Novartis combination adjuvant therapy Tafinlar® + Mekinist® receives FDA Breakthrough Therapy Designation for stage III BRAF V600 mutation-positive melanoma patients

- **Breakthrough Therapy Designation based on Phase III study showing the three-year relapse-free survival (RFS) rate for patients treated with the combination was 58%, compared to 39% with placebo.**

- **First targeted combination therapy to demonstrate a clinical benefit in patients with a BRAF V600E/K mutation in the adjuvant setting.**

- **Discussions with global regulatory authorities are ongoing.**

**Basel, October 23, 2017** – Novartis today announced that the US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation (BTD) for Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) for the adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation following complete resection. Tafinlar in combination with Mekinist is in development to become the first adjuvant treatment specifically for melanoma patients with a BRAF V600 mutation.

The designation is based on results from COMBI-AD, a Phase III study of 870 patients with stage III BRAF V600E/K mutation-positive melanoma after complete surgical resection treated with Tafinlar + Mekinist. Patients received the Tafinlar (150 mg BID) + Mekinist (2 mg QD) combination (n = 438) or matching placebos (n = 432). After a median follow-up of 2.8 years, the primary endpoint of relapse-free survival (RFS) was met. Treatment with the combination therapy significantly reduced the risk of disease recurrence or death by 53% vs. placebo (HR: 0.47 [95% CI: 0.39-0.58]; median not reached vs. 16.6 months, respectively; p<0.001). The RFS benefit among the combination arm was observed across all patient subgroups, including stage III A, B and C. These results were recently presented at the European Society for Medical Oncology Congress (ESMO) and published in the New England Journal of Medicine.

“There is a need for more effective treatment options for stage III melanoma patients at a high risk of recurrence following surgical resection,” said Samit Hirawat, Executive Vice President and Head, Global Drug Development at Novartis Oncology. “We thank the FDA for recognizing the scientific advancement Tafinlar and Mekinist may provide in this adjuvant setting.”

Adverse events (AEs) were consistent with other Tafinlar + Mekinist studies, and no new safety signals were reported. Of patients treated with the combination, 97% experienced an AE; 41% had grade 3/4 AEs and 26% had AEs leading to treatment discontinuation (vs. 88%, 14% and 3%, respectively, with placebo).

According to FDA guidelines, treatments that receive Breakthrough Therapy Designation are those that treat a serious or life threatening disease or condition and demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoints based on preliminary clinical evidence. The designation also indicates that the agency will expedite the development and review of Tafinlar + Mekinist for the adjuvant treatment of...
patients with stage III melanoma with a BRAF V600 mutation following complete resection. The treatment combination has previously received Breakthrough Therapy Designations in non-small cell lung cancer (NSCLC) and anaplastic thyroid cancer (ATC).

**About COMBI-AD**

The COMBI-AD study is a randomized, double-blind, placebo-controlled, Phase III study and included a total of 870 patients with stage III, BRAF V600E/K-mutant melanoma who had undergone prior complete surgical resection, without prior anticancer therapy. Patients were treated for 12 months and stratified based on BRAF mutation (V600E vs. V600K) and stage (IIIA vs. IIIB vs. IIIC).

The primary endpoint was RFS. Secondary endpoints included overall survival (OS), distant metastasis-free survival (DMFS), freedom from relapse (FFR), and safety.

**About Melanoma**

There are about 200,000 new cases of melanoma diagnosed worldwide each year, approximately half of which have BRAF mutations. Gene tests can determine whether a tumor has a BRAF mutation\(^3\). Patients who receive surgical treatment for melanoma may have a high risk of recurrence because melanoma cells can remain in the body after surgery\(^5\). Adjuvant therapy may be recommended for patients with high-risk melanoma to help reduce the risk of melanoma returning\(^5\).

**About Tafinlar + Mekinist Combination**

Combination use of Tafinlar + Mekinist in patients with unresectable or metastatic melanoma who have a BRAF V600 mutation is approved in the US, EU, Australia, Canada and other countries.

The combination of Tafinlar + Mekinist is also approved for the treatment of metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation in the US and advanced NSCLC with a BRAF V600 mutation in the EU.

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.

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 60 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**

Tafinlar + Mekinist combination may cause serious side effects.

Tafinlar in combination with Mekinist should only be used to treat patients with a change (mutation) in the BRAF gene; therefore, doctors should test their patients before treatment, as patients without a BRAF mutation and with a RAS mutation can be at risk of increased cell proliferation in the presence of a BRAF inhibitor.

