2. SYNOPSIS

Name of Sponsor: Amgen, Inc.

Name of Finished Product: Vectibix®

Name of Active Ingredient: Panitumumab

Title of Study: A Randomized, Open-Label, Controlled, Phase II Trial of Combination Chemotherapy with or without Panitumumab as First-line Treatment of Subjects with Metastatic or Recurrent Head and Neck Cancer, and Cross-over Second-line Panitumumab Monotherapy of Subjects who Fail the Combination Chemotherapy Only Arm

Investigators and Study Centers: This study was conducted at 48 centers in the United States and Europe.

Publications: None.

Study Period: 29 January 2007 through 11 June 2012 (data cutoff date for the final analysis); 2 subjects were continuing to receive protocol-specified first-line treatment as 11 June 2012.

Development Phase: 2

Objectives:

The primary objective of this study was to estimate the effect of panitumumab on progression-free survival (PFS) based on the investigator's assessment when added to combination chemotherapy in first-line treatment of metastatic or recurrent squamous cell carcinoma of head and neck (SCCHN). Secondary objectives were to estimate the effect of panitumumab when added to combination chemotherapy in first-line treatment of metastatic or recurrent SCCHN on overall response rate, rate of disease control, duration of response, time to response, and overall survival; to describe the safety of panitumumab when added to combination chemotherapy; and to describe PFS, overall response rate, rate of disease control, duration of response, time to response, and overall survival for second-line panitumumab monotherapy (ie, after failure of combination chemotherapy). [redacted]

Methodology:

This was a randomized, phase 2, controlled, open-label, 2-arm, multicenter study of panitumumab plus docetaxel and cisplatin combination chemotherapy compared to chemotherapy alone in the first-line treatment of subjects with metastatic or recurrent SCCHN, as well as a crossover second-line study of panitumumab monotherapy in subjects who failed the chemotherapy-only arm. Subjects were randomized in a 1:1 ratio to receive panitumumab plus chemotherapy arm or chemotherapy alone. Randomization was stratified by screening Eastern Cooperative Oncology Group (ECOG) performance status score (0 vs 1) and disease status (newly diagnosed/previously untreated vs recurrent).

First-line treatment phase:

- During the first-line treatment phase, subjects received panitumumab plus docetaxel and cisplatin combination chemotherapy or combination chemotherapy alone for a maximum of 6 cycles. Carboplatin could be substituted for cisplatin in subjects who developed grade 2 or 3 neurotoxicity or at the first occurrence of a creatinine clearance < 60 mL/min.
- Subjects randomized to the panitumumab plus chemotherapy arm who had complete response, partial response, or stable disease and completed 6 cycles of treatment and those subjects who discontinued chemotherapy for intolerability prior to progression remained on first-line panitumumab monotherapy until disease progression, unacceptable toxicities, withdrawal of consent, or death, whichever occurred first.

Second-line panitumumab monotherapy:

- Eligible subjects in the chemotherapy alone arm who were determined to have disease progression before or after completing 6 cycles of chemotherapy in first-line treatment received second-line panitumumab monotherapy in cycles until disease progression, unacceptable toxicities, withdrawal of consent, or death, whichever occurred first.

Response evaluation in all treatment groups was performed by the investigator per a modified version of the Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 guidelines. All radiographic images were also reviewed, for analysis and reporting purposes, by an independent central review group. All subjects who received first-line chemotherapy with or without panitumumab and/or second-line treatment with panitumumab monotherapy were followed for tumor response every 6 weeks ± 1 week until disease progression and for survival until death, withdrawal of full consent, or approximately 24 months after the last subject was randomized, whichever occurred first.

Number of Subjects Planned: 110

Number of Subjects Enrolled: 113

Diagnosis and Main Criteria for Eligibility:

Eligible subjects were men and women ≥ 18 and < 70 years of age with histologically or cytologically confirmed SCCHN or its variants and a primary tumor of the oropharynx, oral cavity, hypopharynx, or larynx or SCCHN of unknown primary. Subjects were required to have a diagnosis of metastatic disease and/or recurrent disease determined to be incurable by surgery or radiotherapy, no prior systemic treatment for metastatic and/or recurrent SCCHN, at least 1 unidimensionally measurable lesion, and an ECOG performance status of 0 or 1.

