Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

March 2010 | A SPECIAL MEETING REVIEW EDITION | Volume 8, Issue 3, Supplement 5

Highlights From the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO GI) Symposium

January 22–24, 2010

Orlando, Florida

Special Reporting on:

Integrated Genomic Analyses of Cancer

Pursuit of Novel Treatment Strategies in the KRAS Wild-type Tumor Patient

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PLUS Meeting Abstract Summaries

Integrated Genomic Analyses of Cancer

In the Keynote Lecture at the 2010 American Society of Clinical Oncology Gastrointestinal Cancers (ASCO GI) Symposium, Dr. Victor E. Velculescu discussed integrated genomic analyses of cancers.[1] He focused on the recent developments resulting from these technologies, including the challenges with their use and the potential therapeutic implications.

Dr. Velculescu and other researchers have focused their work on understanding the "cancer genome" with the goal of translating these findings to patient care. Dr. Velculescu explained that the development and progression of cancer is a genetic process involving the activation of oncogenes and the inactivation of tumor suppressor genes. However, he called these changes "the tip of the iceberg," as it is becoming clear that other important changes also occur in cancer cells, including gains and losses of chromosomal arms, amplification of subchromosomal regions, homozygous deletions, and various changes in gene expression. These events suggest that additional driver genes are mediating cancer development.

Using a systematic genome-wide screen for signaling genes associated with human cancers, Davies and colleagues found an association between mutations in the *RAF* gene *BRAF* and various cancers, including malignant melanoma, thyroid cancer, and colorectal cancer.[2] Subsequently, Samuels and colleagues at The Johns Hopkins University reported that mutations in the *PIK3CA* gene are associated with numerous cancers, including cancer of the colon, breast, liver, brain, stomach, and lung.[3] "This currently places *PIK3CA* as one of the most highly mutated oncogenes in human cancer," explained Dr. Velculescu. He said that the discoveries of *BRAF* and *PIK3CA* highlight the need to study the entire coding region of the human genome, rather than specific genes or groups of genes, in order to identify genes relevant to cancer development.

Additional genome-wide analyses have been undertaken in recent years to try to identify gene mutations present in malignant cells but not in normal tissue from the same individual. These studies were originally undertaken using a database of approximately 13,000 genes. In 2006, the Consensus Coding Sequences of Human Breast and Colorectal Cancers was published identifying 189 genes mutated at a significant frequency in cancer cells.[4] Most of these genes were not previously known to be altered in tumors.

The most recent studies have evaluated the expression of approximately 23,000 transcripts, representing the majority of protein-coding genes within the genome. Dr. Velculescu said that although a few thousand non–protein-coding genes or small RNA-encoding genes remained to be analyzed, the genes available for analysis represent a good "first start of the important machinery inside of the genome." These studies have analyzed gene expression in 11 patients with colorectal cancer, 11 patients with breast cancer, 24 patients with pancreatic cancer, and 22 patients with glioblastoma.

The first step in these studies has been to perform a discovery screen to identify tumor-specific mutations—alterations that are present in malignant cells but not in healthy tissue. Identified genes of interest are then analyzed in a larger panel of 96 tumors. Genes with mutations occurring at a frequency above background levels are then studied at a more detailed level.

In order to understand the significance of genetic alterations in cancer cells, other analyses are also performed. For example, copy number analyses, which identify gene amplifications or losses, can reveal oncogenes or tumor suppressor genes. Newer technologies for assessing copy number include high-density oligonuclear-type microarrays and serial analysis of gene expression coupled with next-generation sequencing. These approaches allow a detailed quantitative measurement of gene expression by analyzing several million tags for each sample.

Dr. Velculescu described some of the findings that have resulted from these gene expression studies. An analysis of single nucleotide substitutions in the tumor samples revealed variations in the type of base changes that occur in different tumor types. For example,

C:G to T:A transitions represented over half of evaluated colorectal cancer mutations but only 35% of evaluated breast cancer mutations. Conversely, C:G to G:C transversions represented less than 10% of colorectal cancer mutations but 29% of breast cancer mutations.[5] Dr. Velculescu said that these findings, which are not well understood, suggest the involvement of organ-specific carcinogens or mechanisms of repair.

To analyze genomic alterations on the global level, Dr. Velculescu and colleagues have used a technology called digital karyotyping, which provides a high-resolution analysis of copy number alterations (amplifications and deletions) on a genome-wide scale.

By integrating these various genomic analysis tools, researchers are attempting to identify the genes responsible for driving tumorigenesis in different cancer types. For colorectal cancer, the resulting list of the top 20 candidate genes included some genes already associated with tumor development, such as *RAS*, *p53*, *CDC-4*, and *SMAB-4*, but also identified genes not previously known to be important in any cancer, including kinases, metalloproteinases, and other enzymes.

Dr. Velculescu added that there are challenges with these analyses: many mutations occur at low frequencies, and there is interpatient heterogeneity, with no 2 patients expressing identical alterations. He suggested that it may be advantageous to think about targeting molecular processes or signaling pathways rather than specific genes. For example, in pancreatic cancer, 12 pathways have been identified that are affected in at least two-thirds of all patients. "This is," he said, "the beginning of understanding these pathways and the underlying mechanisms in cancer."

A greater understanding of these pathways could identify therapeutic targets and could be used for diagnostic purposes and for monitoring of disease. For example, Dr. Luis Diaz and colleagues at Johns Hopkins developed a technique for monitoring for recurrence in which a mutation is identified from a resected tumor, and the presence of that mutation can be detected in the plasma at very low levels (1 in 10,000 or lower) in patients developing recurrence after surgery.

Dr. Velculescu said that moving forward, researchers will be expanding their analyses into other gastrointestinal cancers, including gastric cancer, hepatocellular carcinoma, and esophageal cancer, to identify relevant genes and pathways. He concluded that, with the tools available today, the greatest challenge lies not in identifying relevant genes, but in determining the functional and pathway implications of those genes. It is hoped that this research will lead to novel approaches to the diagnosis, evaluation, and treatment of patients with cancer.

ABSTRACT SUMMARY **Panitumumab With FOLFIRI Versus FOLFIRI Alone as Second-line Treatment in Metastatic Colorectal Cancer**

In patients with *KRAS* wild-type metastatic colorectal cancer, the addition of panitumumab to FOLFIRI in the second-line setting provides a significant PFS benefit and a significant improvement in patient-reported outcomes, according to results of an open-label, randomized, global phase III trial presented by Dr. Marc Peeters (Abstract 282). Among the 597 evaluable patients with wild-type *KRAS* tumors, panitumumab plus FOLFIRI was significantly more effective than FOLFIRI alone in regard to median PFS (5.9 vs 3.9 months; HR, 0.73; 95% CI, 0.59–0.90; *P*=.004) and objective response rate (35% vs 10%; *P*< .001), and there was a nonsignificant trend toward improved median OS (14.5 vs 12.5 months; HR, 0.85; 95% CI, 0.70–1.04; *P*=.12). The addition of panitumumab to FOLFIRI provided no benefit among the 486 evaluable patients with mutant *KRAS* tumors. Median PFS in these patients was 5.0 months with panitumumab plus FOLFIRI versus 4.9 months with FOLFIRI alone (*P*=.14), objective response rates were 13% and 14%, respectively, and median OS was 11.8 months and 11.1 months, respectively. The investigators also evaluated the impact of panitumumab on patient-reported outcomes. In *KRAS* wild-type patients, panitumumab was associated with a significant benefit as assessed by the EQ-5D Overall Health Rating (OHR) but not the multidimensional Health State Index (HSI). Panitumumab provided no benefit in patient-reported outcomes in *KRAS*-mutant patients. Dr. Peeters and colleagues reported that the combination of panitumumab and FOLFIRI was well tolerated and revealed no unexpected toxicities. The most common grade 3/4 adverse events in *KRAS* wild-type patients receiving panitumumab plus FOLFIRI were skin toxicities (37%), neutropenia (20%), and diarrhea (14%).

