FDA Approves Vectibix® (Panitumumab) For Use In Wild-Type RAS Metastatic Colorectal Cancer

June 29, 2017

Vectibix Demonstrated an Improvement in Overall Survival in Patients With Wild-Type RAS Metastatic Colorectal Cancer
Predictive Biomarkers Allow Physicians to More Accurately Identify Treatments to Potentially Optimize Cancer Care
Approved Companion Diagnostic Tool Strengthens Precision Medicine Approach

THOUSAND OAKS, Calif., June 29, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the U.S. Food and Drug Administration (FDA) has approved the supplemental Biologics License Application (sBLA) for Vectibix® (panitumumab) for patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) as first-line therapy in combination with FOLFOX and as monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy. Vectibix is the first-and-only fully human monoclonal anti-epidermal growth factor receptor (EGFR) antibody approved by the FDA for this patient population.

As part of this new indication, the FDA approved the first multigene, next-generation sequencing-based test to identify the *RAS* mutation status of a patient's tumor. Next-generation sequencing is a novel diagnostics test technique that makes a more personalized medicine approach possible. This companion diagnostic helps physicians identify patients that are more likely to benefit from treatment with Vectibix.

"Of the few biomarkers in colorectal cancer, *RAS* mutation status provides actionable information when deciding on a first-line treatment option in mCRC patients," said Marwan G. Fakih, M.D., co-director of the Gastrointestinal Cancer Program at City of Hope, Duarte, Calif. "Panitumumab has demonstrated a significant overall survival benefit to patients whose mCRC does not have mutations in *RAS*, providing physicians with a novel targeted treatment option and allowing us to develop a personalized approach as we help patients fight this devastating disease."

The full approval for Vectibix as a treatment for patients with wild-type *KRAS* mCRC was based on results from the Phase 3 PRIME and ASPECCT trials. The approval of a refined indication for the treatment of patients with wild-type *RAS* mCRC was based on a retrospective analysis from the PRIME study and prospective, pre-defined analyses from the Phase 3 '0007 study. The '0007 study evaluated the efficacy of Vectibix plus best supportive care (BSC) versus BSC alone in patients with chemorefractory, wild-type *KRAS* mCRC. Data from a key secondary endpoint showed that patients with wild-type *RAS* (exons 2, 3, and 4 of *KRAS* and *NRAS*) mCRC treated with Vectibix plus BSC resulted in a statistically significant improvement in overall survival (OS) of 10 months compared to 6.9 months for patients treated with BSC alone (HR=0.70; 95 percent CI: 0.53, 0.93, *p*=0.0135). The safety profile of Vectibix in patients with wild-type *RAS* mCRC is consistent with that seen previously in patients with wild-type *KRAS* mCRC.

"Every patient with cancer is unique, and we are committed to utilizing cutting-edge science and technology to target treatments to the patients more likely to benefit," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "This approval for Vectibix reinforces the significance of biomarker testing as a treatment planning tool in metastatic colorectal cancer and further validates the potential for precision medicine to optimize patient outcomes."

Most common adverse reactions (≥ 20 percent) of Vectibix as monotherapy are skin rash with variable presentations, paronychia, fatigue, nausea and diarrhea. Most common adverse reactions (≥ 20 percent) with Vectibix plus FOLFOX are diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus and dry skin. The most common serious adverse reactions (≥ 2 percent difference between treatment arms) were diarrhea and dehydration.

About Colorectal Cancer
Colorectal cancer is the third most common cancer found in both men and women in the U.S., with approximately 135,000 new cases estimated to be diagnosed in 2017.[1] 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.[2] Using molecular approaches to identify unique genetic signatures in mCRC has the potential to help improve treatment outcomes.[3]

About the '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.

