Panitumumab

Vectibix™

20mg/mL Concentrate for Solution for Intravenous Infusion

PRODUCT DESCRIPTION

Each ml of concentrate contains 20 mg panitumumab.

PHARMACOLOGIC PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies.

Mechanism of action

Panitumumab is a recombinant fully human IgG2 monoclonal antibody that binds with high affinity to the ligand binding domain of human epidermal growth factor receptor (EGFR) and competitively inhibits receptor autophosphorylation induced by all known EGFR ligands. The addition of Panitumumab *(Vectibix™)* to chemotherapy, radiation, or other targeted therapeutic agents in animal studies results in an increase in antitumor effects compared to chemotherapy or targeted therapeutic agents alone**.**

KRAS (Kirsten rat sarcoma 2 viral oncogene homologue) and NRAS (Neuroblastoma RAS viral oncogene homologue) are highly related members of the RAS oncogene family.

KRAS and NRAS genes encode a small, GTP-binding protein involved in signal transduction. A variety of stimuli, including that from the EGFR activates *KRAS* and NRAS, which in turn stimulates other intracellular proteins to promote cell proliferation, cell survival, and angiogenesis.

Activating mutations in the *RAS* gene occur frequently in a variety of human tumors and have been implicated in both oncogenesis and tumor progression.

Pharmacodynamic effects

In vitro assays and *in vivo* animal studies have shown that panitumumab inhibits the growth and survival of tumour cells expressing EGFR. No anti-tumour effects of panitumumab were observed in human tumour xenografts lacking EGFR expression. The addition of panitumumab to radiation, chemotherapy or other targeted therapeutic agents, in animal studies resulted in an increase in anti-tumour effects compared to radiation, chemotherapy or targeted therapeutic agents alone.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of Panitumumab *(Vectibix™)* has been evaluated using two different screening immunoassays for the detection of binding anti-panitumumab antibodies: an acid dissociation bridging enzyme-linked immunosorbant assay (ELISA) and a Biacore™ biosensor immunoassay. For patients whose sera tested positive in either screening immunoassay, an *in vitro* biological assay was performed to detect neutralising antibodies.

As Monotherapy

The incidence of binding antibodies (excluding predose and transient positive patients) was < 1% as detected by the acid-dissociation ELISA and 3.8% as detected by the Biacore assay.

- The incidence of neutralising antibodies (excluding predose and transient positive patients) was < 1%.
- There was no evidence of altered pharmacokinetic or toxicity profiles in patients who developed antibodies to Panitumumab *(Vectibix™)*.

In combination with irinotecan- or oxaliplatin-based chemotherapy

The incidence of binding antibodies (excluding predose positive patients) was 1.0% (1.2% in patients with wild-type *KRAS* mCRC) as detected by the acid-dissociation ELISA and < 1% (< 1% in patients with wild-type *KRAS* mCRC) as detected by the Biacore assay.

- The incidence of neutralising antibodies (excluding predose positive patients) was < 1% (< 1% in patients with wild-type *KRAS* mCRC).
- No evidence of an altered safety profile was found in patients who tested positive for antibodies to Panitumumab *(Vectibix™)*.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising 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 subject incidence of antibodies to other products may be misleading.

Pharmacokinetics

Panitumumab *(Vectibix™)* administered as a single agent or in combination with chemotherapy exhibits nonlinear pharmacokinetics. Following a single-dose administration of panitumumab as a 1-hour infusion, the area under the concentration-time curve (AUC) increased in a greater than dose-proportional manner and clearance (CL) of panitumumab decreased from 30.6 to 4.6 ml/day/kg as the dose increased from 0.75 to 9 mg/kg. However, at doses above 2 mg/kg, the AUC of panitumumab increases in an approximately dose-proportional manner.

Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour infusion), panitumumab concentrations reached steady-state levels by the third infusion with mean (± SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 micrograms/ml, respectively. The mean (± SD) AUC0-tau and CL were 1306 ± 374 micrograms day/ml and 4.9 ± 1.4 ml/kg/day, respectively. The elimination half-life was approximately 7.5 days (range: 3.6 to 10.9 days).

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics. Results suggest that age (21-88), gender, race, hepatic function, renal function, chemotherapeutic agents, and EGFR membrane staining intensity (1+, 2+, 3+) in tumour cells had no apparent impact on the pharmacokinetics of panitumumab.

