NOVARTIS

Video: Higher Initial Dose of Gleevec Achieved Better Early Responses than Standard Dose for Patients with Chronic Myeloid Leukemia

Jun 13, 2008

- - Efficacy and safety profile in large randomized Phase III study consistent with landmark IRIS trial, which established Gleevec as standard of care
- - Study did not meet primary endpoint at 1 year, yet shows faster time to molecular responses with 800 vs. 400 mg dose
- - Findings reinforce that monitoring blood levels of Gleevec may help optimize treatment benefit for individual patients
- - Novartis committed to improving first-line treatment through additional study follow-up and completing enrollment to Tasigna vs. Gleevec trial

EAST HANOVER, N.J., June 13 /PRNewswire/ -- New data from a large, international clinical trial find that patients with newly diagnosed chronic myeloid leukemia who received Gleevec® (imatinib meslyate) tablets at 800 mg/day as their initial treatment achieved clinical milestones significantly faster than those receiving the standard 400 mg/day dose.

To view the Multimedia News Release, go to: http://www.prnewswire.com/mnr/novartis/33488/

The Tyrosine Kinase Inhibitor Optimization and Selectivity Study (TOPS) is the first Phase III, randomized, controlled clinical trial designed to evaluate the potential benefits of an 800 mg starting dose across all risk categories of newly diagnosed, previously untreated patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML).

Numerically, more patients achieved a major molecular response (MMR) with the 800 mg dose than the 400 mg dose (46.4% vs. 40.1%); however, the difference between the two arms -- the primary endpoint of the study -- was not statistically significant. This trend of improved MMR rate at 12 months in the 800 mg vs. 400 mg arms was most pronounced in the subset of patients with the highest risk for disease progression (41.1% vs. 26.2%). Further, patients in the 800 mg arm achieved MMR significantly faster than those who started treatment with Gleevec at 400 mg(1). Achievement of a MMR is an important goal of therapy for CML.

"TOPS reaffirms Gleevec as the standard of care for newly diagnosed CML patients," said Jorge Cortes, MD, Professor of Medicine and Deputy Chair of Leukemia at the University of Texas MD Anderson Cancer Center in Houston. "We see a strong trend for rapid response with the 800 mg dose. As with trials like IRIS, further follow up will be needed to assess what this rapid early response will mean in terms of long-term benefit."

TOPS also showed that patients with lower blood levels of Gleevec at one month had a lower molecular response at a year, an observation made in previous studies(2). Cumulatively, these data suggest that maintaining adequate blood levels may help attain better clinical responses(2).

These findings, from the first analysis of the TOPS data set, will be presented on Saturday, June 14, at the 2008 Congress of the European Hematology Association (EHA) in Copenhagen.

"Our robust clinical program with Gleevec continues to provide meaningful insights into the treatment of Ph+ CML and other types of cancer," said Diane Young, MD, Head of Global Medical Affairs at Novartis Oncology. "Novartis continues to invest in trials like ENESTnd, which is comparing Tasigna to Gleevec in the first-line setting, to build on this knowledge and further enhance treatment outcomes for patients."

ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of newly diagnosed Ph+ CML patients) is designed to study the efficacy and safety of Tasigna® (nilotinib) capsules vs. Gleevec in newly diagnosed patients in the chronic phase. ENESTnd is currently underway and will enroll approximately 771 patients at 220 centers worldwide. Tasigna is currently approved for the treatment of Ph+ CML in the chronic or accelerated phase in patients resistant to, or intolerant of, Gleevec.

Chronic myeloid leukemia (CML) is a cancer of the blood and bone marrow in which the body produces cancerous white blood cells. Almost all patients with CML have an abnormality known as the Philadelphia chromosome, which produces a protein called Bcr-Abl that causes malignant white blood cells to proliferate. Gleevec, the first therapy to inhibit the activity of Bcr-Abl, revolutionized the treatment of Ph+ CML and is now the standard of care for this disease.

Study details

TOPS is a Phase III, international, open label, randomized, multi-center clinical trial that included 103 study sites from 19 countries. The 476 patients with newly diagnosed, previously untreated Ph+ CML in chronic phase were randomized to receive Gleevec at either 800 mg/day or the standard 400 mg/day dose in a 2:1 ratio. Patients were stratified by Sokal score for evaluation. Sokal score is a clinical measure that is used to identify those at highest risk for disease progression(1).

