Novartis presents new data at ASCO for Zykadia® and combination of Tafinlar® and Mekinist® in certain NSCLC patients with unmet needs

- In Phase II studies, Zykadia (ceritinib) shrank tumors in patients with ALK+ NSCLC; comparable overall response in those with or without brain metastases\(^1,2\)
- Tafinlar (dabrafenib) and Mekinist (trametinib) combination Phase II data show 63% overall response rate in patients with metastatic BRAF V600E+ NSCLC\(^3\)
- Novartis leadership in lung cancer continues to grow, with research focused on precision medicines that treat aggressive NSCLC tumors

Basel, June 1, 2015 – Novartis today announced new data from two Phase II studies of Zykadia® (ceritinib), as well as one Phase II study of Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) in certain patients with non-small cell lung cancer (NSCLC). Data from these studies were presented at the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago.

The results of the Zykadia studies – ASCEND-2 and ASCEND-3 – reinforce the efficacy of the medicine in patients with anaplastic lymphoma kinase-positive (ALK+) NSCLC who had received previous treatment with an ALK inhibitor and in those receiving an ALK-targeted therapy for the first time. Overall response rates (ORR) seen in these trials were 38.6% and 63.7%, respectively, based upon investigator assessment. Comparable ORR results were observed in patients with ALK+ NSCLC who entered the studies with brain metastases (33% and 58%, respectively)\(^1,2\).

Separately, the study of dabrafenib in combination with trametinib in patients with metastatic BRAF V600E-mutation positive NSCLC who had failed at least one round of chemotherapy demonstrated an ORR of 63% in this population\(^3\).

“As our lung cancer portfolio and pipeline continue to mature and grow, we are impressed by the level of activity these targeted treatments demonstrate in patients with specific genetic mutations in NSCLC,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “Our continued studies of Zykadia and the Tafinlar and Mekinist combination, other targeted medicines, as well as our partnerships with the oncology community to develop practice-changing immunotherapy combinations, demonstrate our strong commitment to patients living with lung cancer.”

About the Zykadia trials
ASCEND-2 is a Phase II single-arm, open-label, multicenter study which included 140 adults with ALK+ NSCLC who had been previously treated with chemotherapy and crizotinib. In addition to the ORR of 38.6% [95% CI: 30.5, 47.2%], patients in the trial demonstrated a median duration of response (DOR) of 9.7 months [95% CI: 7.1, 11.1 months] and a median progression-free survival (PFS) of 5.7 months [95% CI: 5.4, 7.6 months], based on investigator assessment, following treatment with Zykadia. The most frequent adverse events (incidence >50%) were nausea (81.4%), diarrhea (80.0%), and vomiting (62.9%)\(^1\).
ASCEND-3 is a Phase II single-arm, open-label, multicenter study which included 124 patients with ALK+ NSCLC who had received up to three lines of chemotherapy and had no prior experience with an ALK inhibitor. In addition to the ORR of 63.7% [95% CI: 54.6, 72.2%], patients in the trial demonstrated a median DOR of 9.3 months [95% CI: 9.1, not estimable (NE) months] and a median PFS of 11.1 months [95% CI: 9.3, NE months], based on investigator assessment, following treatment with Zykadia. The most frequent adverse events (incidence >50%) were diarrhea (82.3%), nausea (74.2%) and vomiting (66.9%)². Use of Zykadia in this patient population is investigational in the European Union and the United States.

In ASCEND-2 and ASCEND-3, brain metastases at baseline were seen in 71.4% and 40.3% of patients, respectively. The ORR, DOR and PFS for patients with brain metastases at baseline were similar with those reported for the overall population of these studies¹².

“These Phase II results are very useful to clinicians in management of ALK+ NSCLC as they confirm the role of ceritinib in tumors with resistance to chemotherapy and crizotinib,” said Tony S. K. Mok, MD, Professor in Clinical Oncology at The Chinese University of Hong Kong. “In addition, the comparable systemic activity seen in ALK+ NSCLC patients with brain metastases is encouraging, as this is a common and challenging population to manage.”