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Pursuit of Novel Treatment Strategies in the *KRAS* Wild-type Tumor Patient

Dr. Cornelius J.A. Punt discussed novel treatment strategies for patients with *KRAS* wild-type colorectal cancer.[1] Today, chemotherapy plus bevacizumab is often considered to be the standard first-line treatment for patients with metastatic colorectal cancer, based on data from randomized trials. However, multiple recent trials have also demonstrated the efficacy of anti–epidermal growth factor receptor (anti-EGFR) therapy combined with chemotherapy in patients with *KRAS* wild-type tumors. Therefore, Dr. Punt posed the question of which is preferable—chemotherapy plus bevacizumab, or chemotherapy plus an EGFR agent? Moreover, which chemotherapy regimen should be used? To address these questions, Dr. Punt first reviewed the key studies evaluating anti-EGFR therapy in metastatic colorectal cancer.

The randomized, phase III Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) study showed that the addition of cetuximab to FOLFIRI (leucovorin, fluorouracil, irinotecan) in the first-line setting is associated with a modest but significant increase in median progression-free survival (PFS) over FOLFIRI alone (9.9 vs 8.4 months; hazard ratio [HR], 0.696; *P*=.0012) and a more significant increase in median overall survival (OS) (23.5 vs 20.0 months; HR, 0.798; *P*=.0093).[2] (The complete CRYSTAL results are discussed elsewhere in this report.) In patients with *KRAS* mutant tumors, cetuximab had no detrimental effect, but it also was not beneficial.

In the randomized phase II Oxaliplatin and Cetuximab in First-line Treatment of Metastatic Colorectal Cancer (OPUS) trial, the addition of cetuximab to FOLFOX (leucovorin, fluorouracil, oxaliplatin) was also associated with a significant improvement in median PFS over FOLFOX alone (8.3 vs 7.2 months) and a nonsignificant trend toward improved OS.[3] In this trial, the addition of cetuximab to chemotherapy was detrimental in patients with *KRAS* mutated tumors, as it was associated with a significant decrease in median PFS and a shorter OS compared with chemotherapy alone.

In contrast to these findings, results from A Three-arm Randomised Controlled Trial Comparing Either Continuous Chemotherapy Plus Cetuximab or Intermittent Chemotherapy With Standard Continuous Palliative Combination Chemotherapy With Oxaliplatin and a Fluoropyrimidine in First Line Treatment of Metastatic Colorectal Cancer (COIN) presented at the 2009 European Cancer Organisation/European Society for Medical Oncology (ECCO/ESMO) meeting failed to show an efficacy benefit with the addition of cetuximab to FOLFOX in the first-line treatment of metastatic colorectal cancer.[4] There was no difference in median PFS or OS with FOLFOX plus cetuximab compared with FOLFOX alone in patients with *KRAS* wild-type or *KRAS* mutated tumors.

The Randomized Phase III Study of Panitumumab With FOLFOX4 Compared to FOLFOX4 Alone as

ABSTRACT SUMMARY **Safety of Panitumumab in Combination With Chemotherapy in Metastatic Colorectal Cancer Patients With Wild-type *KRAS* Tumors**

The safety of panitumumab and chemotherapy in patients with metastatic colorectal cancer is consistent and as expected for an EGFR monoclonal antibody in combination with chemotherapy, according to a meta-analysis of 5 multicenter clinical trials presented by Dr. Jean-Yves Douillard (Abstract 409). The most common grade 3/4 adverse events among the 763 patients with *KRAS* wild-type tumors randomized to FOLFIRI plus panitumumab (473 patients) or FOLFOX plus panitumumab (322 patients) were skin-related toxicity (20–37%), neutropenia (15–42%), diarrhea (13–24%), pulmonary embolism (0–8%), nausea (3–5%), dehydration (2–10%), and hypomagnesemia (3–8%). Two patients died due to adverse events: 1 due to diarrhea and 1 due to pulmonary embolism. The evaluated studies included 3 randomized trials (1 phase II and 2 phase III) and 2 single-arm phase II trials. The phase II studies evaluated FOLFIRI plus panitumumab and irinotecan plus panitumumab, whereas the phase III studies evaluated FOLFOX or FOLFIRI with or without panitumumab. Common eligibility criteria included a diagnosis of metastatic colorectal cancer, age of 18 years or older, and adequate organ function.

1st-Line Treatment for Metastatic Colorectal Cancer (PRIME), presented at the same meeting, evaluated the addition of the humanized anti-EGFR antibody panitumumab to FOLFOX in patients with previously untreated metastatic colorectal cancer.[5] Compared with FOLFOX alone, FOLFOX plus panitumumab was associated with a significant 1.6-month improvement in PFS in patients with *KRAS* wild-type tumors and a significant decrease in PFS and OS in patients with *KRAS* mutated tumors. (Updated data from the PRIME study, presented the same day as Dr. Punt's talk, confirmed these findings.)

In the Randomized Phase III Study of Capecitabine, Oxaliplatin, and Bevacizumab With or Without Cetuximab in Advanced Colorectal Cancer (CAIRO2), Dr. Punt and his colleagues in the Dutch Colorectal Cancer Group evaluated capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in 755 patients.[6] In the overall population, the addition of cetuximab was associated with a significant reduction in median PFS (9.4 vs 10.7 months). A subgroup analysis by *KRAS* status found no survival differences between treatments in patients with *KRAS* wild-type tumors but a significant detriment in patients with *KRAS* mutated tumors in regards to median PFS (8.1 vs 12.5 months) and median OS (17.2 vs 24.9 months). Dr. Punt noted that toxicity differences did not account for the detrimental effect of cetuximab. However, the incidence of hypertension, an adverse event associated with bevacizumab, was lower in the cetuximab-containing arm, suggesting a negative interaction between the 2 agents.

The Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study used a similar design, evaluating chemotherapy and bevacizumab with or without panitumumab for the first-line treatment of metastatic colorectal cancer.[7] Panitumumab was discontinued after a significant decrease in median PFS was seen in the panitumumab arm versus the control arm (10.0 vs 11.4 months; HR, 1.27; 95% CI, 1.06–1.52). Analyses by *KRAS* status and chemotherapy (oxaliplatin-based vs irinotecan-based) showed that in *KRAS* wild-type patients, the addition of panitumumab to oxaliplatin-based chemotherapy was associated with a decrease in median PFS and OS. Panitumumab was also associated with a reduction in PFS in irinotecan-treated patients, although the patient numbers in these groups were small.

Panitumumab was associated with worse toxicity in the PACCE study. Among oxaliplatin-treated patients, panitumumab was associated with a higher incidence of grade 3/4 skin toxicity (36% vs 1%), diarrhea (24% vs 13%), infections (19% vs 10%), and pulmonary embolism (6% vs 4%).