A secondary endpoint of the study was the rate of complete cytogenetic response (the elimination of Ph+ cells) at 12 months. Patients in the 800 mg arm achieved complete cytogenetic response (CCyR) faster than patients in the 400 mg arm. The response rates for the 800 mg and 400 mg arms were 56.7% vs. 44.6% by six months (p=0.0146) and 69.9% vs. 65.6% by 12 months (p=0.3470), respectively. More than 95% of patients on either dose achieved some cytogenetic response by six months.

The safety profile in the TOPS trial was similar to that previously reported for both doses of Gleevec. At twelve months, discontinuation rates due to adverse events were 5.6% and 1.3% in the 800 mg arm and 400 mg arm, respectively. The 800 mg/day dose was associated with a higher frequency of adverse events, including grade 3/4 hematologic laboratory abnormalities. There was no difference between the two doses in the rate of grade 3/4 biochemical laboratory abnormalities.

About IRIS

The IRIS study (International Randomized Interferon versus STI571) is the largest ongoing clinical trial in newly diagnosed CML patients. IRIS is an open-label, Phase III clinical trial involving 1,106 newly diagnosed patients with Ph+ CML in chronic phase in 177 centers across 16 countries. The results showed that after six years of Gleevec therapy, 93% of patients remained free of progression to advanced disease and an estimated 88% were still alive. When deaths from causes unrelated to CML or following transplantation were excluded, the estimated overall six-year survival rate reported in IRIS was 95%(1). Further, among those who remained on Gleevec after five years, no patients progressed to advanced disease between years five and six. At the six-year follow-up, the type and frequency of adverse events reported in IRIS were similar to previously reported profiles. Newly occurring or worsening grade 3 or 4 hematologic or biochemical adverse events were infrequent.

About Gleevec

Gleevec® (imatinib mesylate) tablets are indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic phase. Follow-up is limited to 5 years. Gleevec is also indicated for the treatment of patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in the chronic phase (CP) after failure of interferon-alpha therapy.

Important Safety Information(3)

Fetal harm can occur when administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking Gleevec tablets and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking Gleevec should use adequate contraception. If the patient does become pregnant while taking Gleevec, the patient should be advised of the potential hazard to the fetus.

Severe (NCI Grades 3/4) lab abnormalities-including neutropenia (3.6%-48%), anemia (1%-42%), thrombocytopenia (< 1%-33%), and hepatotoxicity (approx 5%) -- and severe adverse experiences (NCI Grades 3/4), including severe fluid retention (eg, pleural effusion, pulmonary edema, and ascites) and superficial edema (1.3%-11%), hemorrhage (1.8%-19%), and musculoskeletal pain (2%-9%) were reported among patients receiving Gleevec*. Severe fluid retention appears to be dose-related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly.

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

Dose adjustments may be necessary due to hepatotoxicity, other nonhematologic adverse reactions, or hematologic adverse reactions. Therapy with Gleevec was discontinued for drug-related adverse reactions in 2.4% to 5% of patients. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months).

A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

Patients should be weighed and monitored regularly for signs and symptoms of edema, which can be serious or life-threatening. There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, papilledema, and gastrointestinal (GI) perforation.

Bullous dermatologic reactions (e.g., erythema multiforme and Stevens- Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of Gleevec at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

Consider potential toxicities-specifically liver, kidney, and cardiac toxicity, and immunosuppression from long-term use.

Gleevec is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Dosage of Gleevec should increase by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin. Examples of commonly used drugs that may significantly interact with Gleevec include ketoconazole, acetaminophen, warfarin, erythromycin, and phenytoin. (Please see full Prescribing Information for other potential drug interactions).

For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron.

Common Side Effects of Gleevec Tablets

The majority of adult Ph+ CML patients who received Gleevec in clinical studies experienced adverse reactions at some time, but most were mild to moderate in severity. The most frequently reported adverse reactions (all Grades) were superficial edema (60%-74%), nausea (50%-73%), muscle cramps (28%-62%), vomiting (23%-58%), diarrhea (43%-57%), musculoskeletal pain (38%-49%), and rash and related terms (36%-47%).* +

Supportive care may help management of some mild-to-moderate adverse reactions so that the prescribed dose can be maintained whenever possible. However, in some cases, either a dose reduction or interruption of treatment with Gleevec may be necessary.

Gleevec tablets should be taken with food and a large glass of water to minimize GI irritation. Gleevec tablets should not be taken with grapefruit juice and other foods known to inhibit CYP3A4.

Patients should be informed to take Gleevec exactly as prescribed, not to change their dose or stop taking Gleevec unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose.

* Numbers indicate the range of percentages in 4 studies among adult patients with Ph+ CML in blast crisis, accelerated phase, and chronic phase.

