New Amgen Data In Melanoma And Metastatic Colorectal Cancer To Be Presented At The European Society For Medical Oncology 2016 Congress

October 5, 2016

Interim Data From Phase 2 Trial Provides Further Insight Into IMLYGIC® (Talimogene Laherparepvec) as a Potential Combination Partner With a Checkpoint Inhibitor for Patients With Advanced Melanoma

Retrospective Analyses of Key Studies Evaluating Vectibix® (Panitumumab) Combination Regimen in First- and Second-Line Metastatic Colorectal Cancer Evaluate Impact of Tumor Site of Origin on Treatment Efficacy

THOUSAND OAKS, Calif., Oct. 5, 2016 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that new data on IMLYGIC® (talimogene laherparepvec) in combination with an immune checkpoint inhibitor and results from retrospective analyses on Vectibix® (panitumumab) will be presented at the European Society for Medical Oncology (ESMO) 2016 Congress, Oct. 7-11, 2016, in Copenhagen.

IMLYGIC presentations include interim results from a Phase 2 trial evaluating IMLYGIC in combination with ipilimumab versus ipilimumab alone in patients with unresected stage IIIB-IV melanoma. Vectibix abstracts include retrospective analyses of the first-line Phase 3 PRIME and PEAK studies, evaluating the association between tumor site of origin and treatment efficacy in patients with *RAS* wild-type metastatic colorectal cancer (mCRC).

"We look forward to sharing our research into the combination of a checkpoint inhibitor and Amgen's oncolytic immunotherapy in metastatic melanoma," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "Additionally, we are excited about our data around tumor site of origin as one of a number of potential factors that may inform treatment decisions for patients with metastatic colorectal cancer."

IMLYGIC data:

- **Interim safety and efficacy of a randomized (1:1), open-label phase 2 study of talimogene laherparepvec (T) and ipilimumab (I) vs I alone in unresected, stage IIIB-IV melanoma**
  Abstract #1108PD, Poster Discussion, Monday, Oct. 10 from 11 a.m.-noon CET at Bella Center, Rome

Vectibix data:

- **Outcome according to left vs. right side in the panitumumab studies**
  Special Session, Monday, Oct. 10 from 11:35-11:50 a.m. CET at Bella Center, Copenhagen
- **Primary tumor sidedness impacts on prognosis and treatment outcome: results from three randomized studies of panitumumab plus chemotherapy versus chemotherapy or chemotherapy plus bevacizumab in 1st and 2nd line RAS/BRAF WT mCRC**
  Abstract #89P, Poster, Monday, Oct. 10 from 1-2 p.m. CET at Bella Center, Hall E
- **Importance of tumour symptoms and extent of disease on efficacy of first-line FOLFOX4 ± panitumumab (pmab) in patients (pts) with *RAS* wild-type (WT)/*BRAF* WT metastatic colorectal cancer (mCRC) in the PRIME study**
  Abstract #482P, Poster, Monday, Oct. 10 from 1-2 p.m. CET at Bella Center, Hall E
- **Impact of depth of response (DpR) on survival in patients (pts) with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC) receiving first-line panitumumab + FOLFOX4 vs FOLFOX4**
  Abstract #485P, Poster, Monday, Oct. 10 from 1-2 p.m. CET at Bella Center, Hall E
- **Efficacy of first-line modified FOLFOX6 with panitumumab or bevacizumab in *RAS* wild-type/*BRAF* wild-type metastatic colorectal cancer: Impact of tumour symptoms and extent of disease**
  Abstract #501P, Poster, Monday, Oct. 10 from 1-2 p.m. CET at Bella Center, Hall E
- **Associations between dermatologic toxicity severity, patient characteristics, and efficacy among patients treated with panitumumab (Pmab) and chemotherapy**
  Abstract #531P, Poster, Monday, Oct. 10 from 1-2 p.m. CET at Bella Center, Hall E

Abstracts are currently available on the ESMO website.