Approximately 2-7% of patients with NSCLC harbor the ALK gene rearrangement, which causes cancer growth⁴. These patients are candidates for treatment with a targeted ALK inhibitor. Patients with ALK+ NSCLC are often younger than the average NSCLC patient, and in many cases have never smoked⁵.

About the Tafinlar/Mekinist trial
In the single-arm, two-stage, Phase II trial, patients with metastatic NSCLC who had the BRAF V600E mutation and failed at least one line of chemotherapy took 150 mg of Tafinlar twice daily and 2 mg of Mekinist once daily. The primary endpoint of the trial was investigator-assessed ORR. The ORR among 24 patients evaluable for efficacy was 63% [95% CI: 40.6, 81.2%], with responses being observed by the first scan (6 weeks), and disease control rate for >12 weeks was 88% [95% CI: 67.6, 97.3%]. Independent review response rates were consistent with investigator-assessed response. The most common adverse events (incidence >20%) among patients included in this analysis were pyrexia, diarrhea, nausea, vomiting, decreased appetite, asthenia, cough, peripheral edema, and rash³.

“If no approved therapies for patients with NSCLC who have the BRAF V600E mutation, the lung cancer community is in dire need of targeted treatments,” said David Planchard, MD, PhD, Thoracic Oncology Specialist, Cancer Institute Gustave-Roussy, Villejuif, France. “The initial data from this Phase II study indicate that combination of dabrafenib and trametinib may hold potential for this patient population.”

Up to 3% of patients with NSCLC have the BRAF V600E mutation, which results in constitutive signaling, leading to cell proliferation and escape from apoptosis, or cell death⁶.

Tafinlar and Mekinist are being investigated in combination as a potential treatment for metastatic BRAF V600E-mutation positive NSCLC. Tafinlar and Mekinist are not approved as monotherapies or in combination anywhere in the world to treat NSCLC.

Novartis Commitment to Lung Cancer
Novartis research in precision oncology has helped transform treatment approaches for patients living with genetically-driven types of lung cancer. Zykadia is one of the first medicines to be approved following FDA Breakthrough Therapy designation, and was
commercially available in the US less than three and a half years after the first patient entered a clinical trial.

Novartis continues its commitment to the global lung cancer community through ongoing studies of Zykadia and of Tafinlar and Mekinist in combination, as well as the exploration of investigational compounds that target genetic biomarkers in NSCLC beyond ALK and BRAF V600E. EGF816, targeting EGFR, and INC280, targeting cMET, are currently in Phase I/II clinical trials. Novartis is also collaborating with Bristol-Myers Squibb to study Zykadia, EGF816 and INC280 in combination with Bristol-Myers Squibb's immuno-oncology drug, Opdivo (nivolumab), to gauge whether combining targeted agents with immunotherapy can increase efficacy in certain lung cancer patients.

About Zykadia
Zykadia is an oral, selective inhibitor of anaplastic lymphoma kinase (ALK), a gene that can fuse with others to form an abnormal “fusion protein” that promotes the development and growth of certain tumors in cancers including non-small cell lung cancer (NSCLC). Zykadia is approved by the European Commission for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. Outside the European Union, Zykadia is approved for patients with ALK+ NSCLC in the United States and other countries within North America, South America, Central America and Asia. Additional regulatory reviews for Zykadia are underway worldwide.

Zykadia Important Safety Information
Zykadia may cause serious side effects.

Zykadia may cause stomach upset and intestinal problems in most patients, including diarrhea, nausea, vomiting and stomach-area pain. These problems can be severe. Patients should follow their doctor's instructions about taking medicines to help these symptoms, and should call their doctor for advice if symptoms are severe or do not go away.

Zykadia may cause severe liver injury. Patients should have blood tests prior to the start of treatment with Zykadia, every two weeks for the first month of treatment and monthly thereafter, and should talk to their doctor right away if they experience any of the following symptoms: tiredness (fatigue), itchy skin, yellowing of the skin or the whites of the eyes, nausea or vomiting, decreased appetite, pain on the right side of the abdomen, urine turns dark or brown, or bleeding or bruising more easily than normal.