The key efficacy analysis of the study showed that Vectibix plus BSC (n=189) was statistically significant to BSC alone (n=188). Patients with wild-type *KRAS* (exon 2) mCRC treated with Vectibix plus BSC achieved a median OS of 10 months compared to 7.4 months for patients treated with BSC alone (HR=0.73; 95 percent CI: 0.57, 0.93, *p*=0.0096).

In patients with mutant *RAS* mCRC, no differences in OS or progression-free survival (PFS) were observed between the treatment arms [OS HR=0.99 (95 percent CI: 0.49, 2.00); PFS HR=1.03 (95 percent CI: 0.56, 1.90)].

No new safety signals were seen in the '0007 study. The safety profile was comparable to the known safety profile of Vectibix when administered as a single agent.

About the PRIME Study
PRIME was a randomized, Phase 3, open-label study of Vectibix and FOLFOX combination therapy versus FOLFOX monotherapy in 1,183 adults with untreated mCRC who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The primary endpoints were PFS and OS.

The PRIME study showed that patients with wild-type *KRAS* tumors (exon 2) achieved statistically significant improvement in PFS with Vectibix and FOLFOX versus FOLFOX alone (9.6 versus 8.0 months [HR=0.80; 95 percent CI: 0.66, 0.97, *p*=0.02]) and a significant 4.4 month improvement in OS versus FOLFOX alone (23.8 versus 19.4 months [HR=0.82, 95 percent CI: 0.70, 0.98]).

Analyses from the PRIME study evaluated the treatment effect of Vectibix plus FOLFOX compared with FOLFOX alone in the wild-type *RAS* subgroup and found that Vectibix plus FOLFOX extended the prespecified major efficacy measure of PFS versus FOLFOX alone, 10.1 months versus 7.9 months, respectively (HR=0.72; 95 percent CI: 0.58, 0.90). The study demonstrated that the median OS for patients treated with Vectibix plus FOLFOX was 25.8 months versus 20.2 months for those treated with FOLFOX alone (HR=0.77; 95 percent CI: 0.64, 0.94). There were no OS or PFS benefit in Vectibix-treated patients with mutant *RAS* mCRC.

About the ASPECCT Study

ASPECCT was a global, randomized, multicenter, open-label, Phase 3 non-inferiority trial designed to compare the effect of Vectibix versus Erbitux® (cetuximab) on OS for monotherapy treatment of 1,010 patients with EGFR-expressing, chemorefractory wild-type *KRAS* (exon 2) mCRC.

The ASPECCT study met its primary endpoint of non-inferiority for improving OS in patients taking Vectibix (n=499) versus Erbitux (n=100) as a single agent for the treatment of mCRC in patients with wild-type *KRAS* tumors who have not responded to chemotherapy. Patients treated with Vectibix demonstrated an OS of 10.4 months versus 10 months for patients treated with Erbitux (HR=0.97; 95 percent CI: 0.84-1.11).

About Vectibix® (panitumumab)

Vectibix is the first fully human monoclonal anti-EGFR antibody approved by the FDA for the treatment of 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.

In June 2017, the FDA approved a refined indication for Vectibix for use in in patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use*)* mCRC.

Important U.S. Product Information

Vectibix® is indicated for the treatment of patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC):

- 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% of patients and were severe (NCI-CTC grade 3 or higher) in 15% of patients receiving Vectibix monotherapy.

In Study 20020408, 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 Vectibix®. 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 (eg, 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 *RAS* 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 20050203, 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 20080763) 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 20020408, 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 nonfatal 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.

Vectibix® can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 months after the last dose of Vectibix®.

In monotherapy, the most commonly reported adverse reactions (≥ 20%) in patients with Vectibix® were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.

The most commonly reported adverse reactions (≥ 20%) with Vectibix® + FOLFOX were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin. The most common serious adverse reactions (≥ 2% difference between treatment arms) were diarrhea and dehydration.

To see the Vectibix® Prescribing Information, including Boxed Warning visit www.vectibix.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. 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. Discovery or identification of new product candidates cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate will be successful and become a commercial product. 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.

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