Dr. Punt also discussed the 181 study of FOLFIRI with or without panitumumab in the second-line treatment of metastatic colorectal cancer;

ABSTRACT SUMMARY **Skin Toxicity in Metastatic Colorectal Cancer Patients Taking Panitumumab and FOLFIRI**

In a study evaluating the safety of panitumumab and chemotherapy, Dr. Meinolf Karthaus reported results from a single-arm phase II study showing that panitumumab plus FOLFIRI is well tolerated in patients with previously untreated metastatic colorectal cancer (Abstract 429). Skin toxicities reported with the combination of panitumumab and FOLFIRI were similar to those previously observed with panitumumab monotherapy. Among the 145 patients enrolled, 98% developed any-grade skin nail toxicity or ocular toxicity, with 36% developing grade 3/4 dermatologic toxicities. The most common grade 3/4 dermatologic toxicities included rash (10%), acne (10%), paronychia (6%), and dermatitis acneiform (5%). Of the 145 patients evaluated, 59% had *KRAS* wild-type tumors. The median duration of therapy was 6.9 months for these patients and 5.8 months for patients with *KRAS* mutant tumors. The overall incidence and severity of skin toxicity were similar regardless of *KRAS* status. However, grade 3/4 dermatologic toxicities were more common among patients who responded to therapy than in those who did not respond in both *KRAS* strata. In the overall population, 51% of responders developed grade 3 skin toxicity, compared with 19% of nonresponders. The authors noted, however, that no definitive conclusions regarding the relationship of *KRAS* status, skin toxicity, and response could be drawn from this small sample size. Medications used for the treatment and management of skin and nail toxicities included antibiotics/antifungals (62% of *KRAS* wild-type and 69% of *KRAS* mutant patients), steroids (19% and 39%, respectively), antihistamines (14% in both groups), and other agents. While patients started topical treatments upon the development of any skin toxicity, oral antibiotics were incorporated into the treatment plan for patients developing severe acneiform dermatitis and/or paronychia of at least grade 2 severity. The authors also noted that some of the last patients who enrolled in the trial may have received prophylactic skin toxicity treatments.

ABSTRACT SUMMARY **Correlation of Number of Nodes Examined With Colon Cancer Recurrence**

The number of nodes examined and the 12-gene colon cancer recurrence score both independently predict recurrence in patients with stage II colon cancer, according to an analysis of the Quick and Simple and Reliable (QUASAR) study presented by Dr. Richard Gray (Abstract 331). QUASAR randomized 3,239 patients with resected colorectal cancer (66% stage II colon cancer) to adjuvant chemotherapy with fluorouracil and leucovorin or observation. The current analysis focused on 657 patients with stage II colon cancer, assessing the prognostic value of the number of nodes examined and the recurrence score, which has previously been validated in patients with stage II colon cancer from this study. Overall, patients had a median of 10 nodes examined (interquartile ratio, 7–14); 37% had at least 12 nodes examined. The number of nodes examined increased over time; the proportion of patients with at least 12 nodes examined increased from 21% in 1994–1995 to 54% in 2002–2003. Several parameters were significantly associated with the increased number of nodes examined, including later year of randomization ($P<.001$), younger age ($P<.001$), deficient mismatch-repair ($P<.010$), and higher tumor grade ($P=.001$). After controlling for these factors plus lymphovascular invasion and recurrence score, the number of nodes examined was significantly associated with recurrence risk ($P=.004$). In a multivariate analysis, there was a significant association between recurrence score and risk of recurrence and between nodes examined and risk of recurrence. Recurrence rates were 25% in patients with ≥12 nodes examined, 28% in patients with 8–11 nodes examined, and 37% in patients with <8 nodes examined.

results were presented at the 2009 ECCO-ESMO meeting. Among patients with *KRAS* wild-type tumors, the addition of panitumumab to FOLFIRI was associated with a significant increase in median PFS (5.9 vs 3.9 months) and a nonsignificant trend toward improved OS.[8] In patients with *KRAS* mutated tumors, no significant differences in the 2 treatment groups were noted; thus, this study found no detrimental effects of adding an EGFR inhibitor in these patients.

Overall, these trials indicate that the benefit of anti-EGFR antibodies is limited to patients with *KRAS* wild-type tumors. In patients with *KRAS* mutant tumors, the addition of an anti-EGFR antibody to an oxaliplatin-based regimen is associated with a detrimental effect. Dr. Punt said that "based on CAIRO2 and PACCE, the combination of bevacizumab with cetuximab or panitumumab should not be used." He added that the currently available data suggest "no outright superiority for anti-EGFR agents over bevacizumab." The Cancer and Leukemia Group B (CALGB) trial X0405, which is ongoing in patients with *KRAS* wild-type tumors, is randomizing patients treated with FOLFOX or FOLFIRI to bevacizumab or cetuximab or a combination of the 2. This study should provide important insight into the optimal first-line treatment strategy.

Regarding the role of EGFR-targeted therapy, Dr. Punt concluded that the absolute benefits of anti-EGFR antibodies appear to increase in later-line treatments, with these agents showing the greatest benefit when used as monotherapy in chemotherapy-refractory patients. However, bevacizumab has not been evaluated in this setting, and bevacizumab does appear to be better tolerated than anti-EGFR agents in most patients. "When you want to expose your patients to all of the available drugs," he explained, "there is still a preference for bevacizumab in first-line, and a role for cetuximab or panitumumab in salvage treatments."

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Cetuximab Plus FOLFIRI in the Treatment of Metastatic Colorectal Cancer

The addition of the anti-EGFR monoclonal antibody cetuximab to FOLFIRI in the first-line treatment of metastatic colorectal cancer is associated with a significant survival improvement in patients with *KRAS* wild-type tumors, according to results of the open-label, randomized, multicenter phase III CRYSTAL trial (Abstract 281).[1] These findings show, for the first time in a randomized study, that the addition of cetuximab to FOLFIRI is associated with a significant survival benefit compared with FOLFIRI alone, explained Dr. Eric Van Cutsem in his presentation. In this updated analysis, the CRYSTAL investigators also confirmed the predictive value of *KRAS* mutation status across all efficacy endpoints, and identified *BRAF* mutation status as a poor prognostic factor in previously untreated metastatic colorectal cancer.

The CRYSTAL study evaluated the efficacy and safety of cetuximab plus FOLFIRI versus FOLFIRI alone in 1,198 patients with previously untreated EGFR-expressing metastatic colorectal cancer. In a previous publication of the CRYSTAL data, Van Cutsem and colleagues reported that in patients with *KRAS* wild-type tumors, cetuximab plus FOLFIRI was associated with a significant 32% reduction in risk of disease progression (*P*=.02) and a nearly 2-fold increase in the likelihood of tumor response compared with FOLFIRI alone.[2] The benefit of cetuximab was limited to this subset of patients with *KRAS* wild-type tumors.

At the time of the 2009 publication, *KRAS* mutation status had only been determined in 45% of patients. To further clarify the benefit of cetuximab in this population, the CRYSTAL investigators analyzed *KRAS* status in additional patients and evaluated outcomes after a longer median follow-up of approximately 46 months. Of 1,063 evaluated patients, 63% (666 patients) had *KRAS* wild-type tumors. Updated efficacy analyses for these patients presented at the 2009 ASCO GI Symposium included data from 316 patients randomized to cetuximab plus FOLFIRI and 350 patients randomized to FOLFIRI alone.

These updated analyses confirmed the benefit of cetuximab in patients with *KRAS* wild-type tumors. Compared with FOLFIRI alone, cetuximab plus FOLFIRI was associated with a significant improvement in median OS (23.5 vs 20.0 months; HR, 0.798; 95% confidence interval [CI], 0.670–0.946; *P*=.0093), median PFS (9.9 vs 8.4 months; HR, 0.696; 95% CI, 0.558–0.867; *P*=.0012), and objective response rate (57.3% vs 39.7%; odds ratio, 2.07; 95% CI, 1.52–2.83; *P*<.0001).