No clinical studies have been conducted to examine the pharmacokinetics of panitumumab in patients with renal or hepatic impairment.

Clinical Studies

Clinical efficacy as Monotherapy

The efficacy of Panitumumab *(Vectibix™)* as monotherapy in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in a randomised controlled trial (463 patients) and open-label, single-arm trials (384 patients).

A multinational, randomised, controlled trial was conducted in 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum after confirmed failure of oxaliplatin and irinotecan-containing regimens. Patients were randomised 1:1 to receive Panitumumab *(Vectibix™)* at a dose of 6 mg/kg given once every two weeks plus best supportive care (not including chemotherapy) (BSC) or BSC alone. Patients were treated until disease progression or unacceptable toxicity occurred. Upon disease progression BSC alone patients were eligible to crossover to a companion study and receive Panitumumab *(Vectibix™)* at a dose of 6 mg/kg given once every two weeks.

Of 463 patients, 63% were male. The median age was 62 years (range 27 to 83), and 99% were Caucasian. Three hundred and ninety-six (86%) patients had a baseline ECOG Performance Status of 0 or 1. Sixty-seven percent of patients had colon cancer and 33% had rectal cancer.

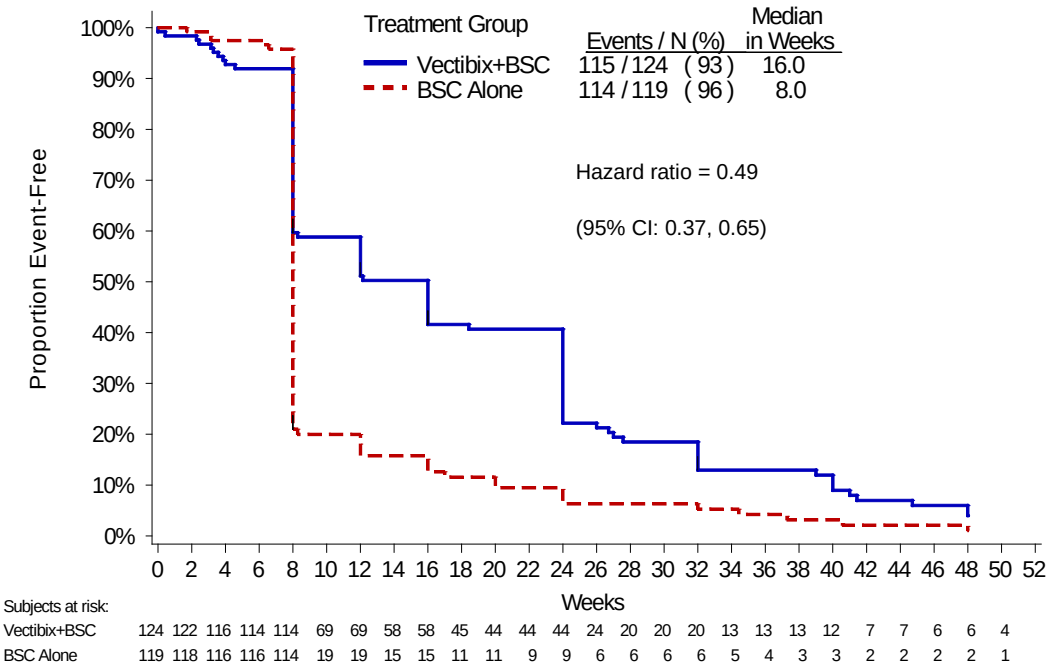
The primary endpoint was progression-free survival (PFS). In an analysis adjusting for potential bias from unscheduled assessments, the rate of disease progression or death in patients who received Panitumumab *(Vectibix™)* was reduced by 40% relative to patients that received BSC [Hazard Ratio = 0.60, (95% CI 0.49, 0.74), stratified log-rank p < 0.0001]. There was no difference seen in median PFS times as more than 50% of patients progressed in both treatment groups before the first scheduled visit.

The study was retrospectively analysed by wild-type *KRAS* status versus mutant *KRAS* status. *KRAS* mutation status was determined by analysis of archived paraffin embedded tumour tissue.

