Analysis Published In New England Journal of Medicine Highlights Discovery Of New Predictive Biomarkers For Vectibix® (Panitumumab)

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Study Links RAS Mutations to Vectibix Clinical Response in Patients With Metastatic Colorectal Cancer

THOUSAND OAKS, Calif., Sept. 11, 2013 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced the publication of a biomarker analysis of Vectibix® (panitumumab) in combination with FOLFOX, a type of oxaliplatin-based chemotherapy, for the first-line treatment of patients with metastatic colorectal cancer (mCRC). Published in the *New England Journal of Medicine,* the analysis found that *RAS* mutations, beyond the known *KRAS* exon 2 mutations, predict lack of response to Vectibix in combination with FOLFOX. *RAS* mutations are mutations occurring in exons 2, 3 and 4 of *KRAS* and *NRAS*.

"While the *KRAS* exon 2 biomarker is well-known and has facilitated selection of patients more likely to respond to anti-EGFR treatment, we found that there were still some patients who didn't benefit from treatment," said Jean-Yves Douillard, M.D., Ph.D., professor of medical oncology, Centre R Gauducheau, France and PRIME trial lead investigator and study author. "This analysis is important as it furthers our understanding of tumor genetics and allows physicians to more accurately match patients to effective treatments."

This predefined retrospective subset analysis of the PRIME ('203) study assessed the safety and efficacy of Vectibix plus FOLFOX, compared to FOLFOX alone based on *RAS* or *BRAF* mutation status. By more precisely narrowing the pool of patients treated with Vectibix plus FOLFOX to those with wild-type *RAS,* greater improvements in overall survival (OS) and progression-free survival (PFS) were observed. Specifically, previous data found that OS was improved by 4.4 months in patients with wild-type *KRAS*. By further narrowing to patients with wild-type *RAS*, an improvement in OS of 5.8 months was observed.

In patients with wild-type *RAS*, OS was 26.0 months and 20.2 months (HR = 0.78; 95 percent CI, 0.62-0.99) and PFS was 10.1 months and 7.9 months (HR = 0.72, 95 percent CI, 0.58-0.90) in the Vectibix plus FOLFOX arm compared to the FOLFOX alone arm, respectively. *BRAF* mutations were not observed to have predictive value.

Conversely, in the patients with *RAS* mutations, inferior OS (HR = 1.25, 95 percent CI, 1.02-1.55) and PFS (HR = 1.34, 95 percent CI, 1.07-1.60) were observed in the Vectibix plus FOLFOX arm compared to the FOLFOX alone arm. Amgen has informed investigators and physicians of this important new safety information, and is working with regulatory agencies regarding appropriate communication of the outcomes of the analysis.

"Amgen is proud of our continuing work to identify and establish predictive biomarkers, like *RAS*, that will help better inform therapeutic decisions," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "As a result of this information, the European Commission has refined the prescribing information for Vectibix to the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer."

No new safety signals were identified in this analysis.

PRIME ('203) Study Design

The PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) ('203) trial is a global, multicenter, randomized Phase 3 study designed to evaluate Vectibix (6.0 mg/kg every two weeks) plus FOLFOX versus FOLFOX alone in patients with wild-type *KRAS* exon 2 mCRC. The primary endpoint is PFS.

The primary objective of this predefined retrospective subset analysis was to determine the effect of Vectibix plus FOLFOX versus FOLFOX alone on OS and PFS in patients with mCRC based on *RAS* or *BRAF* mutation status. The analysis included 512 patients who were identified with wild-type *RAS* tumors.

About *KRAS* and *RAS*

Results from studies performed over the last 30 years indicate that *KRAS* plays an important role in cell growth regulation. In mCRC, EGFR transmits signals through a set of intracellular proteins. Upon reaching the nucleus, these signals instruct the cancer cell to reproduce and metastasize, leading to cancer progression.[1] Anti-EGFR antibody therapies work by inhibiting the activation of EGFR, thereby inhibiting downstream events that lead to malignant signaling. However, in patients whose tumors harbor a mutated *KRAS* gene, the KRAS protein is always turned "on," regardless of whether the EGFR has been activated or therapeutically inhibited. Common *KRAS* mutations occurring in exon 2 (codons 12/13) are present in approximately 40 to 50 percent of mCRC patients.[2,3] Additional *RAS* mutations occurred in approximately 17 percent of patients with wild-type *KRAS* exon 2 tumors.

About Colorectal Cancer

Colorectal cancer is the third most common cancer found in both men and women in the U.S., and is the second leading cause of cancer deaths.[4,5] Approximately 1.2 million cases of colorectal cancer are expected to occur globally. The highest incidence rates are found in Japan, North America, parts of Europe, New Zealand and Australia, and rates are low in Africa and Southeast Asia.[6]

About Vectibix

Vectibix is the first fully human anti-EGFR antibody approved by the U.S. Food and Drug Administration (FDA) for the treatment of mCRC. Vectibix was approved in the U.S. in September 2006 as a single agent for the treatment of patients with EGFR-expressing mCRC with disease progression on or following fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens. The effectiveness of Vectibix as a single agent for the treatment of EGFR-expressing mCRC is based on PFS. More than half of patients who receive Vectibix monotherapy respond to treatment with an average six month PFS benefit. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Vectibix.

Retrospective subset analyses of mCRC trials have not shown a treatment benefit for Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix is not recommended for the treatment of mCRC with these mutations.[7]

Important U.S. Product Information
Vectibix is indicated as a single agent for the treatment of EGFR-expressing mCRC with disease progression on or following fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens. The effectiveness of Vectibix as a single agent for the treatment of EGFR-expressing mCRC is based on progression-free survival. Currently, no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix.

Vectibix is not indicated for the treatment of patients with *KRAS* mutation-positive mCRC or for whom *KRAS* mCRC status is unknown. Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had KRAS mutations in codon 12 or 13. Vectibix in combination with oxaliplatin-based chemotherapy is not indicated for the treatment of patients with *RAS* (*KRAS* or *NRAS*) mutation-positive mCRC or for whom *RAS* status is unknown.

WARNING: DERMATOLOGIC TOXICITY and INFUSION REACTIONS
Dermatologic Toxicity: Dermatologic toxicities occurred in 89 percent of patients and were severe (NCI-CTC grade 3 or higher) in 12 percent of patients receiving Vectibix monotherapy. [See Dosage and Administration (2.1), Warnings and Precautions (5.1), and Adverse Reactions (6.1)].

Infusion Reactions: Severe infusion reactions occurred in approximately one percent of patients. Fatal infusion reactions occurred in postmarketing experience [See Dosage and Administration (2.1), Warnings and Precautions (5.2), and Adverse Reactions (6.1, 6.3)].

The most common adverse events of Vectibix are skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea and diarrhea, including diarrhea resulting in dehydration.

The most serious adverse reactions of Vectibix are pulmonary fibrosis, pulmonary embolism, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting and constipation.

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 the world's largest independent biotechnology company, 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 management's current expectations and beliefs 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, including Amgen'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's most recent Forms 10-K, 10-Q and 8-K for additional information on the uncertainties and risk factors related to our business. Unless otherwise noted, Amgen is providing this information as of Sept. 11, 2013, 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 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 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 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 and there can be no guarantee of our 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.

The scientific information discussed in this news release relating to new indications for our products is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration (FDA) 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. Only the FDA can determine whether the products are safe and effective for these uses. Healthcare professionals should refer to and rely upon the FDA-approved labeling for the products, and not the information discussed in this news release.

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(Logo: http://photos.prnewswire.com/prnh/20081015/AMGENLOGO)

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