Doctors should also consider other treatment options for their patients if they had been previously treated with a BRAF inhibitor as single agent, as the limited data available have shown that the efficacy of Tafinlar + Mekinist is lower in these patients.
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.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause severe 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, or either drug alone, 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.

Tafinlar in combination with Mekinist, or Tafinlar alone, 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.

Tafinlar in combination with Mekinist, or Mekinist alone, can affect how well the heart pumps blood. 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 in combination with Mekinist, or Tafinlar alone, can cause abnormal kidney function or inflammation of the kidney. Abnormal kidney function may happen more often for patients with fever or too much fluid loss. Patients should be advised to call their healthcare provider right away if they have a fever above 38.5°C (101.3°F), decreased urine, fatigue, loss of appetite or discomfort in lower abdomen or back. Tafinlar has not been studied in patients with renal insufficiency (defined as creatinine > 1.5 x ULN) therefore caution should be used in this setting.

Elevations in blood pressure have been reported in association with Mekinist in combination with Tafinlar, or with Mekinist alone, in patients with or without pre-existing hypertension. Patients should be advised to monitor blood pressure during treatment with Mekinist and control potential hypertension by standard therapy, as appropriate.

Elevations in blood pressure have been reported in association with Mekinist in combination with Tafinlar, or with Mekinist alone, in patients with or without pre-existing hypertension. Patients should be advised to monitor blood pressure during treatment with Mekinist and control potential hypertension by standard therapy, as appropriate.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause inflammation of the lung tissue. Patients should notify their doctor if they experience any new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Rash is a common side effect of Tafinlar in combination with Mekinist, or with Mekinist alone. Tafinlar in combination with Mekinist, or Mekinist alone, can also cause other skin reactions which 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.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause muscle breakdown, a condition called Rhabdomyolysis. Patients experiencing muscle pain, tenderness, weakness or a swelling of their muscles should contact their healthcare provider immediately.

Tafinlar in combination with Mekinist, or Tafinlar alone, can uncommonly cause an inflammation of the pancreas (pancreatitis). Patients should be promptly investigated if they experience unexplained abdominal pain and closely monitored if they re-start Tafinlar after a prior episode of pancreatitis.

Tafinlar in combination with Mekinist, or Mekinist alone, 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.

Mekinist in combination with Tafinlar, or Mekinist alone, may increase the risk of developing holes in the stomach or intestine (gastrointestinal perforation). Treatment with Mekinist alone or in combination with Tafinlar should be used with caution in patients with risk factors for gastrointestinal perforation, including concomitant use of medications with a recognized risk of gastrointestinal perforation.

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, diarrhea, fatigue, chills, headache, vomiting, joint pain, high blood pressure, rash 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 doses 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
This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations 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 investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products 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; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; general economic and industry conditions, including the effects of the persistently weak economic and financial environment in many countries; 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 119,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis and @NovartisCancer at https://twitter.com/novartiscancer.

For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

References

Novartis Media Relations
Central media line: +41 61 324 2200
E-mail: media.relations@novartis.com

Eric Althoff
Novartis Global Media Relations
+41 61 324 7999 (direct)
+41 79 593 4202 (mobile)
eric.althoff@novartis.com

Kristen Klasey
Novartis Oncology Communications
+1 862 7784763 (direct)
+1 862 7541732 (mobile)
kristen.klasey@novartis.com
**Novartis Investor Relations**  
Central investor relations line: +41 61 324 7944  
E-mail: investor.relations@novartis.com

<table>
<thead>
<tr>
<th>Central</th>
<th>North America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samir Shah</td>
<td>Richard Pulik</td>
</tr>
<tr>
<td>+41 61 324 7944</td>
<td>+1 212 830 2448</td>
</tr>
<tr>
<td>Pierre-Michel Bringer</td>
<td>Cory Twining</td>
</tr>
<tr>
<td>+41 61 324 1065</td>
<td>+1 212 830 2417</td>
</tr>
<tr>
<td>Thomas Hungerbuehler</td>
<td></td>
</tr>
<tr>
<td>+41 61 324 8425</td>
<td></td>
</tr>
<tr>
<td>Isabella Zinck</td>
<td></td>
</tr>
<tr>
<td>+41 61 324 7188</td>
<td></td>
</tr>
</tbody>
</table>