Subjects were excluded from the study if they had received prior anti-epidermal growth factor receptor (EGFR) antibody therapy or treatment with small-molecule EGFR inhibitors (unless received as part of prior multimodality treatment and completed ≥ 24 weeks prior to randomization) or if they had central nervous system metastases, unresolved toxicities from prior anti-cancer therapy, or a history of other invasive primary cancer.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Panitumumab 9 mg/kg was administered intravenously. The manufacturing batch numbers of panitumumab used in this study are provided in Appendix 18.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

Combination chemotherapy of docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 was administered intravenously. Carboplatin, administered to target an area under the curve of 5 (AUC 5) based on the Calvert formula, could be substituted for cisplatin in subjects who developed grade 2 or 3 neurotoxicity or at the first occurrence of a creatinine clearance < 60 mL/min.

Duration of Treatment:

First-line treatment: panitumumab and combination chemotherapy or combination chemotherapy alone were administered in cycles repeated every 21 ± 3 days for a maximum of 6 cycles.

First-line and second-line panitumumab monotherapy: in eligible subjects, panitumumab monotherapy was administered in cycles repeated every 21 ± 3 days.

Study Endpoints:

Primary Efficacy Endpoint:

• PFS during first-line treatment (investigator assessment)

Secondary Efficacy Endpoints:

• First-line treatment: PFS (central assessment); overall response rate, rate of disease control, duration of response, and time to response (investigator and central assessment); and overall survival

• Second-line panitumumab monotherapy: PFS, overall response rate, rate of disease control, duration of response, and time to response (central and investigator assessment); and overall survival

Safety Endpoints:

• Incidence, severity, and relationship of treatment-emergent adverse events; changes in laboratory values; and incidence of human anti-panitumumab antibody formation

Exploratory Endpoint:

[redacted]

[redacted]

Statistical Methods:

The study was designed to be an estimation study; therefore, there was no hypothesis testing. The primary analyses of all primary and secondary efficacy endpoints for first-line treatment utilized data from investigators' assessments of disease status (radiologic images only).

[redacted]. Efficacy analyses for second-line panitumumab monotherapy were descriptive. Safety data for first-line treatment were reported using the Safety Analysis Set and separately for subjects < 70 and ≥ 70 years of age.

Summary of Results:

Subject Disposition:

A total of 148 subjects were screened; 113 were randomized to first-line treatment, and 111 were included in the Safety Analysis Set and 103 in the Primary Analysis Set. As of the data cutoff date of 11 June 2012, 101 (98%) subjects in the Primary Analysis Set had ended the study: 5 subjects had completed the study, 81 had died, 10 had fully withdrawn consent, 1 ended because of a protocol deviation, 3 were lost to follow-up, and 1 ended for a reason of Other (the subject ended long-term follow-up); and 29 (97%) of 30 subjects in the Evaluable Subset for Second-line Panitumumab Monotherapy had ended the study. Disease progression was the most frequent reason for ending first-line treatment and second-line panitumumab monotherapy.

Baseline Demographics:

First-line Treatment (Primary Analysis Set, N = 103)

Sex: 90 (87%) subjects were male and 13 (13%) were female

Baseline Age: median: 57.0 years (range: 38, 69 years)

Ethnicity/Race: 83 (81%) white; 10 (10%) black or African American; 5 (5%) Hispanic or Latino; 5 (5%) unknown/missing

Second-line Panitumumab Monotherapy (N = 30)

Sex: 28 (93%) subjects were male and 2 (7%) were female

Baseline Age: median: 58.5 years (range: 39, 73 years)

Ethnicity/Race: 25 (83%) white; 1 black or African American; 2 Hispanic or Latino; 2 unknown/missing

Efficacy Results:

Primary Efficacy Endpoint: PFS for First-line Treatment

Median PFS time (95% confidence interval [CI]) during first-line treatment by investigator assessment was estimated at 6.9 months (4.7, 8.3) in the panitumumab plus chemotherapy arm and 5.5 months (4.1, 6.8) in the chemotherapy alone arm. The estimated hazard ratio using the Cox proportional hazards model stratified by randomization factors was 0.629 (95% CI: 0.395, 1.002; p-value: 0.051), favoring the panitumumab plus chemotherapy arm. The Kaplan-Meier curves of PFS time began to separate after the first assessment. A trend toward improved PFS time in the panitumumab plus chemotherapy arm in first-line treatment was generally observed across most of the subpopulations evaluated. The estimated adjusted treatment hazard ratio from the multivariate Cox proportional hazards model for PFS was 0.693 (95% CI: 0.440, 1.091), favoring the panitumumab plus chemotherapy arm; prior use of platinum in the setting of chemoradiotherapy and involuntary weight loss within the last 6 months were the only baseline covariates that had significant prognostic relevance. None of the baseline covariates analyzed was shown to have a significant predictive effect on PFS time in first-line treatment.

