Novartis study shows Zykadia™ shrank tumors in the majority of patients with ALK+ NSCLC, regardless of prior ALK treatment

- Ceritinib achieved overall response rate of 58.5%, with a median progression-free survival of 8.2 months
- Similar findings were observed in patients who started the study with brain metastases, addressing one of the biggest challenges in treating ALK+ NSCLC
- Zykadia is the only FDA-approved therapy for patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib

Basel, June 2, 2014 – Novartis today announced data showing Zykadia™ (ceritinib, previously known as LDK378) shrank tumors in patients with anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC), including those who had received previous treatment with an ALK inhibitor as well as patients receiving one for the first time. Results were also observed in patients with ALK+ NSCLC who entered the study with brain metastases.

The study is being presented at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago.

“Ceritinib demonstrated a high level of activity in patients with ALK+ NSCLC regardless of whether or not they were previously treated with an ALK inhibitor,” said lead investigator Dong-Wan Kim, MD, PhD, Seoul National University Hospital. “Another noteworthy finding in this study population is that ceritinib exhibited activity among patients whose cancer had metastasized to the brain, which is currently one of the biggest challenges in treating ALK+ NSCLC.”

Among a combined population of 246 NSCLC patients, ceritinib achieved an overall response rate (ORR) of 58.5% and a median progression-free survival (PFS) of 8.2 months. Of these, 124 patients entered the trial with brain metastases and achieved an ORR of 54.0% and a median PFS of 6.9 months. The most common adverse events, occurring in more than half of patients, were diarrhea, nausea, vomiting, abdominal pain and fatigue.

Approximately 2-7% of patients with NSCLC harbor the ALK gene rearrangement, which causes cancer growth. 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 smoked.

“We are encouraged that ceritinib has demonstrated consistent activity as we analyze data from additional patients with longer follow-up, further supporting the potential of ceritinib to make a difference in the lives of patients with ALK+ NSCLC,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “The recent FDA approval of Zykadia brought an important new treatment option to patients in..."
the US and we are pleased to be working with regulatory authorities around the world to bring ceritinib to additional patients."

The study presented at ASCO served as the basis for the US Food and Drug Administration (FDA) approval of Zykadia in April 2014, which followed the FDA’s Breakthrough Therapy designation, and occurred less than three and a half years after the first patient entered a clinical trial. Additional ongoing regulatory reviews are currently underway in the European Union, Argentina and Switzerland.

About the study and ceritinib clinical trial program
The 246 patients with ALK+ NSCLC in this Phase I single-arm study received ceritinib 750 mg daily and had a 7-month median duration of follow-up. Of these, 166 (67%) had received at least two prior regimens and 163 (66%) had been previously treated with an ALK inhibitor. Findings from the study showed that patients treated with ceritinib achieved an ORR of 58.5% [95% CI, 52.1-64.8%] and a median PFS of 8.2 months [95% CI, 6.7-10.1 months]. The median duration of response was 9.7 months [95% CI, 7.0-11.4 months], with a median time to first response of 6 weeks after starting treatment.

Among 163 patients receiving 750 mg of ceritinib daily and who were previously treated with the commonly prescribed ALK inhibitor crizotinib, ORR was 54.6% [95% CI, 46.6-62.4%] and PFS was 6.9 months [95% CI, 5.4-8.4 months]. In 83 patients who had not received prior treatment with an ALK inhibitor, ORR was 66.3% [95% CI, 55.1-76.3%] and PFS had not been reached (NR) at the time of data cutoff as the majority of patients were still receiving treatment with ceritinib.

In the 124 patients who started the study with brain metastases, ceritinib achieved an ORR of 54.0% [95% CI, 44.9-63.0%] and a median PFS of 6.9 months [95% CI, 5.4-8.4 months]. Tumor shrinkage was seen in 50.0% of patients [49 of 98 patients; 95% CI, 39.7-60.3%] with brain metastases who had received previous ALK inhibitor therapy, while 69.2% of patients [18 of 26 patients; 95% CI, 48.2-85.7%] with brain metastases who were not previously treated with an ALK inhibitor achieved tumor shrinkage following treatment with ceritinib.

