Second Phase 3 Study Shows KYPROLIS® (Carfilzomib) Regimen Significantly Improves Overall Survival In Patients With Relapsed Multiple Myeloma

July 12, 2017

KYPROLIS, Lenalidomide and Dexamethasone Reduced the Risk of Death by 21 Percent Versus Lenalidomide and Dexamethasone

Patients Treated With the KYPROLIS-Based Regimen Survived 7.9 Months Longer Than Patients on Lenalidomide and Dexamethasone

KYPROLIS-Based Regimens Are the First and Only to Demonstrate Improved Overall Survival Versus Today's Standards of Care in Two Phase 3 Studies in Relapsed Multiple Myeloma

THOUSAND OAKS, Calif., July 12, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced positive results from the final analysis of the Phase 3 ASPIRE trial. The study met the key secondary endpoint of overall survival (OS), demonstrating that KYPROLIS® (carfilzomib), lenalidomide and dexamethasone (KRd) reduced the risk of death by 21 percent over lenalidomide and dexamethasone alone (Rd) (median OS 48.3 months for KRd versus 40.4 months for Rd, HR = 0.79, 95 percent CI, 0.67 – 0.95). Per protocol, patients received 18 cycles of KYPROLIS with Rd before continuing treatment with Rd alone to progression. This KRd regimen of twice-weekly KYPROLIS administered at 27 mg/m^2 is currently approved in the U.S., European Union and other countries based on the primary analysis of progression-free survival (PFS) in the ASPIRE study.

"For multiple myeloma patients, the first relapse is usually the most devastating," said David S. Siegel, M.D., Ph.D., chief of the Division of Multiple Myeloma at John Theurer Cancer Center in Hackensack, N.J., and investigator on the ASPIRE trial. "These data clearly show that the addition of KYPROLIS – for just 18 cycles – to lenalidomide and dexamethasone at relapse gave patients a significantly improved chance of survival. With these results, this KYPROLIS regimen should be considered a new standard of care."

"The ENDEAVOR study has already demonstrated that KYPROLIS is the superior proteasome inhibitor versus Velcade," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "This overall survival benefit from the ASPIRE trial further supports the importance of proteasome inhibition and duration of treatment with KYPROLIS in the treatment of relapsed multiple myeloma."

Adverse events observed in this updated analysis were consistent with those previously reported for ASPIRE. The most common adverse events (greater than or equal to 20 percent) in the KYPROLIS arm were diarrhea, anemia, neutropenia, fatigue, upper respiratory tract infection, pyrexia, cough, hypokalemia, thrombocytopenia, muscle spasms, pneumonia, nasopharyngitis, nausea, constipation, insomnia and bronchitis.

Amgen recently announced OS results from the Phase 3 head-to-head ENDEAVOR trial, which showed KYPROLIS at 56 mg/m^2 in combination with dexamethasone reduced the risk of death by 21 percent over Velcade® (bortezomib) and dexamethasone (Vd). Patients treated with KYPROLIS lived 7.6 months longer than those treated with Velcade (median OS 47.6 months for Kd versus 40.0 months for Vd, HR = 0.79, 95 percent CI, 0.65 – 0.96).

The ASPIRE OS data will be submitted to a future medical conference, for publication, and to regulatory agencies worldwide to support a potential label update.

The KYPROLIS clinical program continues to focus on providing solutions for physicians and patients in treating this frequently relapsing and difficult-to-treat cancer. KYPROLIS is available for patients whose myeloma has relapsed or become resistant to another treatment and continues to be studied in a range of combinations and patient populations.

About ASPIRE

The international, randomized Phase 3 ASPIRE (C**A**rfilzomib, Lenalidomide, and Dexametha**S**one versus Lenalidomide and Dexamethasone for the treatment of **P**at**I**ents with **R**elapsed Multiple My**E**loma) trial evaluated KYPROLIS in combination with lenalidomide and dexamethasone, versus lenalidomide and dexamethasone alone, in patients with relapsed multiple myeloma following treatment with one to three prior regimens. The primary endpoint of the trial was PFS, defined as the time from treatment initiation to disease progression or death. Secondary endpoints included OS, overall response rate (ORR), duration of response (DOR), disease control rate, health-related quality of life (HR-QoL) and safety. Patients were randomized to receive KYPROLIS (20 mg/m^2 on days 1 and 2 of cycle one, escalating to 27 mg/m^2 on days 8, 9, 15 and 16 of cycle one and continuing on days 1, 2, 8, 9, 15 and 16 of subsequent cycles), in addition to a standard dosing schedule of lenalidomide (25 mg per day for 21 days on, 7 days off) and low-dose dexamethasone (40 mg per week in four-week cycles), versus lenalidomide and low-dose dexamethasone alone. The study randomized 792 patients at sites in North America, Europe and Israel.

