Novartis announces Zykadia® first-line study results showing 16.6 month progression-free survival in patients with ALK+ advanced NSCLC

- Patients without brain metastases at diagnosis experienced median progression-free survival of 26.3 months, the longest seen in a global Phase III study in ALK+ NSCLC.

- Patients with measurable brain metastases in the Zykadia arm experienced an intracranial response rate of more than 70%.

- Data will be used to support global regulatory submissions for first-line use of Zykadia in ALK+ advanced NSCLC patients.

Basel, December 6, 2016 – Novartis today announced results from its Phase III open-label, randomized, active-controlled, multi-center ASCEND-4 study, which found that patients with anaplastic lymphoma kinase-positive (ALK+) advanced non-small cell lung cancer (NSCLC) treated with first-line Zykadia® (ceritinib) had a median progression-free survival (PFS) of 16.6 months (95% confidence interval [CI]: 12.6, 27.2), compared to 8.1 months (95% CI: 5.8, 11.1) in patients treated with standard first-line chemotherapy with maintenance. This equated to a 45% reduction in the risk of disease progression (hazard ratio [HR] = 0.55, P<0.001). Results were presented during the Presidential Symposium at the 17th World Conference on Lung Cancer (WCLC), hosted by the International Association for the Study of Lung Cancer (IASLC), in Vienna. These late-breaking results were also featured in an official conference press briefing.

“These data demonstrate the potential to more than double a patient’s progression-free survival when they take Zykadia as their first ALK inhibitor rather than undergoing treatment with chemotherapy,” said lead investigator Dr. Gilberto de Castro Jr., head of Thoracic Oncology and Head and Neck Cancer clinic in the Clinical Oncology Service of the Institute of Cancer of São Paulo (ICESP), in São Paulo, Brazil. “For clinicians, who are constantly working to extend a patient’s response to treatment in the first-line setting, the ASCEND-4 results are very compelling.”

Overall survival data, a key secondary endpoint of the study, are immature; however, a positive trend in favor of Zykadia was observed, despite 72.4% of patients in the chemotherapy arm receiving an ALK inhibitor as their first treatment after discontinuing chemotherapy. Pre-specified secondary endpoints demonstrating the efficacy of Zykadia in ALK+ advanced NSCLC patients included overall response rate (ORR), overall intracranial response rate (OIRR), disease control rate (DCR) and duration of response (DoR).

Patients taking Zykadia had an ORR of 72.5% (95% CI: 65.5, 78.7) compared to 26.7% (95% CI: 20.5, 33.7) in patients treated with standard chemotherapy. Further, patients with measurable brain metastases experienced an OIRR of 72.7% (95% CI: 49.8, 89.3, n=22) with Zykadia compared to 27.3% (95% CI: 10.7, 50.2, n=22) with standard chemotherapy. Patients without brain metastases at screening experienced a median PFS of 26.3 months (95% CI:
15.4, 27.7, n=130) with Zykadia compared to 8.3 months (95% CI: 6.0, 13.7, n=125) with standard chemotherapy. Additionally, patients taking Zykadia demonstrated a DCR of 84.7% (95% CI: 78.7, 89.5) and DoR of 23.9 months (95% CI: 16.6, not estimable)\(^1\). Study results were measured by a blinded independent review committee (BIRC). Patients treated with Zykadia also reported better overall general health status and improvement in lung cancer-specific symptoms compared to patients treated with standard chemotherapy\(^2\).

“The patient response to treatment is high and durable in the first-line setting,” said Bruno Strigini, CEO, Novartis Oncology. “Based on these results, Novartis is initiating discussions with regulatory authorities worldwide regarding this potential use of Zykadia to further improve outcomes for patients with ALK+ advanced NSCLC.”

The safety profile of Zykadia in the ASCEND-4 study was consistent with the previously known safety profile in patients with ALK+ advanced NSCLC. The most common adverse events (AEs) occurring in more than 50% of Zykadia patients were diarrhea (84.7%), nausea (68.8%), vomiting (66.1%), ALT increase (60.3%) and AST increase (52.9%), which were mostly grade 1 and 2 and managed with dose interruption, dose reduction and concomitant medication. No new or unexpected safety concerns were observed\(^3\).

Novartis also presented an initial investigation of the pharmacokinetic (PK) profile of Zykadia 450 mg or 600 mg taken with a low-fat meal versus Zykadia 750 mg taken after fasting, as currently indicated. This Phase I prospective, open-label, multicenter, randomized study found (in Part 1) that relative to the 750 mg fasted arm, the 450 mg fed arm demonstrated comparable steady-state PK, while the 600 mg fed arm showed approximately 25% higher steady-state PK. Further, preliminary safety data found the overall frequency of AEs were comparable between groups; however, incidences of gastrointestinal-related AEs (diarrhea, nausea or vomiting) were lowest in the Zykadia 450 mg group that ate a low-fat meal, with no grade 3/4 AEs reported\(^4\). This study is ongoing and continues to enroll treatment-naïve patients into Part 2, assessing efficacy across the three treatment arms and evaluating safety follow-up.

One of 12 known genetic drivers of NSCLC, the ALK gene arrangement affects approximately 2-7% of people with NSCLC\(^4,5\). These patients are candidates for treatment with a targeted ALK inhibitor\(^5\). To determine a personalized treatment plan, medical organizations recommend genetic testing for patients with lung cancer\(^6\).

**About ASCEND-4**

ASCEND-4 was a Phase III randomized, open-label, multicenter, global clinical trial to evaluate the safety and efficacy of Zykadia compared to standard chemotherapy, including maintenance, in adult patients with Stage IIIb or IV ALK+ advanced NSCLC who received no prior therapy for their advanced disease. Patients received Zykadia orally at 750 mg/daily or standard pemetrexed-based platinum doublet chemotherapy per label (pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 or carboplatin AUC 5-6) for 4 cycles followed by pemetrexed maintenance.

Of 376 patients, 189 (59 with brain metastases) were randomized to Zykadia and 187 (62 with brain metastases) to chemotherapy. Among patients randomized to the chemotherapy arm, 105 (60%) received an ALK inhibitor as their first treatment after chemotherapy.

**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 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.

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.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "will," "potential," "compelling," "initiating," "initial," "ongoing," or similar terms, or by express or implied discussions regarding 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 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, 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 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.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis and @NovartisCancer at http://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
3. Dziadziuszko, R., et al. Phase 1 Study of Ceritinib 450 mg or 600 mg Taken with a Low-Fat Meal versus 750 mg in Fasted State in ALK+ Metastatic NSCLC. Abstract P3.02a-036. IASLC World Conference on Lung Cancer. Vienna, 7 December 2016.

# # #

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
+1 862 778-4763 (direct)
+1 862 754-1732 (mobile)
kristen.klasey@novartis.com

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central
Samir Shah +41 61 324 7944
Pierre-Michel Bringer +41 61 324 1065

North America
Richard Pulik +1 212 830 2448
Sloan Pavsner +1 212 830 2417
Thomas Hungerbuehler  +41 61 324 8425
Isabella Zinck       +41 61 324 7188