Secondary Efficacy Endpoints for First-line Treatment

Median PFS estimates by central assessment were similar in both treatment arms (5.3 months and 5.4 months). A trend toward improved PFS time by central assessment in the panitumumab plus chemotherapy arm in first-line treatment was generally observed across most of the subpopulations evaluated. Median duration of response by investigator assessment was longer in the panitumumab plus chemotherapy arm than in the chemotherapy alone arm. Median overall survival was similar in both treatment arms.

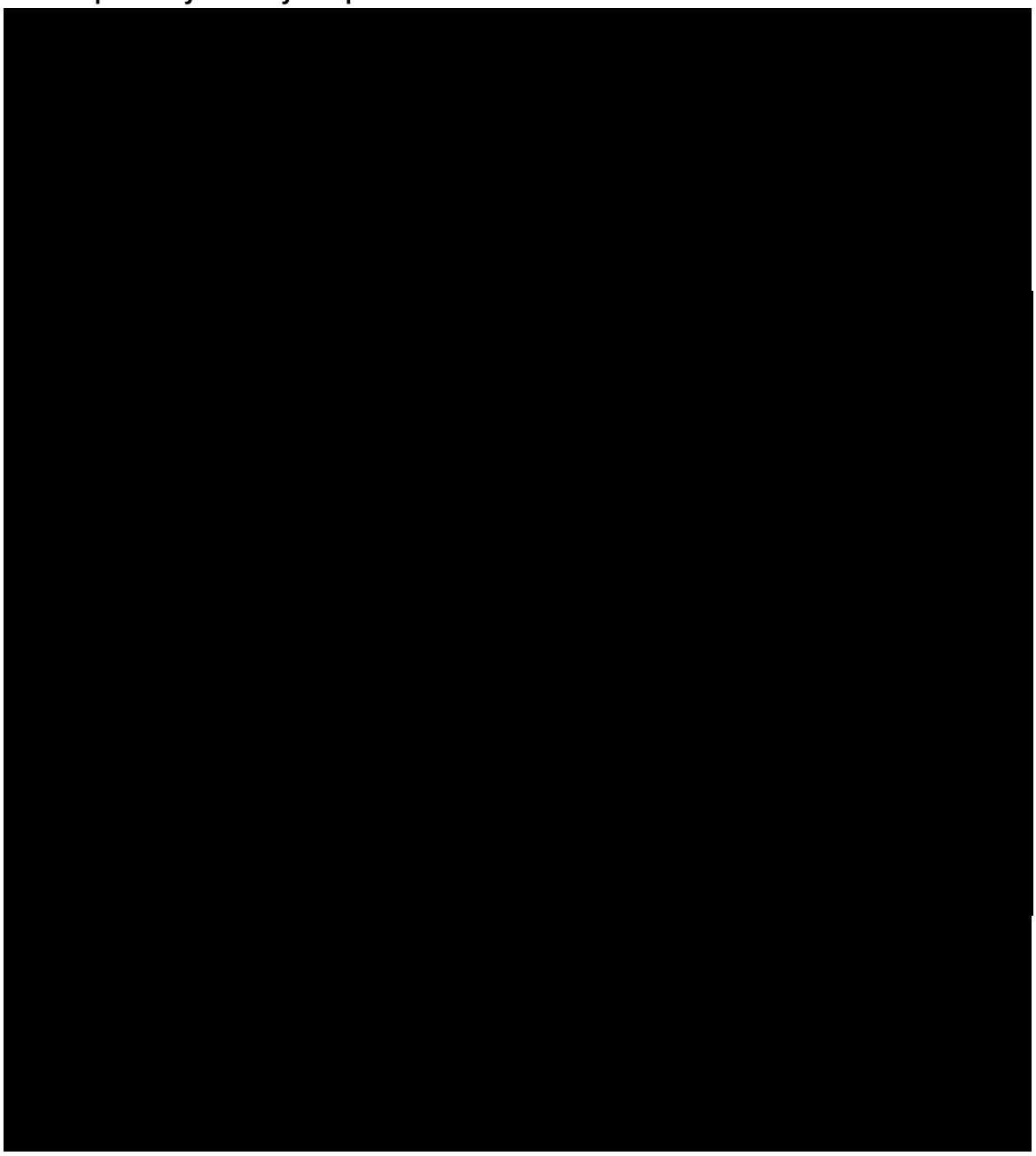
Secondary Efficacy Endpoints in First-lineTreatment	Panitumumab Plus Chemotherapy (N = 52)	Chemotherapy Alone (N = 51)
PFS, median (95% CI): central [a]	5.3 months (4.0, 8.3)	5.4 months (4.1, 7.4)
Hazard ratio (95% CI)	0.863 (0.526, 1.419)	
P-value for treatment effect	0.562	
Objective Response, Rate (95% CI): investigator [b]	44.23% (30.73, 57.73)	37.25% (23.99, 50.52)
Weighted difference in rates (95% CI)	6.23% (–11.67, 24.12)	
Treatment odds ratio (95% CI)	1.37 (0.57, 3.33)	
Objective Response, Rate (95% CI): central [c]	34.62% (21.68, 47.55)	41.67% (27.72, 55.61)
Weighted difference in rates (95% CI)	–6.38% (–24.42, 11.66)	
Treatment odds ratio (95% CI)	0.75 (0.31, 1.85)	
Rate of Disease Control (95% CI): investigator [b]	80.77% (70.06, 91.48)	72.55% (60.30, 84.80)
Weighted difference in rates (95% CI)	7.78% (–8.29, 23.85)	
Treatment odds ratio (95% CI)	1.76 (0.62, 5.26)	
Rate of Disease Control (95% CI): central [c]	80.77% (70.06, 91.48)	79.17% (67.68, 90.66)
Weighted difference in rates (95% CI)	1.48% (–13.94, 16.89)	
Treatment odds ratio (95% CI)	1.21 (0.39, 3.78)	
Time to Response, median (min, max): investigator [d]	6.9 weeks (5.1, 18.0)	11.0 weeks (5.1, 29.1)
Time to Response, median (min, max): central [e]	10.8 weeks (5.7, 26.9)	6.4 weeks (5.0, 35.1)
Duration of Response, median (95% CI): investigator [d]	8.0 months (5.7, 11.1)	5.1 months (4.4, 7.2)
Duration of Response, median (95% CI): central [e]	NE (6.0, NE)	5.8 months (4.2, 10.6)
Overall Survival, median (95% CI) [a]	12.9 months (9.4, 18.5)	13.8 months (11.8, 22.9)
Hazard ratio (95% CI)	1.103 (0.709, 1.717)	
P-value for treatment effect	0.663	

