Vectibix® (panitumumab) And Best Supportive Care Improves Overall Survival Compared To Best Supportive Care In Chemorefractory KRAS And RAS Wild-Type Metastatic Colorectal Cancer

January 23, 2016

First Phase 3 Vectibix Trial to Include a Prespecified Analysis of Efficacy Endpoints by RAS Tumor Status in Primary Analysis

Results Presented at Gastrointestinal Cancers Symposium 2016 Reinforce Importance of RAS Testing

THOUSAND OAKS, Calif., Jan. 23, 2016 /PRNewswire/ -- Amgen (NASDAQ: AMGN) today announced the presentation of detailed results of a Phase 3 study with Vectibix® (panitumumab) and best supportive care (BSC) compared to BSC alone. The study met its primary endpoint, demonstrating a statistically significant improvement in overall survival (OS) in patients with chemorefractory wild-type *KRAS* (exon 2) metastatic colorectal cancer (mCRC; n=377 total). This is the first Phase 3 Vectibix study to include an analysis of efficacy of Vectibix by wild-type *KRAS* (exon 2) and in wild-type *RAS* tumor mutation status in its primary analysis, providing important information about OS in these populations. These results, in addition to secondary endpoint data, were presented at the 2016 Gastrointestinal Cancers Symposium (GICS) in San Francisco.

The study (GICS abstract #642) showed that patients with wild-type *KRAS* (exon 2) mCRC treated with Vectibix and BSC achieved a median OS of 10 months compared to 7.4 months for patients treated with BSC alone (hazard ratio [HR]=0.73, 95 percent confidence interval [CI]=0.57-0.93, *p*=0.0096). Data from a key secondary endpoint showed that patients with wild-type *RAS* (absence of mutations in exons 2, 3 and 4 of *KRAS* and *NRAS*) mCRC treated with Vectibix and BSC achieved a median OS of 10 months compared to 6.9 months for patients treated with BSC alone (n=270; HR=0.70, 95 percent CI=0.53-0.93, *p*=0.0135). Patients with mutant *RAS* mCRC did not benefit from Vectibix treatment (n=54; OS HR=0.99, 95 percent CI=0.49-2.00). The safety profile was comparable to the known safety profile of Vectibix when administered as a single agent, with skin, nail, gastrointestinal and electrolyte disorders being the most frequently reported adverse events.

"Amgen has played a significant role in the advancement of personalized medicine, applying cutting-edge science and technology in our efforts to target therapies to the patients who are most likely to benefit. Amgen is committed to understanding cancer biology through studies like this," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "As well as providing additional insights into the way Vectibix works in mCRC, these data support expanding biomarker screening to include wild-type *RAS*."

Colorectal cancer is the third most common cancer worldwide, with approximately 1.2 million cases occurring globally each year.[1,2] Approximately 20 percent of colon cancers are diagnosed at the metastatic stage, when the disease has already spread to distant organs, a diagnosis associated with only a 12 percent five-year survival rate.[3] Using molecular approaches to identify unique genetic signatures in mCRC has the potential to help improve treatment outcomes. Of the few biomarkers in colorectal cancer, *RAS* genes (*KRAS*, *NRAS*) have a validated impact on treatment outcomes.[4,5]

Abstracts are currently available on the GICS website.

About '0007 Study (NCT01412957)
This Phase 3 global, multicenter, randomized, open-label study was designed to evaluate OS with Vectibix and BSC compared to BSC alone in patients with chemorefractory wild-type *KRAS* (exon 2) mCRC.

Key secondary endpoints included progression-free survival (PFS) in patients with wild-type *KRAS* mCRC, as well as OS and PFS in patients with wild-type *RAS* (absence of mutations in exons 2, 3 and 4 of *KRAS* and *NRAS*) mCRC, objective response rate (ORR) and safety in both wild-type *KRAS* (exon 2) and wild-type *RAS* groups.

Patients were randomized 1:1 to receive 6 mg/kg of Vectibix every 14 days and BSC, or BSC alone (as defined by the investigator). There were a total of 377 patients enrolled:

- 324 out of 377 subjects with *RAS* mutation status determined (86 percent ascertainment rate)
- Out of 324
  - 270 had wild-type *RAS* (83 percent)
  - 54 were found to be mutant *RAS* (17 percent)
- 189 patients for *KRAS* (exon 2) group for Vectibix and BSC

Treatment with Vectibix combined with BSC in patients with wild-type *KRAS* resulted in median PFS of 3.6 months versus 1.7 months with BSC alone (HR=0.51, 95 percent CI=0.41-0.64, *p*=0.0001). In patients with wild-type *RAS*, the Vectibix combination resulted in median PFS of 5.2 months versus 1.7 months with BSC alone (HR=0.46, 95 percent CI=0.35-0.59, *p*=0.0001).