Tumour samples obtained from the primary resection of colorectal cancer were analysed for the presence of the seven most common activating mutations in the codon 12 and 13 (Gly12Asp, Gly12Ala, Gly12Val, Gly12Ser, Gly12Arg, Gly12Cys, and Gly13Asp) of the *KRAS* gene by using an allele-specific polymerase chain reaction. 427 (92%) patients were evaluable for *KRAS* status of which 184 had mutations. In an analysis adjusting for potential bias from unscheduled assessments the hazard ratio for PFS was 0.49 (95% CI: 0.37-0.65) in favour of panitumumab in the wild-type *KRAS* group and 1.07 (95% CI: 0.77-1.48) in the *KRAS* mutant group. The difference in median PFS in the wild-type *KRAS* group was 8 weeks. The progression-free survival rates at the first scheduled visit (week 8) in the wild-type *KRAS* group were 59.7% on Panitumumab *(Vectibix™)* plus BSC and 21.0% on BSC alone, a difference of 38.7% [95% CI: 27.4, 50.0]. The difference in median PFS in the mutant *KRAS* group was 0 weeks. The progression-free survival rates at the first scheduled visit (week 8) in the mutant *KRAS* group were 21.4% on Panitumumab *(Vectibix™)* plus BSC and 28.0% on BSC alone, a difference of -6.6% [95% CI: -19.0, 5.9]. There were no differences in overall survival seen in either group. In the wild-type *KRAS* group the response rate was 17% for panitumumab and 0% for BSC. In the mutant *KRAS* group there were no responses in either treatment arm. Stable disease rates in the wild-type *KRAS* group were 34% for panitumumab and 12% for BSC. The stable disease rates in the mutant *KRAS* group were 12% for panitumumab and 8% for BSC. Response rate (investigator assessment) in patients that crossed over to panitumumab after progression on BSC alone was 22% (95% CI: 14.0, 31.9) for those with wild-type *KRAS* tumours and 0% (95% CI: 0.0, 4.3) for those with mutant *KRAS* tumours.

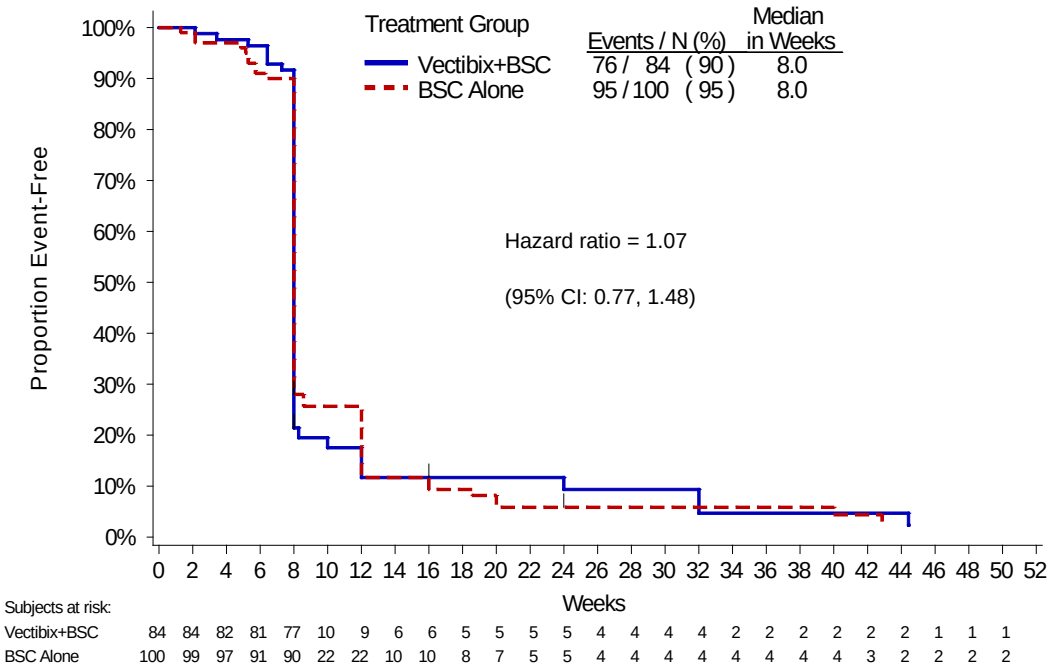
PFS – Patients with mutant and wild-type KRAS