About ENDEAVOR

The randomized ENDEAVOR (Randomiz**E**d, Ope**N** Label, Phase 3 Study of Carfilzomib Plus **DE**xameth**A**sone **V**s Bortezomib Plus Dexamethas**O**ne in Patients With **R**elapsed Multiple Myeloma) trial of 929 patients evaluated KYPROLIS in combination with low-dose dexamethasone (Kd), versus bortezomib with low-dose dexamethasone (Vd) in patients whose multiple myeloma has relapsed after at least one, but not more than three prior therapeutic regimens. The primary endpoint of the trial was PFS, defined as the time from treatment initiation to disease progression or death. The primary analysis was published in The Lancet Oncology and is described in the Prescribing Information.

Patients received treatment until progression with KYPROLIS as a 30-minute infusion on days 1, 2, 8, 9, 15 and 16 of 28 day treatment cycles, along with low-dose dexamethasone (20 mg). For cycle one only, KYPROLIS was administered at 20 mg/m^2 on days 1 and 2, and if tolerated was escalated to 56 mg/m^2 from day 8 cycle one onwards. Patients who received bortezomib (1.3 mg/m^2) with low-dose dexamethasone (20 mg) were treated with bortezomib administered subcutaneously or intravenously at the discretion of the investigator and in accordance with regional regulatory approval of bortezomib. More than 75 percent of the patients in the control arm received bortezomib subcutaneously. This study was conducted at 235 sites worldwide. For information about this trial, please visit www.clinicaltrials.gov under trial identification number NCT01568866.

About Multiple Myeloma

Multiple myeloma is an incurable blood cancer, characterized by a recurring pattern of remission and relapse.[1] It is a rare and very aggressive disease that accounts for approximately one percent of all cancers.[2,3] In the U.S., there are nearly 95,000 people living with, or in remission from, multiple myeloma.[4] Approximately 30,330 Americans are diagnosed with multiple myeloma each year and 12,650 patient deaths are reported on an annual basis.[4]

About KYPROLIS® (carfilzomib)

Proteasomes play an important role in cell function and growth by breaking down proteins that are damaged or no longer needed.[5] KYPROLIS has been shown to block proteasomes, leading to an excessive build-up of proteins within cells.[5] In some cells, KYPROLIS can cause cell death, especially in myeloma cells because they are more likely to contain a higher amount of abnormal proteins.[5,6]

KYPROLIS is approved in the U.S. for the following:

- In combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

KYPROLIS is also approved in Argentina, Australia, Bahrain, Canada, Hong Kong, Israel, Japan, Kuwait, Lebanon, Macao, Mexico, Thailand, Colombia, S. Korea, Canada, Qatar, Switzerland, United Arab Emirates, Turkey, Russia, Brazil, India, Oman and the European Union. Additional regulatory applications for KYPROLIS are underway and have been submitted to health authorities worldwide.

IMPORTANT SAFETY INFORMATION

Cardiac Toxicities

- New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of KYPROLIS administration.
- Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart KYPROLIS at 1 dose level reduction based on a benefit/risk assessment.
- While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.
- Patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with KYPROLIS and remain under close follow-up.

Acute Renal Failure

- Cases of acute renal failure and renal insufficiency adverse events (including renal failure) have occurred in patients receiving KYPROLIS. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome

- Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred in patients receiving KYPROLIS. Patients with multiple myeloma and a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly. Withhold KYPROLIS until TLS is resolved.

Pulmonary Toxicity

- Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving KYPROLIS. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension

- Pulmonary arterial hypertension (PAH) was reported in patients treated with KYPROLIS. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to

restart KYPROLIS based on a benefit/risk assessment.