+ For more detailed study information please see full Prescribing Information.
Please see full Prescribing Information.

About Tasigna

Tasigna (nilotinib) capsules is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included imatinib. The effectiveness of Tasigna is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. Please see Important Safety Information, including WARNING, below.

Tasigna important safety information
WARNING: QT PROLONGATION AND SUDDEN DEATHS

Tasigna prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. Tasigna should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. Use with caution in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

Myelosuppresion

Treatment with Tasigna is associated with Grade 3/4 neutropenia, thrombocytopenia, and anemia. Complete blood counts should be performed every 2 weeks for the first 2 months, then monthly thereafter as clinically indicated. Myelosuppression with Tasigna was generally reversible and usually managed by withholding Tasigna temporarily or dose reduction.

QT prolongation

Tasigna prolongs the QT interval. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically. Avoid drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Use caution in patients with hepatic impairment. Obtain ECGs at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

Sudden deaths

There were sudden deaths reported in the safety population and the expanded access program. Ventricular repolarization abnormalities may have contributed to their occurrence.

Elevated serum lipase

Caution is recommended in patients with history of pancreatitis. Check serum lipase periodically.

Liver function abnormality

Serum bilirubin and hepatic transaminasesThe use of Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Check hepatic function tests periodically.

Electrolyte abnormalities

Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating Tasigna and monitor periodically during therapy.

Hepatic impairment

Metabolism of Tasigna is mainly hepatic. Tasigna has not been investigated in patients with hepatic impairment. Caution is recommended in these patients and QT interval should be monitored closely.

Drug interactions

The concomitant use of QT prolonging drugs and strong inhibitors or inducers of CYP3A4 should be avoided as they may affect serum concentration of Tasigna.

Concomitant strong CYP3A4 inhibitors

The concomitant use of strong CYP3A4 inhibitors should be avoided (including, but not limited to, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted. If interruption of treatment with Tasigna is not possible, patients who require treatment with a drug that prolongs QT or strongly inhibits CYP3A4 should be closely monitored for prolongation of the QT interval, and a dose reduction to 1/2 the daily dose is recommended (400 mg once daily). If the strong inhibitor is discontinued, a washout period should be allowed before Tasigna is adjusted upward to the indicated dose. Close monitoring for prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors. Grapefruit products and other foods that are known to inhibit CYP3A4 should also be avoided.

Concomitant strong CYP3A4 inducers

The concomitant use of strong CYP3A4 inducers should be avoided (including, but not limited to, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital). Patients should also refrain from taking St John's Wort. If patients must be co-administered a strong CYP3A4 inducer, the dose of Tasigna may need to be increased, depending on patient tolerability. If the strong inducer is discontinued, the Tasigna dose should be reduced to the indicated dose. Tasigna is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1. Since warfarin is metabolized by CYP2C9 and CYP3A4, it should be avoided if possible. Tasigna inhibits human P-glycoprotein. If Tasigna is administered with drugs that are substrates of Pgp, increased concentrations of the substrate are likely and caution should be exercised. Tasigna may also induce CYP2B6, CYP2C8, and CYP2C9. Therefore, Tasigna may alter serum concentration of other drugs.

Food effects

Food increases blood levels of Tasigna. Patients should avoid food 2 hours before and 1 hour after taking dose.

Lactose

Since the capsules contain lactose, Tasigna is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency, or of glucose-galactose malabsorption.

Pregnancy

Fetal harm can occur when Tasigna is administered to a pregnant woman. Women should be advised not to become pregnant when taking Tasigna.

Adverse reactions

In chronic phase patients, the most commonly reported adverse reactions (> 10%) were rash (33%), pruritus (29%), nausea (31%), fatigue (28%), headache (31%), constipation (21%), diarrhea (22%), and vomiting (21%). The most common (> 10%) Grade 3/4 adverse reactions were thrombocytopenia (28%), neutropenia (28%), elevated lipase (15%), and hyperglycemia (11%). In accelerated phase patients, the most commonly reported adverse reactions (> 10%) were rash (28%), pruritus (20%), and constipation (18%). The most common (> 10%) Grade 3/4 adverse reactions were thrombocytopenia (37%), neutropenia (37%), anemia (23%), and elevated lipase (17%). Other serious adverse reactions included pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, and pyrexia (Grade 3/4: 2%).

Dose adjustments or modifications

Tasigna may need to be temporarily withheld and/or dose reduced for QT prolongation, hematological toxicities that are not related to underlying leukemia, clinically significant moderate or severe nonhematologic toxicities, laboratory abnormalities, or concomitant use of strong CYP3A4 inhibitors. With concomitant use of strong CYP3A4 inducers, the dose of Tasigna may need to be increased, depending on patient tolerability.