central = central assessment; CI = confidence interval; investigator = investigator assessment; max = maximum; min = minimum; NE = not estimable; PFS = progression-free survival.
[a] Primary Analysis Set.
[b] Evaluable for Local Tumor Response Analysis Set.
[c] Evaluable for Central Tumor Response Analysis Set (N = 52 in the panitumumab plus chemotherapy arm; N = 48 in the chemotherapy alone arm).
[d] Evaluable for Local Tumor Response Analysis Set: Subjects With Objective Responses (N = 23 in the panitumumab plus chemotherapy arm; N = 19 in the chemotherapy alone arm).
[e] Evaluable for Central Tumor Response Analysis Set: Subjects With Objective Responses (N = 18 in the panitumumab plus chemotherapy arm; N = 20 in the chemotherapy alone arm).

Secondary Efficacy Endpoints for Second-line Panitumumab Monotherapy

In second-line treatment, median PFS (95% CI) was estimated at 2.8 months (2.6, 5.5) by central assessment and 4.2 months (1.5, 7.6) by investigator assessment. The overall response rate (95% CI) was 13.79% (1.24, 26.34) by central assessment and 13.33% (1.17, 25.50) by investigator assessment. The rate of disease control (95% CI) was 65.52% (48.22, 82.82) by central assessment and 53.33% (35.48, 71.19) by investigator assessment. Median overall survival was 8.5 months (95% CI: 6.5, 13.2). The response rate with panitumumab monotherapy was comparable to historical rates, but the rate of disease control in this study was significantly higher (65% compared to 46%) compared to historical data.