Dyspnea

- Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KYPROLIS for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Hypertension

- Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with KYPROLIS. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Venous Thrombosis

- Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with KYPROLIS. Thromboprophylaxis is recommended for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.
- Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with KYPROLIS in combination with dexamethasone or lenalidomide plus dexamethasone.

Infusion Reactions

- Infusion reactions, including life-threatening reactions, have occurred in patients receiving KYPROLIS.
- Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS. Premedicate with dexamethasone to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms of an infusion reaction and to contact a physician immediately if they occur.

Hemorrhage

- Fatal or serious cases of hemorrhage have been reported in patients receiving KYPROLIS. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

Thrombocytopenia

- KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in patients receiving KYPROLIS. Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure

- Cases of hepatic failure, including fatal cases, have been reported during treatment with KYPROLIS. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy

- Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred in patients receiving KYPROLIS. Monitor for signs and symptoms of TTP/HUS. Discontinue KYPROLIS if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS therapy in patients previously experiencing TTP/HUS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Cases of PRES have occurred in patients receiving KYPROLIS. PRES was formerly known as Reversible Posterior Leukoencephalopathy Syndrome. Consider a neuro-radiological imaging (MRI) for onset of visual or neurological symptoms. Discontinue KYPROLIS if PRES is suspected and evaluate. The safety of reinitiating KYPROLIS therapy in patients previously experiencing PRES is not known.

Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-ineligible Patients

- In a clinical trial of transplant-ineligible patients with newly diagnosed multiple myeloma comparing KYPROLIS, melphalan, and prednisone (KMP) vs bortezomib, melphalan, and prednisone (VMP), a higher incidence of serious and fatal adverse events was observed in patients in the KMP arm. KYPROLIS in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

Embryo-fetal Toxicity

- KYPROLIS can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals.
- Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. Males of reproductive potential should be advised to avoid fathering a child while being treated with KYPROLIS. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

- The most common adverse reactions occurring in at least 20% of patients treated with KYPROLIS in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia.
- The most common adverse reactions occurring in at least 20% of patients treated with KYPROLIS in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema peripheral.

Please see full prescribing information at www.kyprolis.com.

About Amgen's Commitment to Oncology
Amgen Oncology is committed to helping patients take on some of the toughest cancers, such as those that have been resistant to drugs, those that progress rapidly through the body and those where limited treatment options exist. Amgen's supportive care treatments help patients combat certain side effects of strong chemotherapy, and our targeted medicines and immunotherapies focus on more than a dozen different malignancies, ranging from blood cancers to solid tumors. With decades of experience providing therapies for cancer patients, Amgen continues to grow its portfolio of innovative and biosimilar oncology medicines.

About Amgen
Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

Forward-Looking Statements
This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. We or others could identify safety, side effects or manufacturing

problems with our products after they are on the market. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all. We are increasingly dependent on information technology systems, infrastructure and data security. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock.

CONTACT: Amgen, Thousand Oaks
Kristen Davis, 805-447-3008 (Media)
Kristen Neese, 805-313-8267 (Media)
Arvind Sood, 805-447-1060 (Investors)

References

1. Jakubowiak A. Management Strategies for Relapsed/Refractory Multiple Myeloma: Current Clinical Perspectives. *Seminars in Hematology*. 2012; 49(3)(1),S16-S32.
2. GLOBOCAN 2012. Global Prevalence and Incidence. Available at: http://globocan.iarc.fr/old/summary_table_pop_prev.asp?selection=224900&title=World&sex=0&window=1&sort=0&submit=%C2%A0Execute%C2%A0. Accessed on January 6, 2017.
3. American Cancer Society. Multiple myeloma. Available at: https://www.cancer.org/cancer/multiple-myeloma/about.html. Accessed on July 12, 2017.
4. National Cancer Institute. SEER Stat Fact Sheets: Myeloma. Available at: http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed on January 6, 2017.
5. Moreau P, Richardson PG, Cavo M, et al. Proteasome Inhibitors in Multiple Myeloma: 10 Years Later. *Blood*. 2012; 120(5):947-959.
6. Kortuem KM and Stewart AK. Carfilzomib. *Blood*. 2012; 121(6):893-897.

View original content with multimedia:http://www.prnewswire.com/news-releases/second-phase-3-study-shows-kyprolis-carfilzomib-regimen-significantly-improves-overall-survival-in-patients-with-relapsed-multiple-myeloma-300487224.html

SOURCE Amgen