Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

https://www.novartis.com
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MEDIA & INVESTOR RELEASE

Novartis reports late-breaking data from Phase III COMBI-i trial of spartalizumab (PDR001) with Tafinlar® and Mekinist® in advanced melanoma

- *Based on unprecedented progression-free survival results, Tafinlar (dabrafenib) + Mekinist (trametinib) confirmed as standard-of-care, targeted therapy for advanced BRAF-mutated melanoma*[1-4]

- *Data show positive durable responses and progression-free survival benefit for patients treated with Tafinlar + Mekinist in the comparator arm of the COMBI-i clinical trial despite the study not meeting the primary endpoint for the investigational triplet therapy*

- *Spartalizumab development program continues, investigating the immunotherapy in combination with other anti-cancer agents*

Basel, September 19, 2020 — Novartis announced today detailed results from the Phase III COMBI-i trial evaluating the investigational immunotherapy spartalizumab (PDR001) in combination with the targeted therapies Tafinlar® (dabrafenib) and Mekinist® (trametinib) compared to Tafinlar + Mekinist alone[1]. The efficacy data achieved in the trial's control arm among patients treated with Tafinlar + Mekinist represent the longest progression-free survival results (PFS) observed across multiple Phase III studies. The trial did not meet its primary endpoint of investigator-assessed progression-free survival (PFS) for patients treated with the investigational triplet therapy[1-4].

The COMBI-i study was conducted among treatment-naive patients with advanced BRAF V600 mutation-positive cutaneous melanoma. Results were presented today as a late-breaking oral presentation during the European Society of Medical Oncology (ESMO) Virtual Congress 2020[1].

"For treating physicians and patients alike, the durable, progression-free survival seen with dabrafenib + trametinib in COMBI-i confirms that this targeted therapy combination remains a gold standard treatment for people with advanced BRAF-mutated melanoma," said Dr. Paul Nathan, consultant medical oncologist, Mount Vernon Cancer Centre, United Kingdom, and COMBI-i principal investigator. "The good news is that the control arm of the study performed better than we originally expected, with the efficacy of dabrafenib + trametinib improving consistently over time. Although the study did not meet its primary endpoint, an important trend was seen in favor of the triple therapy arm. There is clearly more for us to learn about patients who may benefit from the potential addition of an immunotherapy."

Findings from this randomized, double-blind, placebo-controlled study showed a median time of PFS of 16.2 months for patients treated with the triple therapy (n=267) compared to 12.0 months for patients receiving the combination Tafinlar + Mekinist alone (n=265; hazard ratio [HR] 0.82; 95% CI 0.655-1.027; p=0.042)[1]. Overall response rate was 68.5% for

spartalizumab with Tafinlar + Mekinist (95% CI, 62.6-74.1%) compared to 64.2% for Tafinlar + Mekinist alone (95% CI, 58.1-69.9%)[1]. A significant duration of response (DOR) was seen in the study as median DOR for the triple therapy was not reached at two-year data cutoff, compared to 20.7 months with Tafinlar + Mekinist[1].

“Working with our clinical investigator partners and melanoma patients around the world, we undertook the COMBI-i study to learn more about how we can continue to improve patient outcomes, and we are proud that it advanced the community’s scientific understanding about potential triplet therapies,” said Jeff Legos, Ph.D., MBA, Senior Vice President and Head of Oncology Drug Development. “The study results reinforce that patients taking Tafinlar + Mekinist continue to see durable responses and a meaningful progression-free survival benefit, consistent with data reported in previous Phase III studies.”

“As we continue to deliver Tafinlar + Mekinist to patients around the world, Novartis will continue to advance the science with bold investigations into uses for immunotherapy in cancer, including the ongoing development of spartalizumab, across a range of tumor types,” Legos added.

About the COMBI-i Study[1]
COMBI-i was a Phase III, double-blinded global study (NCT02967692) evaluating the investigational anti-PD1 therapy spartalizumab in combination with Tafinlar + Mekinist compared to Tafinlar + Mekinist and placebo as first-line therapy in patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The study was conducted in three parts. In the safety run-in (part 1), the primary endpoint was incidence of dose-limiting toxicities, and in the biomarker cohort (part 2), the primary endpoint was immune microenvironment and biomarker modulation. In the randomized portion of the study (part 3), the primary endpoint was investigator-assessed progression-free survival.

COMBI-i study participants were classified as having either Stage IIIC (unresectable) or Stage IV (metastatic) disease and received study treatments as first-line therapy. No new side effects were seen and the safety profile in the control arm was consistent with what has been observed in previous studies. COMBI-i also evaluated a new side effect management protocol to address pyrexia – or fever – a common side effect seen among targeted therapies.

Serious treatment-related adverse events (TRAEs) grade ≥3 occurred in 23.2% of patients in the triple therapy arm compared to 11% in the Tafinlar + Mekinist arm. The most common grade ≥3 adverse events independent of treatment relationship observed in the triple therapy and Tafinlar + Mekinist arms were blood creatine phosphokinase increase (7.9% vs 7.2%), pyrexia (5.2% vs 3.0%), aspartate aminotransferase increase (3.7% vs 1.1%), fatigue (3.4% vs 1.9%), rash (3.4% vs 0.4%), asthenia (2.2% vs. 1.1%), headache (1.1% vs. 1.5%), diarrhea (0.7% vs. 1.9%), nausea (0.7% vs 0.4), arthralgia (0.7% vs 1.5%), and chills (zero vs. 0.8%). TRAEs leading to discontinuation of all 3 study drugs occurred in 12% compared to 8% of patients, respectively.

Visit https://www.virtualcongress.novartis.com/esmo20/ for the latest information from Novartis including our bold approach to reimagining cancer care, and access to our ESMO Virtual Congress 2020 symposia and data presentations (for registered participants).