Wild-Type *KRAS*



Unscheduled tumour assessments were moved to the nearest scheduled timepoint

Mutant *KRAS*



Unscheduled tumour assessments were moved to the nearest scheduled timepoint

Clinical efficacy in combination with chemotherapy

Summary of key efficacy results in pivotal studies: Panitumumab *(Vectibix™)* in combination with chemotherapy

	Oxaliplatin-based chemotherapy ± Panitumumab *(Vectibix™)* wild-type *KRAS* mCRC		**Irinotecan-based chemotherapy ± Panitumumab *(Vectibix™)* wild-type *KRAS* mCRC**	
	Pmab (n=325)	**Control (n=331)**	**Pmab (n = 303)**	**Control (n = 294)**
KRAS Ascertainment	93%		91%	
Response Rate	55%	48%	35%	10 %
PFS Hazard Ratio (95% CI)	0.798 (0.656, 0.971) P = 0.023		0.732 (0.593, 0.903) P = 0.0036	
Median PFS (months) (95% CI)	9.6 (9.2, 11.1)	8.0 (7.5, 9.3)	5.9 (5.5, 6.7)	3.9 (3.7, 5.3)
Absolute benefit (months)	1.6		2.0	
OS Hazard Ratio (95% CI)	0.825 (0.669, 1.018) P=0.0723		0.854 (0.702, 1.039) P=0.1154	
Median OS (months) (95% CI)	23.9 (20.3, 28.3)	19.7 (17.6, 22.6)	14.5 (13.0, 16.0)	12.5 (11.2, 14.2)
Absolute benefit (months)	4.2		2.0	

In combination with Oxaliplatin-based Chemotherapy

The efficacy of Panitumumab *(Vectibix™)* in combination with oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (FOLFOX) was evaluated in a randomised, controlled trial of 1183 patients with mCRC with the primary endpoint of progression-free survival (PFS). Other key endpoints included the overall survival (OS), objective response rate (ORR), time to response, time to progression (TTP), and duration of response. The study was prospectively analysed by tumour *KRAS* status. A summary of results in patients with wild-type *KRAS* mCRC are presented in the table above.

Primary analysis

The efficacy results in patients with wild-type KRAS (exon 2) mCRC and mutant KRAS mCRC are presented in the table below.

	Panitumumab plus FOLFOX	**FOLFOX Alone**
Wild-type KRAS (exon 2) population	(n = 325)	(n = 331)
PFS		
Median (months) (95% CI)	9.6 (9.2, 11.1)	8.0 (7.5, 9.3)

	Panitumumab plus FOLFOX	FOLFOX Alone
Difference in median (months)	1.6	
Hazard ratio (95% CI)	0.798 (0.656, 0.971)	
p-value	0.023	
Estimated rate at 12 months (95% CI)	41% (34%, 47%)	27% (21%, 33%)
OS		
Median (months) (95% CI)	23.9 (20.3, 28.3)	19.7 (17.6, 22.6)
Difference in median (months)	4.2	
Hazard ratio (95% CI)	0.825 (0.669, 1.018)	
p-value	0.0723	
Estimated rate at 24 months (95% CI)	49% (43%, 55%)	40% (35%, 46%)
ORR		
n (%) (95% CI)	175 (55%) (50%, 61%)	154 (48%) (42%, 53%)
Odds ratio (95% CI)	1.35 (0.98, 1.87)	
Stable disease n (%)	95 (30%)	117 (36%)
TTP		
Median (months) (95% CI)	10.8 (9.4, 12.4)	9.2 (7.7, 9.9)
Hazard ratio	0.774	
Time to Response		
Estimated mean (SD) (months)	2.3 (0.9)	2.7 (1.3)
Duration of Response		
Median (months) (95% CI)	11.1 (9.5, 13.0)	8.8 (7.8, 9.7)
Subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine)		
Patients receiving subsequent chemotherapy	53% (n = 173)	62% (n = 205)
Median time to subsequent chemotherapy (months)	10.5	9.7
Subsequent anti-EGFR therapy1		
Patients receiving subsequent anti-EGFR therapy	8% (n = 26)	18% (n = 59)
Median time to anti-EGFR therapy	17.9	10.8
Mutant KRAS (exon 2) population	(n = 221)	(n = 219)
PFS		
Median (months) (95% CI)	7.3 (6.3, 8.0)	8.8 (7.7, 9.4)
p-value	0.0227	
OS2		
Median (months) (95% CI)*	15.5 (13.1, 17.6)	19.3 (16.5, 21.8)

