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Novartis lung cancer drug Zykadia® gains EU approval, providing new therapy for certain patients with ALK+ NSCLC

- Zykadia (ceritinib) is the first treatment option approved for patients in Europe with ALK+ NSCLC previously treated with the ALK inhibitor crizotinib
- Marketing authorization was based on two studies demonstrating Zykadia shrunk tumors in ALK+ NSCLC patients who received prior crizotinib therapy
- Patients with brain metastases at baseline also responded to treatment, with efficacy data comparable to those reported in the overall study populations
- Outside the EU, Zykadia is approved in ten countries including the United States; additional regulatory filings are underway worldwide

Basel, May 8, 2015 – Novartis announced today that the European Commission has approved Zykadia® (ceritinib) to treat adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. The approval of Zykadia in the European Union (EU) provides patients with advanced ALK+ NSCLC previously treated with crizotinib a new treatment option that specifically targets the genetic makeup of their cancer.

“Molecular testing for genetic drivers in lung cancer plays a critical role as patients and physicians determine how to proceed with therapies, especially after they have experienced disease progression following initial treatment,” said Stefania Vallone, international relations, Women Against Lung Cancer in Europe and board member, Lung Cancer Europe (LuCE). “Patients with resistant ALK+ NSCLC have had very few treatment options available that specifically target the genetic makeup of their disease. The approval of Zykadia brings new hope to the lung cancer community as we continue to advocate for innovative therapies.”

Each year, there are 1.6 million people diagnosed worldwide with lung cancer, the leading cause of cancer death. The most common type of lung cancer is NSCLC, accounting for 85-90% of all cases. Of those, 2-7% are driven by a rearrangement of the ALK gene, which increases the growth of cancer cells and can be identified by a molecular test of the cancer tumor. Despite significant treatment advances for patients with ALK+ NSCLC, disease progression is often inevitable and more treatment options are needed.

The EU approval of Zykadia is based on data from two global, multicenter, open-label, single-arm studies [Study A (also known as ASCEND-1) and Study B (also known as ASCEND-2)]. Data from Study A demonstrated patients with ALK+ NSCLC who received Zykadia 750 mg daily after previous treatment with chemotherapy followed by an ALK inhibitor experienced an overall response rate (ORR) of 56.4%. Detailed results from Study B will be presented at an upcoming medical congress.

“The approval of Zykadia in the European Union is significant for ALK+ NSCLC patients who have exhausted the other treatment options for their disease,” said Bruno Strigini,
President, Novartis Oncology. “This approval is yet another example of our commitment to precision oncology and our continued focus on developing treatment approaches that target specific genetic and molecular characteristics of cancer.”

The EU approval follows a positive opinion adopted by the Committee for Medicinal Products for Human Use (CHMP) in February 2015 and applies to all 28 EU member states, plus Iceland, Norway and Liechtenstein. Outside the EU, Zykadia is approved in the United States and other countries within North America, South America, Central America and Asia. Additional regulatory reviews for Zykadia are underway worldwide.

About the Zykadia Clinical Trials
The primary efficacy endpoint for these studies was overall response rate (ORR), including complete response and partial response, for patients who were treated with a 750 mg dose of Zykadia, confirmed by repeat assessments performed not less than four weeks after the criteria for response was first met. Additional evaluations included duration of response (DOR), progression-free survival (PFS) and overall survival (OS). Tumor evaluations were performed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 in Study A and RECIST 1.1 in Study B. Tumor-related endpoints (ORR, DOR and PFS) were assessed by investigator and by blinded independent review committee (BIRC). Comparative efficacy data from randomized clinical studies are not available.

Study A was a Phase I study, which included a dose-escalation phase and an expansion phase at the recommended dose of 750 mg. The study evaluated a total of 246 ALK+ NSCLC patients who were treated with 750 mg of Zykadia: 163 had received prior treatment with an ALK inhibitor and 83 were ALK inhibitor-naive. In patients who had previously received treatment with an ALK inhibitor, the ORR was 56.4% [95% CI, 48.5-64.2%], the median DOR was 8.3 months [95% CI, 6.8-9.7 months] and the median PFS was 6.9 months [95% CI, 5.6-8.7 months] based on investigator assessment.

Study B was a Phase II study designed to evaluate the efficacy and safety of 750 mg Zykadia in patients with locally advanced or metastatic ALK+ NSCLC. Study B evaluated 140 patients who had been previously treated with one to three lines of chemotherapy followed by treatment with crizotinib, and who had then progressed on crizotinib. Detailed results from Study B will be presented at an upcoming medical congress.

In Studies A and B, brain metastases at baseline were seen in 60.1% and 71.4% of patients who had received prior treatment with an ALK inhibitor, respectively. The ORR, DOR and PFS by BIRC assessment for patients with brain metastases at baseline were similar with those reported for the overall population of these studies.

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).

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 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 Zykdia 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 Zykdia. For more information, patients should ask their doctor or pharmacist.

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

Please see full Prescribing Information for Zykdia.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "underway," "hope," "will," "commitment," "continued focus on developing," or similar terms, or by express or implied discussions regarding potential additional marketing approvals for Zykdia, or regarding potential future revenues from Zykdia. 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 Zykdia will be submitted or approved for sale in any additional, or at any particular time. Neither can there be any guarantee that Zykdia will be commercially successful in the future. In particular, management's expectations regarding Zykdia 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 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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