About IMLYGIC® (talimogene laherparepvec) in the EU

IMLYGIC is an oncolytic immunotherapy that is derived from HSV-1, which is commonly called the cold sore virus. IMLYGIC has been modified to replicate within tumors and to produce the immune stimulatory protein human GM-CSF. IMLYGIC causes the death of tumor cells and the release of tumor-derived antigens. It is thought that, together with GM-CSF, it will promote a systemic anti-tumor immune response and an effector T cell response.

Important EU Product Safety Information

▼ This product is subject to additional monitoring. All suspected adverse reactions should be reported in accordance with the national reporting system.

The safety of IMLYGIC was evaluated in the pivotal study where 292 patients received at least one dose of IMLYGIC (see section 5.1). The median duration of exposure to IMLYGIC was 23 weeks (5.3 months). Twenty-six (26) patients were exposed to IMLYGIC for at least one year.

The most commonly reported adverse reactions (≥ 25 percent) in IMLYGIC-treated patients were fatigue (50.3 percent), chills (48.6 percent), pyrexia (42.8 percent), nausea (35.6 percent), influenza-like illness (30.5 percent), and injection site pain (27.7 percent). Overall, ninety-eight percent (98 percent) of these adverse reactions reported were mild or moderate in severity. The most common grade 3 or higher adverse reaction was cellulitis (2.1 percent) (see section 4.4).

Please refer to the Summary of Product Characteristics for full European prescribing information.

About IMLYGIC® (talimogene laherparepvec) in the U.S.
IMLYGIC is a genetically modified herpes simplex type 1 virus that is injected directly into tumors. IMLYGIC replicates inside tumor cells and produces GM-CSF, an immunostimulatory protein. IMLYGIC then causes the cell to rupture and die in a process called lysis. The rupture of the cancer cells causes the release of tumor-derived antigens, which together with virally derived GM-CSF may help to promote an anti-tumor immune response. However, the exact mechanism of action is unknown.

IMLYGIC is the first oncolytic viral therapy approved by the U.S. Food and Drug Administration (FDA) based on therapeutic benefit demonstrated in a pivotal study. IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.

Important U.S. Safety Information Contraindications

- Do not administer IMLYGIC® to immunocompromised patients, including those with a history of primary or acquired immunodeficient states, leukemia, lymphoma, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy, due to the risk of life-threatening disseminated herpetic infection.
- Do not administer IMLYGIC® to pregnant patients.

Warnings and Precautions

- **Accidental exposure to IMLYGIC®** may lead to transmission of IMLYGIC® and herpetic infection, including during preparation and administration. Health care providers, close contacts, pregnant women, and newborns should avoid direct contact with injected lesions, dressings, or body fluids of treated patients. The affected area in exposed individuals should be cleaned thoroughly with soap and water and/or a disinfectant.
- Caregivers should wear protective gloves when assisting patients in applying or changing occlusive dressings and observe safety precautions for disposal of used dressings, gloves, and cleaning materials. Exposed individuals should clean the affected area thoroughly with soap and water and/or a disinfectant.
- To prevent possible inadvertent transfer of IMLYGIC® to other areas of the body, patients should be advised to avoid touching or scratching injection sites or occlusive dressings.
- **Herpetic infections:** Herpetic infections (including cold sores and herpetic keratitis) have been reported in IMLYGIC®-treated patients. Disseminated herpetic infection may also occur in immunocompromised patients. Patients who develop suspicious herpes-like lesions should follow standard hygienic practices to prevent viral transmission.
- Patients or close contacts with suspected signs or symptoms of a herpetic infection should contact their health care provider to evaluate the lesions. Suspected herpetic lesions should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442). Patients or close contacts have the option of follow-up testing for further characterization of the infection.
- IMLYGIC® is sensitive to acyclovir. Acyclovir or other antiviral agents may interfere with the effectiveness of IMLYGIC®. Consider the risks and benefits of IMLYGIC® treatment before administering antiviral agents to manage herpetic infection.
- **Injection Site Complications:** Necrosis or ulceration of tumor tissue may occur during IMLYGIC® treatment. Cellulitis and systemic bacterial infection have been reported in clinical studies. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds.
- Impaired healing at the injection site has been reported. IMLYGIC® may increase the risk of impaired healing in patients with underlying risk factors (e.g., previous radiation at the injection site or lesions in poorly vascularized areas). If there is persistent infection or delayed healing of the injection site, consider the risks and benefits of continuing treatment.
- **Immune-Mediated events** including glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in patients treated with IMLYGIC®. Consider the risks and benefits of IMLYGIC® before initiating treatment in patients who have underlying autoimmune disease or before continuing treatment in patients who develop immune-mediated events.
- **Plasmacytoma at Injection Site:** Plasmacytoma in proximity to the injection site has been reported in a patient with smoldering multiple myeloma after IMLYGIC® administration in a clinical study. Consider the risks and benefits of IMLYGIC® in patients with multiple myeloma or in whom plasmacytoma develops during treatment.

