.5] compared to 10.6 months in the 113 responders receiving monotherapy [95% CI, 9.1-13.8].

The safety results were consistent with the profile observed to date for the combination and consistent with the profile observed for Tafinlar monotherapy; no new safety concerns were observed. The most common adverse events (≥20%) in the combination arm were pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, joint pain (arthralgia), hypertension, vomiting, cough and peripheral edema[1]. More patients had AEs leading to dose modifications in the combination arm compared to Tafinlar monotherapy. Increased incidence (57% vs 33%) and severity (grade 3, 7% (n=15) vs 2% (n=4)) of pyrexia occurred with combination treatment as compared to Tafinlar monotherapy. There was a lower incidence of cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma with the combination arm (3% (n=6)) compared to the Tafinlar monotherapy arm (10% (n=22)). Discontinuation of treatment due to adverse events occurred in 11% (n=24) vs 7% (n=14) of patients in the combination group and the monotherapy group, respectively.

Completion of COMBI-d is a post-marketing requirement for the FDA's accelerated approval for the combination in the US.

About Tafinlar and Mekinist Combination
Combination use of Tafinlar and Mekinist in patients with unresectable or metastatic melanoma who have BRAF V600E/K mutation is approved in the US, Australia, Chile and Canada.

Tafinlar and Mekinist target two different serine/threonine kinases – BRAF and MEK, respectively – in the RAS/RAF/MEK/ERK pathway, which is implicated in NSCLC and melanoma, among other cancers. When Mekinist is used with Tafinlar, the combination has been shown to slow tumor growth more effectively compared with either drug alone. The combination of Tafinlar and Mekinist is currently being investigated in an ongoing clinical trial program conducted in study centers worldwide.

In 2015, Novartis, as successor in interest to GlaxoSmithKline, purchased the worldwide exclusive rights to develop, manufacture, and commercialize trametinib from Japan Tobacco Inc. (JT). JT retains co-promotion rights in Japan.

Tafinlar and Mekinist are registered trademarks of Novartis Pharma AG or its affiliates. The safety and efficacy profile of the Tafinlar and Mekinist combination has not yet been established outside the approved indication.

Tafinlar and Mekinist Combination Important Safety Information
Tafinlar and 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°C (101.3°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 and 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 and Mekinist combination. For more information, patients should ask their doctor or pharmacist.

Patients should take Tafinlar and Mekinist combination exactly as their health care provider tells them. Patients should not change their dose or stop taking Tafinlar and 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 and 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 “can,” “investigational,” “being investigated,” “post-marketing requirement,” “ongoing,” or similar terms, or by express or implied discussions regarding potential new indications or labeling for Tafinlar and Mekinist, or regarding potential future revenues from Tafinlar and Mekinist. 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 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 will be commercially successful in the future. In particular, management's expectations regarding Tafinlar and Mekinist 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 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 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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References

1. Long, G. Overall survival in COMBI-d, a randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib with dabrafenib and placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. Abstract #102. 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA.

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