Other patients in whom Tasigna should be used with caution

Tasigna should not be used during pregnancy. Sexually active female patients should use effective contraception during treatment. Women should not breast feed while taking Tasigna. There are no data to support the use of Tasigna in pediatric patients. Use with caution in patients with hepatic impairment.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "may", "committed", "designed to", "potential", "will", "suggest", "continues to", or similar expressions, or by express or implied discussions regarding potential new indications or labelling for Gleevec or Tasigna or regarding potential future revenues from Gleevec or Tasigna, or regarding the long-term impact of a patient's use of Gleevec or Tasigna. Such forward-looking statements reflect the current views of the Company regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Gleevec or Tasigna to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Gleevec or Tasigna will be submitted or approved for any additional indications or labelling in any market. Nor can there be any guarantee that Gleevec or Tasigna will achieve any particular levels of revenue in the future. Neither can there be any guarantee regarding the long-term impact of a patient's use of Gleevec or Tasigna. In particular, management's expectations regarding Gleevec and Tasigna could be affected by, among other things, unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry and general public pricing pressures, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. 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 Pharmaceuticals Corporation researches, develops, manufactures and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including those in the cardiovascular, metabolic, cancer, organ transplantation, central nervous system, dermatological, GI and respiratory areas. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), which provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on growth areas in healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines and diagnostic tools, and consumer health products. Novartis is the only company with leading positions in these areas. In 2007, the Group's continuing operations (excluding divestments in 2007) achieved net sales of USD 38.1 billion and net income of USD 6.5 billion. Approximately USD 6.4 billion was invested in R&D activities throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 98,200 full-time associates and operate in over 140 countries around the world. For more information, please visit http://www.novartis.com/.

For more information

Additional information regarding Gleevec, Tasigna and Novartis Oncology can be found on the websites http://www.novartisoncologyvpo.com/, http://www.gleevec.com/, http://www.us.tasigna.com/ and http://www.novartisoncology.us/.

References

1. Cortes J. First report of the TOPS study: A randomized phase III trial

of 400mg vs 800mg imatinib in patients with newly diagnosed, previously untreated CML in chronic phase using molecular endpoints. Abstract. 13th Congress of the European Hematology Association, Bella Center, Copenhagen, Denmark, June 12-15, 2008.

2. Larson, R., Druker, B. et al. Imatinib pharmacokinetics and its correlation with response and safety in chronic phase chronic myeloid leukemia: a subanalysis of the IRIS study. Blood, Feb 2008.

3. Gleevec® (imatinib mesylate) tablets prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Nov 2007.

Media Contacts
Media Only:
Kim Fox
Novartis Oncology
P: +1 862 778 7692
C: +1 917 415 2425

Dana Kahn Cooper
P: +1 732 817 1800
C: +1 732 239 6664

Investors only:
Jill Pozarek
Novartis Corporation
P: +1 212 830 2445

Video: http://www.prnewswire.com/mnr/novartis/33488

SOURCE: Novartis

CONTACT: Media, Kim Fox of Novartis Oncology, P, +1-862-778-7692, C, +1-917 415 2425; or Dana Kahn Cooper, P, +1-732-817-1800, C, +1-732-239-6664; or Investors, Jill Pozarek of Novartis Corporation, +1-212-830-2445

Web site: http://www.novartis.com/
http://www.novartisoncologyvpo.com/
http://www.gleevec.com/
http://www.us.tasigna.com/
http://www.novartisoncology.us/

Source URL: *https://qa1.novartis.us/news/media-releases/video-higher-initial-dose-gleevec-achieved-better-early-responses-standard-dose-patients-chronic-myeloid-leukemia*

List of links present in page

1. https://qa1.novartis.us/news/media-releases/video-higher-initial-dose-gleevec-achieved-better-early-responses-standard-dose-patients-chronic-myeloid-leukemia
2. http://www.prnewswire.com/mnr/novartis/33488/
3. http://www.novartis.com/
4. http://www.novartisoncologyvpo.com/
5. http://www.gleevec.com/
6. http://www.us.tasigna.com/

7. http://www.novartisoncology.us/
8. http://www.prnewswire.com/mnr/novartis/33488
9. http://www.novartis.com/
10. http://www.novartisoncologyvpo.com/
11. http://www.gleevec.com/
12. http://www.us.tasigna.com/
13. http://www.novartisoncology.us/