Adverse Reactions

- The most commonly reported adverse drug reactions (≥25%) in IMLYGIC®-treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. Pyrexia, chills, and influenza-like illness can occur at any time during IMLYGIC® treatment, but were more frequent during the first 3 months of treatment.

- The most common Grade 3 or higher adverse reaction was cellulitis.

Please see full U.S. Prescribing Information and Medication Guide for IMLYGIC® at www.IMLYGIC.com.

About Vectibix® (panitumumab) in Europe
Vectibix is a fully human anti-epidermal growth factor receptor (EGFR) antibody approved by the European Medicines Agency (EMA) for the treatment of mCRC.[1] The safety and efficacy of Vectibix have not been studied in patients with renal or hepatic impairment.[1] Vectibix was approved in Europe in December 2007 as a monotherapy for the treatment of patients with EGFR-expressing mCRC with non-mutated (wild-type) *KRAS* genes after failure of standard chemotherapy regimens.[2]

In April 2015, the European Commission (EC) approved a new use of Vectibix as first-line treatment in combination with FOLFIRI for the treatment of adult patients with *RAS* wild-type mCRC.[3] In November 2011, the EC expanded the marketing authorization to include indications for the treatment of patients with *KRAS* wild-type mCRC in first-line in combination with FOLFOX and in second-line in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).[4]

Globally, over 240,000 patients have been treated with Vectibix and more than 6,000 patients have participated in Amgen-sponsored panitumumab clinical trials.[5]

EU Product Safety Information

Summary of safety profile
Based on an analysis of all mCRC clinical trial patients receiving Vectibix monotherapy and in combination with chemotherapy (n = 2,588), the most commonly reported adverse reactions are skin reactions occurring in 93% of patients. These reactions are related to the pharmacologic effects of Vectibix, and the majority are mild to moderate in nature with 25% severe (grade 3 NCI-CTC) and < 1% life threatening (grade 4 NCI-CTC). For clinical management of skin reactions, including dose modification recommendations, see section 4.4. Very commonly reported adverse reactions occurring in ≥ 20% of patients were gastrointestinal disorders [diarrhoea (50%), nausea (41%), vomiting (27%), constipation (23%) and abdominal pain (23%)]; general disorders [fatigue (37%), pyrexia (20%)]; metabolism and nutrition disorders [anorexia (27%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (45%), dermatitis acneiform (39%), pruritus (35%), erythema (30%) and dry skin (22%)].

Special warnings and precautions for use
Dermatologic reactions and soft tissue toxicity
Dermatologic related reactions, a pharmacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients (approximately 90%) treated with Vectibix. Severe (NCI-CTC grade 3) skin reactions were reported in 34% and life-threatening (NCICTC grade 4) skin reactions in < 1% of patients who received Vectibix in combination with chemotherapy (n = 1,536) (see section 4.8). If a patient develops dermatologic reactions that are grade 3 (CTCAE v 4.0) or higher, or that are considered intolerable, the following dose modification is recommended:

Occurrence of skin symptom(s): ≥ grade 3[1]	Administration of Vectibix	Outcome	Dose regulation
Initial occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 100% of original dose
		Not recovered	Discontinue
At the second occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 80% of original dose
		Not recovered	Discontinue
At the third occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 60% of original dose
		Not recovered	Discontinue
At the fourth occurrence	Discontinue	-	-

