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Pivotal data for Novartis' investigational compound LDE225 show marked tumor responses in advanced basal cell carcinoma

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- The study met the primary endpoint with objective response rates of 41.8% and 32.5% respectively in the 200 mg and 800 mg treatment arms(1,2)
- Basal cell carcinoma is the most common form of skin cancer and can be highly disfiguring at advanced stages and life-threatening when metastatic(3,4,5)
- These data, presented for the first time at ASCO, will be used as the basis for worldwide regulatory submissions beginning in 2014

EAST HANOVER, N.J., June 1, 2014 /PRNewswire/ -- Novartis announced today the results of a pivotal Phase II trial demonstrating that patients with locally advanced (laBCC) or metastatic basal cell carcinoma (mBCC) taking the investigational oral compound LDE225 (sonidegib) had marked and sustained tumor shrinkage after a median follow-up of 13.9 months[1]. The data were revealed for the first time today in an oral presentation at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago (abstract #9009a)[1].

"These results represent an important milestone in the clinical development of LDE225, as well as in our research strategy to develop new therapies for patients with unmet needs," said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. "These data will form the basis for the filing of another important new medicine for a skin-related disease in which Novartis is building a leading position."

The trial assessed the efficacy and safety of two oral doses of LDE225, 200 mg and 800 mg, in patients with laBCC or mBCC[6]. The primary endpoint was the objective response rate (ORR), defined as the proportion of patients with complete or partial tumor response, or shrinkage, as measured by a central review committee[1]. The study met the primary endpoint in both treatment arms with ORRs of 41.8% (95% confidence interval [CI]: 30.8, 53.4) in the 200 mg arm and 32.5% (95% CI: 25.1, 40.5) in the 800 mg arm[1,2]. More specifically, 47.0% of patients with laBCC and 15.4% of patients with mBCC, in the 200 mg arm, and 35.2% of patients with laBCC and 17.4% of patients with mBCC in the 800 mg arm, achieved an objective response[1].

Secondary endpoints included duration of response (DoR), progression-free survival (PFS) and time to tumor response (TTR), a measure of how quickly the tumor responded to treatment[1]. Median DoR for patients with laBCC in both treatment arms could not be estimated since the majority of patients who had a response had no event at the time of the analysis (an event is defined as progression or death due to any cause)[1,2]. Median DoR was 8.3 months for patients with mBCC treated with LDE225 800 mg; however, it could not be estimated for patients with mBCC in the 200 mg arm because they had no event at the time of the analysis[1,2]. The median PFS for patients with laBCC in both treatment arms could not be estimated since the majority of patients had no event at the time of the analysis[1,2]. The median PFS per central review for patients with mBCC was 13.1 months in the 200 mg arm and 7.6 months in the 800 mg arm[1]. Median TTR per central review for patients with laBCC was 3.9 months (95% CI: 3.6, 4.2) in the 200 mg arm and 3.7 months (95% CI:

2.6, 3.8) in the 800 mg arm, and 4.6 months (95% CI: 1.8, 7.4) and 1.0 month (95% CI: 1.0, 2.1) for patients with mBCC in the 200 mg and 800 mg arms, respectively[1].

The most common Grade 3/4 adverse events (AEs) reported in ≥2% of patients receiving treatment with the 200 mg dose were elevated levels of creatine phosphokinase (6.3%), increased lipase (5.1%), hypertension (2.5%), asthenia, or weakness (2.5%) and muscle spasms (2.5%)[1,2]. The most common Grade 3/4 AEs, reported in ≥2% of patients receiving treatment with the 800 mg dose were elevated levels of creatine phosphokinase (12.7%), increased lipase (5.3%), muscle spasms (5.3%), decreased weight (5.3%), decreased appetite (4.0%), rhabdomyolysis, or the breakdown of muscle fibers (3.3%), nausea (2.7%), hypertension (2.7%), increased alanine aminotransferase (2.7%), increased aspartate aminotransferase (2.7%), fatigue (2.0%), syncope, or fainting (2%), anemia (2%), dehydration (2%), hyperkalemia (2%) and myalgia, or muscle pain (2.0%)[1,2]. Overall, Grade 3/4 events were observed less frequently in the 200 mg group (30.4%) than in the 800 mg group (56.0%)[1].

Basal cell carcinoma (BCC) accounts for more than 80% of non-melanoma skin cancers[4]. Worldwide incidence of BCC is rising by 10% each year due to factors such as an aging population and increased ultraviolet exposure[7]. Although BCC rarely becomes advanced or metastatic, there are few treatment options at these stages of the disease[8].

"LDE225 showed marked tumor responses in patients with locally advanced or metastatic basal cell carcinoma," said lead investigator, Michael Robert Migden, MD, University of Texas MD Anderson Cancer Center. "If approved, LDE225 could provide an important treatment option for patients suffering from this disease that can be disfiguring and life-threatening in advanced stages."

The data from this pivotal trial will serve as the basis for worldwide regulatory filings for the 200 mg dose of LDE225 in advanced basal cell carcinoma.

About the Study

The Phase II, randomized, double-blind multicenter BOLT (Basal cell carcinoma Outcomes in LDE225 Trial) study was designed to assess the safety and efficacy of two oral doses of LDE225 (200 mg and 800 mg) in patients with locally advanced (n=194) or metastatic basal cell carcinoma (n=36)[1,2]. From July 2011 to January 2013, patients with laBCC not amenable to curative surgery or radiation, as well as patients with mBCC, were randomized 1:2 to receive LDE225 200 mg or 800 mg daily[1,2]. Tumors were assessed every eight weeks until disease progression as determined by a central review committee. Safety was assessed throughout treatment up to approximately 30 days following the last dose[1,2].

The primary endpoint was the proportion of patients achieving an objective response, defined as a confirmed complete or partial tumor response as their best overall response per modified RECIST criteria for patients with laBCC and RECIST 1.1 criteria for patients with mBCC[1]. The trial met the success criteria for the primary endpoint, defined as achieving an ORR of at least 30% in either arm with the lower bound of its 95% CI >20%. Key secondary endpoints of the study included duration of tumor response and rate of complete response[1]. Other secondary endpoints included PFS, time to tumor response and overall survival[1].

About LDE225

LDE225 (sonidegib) is an oral, investigational, selective smoothened inhibitor being studied in a variety of cancers[10,11]. Smoothened (SMO) is a molecule that regulates the hedgehog (Hh) signaling pathway, which plays a critical role in stem cell maintenance and tissue repair, as well as in advanced basal cell

carcinoma[10,12,13]. LDE225 is currently in clinical development for a variety of diseases including myelofibrosis, leukemia and solid tumors[11].

Since LDE225 is an investigational compound, the safety and efficacy profile has not yet been fully established. Access to this investigational compound is available only through carefully controlled and monitored clinical trials. These trials are designed to better understand the potential benefits and risks of the compound. Given the uncertainty of clinical trials, there is no guarantee that LDE225 will ever be commercially available anywhere in the world.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "investigational," "can," "will," "strategy," "look forward," "rising," "could," "has not yet," "designed," "potential," or similar terms, or by express or implied discussions regarding potential marketing approvals for LDE225, or regarding potential future revenues from LDE225. 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 LDE225 will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that LDE225 will be commercially successful in the future. In particular, management's expectations regarding LDE225 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.

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