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Novartis drug PKC412 (midostaurin) improves overall survival by 23% in global Phase III study of AML patients with FLT3 mutations

- Study in partnership with the Alliance for Clinical Trials in Oncology is the first large controlled trial to show overall survival benefit in FLT3-mutated AML
- AML is the most common acute leukemia in adults, but has the lowest survival rate; no change in treatment strategy in more than 25 years2,3
- Currently there are no approved targeted AML treatments; worldwide regulatory submissions for PKC412 (midostaurin) to begin in 2016

Basel, December 6, 2015 – Novartis today announced positive results from the global Phase III RATIFY (CALGB 10603) clinical trial. In the study, adult patients under 60 years of age with newly-diagnosed FLT3-mutated acute myeloid leukemia (AML) who received the investigational compound PKC412 (midostaurin) plus standard induction and consolidation chemotherapy experienced a 23% improvement in overall survival (OS) (hazard ratio [HR] = 0.77, P = 0.0074) compared to those treated with standard induction and consolidation chemotherapy alone4. The median OS for patients in the PKC412 (midostaurin) treatment group was 74.7 months (95% confidence interval [CI]: 31.7, not attained), versus 25.6 months (95% CI: 18.6, 42.9) for patients in the placebo group4.

The trial evaluated the addition of either PKC412 (midostaurin) or placebo to daunorubicin/cytarabine in the induction phase, followed by high-dose cytarabine in the consolidation phase; patients who achieved complete remission after consolidation chemotherapy continued treatment with PKC412 (midostaurin) or placebo as a single agent for up to one year4.

The data, collected and analyzed in partnership with the Alliance for Clinical Trials in Oncology, are from the largest clinical trial in FLT3-mutated AML to date, with 3,279 patients screened and 717 study participants from around the world4. Results will be presented today at the 57th American Society of Hematology (ASH) Annual Meeting in Orlando, Florida, first during the official ASH media briefing at 11:00 am EST and then during the plenary session at 2:00 pm EST.

“The overall survival results for midostaurin, plus standard chemotherapy, in treating FLT3-mutated AML is a long-awaited advancement for hematologists and the AML community,” said Richard M. Stone, MD, Professor of Medicine at the Dana-Farber Cancer Institute and Alliance for Clinical Trials in Oncology study chair for the RATIFY trial. “FLT3 is a common genetic mutation in AML and is currently associated with poorer prognoses, underscoring the critical need for new treatment options.”

The treatment strategy in AML has remained unchanged for more than 25 years2,3. Of the approximately 350,000 people with leukemias worldwide5, about 25% have AML1. One-third of AML patients also harbor a FLT3 gene mutation6, which is associated with worse outcomes and shorter survival than in those without the mutation7. PKC412
(midostaurin) is the first drug to illustrate an overall survival benefit targeting FLT3 in AML – a hematological malignancy with no approved targeted treatments.

In addition to meeting the primary endpoint of OS, event free survival (EFS, defined as the earliest death, relapse or no complete response within 60 days of the start of induction therapy) was significantly higher in the PKC412 (midostaurin) treatment group versus the placebo group [HR = 0.79, P = 0.0025 and median of 8.0 months (95% CI: 5.14, 10.6) vs. 3.0 months (95% CI: 1.9, 5.9)]4.

No statistically significant differences were observed in the overall rate of grade 3 or higher hematologic and non-hematologic adverse events (AEs)4. A total of 37 deaths were reported, with no difference in treatment-related deaths observed between groups4.

“The RATIFY study, in partnership with the Alliance for Clinical Trials in Oncology, reflects our relentless pursuit to develop targeted therapies that can improve and extend people’s lives,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “Based on the results of this trial, we plan to move forward with global regulatory submissions for PKC412 (midostaurin) in the first half of 2016.”

In order to help identify patients who may have a FLT3 mutation and potentially benefit from treatment with PKC412 (midostaurin), Novartis is collaborating with Invivoscribe Technologies, Inc. who will lead regulatory submissions for a companion diagnostic.

About the RATIFY trial
RATIFY (Randomized AML Trial In FLT3 in patients <60 Years old; also known as CALGB 10603) was a Phase III, international, randomized, placebo-controlled, double-blind group trial of newly-diagnosed AML patients aged 18 to less than 60 with a FLT3 mutation4. The study compared PKC412 (midostaurin) to placebo administered orally with up to two cycles of standard induction (daunorubicin/cytarabine) chemotherapy, and up to four cycles of consolidation (high-dose cytarabine) chemotherapy, followed by PKC412 (midostaurin) or placebo treatment as a single agent for up to one year in patients who continue in complete remission after consolidation chemotherapy4. The primary endpoint was OS and the key secondary endpoint was EFS4.

The data were collected by the Alliance for Clinical Trials in Oncology (“Alliance”) on behalf of 13 contributing international cooperative groups. The Alliance was the sponsor of the study in North America and Novartis was the sponsor in Europe and Australia. A total of 225 sites from 17 countries participated in this study, spanning North America, Europe and Australia. A total of 3,279 patients with AML were screened, and 717 patients with an activating FLT3 mutation aged 18 to less than 60 were enrolled4.

Patients were stratified according to the following mutation subtypes: tyrosine kinase domain (TKD), internal tandem duplications (ITD) high allelic mutation fraction (>0.7) and ITD low allelic mutation fraction (0.05-0.7)4. All three subtypes treated with PKC412 (midostaurin) demonstrated improved OS versus placebo4. Allogeneic hematopoietic stem cell transplantation (SCT) was allowed4. PKC412 (midostaurin) benefited patients regardless of whether they went on to receive a SCT4.

About acute myeloid leukemia (AML) and the FLT3 mutation
AML is an aggressive cancer of the blood and bone marrow4. It prevents white blood cells from maturing, causing an accumulation of “blasts” which do not allow room for the normal blood cells4. AML is the most common acute leukemia in adults, but also has the lowest survival rate4. AML accounts for approximately 25% of all adult leukemias worldwide, with the highest incidence rates occurring in the United States, Europe and Australia1.

Mutations in specific genes are found in many cases of AML, and biomarker testing is considered standard of care for newly-diagnosed patients to help determine the best
possible treatment option. FLT3 is a receptor tyrosine kinase, a type of cell-surface receptor, which plays a role in the proliferation, or increase, in the number of certain blood cells.

**About PKC412 (midostaurin)**

PKC412 (midostaurin) is an investigational, oral, multi-targeted kinase inhibitor in development for the treatment of patients with AML with a FLT3 mutation. PKC412 (midostaurin) inhibits multiple kinases, or enzymes, including FLT3, that help regulate many essential cell processes, thereby interrupting cancer cells’ ability to grow and multiply.

PKC412 (midostaurin) is also being investigated for the treatment of aggressive systemic mastocytosis/mast cell leukemia.

PKC412 (midostaurin) is an investigational compound; the safety and efficacy profile have not been fully established.

**Disclaimer**

The foregoing release contains forward-looking statements that can be identified by words such as "to begin," "will," "can," "relentless pursuit," "plan," or similar terms, or by express or implied discussions regarding potential marketing submissions or approvals for PKC412, or regarding potential future revenues from PKC412. 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 PKC412 will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that PKC412 will receive additional regulatory approvals or be commercially successful in the future. In particular, management's expectations regarding PKC412 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 or quality issues; unexpected safety 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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**References**

4. Stone RM, et al. The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 with FLT3 Mutations (muts): An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance]). Presented at the 57th Annual Meeting of the American Society of Hematology.


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