HPV Exploratory Efficacy Endpoints in First-line Treatment



Safety Results:

First-line Treatment

Safety data for first-line treatment are reported separately for subjects < 70 years of age and for all subjects in the Safety Analysis Set. Eight subjects 70 years of age or older (4 in the panitumumab plus chemotherapy arm and 4 in the chemotherapy alone arm) were enrolled prior to Amendment 2, which excluded subjects 70 years of age or older.

In first-line treatment, 4 of the 9 on-treatment fatal adverse events in the panitumumab plus chemotherapy arm were reported in subjects 70 years of age or older. All 4 of the 4 subjects 70 years of age or older who received panitumumab experienced on-treatment fatal adverse events; the deaths were attributed to sepsis (n = 2), pulmonary embolism (n = 1), and renal failure acute (n = 1). One of the 4 on-treatment fatal adverse events in the chemotherapy alone arm was reported in a subject 70 years of age or older (neoplasm progression). The on-treatment

fatal adverse events that occurred in the 5 subjects < 70 years of age in the panitumumab plus chemotherapy arm were reflective of complications associated with the underlying disease (pneumonia staphylococcal due to aspiration [n = 1], general physical health deterioration [n = 2]) or reflective of progression of the underlying disease (neoplasm progression; arterial hemorrhage in the context of local disease progression). No on-treatment fatal adverse events were considered by the investigator to be related to panitumumab.

Adverse Events in First-line Treatment n (%)	Panitumumab Plus Chemotherapy		Chemotherapy Alone		Total	
	< 70 y [a] (N = 52)	All [b] (N = 56)	< 70 y [a] (N = 51)	All [b] (N = 55)	< 70 y [a] (N = 103)	All [b] (N = 111)
On-treatment fatal adverse event [c]	5 (10)	9 (16)	3 (6)	4 (7)	8 (8)	13 (12)
Serious adverse event [d]	30 (58)	34 (61)	26 (51)	27 (49)	56 (54)	61 (55)
Adverse events leading to discontinuation of any study drug [d]	12 (23)	13 (23)	11 (22)	12 (22)	23 (22)	25 (23)
Events of interest (any grade) [d]	46 (88)	50 (89)	38 (75)	39 (71)	84 (82)	89 (80)
Non-infectious diarrhea	26 (50)	29 (52)	18 (35)	18 (33)	44 (43)	47 (42)
Hypomagnesaemia	22 (42)	23 (41)	13 (25)	13 (24)	35 (34)	36 (32)
Hypokalemia	15 (29)	17 (30)	7 (14)	7 (13)	22 (21)	24 (22)
Dehydration	15 (29)	17 (30)	7 (14)	7 (13)	22 (21)	24 (22)
Skin Disorders per SOC	43 (83)	45 (80)	19 (37)	20 (36)	62 (60)	65 (59)
Stomatitis/Oral mucositis	26 (50)	28 (50)	13 (25)	14 (25)	39 (38)	42 (38)
Events of interest (grade 3 or higher) [d,e]	25 (48)	29 (52)	14 (27)	14 (25)	39 (38)	43 (39)

The data cutoff date for this analysis is 11 June 2012. SOC = System Organ Class.
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v15.
[a] Includes subjects in the Safety Analysis Set: Subjects With Age < 70.
[b] Includes subjects in the Safety Analysis Set.
[c] Fatal adverse events that occurred from the first-line first dose date to 30 days since the first-line last dose date.
[d] Reporting period is from the first-line first dose date to 30 days since the first-line last dose date.
[e] Severity graded using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0, with the exception of some dermatology/skin adverse events that were graded using the CTCAE 3.0 with modifications.

Serious adverse events were reported more frequently in the panitumumab plus chemotherapy arm than in the chemotherapy alone arm. Serious adverse events reported with at least a 5% greater frequency in the panitumumab plus chemotherapy arm included dehydration, hypotension, diarrhea, general physical health deterioration, and sepsis (dehydration, general physical health deterioration, and diarrhea in subjects with age < 70 years).