Discontinuation of treatment due to adverse events occurred in 10% of patients.

Among 255 patients treated with ceritinib, including 246 patients with NSCLC and nine patients with other types of cancer, 150 (59%) required at least one dose reduction. The most frequent adverse events (incidence >50%) among 255 patients were diarrhea (86%), nausea (80%), vomiting (60%), abdominal pain (54%) and fatigue (52%). The most common lab abnormalities (incidence >50%) were decreased hemoglobin (84%), increased ALT (80%), AST increased (75%) and increased creatinine (58%). The most common Grade 3/4 lab abnormalities (incidence >10%) were increased ALT (27%), increased AST (13%) and increased glucose (13%).

This study is part of the ongoing Novartis clinical trial program in this patient population. Several major studies evaluating treatment with ceritinib are being conducted in more than 300 study centers across more than 30 countries. Two Phase II single-arm clinical trials in previously treated and treatment-naïve ALK+ NSCLC patients, (www.clinicaltrials.gov identifiers NCT01685060 and NCT01685138), are fully enrolled and ongoing. In addition, two Phase III clinical trials comparing ceritinib with chemotherapy in treatment-naïve and in previously-treated patients, (www.clinicaltrials.gov identifiers NCT01828099 and NCT01828112), are ongoing and actively recruiting patients worldwide.

About Zykadia
Zykadia (ceritinib) is indicated in the US for the treatment of patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of
response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Zykadia is an FDA-approved prescription medicine that is currently available through a number of specialty pharmacies in the US. Outside of the US, Zykadia (LDK378) is an investigational agent and has not been approved by regulatory authorities.

**Zykadia Important Safety Information**

Zykadia may cause serious side effects, such as:

Zykadia causes stomach and intestinal problems in most people, including diarrhea, nausea, vomiting, and stomach-area pain. These problems can sometimes 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 liver injury. Patients should have blood tests at least every month while taking Zykadia, and should talk to their doctor right away if they experience any of the following symptoms: tiredness (fatigue), itchy skin, yellow skin and eyes, nausea or vomiting, decreased appetite, pain on the right side of the stomach, urine turns dark or brown, 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, or if they start to take or have any changes in heart or blood pressure medicines.

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 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, increased hunger, headaches, trouble thinking or concentrating, urinating often, blurred vision, tiredness, or breath that smells like fruit.

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; are pregnant, think they may be pregnant, or plan to become pregnant; are breastfeeding or plan to breastfeed.

Zykadia may harm unborn babies. Women who are able to become pregnant must use an effective method of birth control during treatment with Zykadia and for at least 2 weeks 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.

The most common side effects of Zykadia include diarrhea, nausea, vomiting, abdominal pain, tiredness (fatigue), decreased appetite and constipation.
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 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. 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.

Please see full Prescribing Information for Zykadia.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as “being presented,” “encouraged,” “potential,” “Breakthrough Therapy,” “underway,” “ongoing,” “being conducted,” “may,” “contingent,” “investigational,” “can,” or similar terms, or by express or implied discussions regarding potential additional marketing authorizations for Zykadia, potential new indications or labeling for Zykadia, or regarding potential future revenues from Zykadia. 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 will be approved for sale in any market where it has been submitted, or that it will be submitted or approved for sale in any additional markets, or at any particular time. Neither can there be any guarantee that Zykadia 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 Zykadia will be commercially successful in the future. In particular, management’s expectations regarding Zykadia could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; 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, cost-saving generic pharmaceuticals, preventive vaccines, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2013, the Group achieved net sales of USD 57.9 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 135,000 full-time-equivalent associates and sell products in more than 150 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.

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