FDA Approves New KYPROLIS® (carfilzomib) Combination Regimen With DARZALEX® (daratumumab) And Dexamethasone In Both Once- And Twice-Weekly Dosing Regimens

August 20, 2020

Approval Based on the CANDOR and EQUULEUS Studies in Patients With Relapsed/Refractory Multiple Myeloma

THOUSAND OAKS, Calif., Aug. 20, 2020 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced the U.S. Food and Drug Administration (FDA) has approved the expansion of the KYPROLIS® (carfilzomib) U.S. prescribing information to include its use in combination with DARZALEX® (daratumumab) plus dexamethasone (DKd) in two dosing regimens — once weekly and twice weekly — for the treatment of patients with relapsed or refractory multiple myeloma (R/R MM) who have received one to three previous lines of therapy.

"This expanded approval for KYPROLIS demonstrates a leap forward in the treatment paradigm for this complex disease by combining two potent agents in their respective drug classes indicated for patients with relapsed or refractory multiple myeloma," said David M. Reese, M.D., executive vice president of Research and Development at Amgen.

Multiple myeloma is a blood cancer characterized by patterns of remission and relapse. Patient outcomes worsen with each relapse.[1] With the increasing use of frontline immunomodulatory drug based (IMiD) therapies through progression, the number of patients treated with these agents who will progress is likely to increase with time. This creates an emerging need for efficacious IMiD-free regimens upon relapse.[2]

"Now, we can provide healthcare professionals and patients with an efficacious regimen with two dosing options at a critical time in a patient's treatment journey: first relapse," Reese continued.

"The DKd regimen provides an important potent triplet option in the setting of relapse following IMiD combination frontline therapy," said Brian G.M. Durie, M.D., chairman, International Myeloma Foundation.

The Phase 3 CANDOR trial was the first Phase 3 randomized trial to compare DKd versus KYPROLIS and dexamethasone (Kd) alone in R/R MM patients. The study met its primary endpoint and resulted in a 37% reduction in the risk of disease progression or death in patients receiving DKd (HR=0.63; 95% CI: 0.464, 0.854; p-value [1-sided]=0.0014) compared to Kd alone.

"Despite ongoing advances in the treatment of multiple myeloma, the disease remains incurable and is especially challenging for patients who relapse or become refractory to established therapies," said Saad Z. Usmani, M.D., director of clinical research in hematologic malignancies; director of plasma cell disorders; clinical professor of medicine, Atrium Health's Levine Cancer Institute. "As a clinician, having the DKd regimen as an option means we can now combine two efficacious, targeted agents in a new, immunomodulatory drug-free triplet regimen that has demonstrated deep and durable responses for patients upon relapse."

In CANDOR, the safety of DKd was generally consistent with the known safety profiles of the individual agents. The most frequently reported (≥ 20% of subjects in either treatment arm [DKd, Kd]) treatment-emergent adverse events (AEs) included infusion-related reactions, anemia, diarrhea, fatigue, hypertension, pyrexia, upper respiratory tract infection, thrombocytopenia, neutropenia, lymphopenia, cough, dyspnea, and insomnia, headache and back pain. The incidence of treatment-emergent Grade 3 or higher, serious and fatal AEs was higher in the DKd arm compared to the Kd arm. The most common reason for fatal treatment-emergent AEs in both arms was infection. The rate of treatment discontinuation due to AEs was similar in both arms.

The expansion of KYPROLIS's prescribing information to include once-weekly dosing of KYPROLIS within the DKd regimen was supported by the open-label, multi-cohort Phase 1b EQUULEUS trial, in which the safety and efficacy of DKd was assessed among R/R MM patients using a once-weekly dosing regimen for KYPROLIS.

Amgen has submitted marketing applications globally.

DARZALEX® is a registered trademark of Janssen Pharmaceutica NV.

About CANDOR
CANDOR, a randomized, open-label Phase 3 study of KYPROLIS, DARZALEX and dexamethasone (DKd) compared to KYPROLIS and dexamethasone (Kd), has evaluated 466 relapsed or refractory multiple myeloma patients who have received one to three prior therapies. Patients were treated until disease progression. The primary endpoint was progression-free survival (PFS), and the key secondary endpoints were overall response rate, minimal residual disease and overall survival. PFS was defined as time from randomization until disease progression or death from any cause.

In the first arm, patients received KYPROLIS twice weekly at 56 mg/m^2 and dexamethasone in combination with DARZALEX. In the second arm (control), patients received KYPROLIS twice weekly at 56 mg/m^2 and dexamethasone.

CANDOR was initiated as part of a collaboration with Janssen, and under the terms of the agreement, Janssen co-funded the study. For more information about this trial, please visit www.clinicaltrials.gov under trial identification number NCT03158688.

About EQUULEUS
EQUULEUS was an open label, Phase 1b, multi-cohort trial which evaluated the combination of KYPROLIS with intravenous DARZALEX and dexamethasone in 85 patients with relapsed or refractory multiple myeloma who had received one to three prior lines of therapy.

KYPROLIS was evaluated at a starting dose of 20 mg/m^2, which was increased to 70 mg/m^2 on Cycle 1, Day 8 and onward.

The most frequently reported all-grade, treatment-emergent AEs (occurring in 20% or more of patients) were thrombocytopenia, respiratory tract

infection, anemia, nausea, fatigue, vomiting, diarrhea, pyrexia, neutropenia, lymphopenia, infusion related reactions, dyspnea, cough, insomnia, hypertension, headache and back pain.