An analysis of tumor regression showed a qualitative and quantita-

ABSTRACT SUMMARY **Cetuximab With Chemotherapy as First-line Treatment for Metastatic Colorectal Cancer**

Cetuximab plus chemotherapy is superior to chemotherapy alone for the first-line treatment of patients with wild-type *KRAS* metastatic colorectal cancer, according to a meta-analysis of the CRYSTAL and OPUS trials (Abstract 406). In a pooled analysis of 845 *KRAS* wild-type patients randomized to FOLFOX4 (OPUS) or FOLFIRI (CRYSTAL) with or without cetuximab, the addition of cetuximab was associated with significant improvements over chemotherapy alone in regard to objective response rate (57.3% vs 38.5%; odds ratio, 2.16; 95% CI, 1.64–2.86; *P*<.0001), median PFS (9.6 vs 7.6 months; HR, 0.66; 95% CI, 0.55–0.80; *P*<.0001), and median OS (23.5 vs 19.5 months; HR, 0.81; 95% CI, 0.69–0.94; *P*=.0062). These findings are based on an expanded number of samples evaluable for *KRAS* mutation status in both trials, which included 89% of samples from the CRYSTAL study (1,063 of 1,198) and 93% of samples from the OPUS study (315 of 337). Previous analyses were based on 45% of patients from CRYSTAL and 69% of patients from OPUS. In their analysis, Dr. Claus-Henning Köhne and colleagues also evaluated the effect of *BRAF* mutations on responses to cetuximab. However, as in the CRYSTAL analysis by Dr. Eric Van Cutsem and colleagues, the current analysis found no difference in the cetuximab treatment effect according to *BRAF* mutation status. *BRAF* mutation status appeared to have negative prognostic value, with shorter survival and lower response rates in both treatment arms in the 8% of patients with *BRAF* mutant tumors. However, even in this small subset of patients, there was a trend toward better outcomes with the addition of cetuximab to chemotherapy.

ABSTRACT SUMMARY **Neoadjuvant or Adjuvant Chemoradiotherapy and Bevacizumab in Rectal Cancer**

Bevacizumab can be added to standard neoadjuvant or adjuvant chemoradiotherapy in most patients with localized rectal cancer and may provide an efficacy benefit, although toxicities are a concern, according to a nonrandomized phase II trial presented by Dr. David Spigel (Abstract 459). Among 66 patients with stage II/III rectal cancer treated with bevacizumab in the neoadjuvant setting (35 patients) or the adjuvant setting (31 patients), 62 patients (94%) remained alive and free of recurrence after a median follow-up of 14 months. Post-combined modality treatment for all patients included FOLFOX6 plus bevacizumab for up to 4 cycles. Those patients with no evidence of disease could continue single-agent bevacizumab for up to 1 year of total treatment. Of the 35 patients who received bevacizumab in the neoadjuvant setting, 4 patients did not undergo surgery due to disease progression, coagulopathy, bowel perforation, and patient request (1 patient each). Of the 31 patients undergoing surgery, 10 patients (29%) had a pathologic complete response and 21 patients had residual disease (17 with gross residual disease and 4 with microscopic residual disease). Grade 3/4 toxicities reported in the neoadjuvant cohort were stomatitis/mucositis (23%), neutropenia (15%), diarrhea (14%), leukopenia (11%), postoperative infection (9%), dehydration (6%), and fatigue (6%). Grade 3/4 toxicities reported in the adjuvant cohort included diarrhea (29%), neutropenia (22%), fatigue (10%), hypertension (9%), dehydration (6%), and stomatitis/mucositis (6%). Eight patients discontinued neoadjuvant therapy due to treatment-related toxicities that included small-bowel perforations, prolonged surgical healing, postoperative wound complications, perirectal abscess, nausea/vomiting/diarrhea, methicillin-resistant *Staphylococcus aureus* infection, and coagulopathy. Five patients receiving adjuvant bevacizumab discontinued therapy due to rectovaginal fistula, perianal infection, hypoxia, hematochezia, and dehydration. The investigators concluded that although "the addition of bevacizumab may add to treatment efficacy . . . bowel perforations, infection, and wound-healing complications are potential serious toxicities that warrant cautious use of these regimens."

tive improvement in response rate with cetuximab plus FOLFIRI versus FOLFIRI alone, with a 13.9% difference in the best percentage change in lesion size based on the World Health Organization (WHO) criteria.

The analysis also confirmed the predictive value of *KRAS* status, showing significant interactions between treatment outcomes and *KRAS* mutation status for all efficacy measures, including tumor response (*P*=.0005), PFS (*P*=.003), and OS (*P*=.046).

The investigators also explored the association of another potential biomarker, *BRAF*, for predicting responses to cetuximab and FOLFIRI. *BRAF* is a serine-threonine kinase that is a downstream effector of *KRAS*. Previous data have suggested that *BRAF* mutations, which are present in approximately 8% of colorectal tumors, are predictive of responses to cetuximab in previously treated patients. Van Cutsem and colleagues determined *BRAF* mutation status in 83% of patients in the CRYSTAL trial (1,000 of 1,198). *BRAF* mutations were detected in 6% of evaluable samples, including in 1 patient with a *KRAS*-mutant tumor. Of the 625 *KRAS* wild-type tumors, 555 (88%) were *BRAF* wild-type and 59 (9%) were *BRAF* mutant.

BRAF mutation status had a clear prognostic value in this study, explained Dr. Van Cutsem in his presentation, noting a striking difference in survival and response rates in both treatment arms. In *KRAS* mutation-positive patients receiving cetuximab and FOLFIRI, median OS was 25.1 months in *BRAF* wild-type patients and 14.1 months in *BRAF*-mutant patients. Median PFS was 10.9 months and 8.0 months, respectively, and the overall response rates were 61.0% and 19.2%, respectively. *BRAF* status was also a negative prognostic factor in patients receiving chemotherapy alone.

Although the small sample size of *BRAF* mutant tumors precludes statistical comparisons of the treatment arms, the poor outcomes in these patients are evident. Dr. Van Cutsem concluded that *BRAF* mutation status "does not appear to be a strong predictive biomarker for the addition of cetuximab to FOLFIRI in the first-line treatment of metastatic colorectal cancer," considering also the low frequency of *BRAF* mutations in this population.

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Panitumumab With FOLFOX4 Compared to FOLFOX4 Alone as First-line Treatment in Metastatic Colorectal Cancer

In the first-line treatment of metastatic colorectal cancer, the addition of panitumumab to FOLFOX4 appears beneficial in patients with *KRAS* wild-type tumors but detrimental in patients with *KRAS* mutant tumors, according to a prospective analysis of the open-label, randomized, global phase III PRIME trial presented by Dr. Salvatore Siena (Abstract 283).[1]

Panitumumab, a fully human monoclonal antibody targeting EGFR, is currently approved for use as a single agent in patients with metastatic colorectal cancer with wild-type *KRAS* tumors. The PRIME trial was designed to evaluate panitumumab in combination with chemotherapy in the first-line setting, and prospectively analyzed outcomes according to *KRAS* status.

The study enrolled 1,183 patients with previously untreated metastatic colorectal cancer who were randomized to FOLFOX4 with panitumumab (593 patients) or FOLFOX4 alone (590 patients). Availability of paraffin-embedded tumor tissue was an eligibility requirement, although EGFR expression and *KRAS* status were not required for study entry. "The role of *KRAS* as a biomarker for clinical outcome was found . . . while this study was enrolling," explained Dr. Siena in his presentation, "and therefore the decision was made to amend the protocol to focus primarily on the efficacy by *KRAS* status." Thus, the study was amended prior to efficacy analyses and completion of enrollment to focus on the subset of patients with *KRAS* wild-type tumors.

