Novartis combination targeted therapy Tafinlar® + Mekinist® receives FDA approval for BRAF V600E mutant metastatic non-small cell lung cancer (NSCLC)

- Approval provides first targeted treatment in the US specifically for BRAF V600E mutation-positive metastatic NSCLC
- More than 60% of treatment-naïve and previously treated patients with BRAF V600E mutant metastatic NSCLC responded to Tafinlar + Mekinist in a pivotal study¹
- BRAF V600E is an aggressive mutation that may be associated with a poorer prognosis in patients with NSCLC²

Basel, June 22, 2017 – Novartis today announced the US Food and Drug Administration (FDA) approval of Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) to treat patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express the BRAF V600E mutation. The FDA granted Tafinlar + Mekinist Breakthrough Therapy designation in July 2015 for the treatment of patients with advanced or metastatic BRAF V600E mutation-positive NSCLC who received previous treatment with chemotherapy.

“Patients with BRAF V600E mutation-positive metastatic NSCLC have responded less favorably to standard chemotherapy, suggesting that there is a critical need for a targeted therapy,” said Bruno Strigini, CEO, Novartis Oncology. “Today’s approval of the Tafinlar + Mekinist combination validates our expertise in tumor biology, which enabled us to develop the first targeted treatment for people with this rare mutation.”

“The approval of Tafinlar + Mekinist makes BRAF V600E the fourth actionable genomic biomarker in metastatic NSCLC – along with EGFR, ALK and ROS-1,” said Bruce Johnson, MD, Professor of Medicine, Chief Clinical Research Officer, Dana-Farber Cancer Institute and Harvard Medical School at Dana-Farber Cancer Institute. “This is an important milestone for the lung cancer community as we are continuing to better understand the genomic drivers of cancer and develop effective treatments targeted for these biomarkers.”

The FDA approval is based on safety and efficacy of Tafinlar in combination with Mekinist in a Phase II, three-cohort, multicenter, non-randomized, non-comparative and open-label study in which patients with stage IV BRAF V600E mutant NSCLC were enrolled (36 treatment-naïve [previously untreated] and 57 previously treated with chemotherapy)¹.

Among the 36 treatment-naïve patients receiving 150 mg of Tafinlar twice daily and 2 mg of Mekinist once daily, the overall response rate (ORR) was 61% (95% confidence interval [CI]: 44%, 77%)¹. In the previously treated population receiving the same dosage, patients demonstrated an ORR of 63% (95% CI: 49%, 76%)¹. The ORR was assessed by independent review committee. The median duration of response in the treatment naïve cohort was not estimable (95% CI: 6.9, not estimable) and in the previously treated patient cohort was 12.6...
months (95% CI: 5.8, not estimable)\(^1\). An in-depth analysis of data from the treatment-naïve cohort will be presented at an upcoming medical meeting.

The most common adverse events (incidence >20%) were pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough and dyspnea.

BRAF mutations appear in approximately 1-3% of NSCLC cases worldwide\(^3\). There is an urgency to treat people with this mutation, as BRAF V600E mutation-positive tumors have been shown to be more aggressive and may lead to a poorer prognosis\(^2\).

The treatment combination was approved with Thermo Fisher Scientific’s Oncomine™ Dx Target Test to identify a BRAF V600E mutation in eligible patients. This qualitative in vitro diagnostic test uses targeted high throughput, parallel-sequencing technology to detect sequence variations in select genes, including BRAF V600E, in DNA and RNA isolated from formalin-fixed, paraffin-embedded tumor (FFPE) tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System.

Tafinlar + Mekinist was approved by the European Commission (EC) in March 2017 for the treatment of patients with BRAF V600 advanced mutation-positive NSCLC.

**Novartis Commitment to Lung Cancer**

Worldwide, lung cancer causes more deaths than colon, breast and prostate cancer combined, and an estimated 1.8 million new cases of lung cancer are diagnosed each year\(^4,5\). Among patients with NSCLC, roughly 30% have an actionable mutation that may be targeted with available therapies\(^6,9\). To determine the most appropriate treatment, medical organizations recommend genomic testing for patients with lung cancer\(^10\).

