

Long-term Survival Benefit Shown for Metastatic Melanoma Patients Treated with Novartis Tafenlar® + Mekinist®

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- - Five-year Tafenlar + Mekinist survival data presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting and published simultaneously in The New England Journal of Medicine
- - Results are from the largest dataset and longest follow-up of more than 500 patients with BRAF-mutated metastatic melanoma, a genetic mutation common for this aggressive skin cancer
- - Additional Novartis melanoma research presented at ASCO includes efficacy and safety data investigating the immunotherapy spartalizumab (PDR001) combined with Tafenlar + Mekinist

BASEL, Switzerland, June 4, 2019 /PRNewswire/ -- Novartis announced today results from the landmark COMBI-d and COMBI-v clinical trials, concluding that first-line treatment with Tafenlar (dabrafenib) and Mekinist (trametinib) offers both overall and progression-free long-term survival benefits to patients with unresectable or metastatic BRAF-mutation positive melanoma. Researchers reported that 34% (95% CI: 30-38%) of all patients in the pooled analysis who were treated with Tafenlar + Mekinist survived at five years¹. Study authors also reported on prolongation in progression-free survival (PFS), with 19% (95% CI: 15-22%) of patients showing no sign of disease progression or death at five years. Five-year overall survival and PFS were similar in the pooled patient population^{1,4}.

The results, from a pooled analysis of 563 patients from the COMBI-d and COMBI-v trials, represented the largest collection of data and longest follow-up among patients with advanced melanoma with BRAF V600-mutated unresectable or metastatic melanoma who were treated with Tafenlar + Mekinist. These data were presented at the 2019 ASCO Annual Meeting (Abstract #9507) and published simultaneously in The New England Journal of Medicine^{1,4}.

"Our analysis demonstrates that first-line therapy with Tafenlar + Mekinist leads to five-year disease control in about one-fifth of the patients and five-year survival in about one-third of those treated," said Caroline Robert, MD, Ph.D., Head of the Dermatology Unit at the Institut Gustave Roussy in Paris. "While metastatic melanoma has historically had a very poor prognosis for patients, there are many reasons to be encouraged today. Our analysis demonstrates a clinically meaningful and positive impact on patient survival. These results show that targeted therapies may provide long-term survival and offer durable outcomes."

Of patients who achieved a complete response with Tafenlar + Mekinist, 19% (n=109) had five-year PFS and overall survival rates of 49% and 71%, respectively, compared with 19% and 34% in the overall population. Researchers also observed that the efficacy of subsequent treatment was preserved in patients who progressed on study treatment and subsequently received immune checkpoint inhibitor therapy.

Adverse events (regardless of causality) were reported in 548 of 559 patients (98%) with no new safety signals. Adverse events (AEs) led to permanent discontinuation of study treatment in 99 of 559 patients (18%); the most common events were pyrexia (4%), decreased ejection fraction (4%) and increased alanine aminotransferase (1%). No treatment-related deaths were reported in patients treated with dabrafenib plus trametinib.

"The five-year COMBI-d/v analysis is truly gratifying, as it shows us that many BRAF+ melanoma patients on Tafenlar + Mekinist are living much longer than what may have been expected when originally diagnosed," said John Tsai, MD, Head of Global Drug Development and Chief Medical Officer, Novartis. "Other Novartis-sponsored melanoma research at ASCO this week illustrates our drive to do even more in melanoma. Efficacy results from the study of the immunotherapy spartalizumab were encouraging as the oncology community learns more about how immunotherapies may be combined with established targeted therapies to provide an even greater benefit to patients."

About COMBI-d and COMBI-v

COMBI-d is a pivotal Phase III randomized, double-blinded study (NCT01584648) comparing the combination of the BRAF inhibitor, Tafenlar, and the MEK inhibitor, Mekinist, to single-agent therapy with Tafenlar 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 randomized 422 patients from 121 investigative sites.