At a median follow-up of 16.6 months, the overall response rate was 81% in all treated patients: 21% achieved a stringent complete response, 14% a complete response, 33% a very good partial response and 13% a partial response.

About Multiple Myeloma

Multiple myeloma is an incurable blood cancer, characterized by a recurring pattern of remission and relapse.[3] It is a rare and life-threatening disease that accounts for approximately one percent of all cancers.[4,5] Worldwide, approximately 160,000 people are diagnosed with multiple myeloma each year, and 106,000 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.[6] KYPROLIS has been shown to block proteasomes, leading to an excessive build-up of proteins within cells.[7] 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.[6,7]

Since its first approval in 2012, approximately 150,000 patients worldwide have received KYPROLIS.[8] KYPROLIS is approved in the U.S. for the following:

- for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with
  - Lenalidomide and dexamethasone; or
  - Dexamethasone; or
  - Daratumumab and dexamethasone.
- 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 Algeria, Argentina, Australia, Bahrain, Belarus, Brazil, Canada, Chile, Colombia, Ecuador, Egypt, European Union, Hong Kong, India, Israel, Japan, Jordan, Kazakhstan, Kuwait, Lebanon, Macao, Malaysia, Mexico, Morocco, New Zealand, Oman, Peru, Philippines, Qatar, Russia, Saudi Arabia, Serbia, Singapore, S. Africa, S. Korea, Switzerland, Taiwan, Thailand, Turkey and United Arab Emirates.

U.S. KYPROLIS® (carfilzomib) Important Safety Information

INDICATIONS

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- KYPROLIS® is indicated as a single agent for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

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 administration.
- Monitor patients for signs or symptoms of cardiac failure or 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 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.
- For 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 prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

Acute Renal Failure

- Cases of acute renal failure, including some fatal renal failure events, and renal insufficiency adverse events (including renal failure) have occurred. 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. Patients with 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, and withhold until 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. Some events have been fatal. In the event of drug–induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension

- Pulmonary arterial hypertension (PAH) was reported. 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 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 based on a benefit/risk assessment.

Hypertension

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

Venous Thrombosis

- Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed. 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 hormonal contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment.

Infusion Reactions

- Infusion reactions, including life–threatening reactions, have occurred. Signs and symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, laryngeal 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. Premedicate with dexamethasone to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and seek immediate medical attention if they occur.

Hemorrhage

- Fatal or serious cases of hemorrhage have been reported. 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. Monitor platelet counts frequently during treatment. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure

- Cases of hepatic failure, including fatal cases, have occurred. 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. Monitor for signs and symptoms of TTP/HUS. Discontinue if diagnosis

is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Cases of PRES have occurred in patients receiving KYPROLIS. If PRES is suspected, discontinue and evaluate with appropriate imaging. The safety of reinitiating KYPROLIS 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. KMP 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.
- Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS and for 6 months following the final dose. Males of reproductive potential should be advised to avoid fathering a child while being treated with KYPROLIS and for 3 months following the final dose. 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 in the combination therapy trials: anemia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, cough, upper respiratory tract infection, hypertension.
- The most common adverse reactions in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema peripheral.

Please see accompanying full Prescribing Information at www.kyprolis.com.

About Amgen Oncology
Amgen Oncology is searching for and finding answers to incredibly complex questions that will advance care and improve lives for cancer patients and their families. Our research drives us to understand the disease in the context of the patient's life – not just their cancer journey – so they can take control of their lives.

For the last four decades, we have been dedicated to discovering the firsts that matter in oncology and to finding ways to reduce the burden of cancer. Building on our heritage, Amgen continues to advance the largest pipeline in the Company's history, moving with great speed to advance those innovations for the patients who need them.

At Amgen, we are driven by our commitment to transform the lives of cancer patients and keep them at the center of everything we do.

For more information, follow us on www.twitter.com/amgenoncology.

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 any statements on the outcome, benefits and synergies of collaborations, or potential collaborations, with any other company, including Adaptive Biotechnologies (including statements regarding such collaboration's ability to discover and develop fully-human neutralizing antibodies targeting SARS-CoV-2 to potentially prevent or treat COVID-19), BeiGene, Ltd., or the Otezla® (apremilast) acquisition, including anticipated Otezla sales growth and the timing of non-GAAP EPS accretion, as well as 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, effects of pandemics or other widespread health problems such as the ongoing COVID-19 pandemic on our business, outcomes, progress, or effects relating to studies of Otezla as a potential treatment for COVID-19, 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 current reports on 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, including our devices, 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. 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, including in Puerto Rico, 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. An outbreak of disease or similar public health threat, such as COVID-19, and the public and governmental effort to mitigate against the spread of such disease, could have a significant adverse effect on the supply of materials for our manufacturing activities, the distribution of our products, the commercialization of our product candidates, and our clinical trial operations, and any such events may have a material adverse effect on our product development, product sales, business and results of operations. We rely on collaborations with third parties for the development of some of our product candidates and for the commercialization and sales of some of our commercial products. 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 collaborate with or acquire other companies, products or technology and to integrate the operations of companies or to support the products or technology we have acquired, may not be successful. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our systems and our data. 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. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

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