For patients with wild-type *KRAS*, ORRs were 27.0 percent with Vectibix versus 1.6 percent with BSC (HR=24.9, 95 percent CI=7.5-123.8, *p*<0.0001). For patients with wild-type *RAS*, ORRs were 31.0 percent with Vectibix versus 2.3 percent for BSC (ODDS Ratio=20.0, 95 percent CI=5.9-101.6, *p*<0.0001).

Patients with mutant *RAS* mCRC did not benefit from Vectibix treatment (OS HR=0.99, 95 percent CI=0.49-2.00). No new safety signals were seen in this study. The safety profile was comparable to the known safety profile of Vectibix when administered as a single agent, with skin, nail, gastrointestinal and electrolyte disorders being the most frequently reported adverse events.

About Vectibix® (panitumumab)
Vectibix is the first fully human monoclonal anti-epidermal growth factor receptor (EGFR) antibody approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer (mCRC). Vectibix was approved in the U.S. in September 2006 as a monotherapy for the treatment of patients with EGFR-expressing mCRC after disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-

containing chemotherapy.

In May 2014, the FDA approved Vectibix for use in combination with FOLFOX, as first-line treatment in patients with wild-type *KRAS* (exon 2) mCRC. With this approval, Vectibix became the first-and-only biologic therapy indicated for use with FOLFOX, one of the most commonly used chemotherapy regimens, in the first-line treatment of mCRC for patients with wild-type *KRAS* mCRC.

Important U.S. Product Information
Vectibix is indicated for the treatment of patients with wild-type *KRAS* (exon 2 in codons 12 or 13) metastatic colorectal cancer (mCRC) as determined by an FDA-approved test for this use:

- As first-line therapy in combination with FOLFOX
- As monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy

Limitation of Use: Vectibix is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

WARNING: DERMATOLOGIC TOXICITY
Dermatologic Toxicity: Dermatologic toxicities occurred in 90 percent of patients and were severe (NCI-CTC grade 3 or higher) in 15% of patients receiving Vectibix monotherapy.

In Study 1, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients with mCRC receiving Vectibix. The clinical manifestations included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin and skin fissures.

Monitor patients who develop dermatologic or soft tissue toxicities while receiving Vectibix for the development of inflammatory or infectious sequelae. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses and sepsis have been observed in patients treated with Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions and skin sloughing has also been observed in patients treated with Vectibix. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis). Withhold or discontinue Vectibix for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications. Dose modifications for Vectibix concerning dermatologic toxicity are provided in the product labeling. Vectibix is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either *KRAS* or *NRAS* and hereafter is referred to as "*RAS*."

Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of *RAS* mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing *RAS* mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents.

Additionally, in Study 3, 272 patients with *RAS*-mutant mCRC tumors received Vectibix in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI 1.01-1.45) in patients with *RAS*-mutant mCRC who received Vectibix and FOLFOX versus FOLFOX alone.

Progressively decreasing serum magnesium levels leading to severe (Grade 3-4) hypomagnesemia occurred in up to 7% (in Study 2) of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating Vectibix treatment, periodically during Vectibix treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

In Study 1, 4% of patients experienced infusion reactions and 1% of patients experienced severe infusion reactions (NCI-CTC grade 3-4). Infusion reactions, manifesting as fever, chills, dyspnea, bronchospasm, and hypotension, can occur following Vectibix administration. Fatal infusion reactions occurred in postmarketing experience. Terminate the infusion for severe infusion reactions.

Severe diarrhea and dehydration, leading to acute renal failure and other complications, have been observed in patients treated with Vectibix in combination with chemotherapy.

Fatal and non-fatal cases of interstitial lung disease (ILD) (1%) and pulmonary fibrosis have been observed in patients treated with Vectibix. Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix. In the event of acute onset or worsening of pulmonary symptoms, interrupt Vectibix therapy. Discontinue Vectibix therapy if ILD is confirmed.

In patients with a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with Vectibix versus the risk of pulmonary complications must be carefully considered.

Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving Vectibix.

Keratitis and ulcerative keratitis, known risk factors for corneal perforation, have been reported with Vectibix use. Monitor for evidence of keratitis or ulcerative keratitis. Interrupt or discontinue Vectibix for acute or worsening keratitis.