COMBI-v is a two-arm, open-label, Phase III study comparing the combination of Tafenlar + Mekinist with vemurafenib monotherapy in patients with BRAF V600E/K mutation-positive unresectable or metastatic melanoma (NCT01597908). The primary endpoint of this study was OS¹.

Efficacy Findings for Investigational Anti-PD-1 Antibody Spartalizumab (PDR001) Used in Combination With Tafenlar + Mekinist Also Reported

Also presented at ASCO were findings from the COMBI-i study evaluating Tafenlar + Mekinist in combination with spartalizumab in metastatic melanoma patients with known BRAF mutation (Abstract #9531). Results from the 36 patients enrolled in the safety run-in cohort (part 1) and biomarker cohort (part 2) showed a confirmed objective response rate by investigator assessment of 78% (n=28), with 42% (n=15) of patients exhibiting complete responses. All patients experienced at least one AE, 28 had grade ≥ 3 AEs and six had AEs leading to discontinuation of all three study drugs. The most common AEs ($\geq 20\%$) included pyrexia, cough, arthralgia, rash, chills and fatigue. One patient died of cardiac arrest that was not considered related to study treatment. The clinical trial is ongoing⁵.

About the COMBI-i Study

COMBI-i is a pivotal Phase III, double-blinded global study (NCT02967692) comparing the combination of Tafenlar + Mekinist to the same combination along with the investigational anti-PD1 therapy spartalizumab as first-line therapy in patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The study is being 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. The randomized portion of the study (part 3) is ongoing, and the primary endpoint is investigator-assessed progression-free survival⁵.

About Melanoma

There are about 280,000 new diagnoses of melanoma (Stages 0-IV) worldwide each year⁶, approximately half of which have BRAF mutations⁷. Biomarker tests can determine whether a tumor has a BRAF mutation⁸.

One way melanoma is staged is by how far it has metastasized. In Stage III melanoma, tumors have spread to the regional lymph nodes, presenting a higher risk of recurrence or metastases⁹. Patients who receive surgical treatment for Stage III melanoma may have a high risk of recurrence because melanoma cells can remain in the body after surgery^{10,11}. Patients should ask their doctor if they are at risk for melanoma returning.

About Tafenlar + Mekinist

Tafenlar + 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 melanoma and NSCLC, among other

cancers. When Tafenlar is used with Mekinist, the combination has been shown to slow tumor growth more than either drug alone.

Tafenlar + Mekinist have been investigated for the treatment of a variety of cancers as part of an ongoing clinical trial program. Tafenlar + Mekinist are approved in more than 60 countries, for uses including:

- as monotherapy and in combination for the treatment of subjects with unresectable or metastatic melanoma with a BRAFV600 mutation
- in combination for the adjuvant treatment of patients with Stage III melanoma with a BRAFV600 mutation, following complete resection
- in combination for the treatment of patients with advanced NSCLC with a BRAFV600 mutation
- in combination for the treatment of patients with locally advanced or metastatic ATC with a BRAFV600 mutation

Approved indications vary worldwide. Please refer to local labeling for indication language in a particular country.

Tafenlar + Mekinist Combination Important Safety Information

Tafenlar 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 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 Tafenlar 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 Tafenlar, 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.

Tafenlar, 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 Tafenlar 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.

Tafenlar, 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.

Tafenlar, 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 Tafenlar 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 Tafenlar in combination with Mekinist. In some cases, these rashes and other skin reactions can be severe or serious, and may need to be treated in a hospital. Patients should be advised to call their health care 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, or skin redness.

Some people may develop high blood sugar or worsening diabetes during treatment with Tafenlar 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.

Tafenlar, in combination with Mekinist, 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.

Tafenlar, 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.

The most common side effects of Tafenlar, in combination with Mekinist, include fever, rash, nausea, fatigue, headache, chills, diarrhea, vomiting, high blood pressure (hypertension), joint aches, muscle aches, swelling of the face, arms, or legs, and cough.

Please see full Prescribing Information for Tafenlar and Mekinist.

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List of links present in page

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