About Spartalizumab (PDR001)
Spartalizumab is an investigational monoclonal antibody directed against the human programmed death-1 (PD-1) receptor. Its development program continues, investigating the immunotherapy across a range of tumor types.

About Tafinlar + Mekinist[2-4]
The combination of the targeted therapies Tafinlar + Mekinist, the worldwide leader in BRAF/MEK-inhibition, is approved for the treatment of patients with unresectable or metastatic BRAF-mutated melanoma by the US Food and Drug Administration (FDA) and European Commission based on data from the pivotal Phase III COMBI-d and COMBI-v trials.

In COMBI-d, Tafinlar + Mekinist achieved a statistically significant overall survival (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=0.01). The median progression-free survival (PFS) was 9.3 months in the 211 patients receiving combination therapy compared to 8.8 months in the 212 patients receiving monotherapy (HR 0.75 [95% CI, 0.57-0.99], p=0.035).

In COMBI-v, Tafinlar + Mekinist demonstrated a statistically significant OS benefit compared to vemurafenib monotherapy (median not reached vs 17.2 months; HR 0.69 [95% CI, 0.53-0.89], p=0.005). The median PFS was 11.4 months in the 352 patients receiving the Tafinlar + Mekinist combination compared to 7.3 months in the 352 patients receiving vemurafenib monotherapy (HR 0.56 [95% CI, 0.46-0.69], p<0.001).

Tafinlar + Mekinist Indication and Important Safety Information
Tafinlar and Mekinist are prescription medicines that can be used in combination to treat people with a type of skin cancer called melanoma:

- That has spread to other parts of the body (metastatic) or cannot be removed by surgery (unresectable), and
- That has a certain type of abnormal "*BRAF*" (V600E or V600K mutation-positive) gene

Tafinlar and Mekinist are prescription medicines that can be used in combination to help prevent melanoma that has a certain type of abnormal "*BRAF*" gene from coming back after the cancer has been removed by surgery.

Tafinlar and Mekinist are prescription medications that can be used in combination to treat a type of lung cancer called non-small cell lung cancer (NSCLC) that has spread to other parts of the body (metastatic NSCLC), and that has a certain type of abnormal "*BRAF* V600E" gene.

Tafinlar and Mekinist are prescription medications that can be used in combination to treat a type of thyroid cancer called anaplastic thyroid cancer (ATC):

- That has spread to other parts of the body and you have no satisfactory treatment options, and
- That has a certain type of abnormal "*BRAF*" gene

Tafinlar, in combination with Mekinist, should not be used to treat people with wild-type *BRAF* melanoma. Mekinist should not be used to treat people who already have received a *BRAF* inhibitor for treatment of their melanoma and it did not work or is no longer working.

Your health care provider will perform a test to make sure that Tafinlar and Mekinist, in combination, are right for you.

It is not known if Tafinlar and Mekinist are safe and effective in children.

Tafinlar and Mekinist, in combination, may cause serious side effects such as the risk of new cancers, including both skin cancer and nonskin cancer. Patients should be advised to contact their health care provider immediately for any skin changes, including 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, that can lead to death. Patients should be advised to call their health care provider and get medical help right away if they have any signs of bleeding, including headaches, dizziness, or feel weak, cough up blood or blood clots, vomit blood or their vomit looks like "coffee grounds," or red or black stools that look like tar.

Mekinist, alone or in combination with Tafinlar, can cause inflammation of the intestines or tears in the stomach or intestines that can lead to death. Patients should report to their health care provider immediately if they have any of the following symptoms: bleeding, diarrhea (loose stools) or more bowel movements than usual, stomach-area (abdomen) pain or tenderness, 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 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 and other skin reactions are common side effects of Tafinlar in combination with Mekinist. In some cases, these rashes and other skin reactions can be severe or serious, may need to be treated in a hospital, or lead to death. Patients should be advised to call their health care provider if they get any of the following symptoms: blisters or peeling of skin, mouth sores, blisters on the lips or around the mouth or eyes, high fever or flu-like symptoms, and/or enlarged lymph nodes.

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 may cause healthy red blood cells to break down too early in people with glucose-6-phosphate dehydrogenase 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, blurry vision, or dizziness.

Men (including those who have had a vasectomy) should use condoms during sexual intercourse during treatment with Tafinlar and Mekinist and for at least 4 months after the last dose of Tafinlar and Mekinist. For women of reproductive potential, Tafinlar and Mekinist, in combination, may harm your unborn baby. Use effective birth control (contraception) during treatment with Tafinlar and Mekinist in combination, and for 4 months after stopping treatment with Tafinlar and Mekinist. The most common side effects for patients with metastatic melanoma are: pyrexia, nausea, rash, chills, diarrhea, headache, vomiting, hypertension, arthralgia, peripheral edema, and cough. The most common side effects for patients with stage III melanoma receiving the combination as adjuvant therapy are: pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia. The most common side effects for patients with NSCLC: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea.

Please see full Prescribing Information for Tafinlar at https://www.novartis.us/sites/www.novartis.us/files/tafinlar.pdf and Mekinist at https://www.novartis.us/sites/www.novartis.us/files/mekinist.pdf.

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Novartis Media Relations
E-mail: media.relations@novartis.com

Anja von Treskow
Novartis External Communications
+41 79 392 8697
anja.von_treskow@novartis.com

Mary Curtin Creaser
Novartis Oncology Communications
+1 862 345 4102
mary.curtin_creaser@novartis.com

Eric Althoff
Novartis US External Communications
+1 646 438 4335
eric.althoff@novartis.com

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 778 5052
Thomas Hungerbuehler	+41 61 324 8425		
Isabella Zinck	+41 61 324 7188		

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