In the 60% of patients with *KRAS* wild-type tumors, the addition of cetuximab to FOLFOX4 was associated with a significant 20% reduction in the risk of progression or death over FOLFOX4 alone (median PFS, 9.6 vs 8.0 months; HR, 0.80; 95% CI, 0.66–0.97; *P*=.02). There was also a trend toward an improvement in OS with panitumumab (median OS, 23.9 vs 19.7 months; HR, 0.83; 95% CI, 0.67–1.02; *P*=.07) and a numerical

ABSTRACT SUMMARY Panitumumab Immunogenicity in Metastatic Colorectal Cancer

The development of anti-panitumumab antibodies in patients with metastatic colorectal cancer receiving panitumumab plus FOLFOX or FOLFIRI is rare and independent of *KRAS* status, according to an analysis of 2 phase III trials presented by Dr. Marta Starcevic (Abstract 433). Of 559 patients receiving panitumumab plus FOLFIRI, 22 patients (3.9%) tested positive for anti-panitumumab antibodies via Biacore (16 patients) or enzyme-linked immunosorbent assay (ELISA; 7 patients). However, 19 of these patients (3.8%) had pre-existing antibodies detectable at or before baseline. Thus, only 4 patients (0.8%) had newly developing anti-panitumumab antibodies. The incidence of anti-panitumumab antibodies was similar among *KRAS* wild-type and *KRAS* mutant patients in regards to pre-existing antibodies (4.4% and 3.3%, respectively) and developing antibodies (0% and 1.5%, respectively). Similar trends were observed in FOLFOX-treated patients. Of 558 patients evaluated, 36 (6.5%) had detectable anti-panitumumab antibodies, with 22 patients (4.3%) harboring pre-existing antibodies and 14 patients (3.0%) developing new antibodies. The incidence of anti-panitumumab antibodies was similar among *KRAS* wild-type and *KRAS* mutant patients for pre-existing antibodies (3.9% and 3.7%, respectively) and developing antibodies (3.9% and 1.7%, respectively). "Panitumumab monotherapy is associated with a low rate of immunogenicity . . . the rate appears to be even lower among patients receiving combination chemotherapy," concluded the researchers in their report. The investigators used a neutralizing antibody bioassay to measure the ability of panitumumab to mediate EGFR phosphorylation in vitro. By this assay, anti-panitumumab antibody activity was detected in 0 of 501 samples from patients receiving panitumumab plus FOLFIRI and in 2 of 470 samples from patients receiving panitumumab plus FOLFOX. The presence of anti-panitumumab antibodies did not appear to alter the safety of the regimens, and the low incidence of these antibodies precluded an evaluation of their impact on efficacy endpoints.

Grade 3/4 Adverse Event	Panitumumab + FOLFOX4		FOLFOX 4	
	KRAS Wild-type (n=322)	*KRAS* Mutant (n=217)	*KRAS* Wild-type (n=322)	*KRAS* Mutant (n=217)
Any event	84	80	69	73
Skin toxicity	36	30	2	1
Neutropenia	42	37	41	47
Diarrhea	18	20	9	10
Neurologic toxicity	16	17	16	17

Table 1. Most Common Grade 3/4 Adverse Events With FOLFOX4 Plus Panitumumab*

*Adverse events that were observed in ≥10% of patients in any arm. FOLFOX=leucovorin, fluorouracil, oxaliplatin.
Data from Siena S. Randomized phase III study of panitumumab (pmab) with FOLFOX4 compared to FOLFOX4 alone as first-line treatment (tx) for metastatic colorectal cancer (mCRC): PRIME trial. Paper presented at: 2010 American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, FL.

improvement in response rate (55% vs 48%; *P*=.07).

However, in the 40% of patients with *KRAS* mutant tumors, median PFS was significantly shorter with panitumumab plus FOLFOX4 vs FOLFOX4 alone (7.3 vs 8.8 months; HR, 1.29; 95% CI, 1.04–1.62; *P*=.02). There was also a trend toward a shorter median OS (15.5 vs 19.3 months; HR, 1.24; 95% CI, 0.98–1.57; *P*=.07). Dr. Siena said that these results could not be explained by treatment exposure, as the median number of cycles and dose intensity were similar regardless of *KRAS* status.

The adverse event profile of the combination was as expected for an anti-EGFR antibody plus chemotherapy. The most common grade 3/4 adverse events were neutropenia, skin toxicity, diarrhea, and neurologic toxicities. Three patients receiving panitumumab died from treatment-related adverse events, including 2 due to pulmonary embolism and 1 from febrile neutropenia. Two patients developed grade 3 panitumumab-related infusion reactions, for a total incidence of less than 1%.

Subgroup analyses calculated in the subset of patients with *KRAS* wild-type tumors showed a consistent benefit in favor of panitumumab in most planned subgroups. The PFS benefit was not significant in women (HR, 1.00; 95% CI, 0.73–1.39), patients ages 65 years or older (HR, 1.02; 95% CI, 0.75–1.38), and a small population (38 patients) with Eastern Cooperative Oncology Group (ECOG) performance status 2 (HR, 1.99; 95% CI, 0.96–4.15).

Reference

1. Siena S. Randomized phase III study of panitumumab (pmab) with FOLFOX4 compared to FOLFOX4 alone as first-line treatment (tx) for metastatic colorectal cancer (mCRC): PRIME trial. Paper presented at: 2010 American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, FL.

ABSTRACT SUMMARY Capecitabine Versus 5-Fluorouracil in Colorectal and Gastric Cancers

A meta-analysis of 6,171 patients enrolled in 6 large, multicenter, randomized, noninferiority, phase III clinical trials confirmed the efficacy of capecitabine in patients with colorectal and gastric cancer (Abstract 404). In this analysis, which was undertaken on the advice of European health authorities, Dr. James Cassidy and colleagues compared outcomes in 3,097 patients receiving capecitabine-containing regimens and 3,074 patients receiving 5-fluorouracil/leucovorin (5-FU/LV)-containing regimens. The analysis comprised 3 trials in first-line metastatic colorectal cancer, 1 trial in resected stage III colon cancer, 1 trial in second-line metastatic colorectal cancer, and 1 trial in first-line advanced gastric cancer. In an unadjusted analysis stratified by study, there was no significant difference in median OS with capecitabine (23.1 months) versus 5-FU/LV (22.4 months), with a hazard ratio of 0.94 (95% CI, 0.89–2.00; *P*=.0489). A multivariate Cox regression analysis evaluating the influence of various prognostic factors on OS found that only Eastern Cooperative Oncology Group (ECOG) performance score at baseline was significantly associated with OS. Treatment arm (capecitabine vs 5-FU/LV), age, and sex were not independent prognostic factors. Compared with an ECOG performance score of 0, a score of 1 or higher was associated with a significant increase in the risk of death, with a hazard ratio of 1.56 (95% CI, 1.46–1.66; *P*<.0001). Overall, 66% of 5-FU/LV-treated patients and 67% of capecitabine-treated patients had an ECOG performance score of 0 at baseline; 33% and 32%, respectively, had an ECOG performance score of 1. The investigators concluded that these findings support the "already extensive evidence" regarding the therapeutic equivalence of intravenous 5-FU and oral capecitabine, and suggested that capecitabine can be considered a suitable alternative to 5-FU.