[1] The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS treatment effect is unknown
[2] See Contraindications

The results of an exploratory covariate analysis according to ECOG status in patients with wild-type KRAS (exon 2) mCRC are shown below:

	ECOG PS of 0 or 1 (n = 616)		ECOG 2 PS (n = 40)	
	Panitumumab plus FOLFOX (n = 305)	FOLFOX Alone (n = 311)	Panitumumab plus FOLFOX (n = 20)	FOLFOX Alone (n = 20)
Median OS (months)	25.8	20.7	7.0	11.7
OS Hazard ratio (95% CI)	0.767 (0.616; 0.955)		1.834 (0.896, 3.753)	
p-value	0.0176		0.0937	

Final analysis

The efficacy results from the pre-specified final analysis which occurred 2 years after the last patient was enrolled in patients with wild-type KRAS (exon 2) mCRC and mutant KRAS mCRC are presented in the table below.

	Panitumumab plus FOLFOX	**FOLFOX Alone**
Wild-type KRAS (exon 2) population	(n = 325)	(n = 331)
PFS		
Median (months) (95% CI)	10.0 (9.3, 11.4)	8.6 (7.5, 9.5)
Difference in median (months)	1.4	
Hazard ratio (95% CI)	0.799 (0.674, 0.946)	
p-value	0.009	
Estimated rate at 12 months (95% CI)	44% (38%, 49%)	32% (27%, 38%)
OS		
Median (months) (95% CI)	23.9 (20.3, 27.7)	19.7 (17.6, 22.7)
Difference in median (months)	4.2	
Hazard ratio (95% CI)	0.878 (0.728, 1.058)	
p-value	0.171	
Estimated rate at 24 months (95% CI)	50% (44%, 55%)	41% (36%, 47%)
ORR		
n (%) (95% CI)	181 (57%) (51%, 63%)	154 (48%) (42%, 53%)
Odds ratio (95% CI)	1.47 (1.07, 2.04)	
Stable disease n (%)	91 (29%)	117 (36%)
Mutant KRAS (exon 2) population	(n = 221)	(n = 219)
PFS		
Median (months) (95% CI)	7.4 (6.9, 8.1)	9.2 (8.1, 9.9)
p-value	0.019	
OS2		
Median (months) (95% CI)*	15.5 (13.1, 17.6)	19.2 (16.5, 21.7)

[1] The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS treatment effect is unknown
[2] See Contraindications

The results of an exploratory covariate analysis according to ECOG status in patients with wild-type KRAS (exon 2) mCRC are shown below:

	ECOG PS of 0 or 1 (n = 616)		ECOG 2 PS (n = 40)	
	Panitumumab plus FOLFOX (n = 305)	FOLFOX Alone (n = 311)	Panitumumab plus FOLFOX (n = 20)	FOLFOX Alone (n = 20)
Median OS (months)	25.8	20.6	7.0	11.7
OS Hazard ratio (95% CI)	0.837 (0.690, 1.017)		1.589 (0.800, 3.157)	
p-value	0.074		0.185	

Exploratory analysis of overall survival (OS)

An exploratory analysis of mature overall survival (>80% OS events) estimated the treatment effect of panitumumab plus FOLFOX compared with FOLFOX alone on OS by KRAS (exon 2) status. Previous analyses in patients with wild-type KRAS (exon 2) tumor status reported OS with an event rate of 54% of patients in the primary analysis and 68% of patients in the final analysis. 535/656 patients (82%) with wild-type KRAS (exon 2) mCRC had an OS event at the time of this analysis. Results are shown below.

	Panitumumab plus FOLFOX	FOLFOX Alone
Wild-type KRAS (exon 2) population	(n = 325)	(n = 331)
Death (any cause) - n (%)	256 (79)	279 (84)
Median OS - months (95% CI)	23.8 (20.0 – 27.7)	19.4 (17.4 – 22.6)
Hazard ratio (95% CI)	0.825 (0.695, 0.979)	
Mutant KRAS (exon 2) population	(n = 221)	(n = 219)
Death (any cause) - n (%)	193 (87)	195 (89)
Median OS - months (95% CI)	15.5 (13.1 – 17.6)	19.2 (16.2 – 21.5)
Hazard ratio (95% CI)	1.155 (0.943, 1.414)	

