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Novartis pivotal data for Tafinlar® + Mekinist® demonstrated a 63 percent overall response rate in treating rare form of lung cancer

- The median Duration of Response for BRAF V600E-mutant NSCLC patients treated with Tafinlar® + Mekinist® combination therapy was 9 months
- Efficacy analyses also presented for INC280 (capmatinib) in cMET+ NSCLC
- Novartis’ growing commitment in treating NSCLC supported by data for three distinct targeted therapies

Basel, June 6, 2016 – Novartis today announced new data for multiple investigational and established non-small cell lung cancer (NSCLC) treatments, including results from a pivotal, Phase II study of Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) in patients with BRAF V600E-mutation positive (BRAF V600E+) NSCLC. In the study, patients treated with Tafinlar + Mekinist demonstrated an overall response rate (ORR) of 63% (95% CI, 49%-76%)1. Data were presented during an oral session at the 52nd Annual Meeting of the American Society of Clinical Oncology (ASCO) and also published simultaneously in The Lancet Oncology.

“This study confirms a fourth actionable biomarker in NSCLC – BRAFV600E – after EGFR, ALK and ROS-1,” said David Planchard, MD, PhD, Thoracic Oncology Specialist, Cancer Institute Gustave-Roussy, Villejuif, France and trial's principal investigator. “The potential to treat this oncogene gives hope to a very small, underserved patient population.”

One-to-two percent (1-2%) of patients with NSCLC have a BRAF V600E mutation2, which is associated with more aggressive tumors and a poorer prognosis, independent of smoking status3.

In this Phase II, multicenter, non-randomized, open-label study (NCT01336634), 57 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, and key secondary endpoints were Duration of Response (DoR) and Progression-Free Survival (PFS). Independent review response rates were consistent with investigator-assessed response1.

The investigator-assessed median DoR and PFS were 9.0 months (95% CI, 6.9 to 18.3) and 9.7 months (95% CI, 6.9 to 19.6), respectively. Thirty-six of 57 patients (63%) demonstrated a clinical response; of these patients, 50% (18 of 36) continued to respond to treatment at the time of analysis. The most common adverse events (incidence >20%) were pyrexia, nausea, vomiting, diarrhea, asthenia, decreased appetite, dry skin, chills, peripheral edema, cough and rash1. Four patients (7%) died from fatal adverse events not related to study treatment as assessed by the investigator1.
“Lung cancer is the number one cause of cancer death world-wide, and more than half of NSCLC patients’ tumors occur as a result of a genetic mutation,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “Novartis is fully committed to bringing forth new, targeted options for NSCLC patients, many of whom remain underserved by today’s available therapies.”

**Additional Novartis NSCLC Data at ASCO**

Novartis presented several additional key pieces of data for INC280 (capmatinib) as well as one poster for Zykadia® (ceritinib).

The INC280 (capmatinib) data, from a Phase I, single agent study (NCT01324479) in patients with advanced cMET+ NSCLC and a Phase Ib/II combination study (NCT01610336) with gefitinib in patients with EGFR-mutated, cMET+ NSCLC, demonstrated encouraging early signs of clinical activity. Based on these data, Novartis initiated ongoing Phase II studies to prospectively explore the predictive value of different mechanisms of cMET dysregulation (including cMET amplification and cMETΔex14 mutation) in advanced NSCLC. INC280 is a potent and selective, oral cMET inhibitor licensed by Novartis from Incyte Corporation.

Separately, a planned exploratory analysis from the Phase I, global, multicenter, open-label, single-arm ASCEND-1 trial (NCT01283516) reviewed genetic biomarkers of study participants to better understand determinants of response to Zykadia®.

**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 additional countries.

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 indication. Because of the uncertainty of clinical trials, there is no guarantee that the combination will become commercially available with additional indications.

Tafinlar and Mekinist are also indicated in more than 35 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 for Metastatic Melanoma**

Tafinlar + Mekinist combination may cause serious side effects.

Tafinlar in combination with Mekinist should only be used to treat melanoma 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.

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.

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.

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, tiredness, nausea, headache, chills, diarrhea, rash, joint pain, high blood pressure, vomiting 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.

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 was granted conditional approval in the EU for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib. In the US, Zykadia was granted accelerated approval for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Zykadia is currently approved in over 50 countries worldwide. Please visit www.NovartisOncology.com/news/product-portfolio/zykadia for additional information.

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.

Zykadia may cause high levels of pancreatic enzymes in the blood and may cause pancreatitis. Patients should have blood tests prior to the start of treatment with Zykadia and as needed during their treatment with Zykadia. Patients should talk to their doctor if they experience signs and symptoms of pancreatitis which including upper abdominal pain that may spread to the back and get worse with eating.

Before patients take Zykadia, 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; are breastfeeding or plan to breastfeed.

Zykadia may harm unborn babies. Women who are able to become pregnant must use a highly effective method of birth control (contraception) during treatment with Zykadia and up to 3 months after stopping Zykadia. It is not known if Zykadia passes into breast milk. Patients and their doctor should decide whether to take Zykadia 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 Zykadia 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 Zykadia 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 Zykadia. For more information, patients should ask their doctor or pharmacist.

Patients should take Zykadia exactly as their health care provider tells them. Patients should not change their dose or stop taking Zykadia unless their health care provider advises them to. Zykadia 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 Zykadia. If a dose of Zykadia 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 Zykadia, as it may make the amount of Zykadia in their blood increase to a harmful level. If patients have to vomit after swallowing Zykadia capsules, they should not take more capsules until their next scheduled dose.

Please see full Prescribing Information for Zykadia.

About INC280

INC280 (capmatinib) is an investigational, highly selective cMET inhibitor currently in Phase II clinical development. Efficacy and safety have not been established. There is no guarantee that INC280 will become commercially available. INC280 is licensed by Novartis from Incyte Corporation.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as “growing,” “commitment,” “investigational,” “actionable,” “potential,” “hope,” “committed,” “encouraging,” “initiated,” “ongoing,” “prospectively,” “planned,” “exploratory,” “being investigated,” “yet,” “may,” “can,” “currently,” “will,” or similar terms, or by express or implied discussions regarding potential marketing approvals or new indications or labeling for Tafinlar and Mekinist, either in combination or as single agents, or for Zykadia, regarding potential marketing approvals for INC280, or regarding potential future revenues from Tafinlar and Mekinist, either in combination or as single agents, Zykadia and INC280. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding 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 and Mekinist, either in combination or as single agents, 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 Tafinlar and Mekinist, either in combination or as single agents, or Zykadia, will be submitted or approved for sale in any additional markets, or at any particular time. Nor can there be any guarantee that INC280 will be submitted or approved for sale in any market, or at any particular time. Neither can there be any guarantee that any of Tafinlar and Mekinist, either in combination or as single agents, Zykadia and INC280 will be commercially successful in the future. In particular, management’s expectations regarding such products and the investigational compound INC280 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; general trends toward health care cost containment, including
ongoing pricing pressures; unexpected 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, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 118,000 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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