Vectibix® (panitumumab)
Injection for Intravenous Use

Vectibix® (panitumumab)

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: DERMATOLOGIC TOXICITY and INFUSION REACTIONS

Dermatologic Toxicity: Dermatologic toxicities occurred in 89% of patients and were severe (NCI-CTC grade 3 and higher) in 12% of patients receiving Vectibix monotherapy. *[see Dosage and Administration, Warnings and Precautions, and Adverse Reactions].*

Infusion Reactions: Severe infusion reactions occurred in approximately 1% of patients. *[see Warnings and Precautions and Adverse Reactions].* Although not reported with Vectibix, fatal infusion reactions have occurred with other monoclonal antibody products. *[see Dosage and Administration].*

INDICATIONS AND USAGE

Vectibix is indicated as a single agent for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens *[see Clinical Studies (14) in Full Prescribing Information].*

The effectiveness of Vectibix as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma is based on progression-free survival *[see Clinical Studies (14) in Full Prescribing Information]*. Currently, no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix.

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. Use of Vectibix is not recommended for the treatment of colorectal cancer with these mutations.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dose Modifications: The recommended dose of Vectibix is 6 mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. Doses higher than 1000 mg should be administered over 90 minutes *[see Dosage and Administration]*.

Appropriate medical resources for the treatment of severe infusion reactions should be available during Vectibix infusions.

Dose Modifications for Infusion Reactions *[see Adverse Reactions]*

- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.
- Immediately and permanently discontinue Vectibix infusion in patients experiencing severe (grade 3 or 4) infusion reactions.

Dose Modifications for Dermatologic Toxicity *[see Adverse Reactions]*

- Withhold Vectibix for dermatologic toxicities that are grade 3 or higher or are considered intolerable. If toxicity does not improve to ≤ grade 2 within 1 month, permanently discontinue Vectibix.
- If dermatologic toxicity improves to ≤ grade 2, and the patient is symptomatically improved after withholding no more than two doses of Vectibix, treatment may be resumed at 50% of the original dose.
  - If toxicities recur, permanently discontinue Vectibix.
  - If toxicities do not recur, subsequent doses of Vectibix may be increased by increments of 25% of the original dose until the recommended dose of 6 mg/kg is reached.

Preparation and Administration: Do not administer Vectibix as an intravenous push or bolus.

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although Vectibix should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration; see below). Do not shake. Do not administer Vectibix if discoloration is observed.
- Withdraw the necessary amount of Vectibix for a dose of 6 mg/kg.
- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.

Administration

- Administer using a low-protein-binding 0.2 µm or 0.22 µm in-line filter.
- Vectibix must be administered via infusion pump.
  - Flush line before and after Vectibix administration with 0.9% sodium chloride injection, USP, to avoid mixing with other drug products or intravenous solutions. Do not mix Vectibix with, or administer as an infusion with, other medicinal products. Do not add other medications to solutions containing panitumumab.
  - Infuse over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. Doses higher than 1000 mg should be infused over 90 minutes.

Use the diluted infusion solution of Vectibix within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). DO NOT FREEZE.

Discard any unused portion remaining in the vial.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Dermatologic Toxicity: In Study 1, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 16% of patients with mCRC receiving Vectibix. The clinical manifestations included, but were not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage were reported. Withhold Vectibix for severe or life-threatening dermatologic toxicity. *[see Boxed Warning, Adverse Reactions, and Dosage and Administration].*

Infusion Reactions: In Study 1, 4% of patients experienced infusion reactions and in 1% of patients, these reactions were graded as severe (NCI-CTC grade 3–4).

Across all clinical studies, severe infusion reactions occurred with the administration of Vectibix in approximately 1% of patients. Severe infusion reactions included anaphylactic reactions, bronchospasm, and hypotension *[see Boxed Warning and Adverse Reactions]*. Although fatal infusion reactions have not been reported with Vectibix, fatalities have occurred with other monoclonal antibody products. Stop infusion if a severe infusion reaction occurs. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix *[see Dosage and Administration]*.

Increased Toxicity With Combination Chemotherapy: Vectibix is not indicated for use in combination with chemotherapy. In an interim analysis of Study 2, the addition of Vectibix to the combination of bevacizumab and chemotherapy resulted in decreased overall survival and increased incidence of NCI-CTC grade 3–5 (87% vs 72%) adverse reactions *[see Clinical Studies (14) in Full Prescribing Information]*. NCI-CTC grade 3–4 adverse drug reactions occurring at a higher rate in Vectibix-treated patients included rash/dermatitis acneiform (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 4%) 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.

In a single-arm study of 19 patients receiving Vectibix in combination with IFL, the incidence of NCI-CTC grade 3–4 diarrhea was 58%; in addition, grade 5 diarrhea occurred in one patient. In a single-arm study of 24 patients receiving Vectibix plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhea was 25%.

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

Pulmonary Fibrosis: Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix. Following the initial fatality described below, patients with a history of interstitial pneumonitis, pulmonary fibrosis, evidence of interstitial pneumonitis, or pulmonary fibrosis were excluded from clinical studies. Therefore, the estimated risk in a general population that may include such patients is uncertain.

One case occurred in a patient with underlying idiopathic pulmonary fibrosis who received Vectibix in combination with chemotherapy and resulted in death from worsening pulmonary fibrosis after four doses of Vectibix. The second case was characterized by cough and wheezing 8 days following the initial dose, exertional dyspnea on the day of the seventh dose, and persistent symptoms and CT evidence of pulmonary fibrosis following the 11th dose of Vectibix as monotherapy. An additional patient died with bilateral pulmonary infiltrates of uncertain etiology with hypoxia after 23 doses of Vectibix in combination with chemotherapy. Permanently discontinue Vectibix therapy in patients developing interstitial lung disease, pneumonitis, or lung infiltrates.

Electrolyte Depletion/Monitoring: In Study 1, median magnesium levels decreased by 0.1 mmol/L in the Vectibix arm; hypomagnesemia (NCI-CTC grade 3 or 4) requiring oral or intravenous electrolyte repletion occurred in 2% of patients. Hypomagnesemia occurred 6 weeks or longer after the initiation of Vectibix. In some patients, both hypomagnesemia and hypocalcemia occurred. Patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of Vectibix therapy. Institute appropriate treatment, eg, oral or intravenous electrolyte repletion, as needed.

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

EGF Receptor Testing: Detection of EGFR protein expression is necessary for selection of patients appropriate for Vectibix therapy because these are the only patients studied and for whom benefit has been shown *[see Indications and Usage and Clinical Studies (14) in Full Prescribing Information]*. Patients with colorectal cancer enrolled in Study 1 were required to have immunohistochemical evidence of EGFR expression using the Dako EGFR pharmDx® test kit.

Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specific reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the package insert for the Dako EGFR pharmDx® test kit, or other test kits approved by FDA, for identification of patients eligible for treatment with Vectibix and for full instructions on assay performance.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Dermatologic Toxicity *[see Boxed Warning, and Warnings and Precautions]*
- Infusion Reactions *[see Boxed Warning, and Warnings and Precautions]*
- Increased Toxicity With Combination Chemotherapy *[see Warnings and Precautions]*
- Pulmonary Fibrosis *[see Warnings and Precautions]*
- Electrolyte Depletion/Monitoring *[see Warnings and Precautions]*
- Photosensitivity *[see Warnings and Precautions]*

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 events 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. Adverse reactions requiring discontinuation of Vectibix were infusion reactions, severe skin toxicity, paronychia, and pulmonary fibrosis.

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Safety data are available from 15 clinical trials in which 1467 patients received Vectibix; of these, 1293 received Vectibix monotherapy and 174 received Vectibix in combination with chemotherapy *[see Warnings and Precautions]*.