In an interim analysis of an open-label, multicenter, randomized clinical trial in the first-line setting in patients with mCRC, the addition of Vectibix to the combination of bevacizumab and chemotherapy resulted in decreased OS and increased incidence of NCI-CTC grade 3–5 (87% vs 72%) adverse reactions. NCI-CTC grade 3–4 adverse reactions occurring at a higher rate in Vectibix-treated patients included rash/acneiform dermatitis (26% vs 1%), diarrhea (23% vs 12%), dehydration (16% vs 5%; primarily occurring in patients with diarrhea), hypokalemia (10% vs 4%), stomatitis/mucositis (4% vs < 1%), and hypomagnesemia (4% vs 0).

NCI-CTC grade 3–5 pulmonary embolism occurred at a higher rate in Vectibix-treated patients (7% vs 3%) and included fatal events in three (< 1%) Vectibix-treated patients.

As a result of the toxicities experienced, patients randomized to Vectibix, bevacizumab and chemotherapy received a lower mean relative dose intensity of each chemotherapeutic agent (oxaliplatin, irinotecan, bolus 5-FU, and/or infusional 5-FU) over the first 24 weeks on study, compared with those randomized to bevacizumab and chemotherapy.

Advise patients of the need for adequate contraception in both males and females while receiving Vectibix and for 6 months after the last dose of Vectibix therapy. Vectibix may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women.

Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from Vectibix, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If nursing is interrupted, it should not be resumed earlier than 2 months following the last dose of Vectibix.

Women who become pregnant during Vectibix treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Women who are nursing during Vectibix treatment are encouraged to enroll in Amgen's Lactation Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

In Study 1, the most common adverse reactions (≥ 20%) with Vectibix were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea. The most common (> 5%) serious adverse reactions in the Vectibix arm were general physical health deterioration and intestinal obstruction.

In Study 3, the most commonly reported adverse reactions (> 20%) in patients with wild-type *KRAS* mCRC receiving Vectibix (6 mg/kg every 2 weeks) and FOLFOX therapy (N = 322) were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus and dry skin. Serious adverse reactions (> 2% difference between treatment arms) in Vectibix-treated patients with wild-type *KRAS* mCRC were diarrhea and dehydration.

To see the Vectibix Prescribing Information, including Boxed Warning visit www.vectibix.com.
In the EU, Vectibix is currently indicated for the treatment of adult patients with wild-type *RAS* mCRC:

- in first-line in combination with FOLFOX and FOLFIRI.
- in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
- as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

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 biologics manufacturing 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 Inc. and its subsidiaries (Amgen, we or us) and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described. 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 (SEC) reports filed by Amgen Inc., including Amgen Inc.'s most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Please refer to Amgen Inc.'s most recent Forms 10-K, 10-Q and 8-K for additional information on the uncertainties and risk factors related to Amgen's business. Unless otherwise noted, Amgen is providing this information as of Jan. 23, 2016, and expressly disclaims any duty to update information contained in this news release.

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 and our partners to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. 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 business may be impacted by government investigations,

litigation and product liability claims. 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. We depend on third parties for a significant portion of our manufacturing capacity for the supply of certain of our current and future products and limits on supply may constrain sales of certain of our current products and product candidate development.

In addition, sales of our products (including products of our wholly-owned subsidiaries) are affected by the 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 as well as U.S. legislation affecting pharmaceutical pricing and reimbursement. Government and others' regulations and reimbursement policies may affect the development, usage and pricing of our products. In addition, we compete with other companies with respect to some of our marketed products as well as for the discovery and development of new products. We believe that some of our newer products, product candidates or new indications for existing products, may face competition when and as they are approved and marketed. Our products may compete against products that have lower prices, established reimbursement, superior performance, are easier to administer, or that are otherwise competitive with our products. In addition, while we and our partners routinely obtain patents for our and their products and technology, the protection of our products offered by patents and patent applications may be challenged, invalidated or circumvented by our or our partners' competitors and there can be no guarantee of our or our partners' ability to obtain or maintain patent protection for our products or product candidates. We cannot guarantee that we will be able to produce commercially successful products or maintain the commercial success of our existing products. Our stock price may be affected by actual or perceived market opportunity, competitive position, and success or failure of our products or product candidates. Further, 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 integrate the operations of companies we have acquired may not be successful. We may experience difficulties, delays or unexpected costs and not achieve anticipated benefits and savings from our ongoing restructuring plans. 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 common stock.

The scientific information discussed in this news release relating to new indications for Amgen's products is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration for the products. The products are not approved for the investigational use(s) discussed in this news release and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

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