Events of interest in first-line treatment were reported more frequently in the panitumumab plus chemotherapy arm than in the chemotherapy alone arm. Non-infectious diarrhea, hypomagnesemia, hypokalemia, dehydration, skin disorders, and stomatitis/oral mucositis were among the events of interest reported more frequently in the panitumumab plus chemotherapy arm than in the chemotherapy alone arm.

The changes from baseline in hematology results in first-line treatment were generally similar between the panitumumab plus chemotherapy and the chemotherapy alone arms, and no notable trends were observed. The chemistry analytes with the highest frequencies of subjects with grade 3 or higher toxicities included decreases in serum magnesium and sodium. As expected, grade 3 or higher decreases in serum magnesium were observed in a greater proportion of subjects in the panitumumab plus chemotherapy arm than in the chemotherapy alone arm (20% vs 9%).

No clinically significant changes from baseline in vital signs were observed.

Second-line Panitumumab Monotherapy

One subject experienced an on-treatment fatal adverse event (cerebrovascular accident) during second-line panitumumab monotherapy, and serious adverse events were reported in 10 (33%)

of 30 subjects. Pneumonia occurred in 3 subjects and was the only serious adverse event that occurred in more than 1 subject in second-line treatment. No clinically significant changes from baseline in vital signs were observed.

Anti-panitumumab Antibodies

There were no neutralizing anti-panitumumab antibodies detected in any subject. In first-line treatment, 2 subjects had pre-existing anti-panitumumab binding antibodies, and 2 subjects developed anti-panitumumab binding antibodies. There was no evidence of a change in safety profile found in subjects who tested positive for anti-panitumumab antibodies when compared to that of subjects who tested negative.

[redacted]

Conclusions:

The primary objective of this study was to estimate the effect of panitumumab on PFS based on the investigator's assessment when added to combination chemotherapy in first-line treatment of metastatic or recurrent SCCHN.

Efficacy analyses for first-line treatment showed improved PFS in the panitumumab plus chemotherapy arm (median PFS [95% CI] by investigator assessment: 6.9 months [4.7, 8.3] vs 5.5 months [4.1, 6.8] in the chemotherapy alone arm; hazard ratio: 0.629 [95% CI: 0.395, 1.002]). Median PFS estimates by central assessment were similar in both treatment arms (5.3 months and 5.4 months). Response rates were high in both treatment arms. PFS favored the panitumumab plus chemotherapy arm for subjects in most of the subgroups analyzed; however, interpretation of the results is limited by the small sample size in the subgroups. Analyses of efficacy results by HPV status were also limited by the small sample size.

During the course of this study, a pre-planned interim analysis of safety data for the first 30 subjects revealed an apparent imbalance in deaths and serious adverse events between the panitumumab plus chemotherapy and chemotherapy alone arms. The imbalance was chiefly due to infectious/febrile neutropenic episodes in the subjects 70 years of age or older. The protocol was amended to increase the entry criterion for creatinine clearance to ≥ 60 mL/min, exclude subjects 70 years of age or older, add mandatory growth factor support following chemotherapy administration, and include an additional safety visit at day 11 (nadir of chemotherapy effect).

Among subjects with age <70 years, safety results were consistent with those observed in other clinical studies evaluating panitumumab in combination with chemotherapy, and no new safety risks were identified. When subjects 70 years of age or older were excluded from the safety analyses, the number of on-treatment fatal adverse events (5 subjects and 3 subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively) and the frequencies of serious adverse events (58% and 51% of subjects in the panitumumab plus chemotherapy and chemotherapy alone arms, respectively) were comparable in the 2 treatment arms. As expected, events of interest reported at a greater frequency in the panitumumab plus chemotherapy arm included non-infectious diarrhea, hypomagnesemia, hypokalemia, dehydration, skin disorders, and stomatitis/oral mucositis.

In light of the efficacy and safety results from this small, phase 2, estimation study (N = 103 in the Primary Analysis Set), there was clear evidence of antitumor activity with the addition of panitumumab to cisplatin/docetaxel based on the improved PFS (hazard ratio: 0.629) and objective response [redacted] The suggestion of incremental activity needs to be weighed against the observed toxicity and the requirement for growth factor support.