Predefined retrospective subset analysis of efficacy and safety by RAS (i.e., KRAS and NRAS) and RAS/BRAF biomarker status

A predefined retrospective subset analysis of 641 patients of the 656 patients with wild-type KRAS (exon 2) mCRC was performed. The primary objective of this analysis was to examine the treatment effect of panitumumab plus FOLFOX compared with FOLFOX alone in patients who were wild-type for RAS (KRAS and NRAS exons 2, 3, and 4) or wild-type for RAS and BRAF (KRAS and NRAS exons 2, 3, and 4 and BRAF exon 15). In this analysis, patient tumor samples with wild-type KRAS exon 2 (codons 12/13) status were tested using Sanger bidirectional sequencing and Surveyor®/WAVE® analysis in parallel for additional RAS mutations in KRAS exon 3 (codon 61) and exon 4 (codons 117/146) and NRAS exon 2 (codons 12/13), exon 3 (codon 61), and exon 4 (codons 117/146). In the analysis, the incidence of these additional RAS mutations in the wild-type KRAS (exon 2) population was approximately 16%.

In this analysis, BRAF mutation was not found to be predictive of negative outcome for panitumumab treatment.

Results in patients with wild-type RAS mCRC, mutant RAS mCRC and wild-type KRAS (exon 2) mutant RAS mCRC from the primary analysis are presented in the table below.

	Panitumumab plus FOLFOX Median (95% CI), (months)	FOLFOX Alone Median (95% CI), (months)	Hazard Ratio (95% CI)
Wild-type RAS population			
PFS	10.1 (9.3, 12.0)	7.9 (7.2, 9.3)	0.72 (0.58, 0.90)
OS	26.0 (21.7, 30.4)	20.2 (17.7, 23.1)	0.78 (0.62, 0.99)
Mutant RAS population			
PFS	7.3 (6.3, 7.9)	8.7 (7.6, 9.4)	1.31 (1.07, 1.60)
OS	15.6 (13.4, 17.9)	19.2 (16.7, 21.8)	1.25 (1.02, 1.55)
Wild-type KRAS (exon 2) Mutant RAS population			
PFS	7.3 (5.3, 9.2)	8.0 (6.4, 11.3)	1.28 (0.79, 2.07)
OS	17.1 (10.8, 19.4)	18.3 (13.0, 23.2)	1.29 (0.79, 2.10)

Subsequent to the predefined analysis, additional mutations in KRAS and NRAS at exon 3 (codon 59) were identified (n = 7). In an exploratory analysis, adding codon 59 also appeared to be predictive of negative outcomes for panitumumab treatment.

In combination with Irinotecan-based Chemotherapy

The efficacy of Panitumumab *(Vectibix™)* in combination with irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) was evaluated in a randomised, controlled trial of 1186 patients with mCRC with the primary endpoints of overall survival (OS) and progression-free survival (PFS). Other key endpoints included the objective response rate (ORR), time to response, time to progression (TTP), and duration of response. The study was prospectively analysed by tumour *KRAS* status. A summary of results in patients with wild-type *KRAS* mCRC are presented in the table above.

In patients with wild-type *KRAS* mCRC (n = 597) a statistically significant difference in PFS in favour of panitumumab was demonstrated (p = 0.0036). The estimated median PFS times were 5.9 months (95% CI: 5.5, 6.7) in the panitumumab plus FOLFIRI arm and 3.9 months (95% CI: 3.7, 5.3) in the FOLFIRI alone arm, an absolute difference of 2.0 months. The hazard ratio was 0.732 (95% CI: 0.593, 0.903), favouring the panitumumab plus FOLFIRI arm. Estimated PFS rate (95% CI) at six (6) months was 49% (42%, 55%) in the panitumumab plus FOLFIRI arm and 35% (29%, 41%) in the FOLFIRI alone arm.