The data described in Table 1 and in other sections below, except where noted, reflect exposure to Vectibix administered as a single agent at the recommended dose and schedule (6 mg/kg every 2 weeks) in 229 patients with mCRC enrolled in Study 1, a randomized, controlled trial. The median number of doses was five (range: one to 26 doses), and 71% of patients received eight or fewer doses. The population had a median age of 62 years (range: 27 to 82 years), 63% were male, and 99% were white with < 1% black, < 1% Hispanic, and 0% other.

Table 1. Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients With a Between-Group Difference of ≥ 5% (Study 1)

		Patients Treated With Vectibix Plus BSC (n = 229)		Best Supportive Care (BSC) Alone (n = 234)	
		Grade*			
Body System		All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Body as a Whole	Fatigue	26	4	15	3
	General Deterioration	11	8	4	3
Digestive	Abdominal Pain	25	7	17	5
	Nausea	23	1	16	< 1
	Diarrhea	21	2	11	0
	Constipation	21	3	9	1
	Vomiting	19	2	12	1
	Stomatitis	7	0	1	0
	Mucosal Inflammation	6	< 1	1	0
Metabolic/Nutritional	Hypomagnesemia (Lab)	38	4	2	0
	Peripheral Edema	12	1	6	< 1
Respiratory	Cough	14	< 1	7	0
Skin/Appendages	All Skin/Integument Toxicity	90	16	9	0
	Skin	90	14	6	0
	Erythema	65	5	1	0
	Dermatitis Acneiform	57	7	1	0
	Pruritus	57	2	2	0
	Nail	29	2	0	0
	Paronychia	25	2	0	0
	Skin Exfoliation	25	2	0	0
	Rash	22	1	1	0
	Skin Fissures	20	1	< 1	0
	Eye	15	< 1	2	0
	Acne	13	1	0	0
	Dry Skin	10	0	0	0
	Other Nail Disorder	9	0	0	0
	Hair	9	0	1	0
	Growth of Eyelashes	6	0	0	0

*Version 2.0 of the NCI-CTC was used for grading toxicities. Skin toxicity was coded based on a modification of the NCI-CTCAE, version 3.0.

Dermatologic, Mucosal, and Ocular Toxicity: In Study 1, dermatologic toxicities occurred in 90% of patients receiving Vectibix. Skin toxicity was severe (NCI-CTC grade 3 and higher) in 16% of patients. Ocular toxicities occurred in 15% of patients and included, but were not limited to, conjunctivitis (4%), ocular hyperemia (3%), increased lacrimation (2%), and eye/eyelid irritation (1%). Stomatitis (7%) and oral mucositis (6%) were reported. One patient experienced an NCI-CTC grade 3 event of mucosal inflammation. The incidence of paronychia was 25% and was severe in 2% of patients. Nail disorders occurred in 9% of patients *[see Warnings and Precautions]*.

Median time to the development of dermatologic, nail, or ocular toxicity was 14 days after the first dose of Vectibix; the median time to most severe skin/ocular toxicity was 15 days after the first dose of Vectibix; and the median time to resolution after the last dose of Vectibix was 84 days. Severe toxicity necessitated dose interruption in 11% of Vectibix-treated patients *[see Dosage and Administration]*.

Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage, were reported.

Infusion Reactions: Infusional toxicity was defined as any event within 24 hours of an infusion during the clinical study described as allergic reaction or anaphylactoid reaction, or any event occurring on the first day of dosing described as allergic reaction, anaphylactoid reaction, fever, chills, or dyspnea. Vital signs and temperature were measured within 30 minutes prior to initiation and upon completion of the Vectibix infusion. The use of premedication was not standardized in the clinical trials. Thus, the utility of premedication in preventing the first or subsequent episodes of infusional toxicity is unknown. Across several clinical trials of Vectibix monotherapy, 3% (43/1336) experienced infusion reactions of which approximately 1% (6/1336) were severe (NCI-CTC grade 3–4). In one patient, Vectibix was permanently discontinued for a serious infusion reaction *[see Dosage and Administration]*.

Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of Vectibix has been evaluated using two different screening immunoassays for the detection of anti-panitumumab antibodies: an acid dissociation bridging enzyme-linked immunosorbent assay (ELISA) (detecting high-affinity antibodies) and a Biacore® biosensor immunoassay (detecting both high- and low-affinity antibodies). The incidence of binding antibodies to panitumumab (excluding predose and transient positive patients), as detected by the acid dissociation ELISA, was 3/613 (< 1%) and as detected by the Biacore® assay was 28/613 (4.6%).

For patients whose sera tested positive in screening immunoassays, an in vitro biological assay was performed to detect neutralizing antibodies. Excluding predose and transient positive patients, 10/613 patients (1.6%) with postdose samples and 3/356 (0.8%) of the patients with follow-up samples tested positive for neutralizing antibodies.

No evidence of altered pharmacokinetic profile or toxicity profile was found between patients who developed antibodies to panitumumab as detected by screening immunoassays and those who did not.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to panitumumab with the incidence of antibodies to other products may be misleading.

Postmarketing experience: The following adverse reaction has been identified during post-approval use of panitumumab. Because these reactions are reported in a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Angioedema

DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted with Vectibix.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: There are no studies of Vectibix in pregnant women. Reproduction studies in cynomolgus monkeys treated with 1.25 to 5 times the recommended human dose of panitumumab resulted in significant embryolethality and abortions; however, no other evidence of teratogenesis was noted in offspring. *[see Reproductive and Developmental Toxicology]*. Vectibix should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on animal models, EGFR is involved in prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Human IgG is known to cross the placental barrier; therefore, panitumumab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women.

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

Nursing Mothers: It is not known whether panitumumab is excreted into human milk; however, human IgG is excreted into human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. 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, based on the mean half-life of panitumumab, nursing should not be resumed earlier than 2 months following the last dose of Vectibix *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Pediatric Use: The safety and effectiveness of Vectibix have not been established in pediatric patients. The pharmacokinetic profile of Vectibix has not been studied in pediatric patients.

Geriatric Use: Of 229 patients with mCRC who received Vectibix in Study 1, 96 (42%) were ≥ age 65. Although the clinical study did not include a sufficient number of geriatric patients to determine whether they respond differently from younger patients, there were no apparent differences in safety and effectiveness of Vectibix between these patients and younger patients.

OVERDOSAGE

Doses up to approximately twice the recommended therapeutic dose (12 mg/kg) resulted in adverse reactions of skin toxicity, diarrhea, dehydration, and fatigue.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenicity or mutagenicity studies of panitumumab have been conducted. It is not known if panitumumab can impair fertility in humans. Prolonged menstrual cycles and/or amenorrhea occurred in normally cycling, female cynomolgus monkeys treated weekly with 1.25 to 5 times the recommended human dose of panitumumab (based on body weight). Menstrual cycle irregularities in panitumumab-treated female monkeys were accompanied by both a decrease and delay in peak progesterone and 17β-estradiol levels. Normal menstrual cycling resumed in most animals after discontinuation of panitumumab treatment. A no-effect level for menstrual cycle irregularities and serum hormone levels was not identified. The effects of panitumumab on male fertility have not been studied. However, no adverse effects were observed microscopically in reproductive organs from male cynomolgus monkeys treated for 26 weeks with panitumumab at doses of up to approximately 5-fold the recommended human dose (based on body weight).

Animal Toxicology and/or Pharmacology: Weekly administration of panitumumab to cynomolgus monkeys for 4 to 26 weeks resulted in dermatologic findings, including dermatitis, pustule formation and exfoliative rash, and deaths secondary to bacterial infection and sepsis at doses of 1.25 to 5-fold higher (based on body weight) than the recommended human dose.

