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

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Special Reporting on:

Integrated Genomic Analyses of Cancer
Pursuit of Novel Treatment Strategies in the KRAS Wild-type Tumor Patient
Cetuximab Plus FOLFIRI in the Treatment of Metastatic Colorectal Cancer
Panitumumab With FOLFOX4 Compared to FOLFOX4 Alone as First-line Treatment in Metastatic Colorectal Cancer

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. 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 various cancers, including melanoma, thyroid cancer, and colorectal cancer. 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. “This currently places PIK3CA as one of the most highly mutated oncogenes in human cancer,” explained Dr. Velculescu.

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 oligonucleotide-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,
For example, Dr. Luis Diaz and colleagues at Johns Hopkins developed a technique for monitoring for recurrence of cancer. 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.

**References**

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. 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; \( P=0.0012 \)) and a more significant increase in median overall survival (OS) (23.5 vs 20.0 months; HR, 0.798; \( P=0.0093 \)). (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. 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 Pursuit of Novel Treatment Strategies in the KRAS Wild-type Tumor Patient...
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. 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. 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. 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  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 to improved OS. 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.”

References

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). 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. The benefit of cetuximab was limited to this subset of 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, 0.696; 95% CI, 0.558–0.867; 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.
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 ($P=0.005$), PFS ($P=0.003$), and OS ($P=0.046$).

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 CRYS-TAL 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.

References

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.
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, 1.19; 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).

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

<table>
<thead>
<tr>
<th>Grade 3/4 Adverse Event</th>
<th>Panitumumab + FOLFOX4</th>
<th>FOLFOX 4</th>
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<tbody>
<tr>
<td>Any event (n=639)</td>
<td>84 (KRAS Wild-type)</td>
<td>80 (KRAS Wild-type)</td>
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<tr>
<td></td>
<td>73 (KRAS Mutant)</td>
<td>69 (KRAS Mutant)</td>
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<tr>
<td>Skin toxicity</td>
<td>36 (KRAS Wild-type)</td>
<td>30 (KRAS Wild-type)</td>
</tr>
<tr>
<td></td>
<td>1 (KRAS Mutant)</td>
<td>2 (KRAS Mutant)</td>
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<tr>
<td>Neutropenia</td>
<td>42 (KRAS Wild-type)</td>
<td>37 (KRAS Wild-type)</td>
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<tr>
<td></td>
<td>41 (KRAS Mutant)</td>
<td>47 (KRAS Mutant)</td>
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<tr>
<td>Diarrhea</td>
<td>18 (KRAS Wild-type)</td>
<td>20 (KRAS Wild-type)</td>
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<td></td>
<td>9 (KRAS Mutant)</td>
<td>10 (KRAS Mutant)</td>
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<tr>
<td>Neurologic toxicity</td>
<td>16 (KRAS Wild-type)</td>
<td>17 (KRAS Wild-type)</td>
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<td>16 (KRAS Mutant)</td>
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*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.

**Reference**


**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.
The effectiveness of Vectibix as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma is based on progression-free survival.

Dose Modifications for Infusion Reactions

Do not exceed 4 mg/kg administered as an intravenous infusion over 60 minutes, every 14 days. Doses higher than 4 mg/kg should be administered over 90 minutes. Use the diluted infusion solution of Vectibix within 8 hours of preparation at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). Do not freeze.

− Infuse over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. Doses higher than 1000 mg should be infused over 90 minutes.

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**The first fully human anti-EGFR monoclonal antibody**

**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 88% 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].

**Boxed WARNINGS for infusion reactions**

- Statistically significant prolongation in PFS time vs BSC alone
- The recommended dose of Vectibix® is 6 mg/kg administered over 90 minutes (for doses >1000 mg infuse over 90 minutes) as an intravenous infusion every 14 days
- Use of premedication was not standardized in clinical trials (the utility of premedication in preventing infusional toxicity is unknown)
- ~1% incidence of severe infusion reactions reported
  - Please see Important Safety Information including Boxed WARNINGS for infusion reactions

**Prolonged PFS**

**Q2W dosing**

**Infusion reactions**

*Correlation with safety and efficacy is unknown*


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