[1]Greater than or equal to grade 3 is defined as severe or life-threatening

In clinical studies, subsequent to the development of severe dermatologic reactions (including stomatitis), infectious complications including sepsis and necrotising fasciitis, in rare cases leading to death, and local abscesses requiring incisions and drainage were reported. Patients who have severe dermatologic reactions or soft tissue toxicity or who develop worsening reactions whilst receiving Vectibix should be monitored for the development of inflammatory or infectious sequelae (including cellulitis and necrotising fasciitis), and appropriate treatment promptly initiated. Life threatening and fatal infectious complications including necrotising fasciitis and sepsis have been observed in patients treated with Vectibix. Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients treated with Vectibix in the post-marketing setting. Withhold or discontinue Vectibix in the event of dermatologic or soft tissue toxicity associated with severe or life threatening inflammatory or infectious complications.

Treatment of dermatologic reactions should be based on severity and may include a moisturiser, sun screen (SPF > 15 UVA and UVB), and topical steroid cream (not stronger than 1% hydrocortisone) applied to affected areas, and/or oral antibiotics. It is also recommended that patients experiencing rash/dermatological toxicities wear sunscreen and hats and limit sun exposure as sunlight can exacerbate any skin reactions that may occur.

Proactive skin treatment including skin moisturiser, sun screen (SPF > 15 UVA and UVB), topical steroid cream (not stronger than 1% hydrocortisone) and an oral antibiotic (e.g. doxycycline) may be useful in the management of dermatologic reactions. Patients may be advised to apply moisturiser and sunscreen to face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night during treatment.

Pulmonary complications
Patients with a history of, or evidence of, interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies. Cases of interstitial lung disease (ILD), both fatal and non-fatal, have been reported, mainly from the Japanese population. In the event of acute onset or worsening pulmonary

symptoms, Vectibix treatment should be interrupted and a prompt investigation of these symptoms should occur. If ILD is diagnosed, Vectibix should be permanently discontinued and the patient should be treated appropriately. In patients with a history of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with panitumumab versus the risk of pulmonary complications must be carefully considered.

Electrolyte disturbances
Progressively decreasing serum magnesium levels leading to severe (grade 4) hypomagnesaemia have been observed in some patients. Patients should be periodically monitored for hypomagnesaemia and accompanying hypocalcaemia prior to initiating Vectibix treatment, and periodically thereafter for up 5 to 8 weeks after the completion of treatment. Magnesium repletion is recommended, as appropriate.

Other electrolyte disturbances, including hypokalaemia, have also been observed. Monitoring as above and repletion as appropriate of these electrolytes is also recommended.

Infusion related reactions
Across monotherapy and combination mCRC clinical studies (n = 2,588), infusion-related reactions (occurring within 24 hours of an infusion) were reported in approximately 4% of Vectibix-treated patients, of which < 1% were severe (NCI-CTC grade 3 and grade 4).

In the post-marketing setting, serious infusion-related reactions have been reported, including rare post-marketing reports with a fatal outcome. If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion [e.g. presence of bronchospasm, angioedema, hypotension, need for parenteral treatment, or anaphylaxis], Vectibix should be permanently discontinued.

In patients experiencing a mild or moderate (CTCAE v 4.0 grades 1 and 2) infusion-related reaction the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Hypersensitivity reactions occurring more than 24 hours after infusion have been reported including a fatal case of angioedema that occurred more than 24 hours after the infusion. Patients should be informed of the possibility of a late onset reaction and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.

Acute renal failure
Acute renal failure has been observed in patients who develop severe diarrhoea and dehydration. Patients who experience severe diarrhoea should be instructed to consult a healthcare professional urgently.

Vectibix in combination with irinotecan, bolus 5-fluorouracil, and leucovorin (IFL) chemotherapy
Patients receiving Vectibix in combination with the IFL regimen [bolus 5-fluorouracil (500 mg/m2), leucovorin (20 mg/m2) and irinotecan (125 mg/m2)] experienced a high incidence of severe diarrhoea. Therefore administration of Vectibix in combination with IFL should be avoided.