Novartis Oncology’s research in targeted therapies has helped transform treatment approaches for patients living with mutation-driven types of lung cancer. Patients with mutation-driven NSCLC may be candidates for treatment with targeted therapies\(^6\).

Novartis continues its commitment to the global lung cancer community through ongoing studies, as well as the exploration of investigational compounds that target genetic biomarkers in NSCLC.

**About Tafinlar + Mekinist Combination**

Combination use of Tafinlar + Mekinist in patients with unresectable or metastatic melanoma who have a BRAF V600E mutation is approved in the US, EU, Australia, Canada, and additional countries. The combination of Tafinlar and Mekinist is also approved for the treatment of advanced non-small cell lung cancer with a BRAF V600 mutation in Europe.

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 indications.

Tafinlar and Mekinist are also indicated in more than 50 countries worldwide, including the US and EU, as single agents to treat patients with unresectable or metastatic melanoma with a BRAF V600E mutation.
INDICATIONS
TAFINLAR, in combination with MEKINIST, is a prescription medicine used to treat people with a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery, and that has a certain type of abnormal “BRAF” gene.

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.

TAFINLAR, in combination with MEKINIST, is a prescription medication used 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.

IMPORTANT SAFETY INFORMATION for TAFINLAR® (dabrafenib) capsules and MEKINIST® (trametinib) tablets
TAFINLAR, in combination with MEKINIST, may cause serious side effects such as the risk of new cancers, including a type of skin cancer called cutaneous squamous cell carcinoma (cuSCC) and a type of skin cancer called basal cell carcinoma. Patients should be advised to contact their doctor 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.

TAFINLAR, in combination with MEKINIST, can cause serious bleeding problems, especially in the brain or stomach, and can lead to death. Patients should be advised to call their health care 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,” or have red or black stools that look like tar.

TAFINLAR, in combination with MEKINIST, can cause inflammation of the intestines, or tears in the stomach or intestines that can lead to death. Patients should tell their health care provider immediately if they have any of the following symptoms: bleeding (see bleeding problems below); diarrhea (loose stools) or more bowel movements than usual, stomach-area (abdomen) pain or tenderness; fever, and nausea.

Fever is common during treatment with TAFINLAR in combination with MEKINIST, but may also be more serious. Fever may happen often or may be 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 health care provider right away if they get a fever.

Rash and other skin reactions are common serious side effects of TAFINLAR, 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 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, in combination with MEKINIST, 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 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, or dizziness.

Common side effects of TAFINLAR, in combination with MEKINIST, in people with melanoma include: fever, nausea, chills, headache, joint aches, cough, diarrhea, rash, vomiting, high blood pressure (hypertension), and swelling of the face, arms, or legs.

Common side effects of TAFINLAR, in combination with MEKINIST, in people with NSCLC include: fever, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, rash, swelling of the face, arms and legs, diarrhea, chills, bleeding, cough, and shortness of breath.

Please see full prescribing information for TAFINLAR and MEKINIST at https://www.hcp.novartis.com/products/tafinlar-mekinist/.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "may," "Breakthrough Therapy designation," "suggesting," "continuing," "will," "upcoming," "commitment," "recommend," "continues," "ongoing," "exploration," "investigational," "being investigated," "yet," "contingent," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Tafinlar + Mekinist, or regarding potential future revenues from Tafinlar and Mekinist, both as single agents and in combination with the other. 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 + 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, either as single agents or in combination with the other will be commercially successful in the future. In
particular, management’s expectations regarding Tafinlar and Mekinist, both as single agents and in combination with the other could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; 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 and reimbursement pressures; 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, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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For questions about the site or required registration, please contact media.relations@novartis.com

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References

1. Tafinlar + Mekinist Important Safety Information.

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