Zykadia may cause severe or life-threatening swelling (inflammation) of the lungs during treatment that can lead to death. Symptoms may be similar to those symptoms from lung cancer. Patients should tell their doctor right away about any new or worsening symptoms, including trouble breathing or shortness of breath, fever, cough, with or without mucous, or chest pain.

Zykadia may cause very slow, very fast, or abnormal heartbeats. Doctors should check their patient's heart during treatment with Zykadia. Patients should tell their doctor right away if they feel new chest pain or discomfort, dizziness or lightheadedness, faint, or have abnormal heartbeats, blue discoloration of lips, shortness of breath, swelling of lower limbs or skin, or if they start to take or have any changes in heart or blood pressure medicines.

Zykadia may cause high levels of glucose in the blood. People who have diabetes or glucose intolerance, or who take a corticosteroid medicine have an increased risk of high blood sugar with Zykadia. Patients should have glucose blood tests prior to the start of treatment with Zykadia and during treatment. Patients should follow their doctor's instructions about blood sugar monitoring and call their doctor right away with any symptoms of high blood sugar, including increased thirst and/or urinating often.
Before patients take Zyka\'dia, they should tell their doctor about all medical conditions, including liver problems; diabetes or high blood sugar; heart problems, including a condition called long QT syndrome; if they are pregnant, if they think they may be pregnant, or if they plan to become pregnant; and are breastfeeding or plan to breastfeed.

Zyka\'dia may harm unborn babies. Women who are able to become pregnant must use a highly effective method of birth control (contraception) during treatment with Zyka\'dia and up to 3 months after stopping Zyka\'dia. It is not known if Zyka\'dia passes into breast milk. Patients and their doctor should decide whether to take Zyka\'dia or breastfeed, but should not do both.

Patients should tell their doctor about medicines they take, including prescription medicines, over-the-counter medicines, vitamins and herbal supplements. If they take Zyka\'dia while using oral contraceptives, the oral contraceptives may become ineffective.

The most common adverse reactions with an incidence of ≥10% were diarrhea, nausea, vomiting, tiredness (fatigue), liver laboratory test abnormalities (requires blood test monitoring), abdominal pain, decreased appetite, constipation, rash, kidney laboratory test abnormalities (requires blood test monitoring), heartburn and anemia. Grade 3-4 adverse reactions with an incidence of ≥5% were liver laboratory test abnormalities, tiredness (fatigue), diarrhea, nausea and hyperglycemia (requires blood test monitoring).

Patients should stop taking Zyka\'dia and seek medical help immediately if they experience any of the following, which may be signs of an allergic reaction:

- Difficulty in breathing or swallowing
- Swelling of the face, lips, tongue or throat
- Severe itching of the skin, with a red rash or raised bumps

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 Zyka\'dia. For more information, patients should ask their doctor or pharmacist.

Patients should take Zyka\'dia exactly as their health care provider tells them. Patients should not change their dose or stop taking Zyka\'dia unless their health care provider advises them to. Zyka\'dia should be taken once a day on an empty stomach. Patients should not eat for at least 2 hours before and 2 hours after taking Zyka\'dia. If a dose of Zyka\'dia is missed, they should take it as soon as they remember. If their next dose is due within the next 12 hours, they should skip the missed dose and take the next dose at their regular time. They should not take a double dose to make up for a forgotten dose. Patients should not drink grapefruit juice or eat grapefruit during treatment with Zyka\'dia, as it may make the amount of Zyka\'dia in their blood increase to a harmful level. If patients have to vomit after swallowing Zyka\'dia capsules, they should not take more capsules until their next scheduled dose.

*Please see full Prescribing Information for Zyka\'dia.*

**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 "continues," "focused on," "continue," "continued," "commitment," "encouraging," "indicate," "may," "potential," "being investigated," "ongoing," "exploration," "investigational," "can," "yet," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Zykadia, Tafinlar and Mekinist, potential marketing approvals for EGF816 and INC280, or regarding potential future revenues from such products and investigational compounds. 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 Zykadia, Tafinlar or Mekinist will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that EGF816 or INC280 will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that such products and investigational compounds will be commercially successful in the future. In particular, management’s expectations regarding such products and investigational compounds 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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