Vectibix in combination with bevacizumab and chemotherapy regimens
A randomised, open-label, multicentre study of 1,053 patients evaluated the efficacy of bevacizumab and oxaliplatin- or irinotecan-containing chemotherapeutic regimens with and without Vectibix in the first-line treatment of metastatic colorectal cancer. Shortened progression free survival time and increased deaths were observed in the patients receiving Vectibix in combination with bevacizumab and chemotherapy. A greater frequency of pulmonary embolism, infections (predominantly of dermatologic origin), diarrhoea, electrolyte imbalances, nausea, vomiting and dehydration was also observed in the treatment arms using Vectibix in combination with bevacizumab and chemotherapy. An additional analysis of efficacy data by *KRAS* status did not identify a subset of patients who benefited from Vectibix in combination with oxaliplatin- or irinotecan-based chemotherapy and bevacizumab. A trend towards worse survival was observed with Vectibix in the wild-type *KRAS* subset of the bevacizumab and oxaliplatin cohort, and a trend towards worse survival was observed with Vectibix in the bevacizumab and irinotecan cohort regardless of *KRAS* mutational status. Therefore, Vectibix should not be administered in combination with bevacizumab containing chemotherapy.

Vectibix in combination with oxaliplatin-based chemotherapy in patients with mutant *RAS* mCRC or for whom *RAS* tumour status is unknown
The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown.

In the primary analysis of a study (n = 1,183, 656 patients with wild-type *KRAS* (exon 2) and 440 patients with mutant KRAS tumours) evaluating panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) compared to FOLFOX alone as first-line therapy for mCRC, a shortened progression-free survival (PFS) and overall survival (OS) time were observed in patients with mutant *KRAS* tumours who received panitumumab and FOLFOX (n = 221) vs. FOLFOX alone (n = 219).

A predefined retrospective subset analysis of 641 patients of the 656 patients with wild-type *KRAS* (exon 2) tumours from this study identified additional *RAS* (*KRAS* [exons 3 and 4] or *NRAS* [exons 2, 3, 4]) mutations in 16% (n = 108) of patients. A shortening of PFS and OS was observed in patients with mutant *RAS* tumours who received panitumumab and FOLFOX (n = 51) versus FOLFOX alone (n = 57).

RAS mutational status should be determined using a validated test method by an experienced laboratory (see section 4.2). If Vectibix is to be used in combination with FOLFOX then it is recommended that mutational status be determined by a laboratory that participates in a *RAS* External Quality Assurance programme or wild-type status be confirmed in a duplicate test.

Ocular toxicities
Serious cases of keratitis and ulcerative keratitis have been rarely reported in the post-marketing setting. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with Vectibix should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Vectibix should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Patients with ECOG 2 performance status treated with Vectibix in combination with chemotherapy
For patients with ECOG 2 performance status, assessment of benefit-risk is recommended prior to initiation of Vectibix in combination with

chemotherapy for treatment of mCRC. A positive benefitrisk balance has not been documented in patients with ECOG 2 performance status.

Elderly patients
No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Vectibix monotherapy. However, an increased number of serious adverse events were reported in elderly patients treated with Vectibix in combination with FOLFIRI or FOLFOX chemotherapy compared to chemotherapy alone.

Other precautions
This medicinal product contains 0.150 mmol sodium (which is 3.45 mg sodium) per ml of concentrate. To be taken into consideration by patients on a controlled sodium diet.

To see the full prescribing information, visit http://www.vectibix.eu/.

About Vectibix® (panitumumab) in the U.S.
Vectibix is the first fully human monoclonal anti-epidermal growth factor receptor (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.

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% 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 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 (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 (CTCAE v 3.0 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.

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.

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.

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. 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.

The scientific information discussed in this news release related to our product candidates is preliminary and investigative. Such product candidates are not approved by the U.S. Food and Drug Administration, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidates. Further, 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 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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