Reproductive and Developmental Toxicology: Pregnant cynomolgus monkeys were treated weekly with panitumumab during the period of organogenesis (gestation day [GD] 20–50). While no panitumumab was detected in serum of neonates from panitumumab-treated dams, anti-panitumumab antibody titers were present in 14 of 27 offspring delivered at GD 100. There were no fetal malformations or other evidence of teratogenesis noted in the offspring. However, significant increases in embryolethality and abortions occurred at doses of approximately 1.25 to 5 times the recommended human dose (based on body weight).

PATIENT COUNSELING INFORMATION

Advise patients to contact a healthcare professional for any of the following:

- Skin and ocular/visual changes *[see Boxed Warning and Warnings and Precautions]*,
- Signs and symptoms of infusion reactions including fever, chills, or breathing problems *[see Boxed Warning and Warnings and Precautions]*,
- Diarrhea and dehydration *[see Warnings and Precautions]*,
- Persistent or recurrent coughing, wheezing, dyspnea, or new onset facial swelling *[see Warnings and Precautions, and Adverse Reactions]*,
- Pregnancy or nursing *[see Use in Specific Populations]*.

Advise patients of the need for:

- Periodic monitoring of electrolytes *[see Warnings and Precautions]*,
- Limitation of sun exposure (use sunscreen, wear hats) while receiving Vectibix and for 2 months after the last dose of Vectibix therapy. *[see Warnings and Precautions]*,
- Adequate contraception in both males and females while receiving Vectibix and for 6 months after the last dose of Vectibix therapy *[see Use in Specific Populations]*.

This brief summary is based on the Vectibix® prescribing information v8, 7/2009

Rx Only This product, its production, and/or its use may be covered by one or more US Patents, including US Patent No. 6,235,883, as well as other patents or patents pending.

AMGEN®

Manufactured by:
Amgen Inc.
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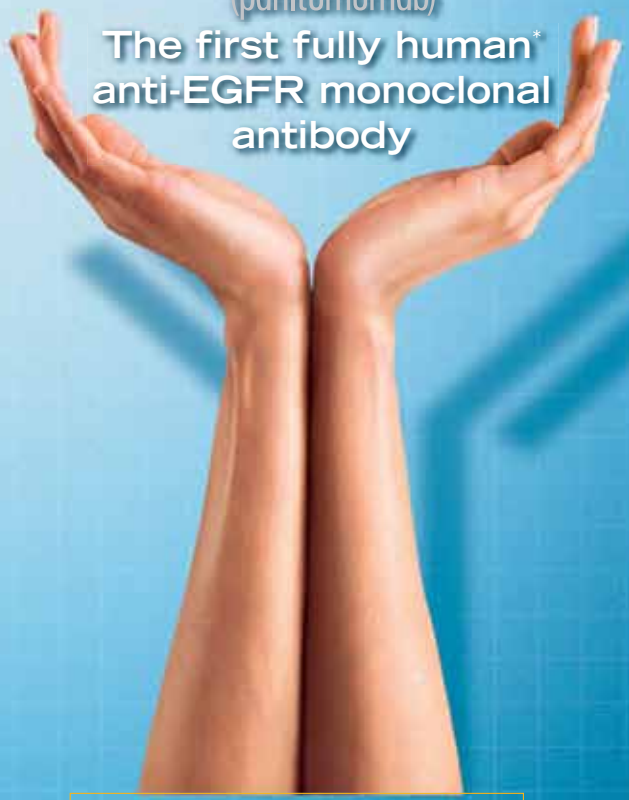
Thousand Oaks, CA 91320-1799
USA

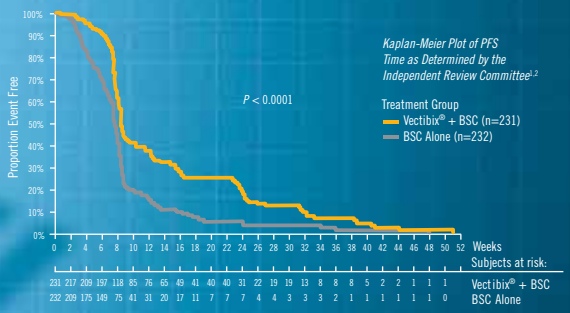
Vectibix® (panitumumab)

The first fully human* anti-EGFR monoclonal antibody



*Correlation with safety and efficacy is unknown

Based on independent review of disease progression, a statistically significant prolongation in PFS was observed in patients receiving Vectibix® plus BSC vs those patients receiving BSC alone[1,2]



Prolonged PFS

- **Statistically significant prolongation in PFS time vs BSC alone[1,2]**

Q2W dosing

- **The recommended dose of Vectibix® is 6 mg/kg administered over 60 minutes (for doses >1000 mg infuse over 90 minutes) as an intravenous infusion every 14 days[1]**
- **Use of premedication was not standardized in clinical trials (the utility of premedication in preventing infusional toxicity is unknown)[1]**

Infusion reactions

- **~1% incidence of severe infusion reactions reported[1] - Please see Important Safety Information including Boxed WARNINGS for infusion reactions**

INDICATION: Vectibix® (panitumumab) is indicated as a single agent for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma (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®.

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. Use of Vectibix® is not recommended for the treatment of colorectal cancer with these mutations.

Important Safety Information, including **Boxed WARNINGS**

WARNING: DERMATOLOGIC TOXICITY and INFUSION REACTIONS

Dermatologic Toxicity: Dermatologic toxicities occurred in 89% of patients and were severe (NCI-CTC grade 3 or higher) in 12% of patients receiving Vectibix® monotherapy. [See Brief Summary: Dosage and Administration, Warnings and Precautions, and Adverse Reactions].

Infusion Reactions: Severe infusion reactions occurred in approximately 1% of patients. [See Brief Summary: Warnings and Precautions and Adverse Reactions]. Although not reported with Vectibix®, fatal infusion reactions have occurred with other monoclonal antibody products. [See Brief Summary: Dosage and Administration].

Vectibix® is not indicated for use in combination with chemotherapy. In an interim analysis of a randomized clinical trial, the addition of Vectibix® to the combination of bevacizumab and chemotherapy resulted in decreased overall survival 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/dermatitis/acneiform (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 4%) and included fatal events in 3 (< 1%) Vectibix®-treated patients.

In a single-arm study of 19 patients receiving Vectibix® in combination with IFL, the incidence of NCI-CTC grade 3-4 diarrhea was 58%; in addition, grade 5 diarrhea occurred in 1 patient. In a single-arm study of 24 patients receiving Vectibix® plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhea was 25%.

Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix®. Of the 2 cases, 1 involved a patient with underlying idiopathic pulmonary fibrosis and resulted in death. The second patient had symptoms of pulmonary fibrosis, which was confirmed by CT. Additionally, a third patient died with bilateral pulmonary infiltrates of uncertain etiology with hypoxia.

In the randomized, controlled clinical trial, median magnesium levels decreased by 0.1 mmol/L in the Vectibix® arm; hypomagnesemia (NCI-CTC grade 3 or 4) requiring oral or IV electrolyte repletion occurred in 2% of patients. Patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of Vectibix® therapy.

Exposure to sunlight can exacerbate dermatologic toxicity. It is recommended that patients wear sunscreen and hats, and limit sun exposure while receiving Vectibix®.

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 events of Vectibix® are pulmonary fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.

Please see brief summary of Prescribing Information on next page.

References: 1. Vectibix® (panitumumab) prescribing information, Amgen. **2.** Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol.* 2007;25:1658-1664.

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