The estimated median OS was 14.5 months (95% CI: 13.0, 16.0) in the panitumumab plus FOLFIRI arm and 12.5 months (95% CI: 11.2, 14.2) in the FOLFIRI alone arm, an absolute difference of 2.0 months. The OS difference did not achieve statistical significance (p = 0.1154). The hazard ratio was 0.854 (95% CI: 0.702, 1.039), favouring the panitumumab plus FOLFIRI arm. Estimated OS rate (95% CI) at twelve (12) months was 59% (53%, 64%) in the panitumumab plus FOLFIRI arm and 53% (47%, 59%) in the FOLFIRI alone arm. Estimated OS rate (95% CI) at eighteen (18) months was 40% (35%, 46%) in the panitumumab plus FOLFIRI arm and 33% (27%, 39%) in the FOLFIRI alone arm. Subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine) was given to 142 (47%) subjects in the panitumumab plus FOLFIRI arm and 142 (48%) subjects in the FOLFIRI alone arm. Subsequent anti-EGFR therapy was received by 31 (10%) subjects in the panitumumab plus FOLFIRI arm and 90 (31%) subjects in the FOLFIRI alone arm. The median time to subsequent chemotherapy was 9.9 months in the panitumumab plus FOLFIRI arm and 7.6 months in the FOLFIRI alone arm. The median time to anti-EGFR therapy was 11.8 months (panitumumab plus FOLFIRI) and 7.6 months (FOLFIRI alone). The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS treatment effect is unknown.

The objective response rate was 35% for patients receiving panitumumab plus FOLFIRI and 10% for patients receiving FOLFIRI alone (all partial responses). The odds ratio for objective response was 5.33 (95% CI: 3.21, 8.60), favouring the panitumumab plus FOLFIRI arm. Stable disease was seen in 116 (39%) patients in the panitumumab plus FOLFIRI arm and 156 (55%) patients in the FOLFIRI alone arm.

The estimated mean (SD) for time to response for responding patients was 2.8 (1.6) months (panitumumab plus FOLFIRI) versus 3.3 (1.4) months (FOLFIRI alone). The duration of response was longer in the panitumumab plus FOLFIRI arm (median 7.6 months [95% CI: 6.7, 9.4]) than in the FOLFIRI alone arm (median 6.6 months [95% CI: 5.7, 10.4]). Time to disease progression was also longer in the panitumumab plus FOLFIRI arm (median 7.3 months [95% CI: 5.9, 7.5]) compared with the FOLFIRI alone arm (median 5.3 months [95% CI: 3,9, 5.7]; hazard ratio 0.683), favouring the panitumumab plus FOLFIRI arm. Eighteen% (18%) (n = 115) of panitumumab patients had been exposed to prior bevacizumab treatment. PFS and Response Rate were similar regardless of prior bevacizumab treatment.

In an exploratory covariate analysis, longer median OS was observed in the panitumumab plus FOLFIRI arm than in the FOLFIRI alone arm regardless of ECOG performance status (ECOG 0 or 1: 14.7 months vs. 12.8 months, hazard ratio 0.839; 95% CI: 0.685, 1.027; p = 0.0885; ECOG 2: 5.7 months vs. 4.8 months, hazard ratio 1.135; 95% CI: 0.512, 2.517; p = 0.7549).

In patients with mutant *KRAS* mCRC (n = 486), no significant difference in PFS (HR (95% CI): 0.85 (0.68, 1.06)) and OS (HR (95% CI): 0.94 (0.76, 1.15)) was observed between treatment arms.

Predefined retrospective subset analysis of efficacy and safety by RAS (i.e., KRAS and NRAS) and RAS/BRAF biomarker status

A predefined retrospective subset analysis of 586 patients of the 597 patients with wild-type KRAS (exon 2) mCRC was performed. Additional RAS mutations beyond KRAS exon 2 (ie, KRAS exons 3, 4 and NRAS exons 2, 3, 4) and mutations in BRAF exon 15 were examined to assess the effect of panitumumab when added to the FOLFIRI chemotherapy backbone in the second-line mCRC treatment setting. In this analysis, patient tumor samples with wild-type KRAS exon 2 status were tested using Sanger bidirectional sequencing for additional RAS mutations in KRAS exon 3 (codons 59 and 61) and exon 4 (codons 117 and 146), NRAS exon 2 (codons12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146), and BRAF exon 15 (codon 600). The RAS ascertainment rate was 85% overall (1014 of 1186 randomized patients). The RAS/BRAF ascertainment was also 85% (1014 of 1186 randomized patients). In this analysis, the incidence of these additional RAS mutations (KRAS exons 3, 4 and NRAS exons 2, 3, 4) in the wild-type KRAS (exon 2) population was approximately 19%. The incidence of BRAF exon 15 mutation in the wild-type KRAS (exon 2) population was approximately 8%. Efficacy results for the RAS analysis sets are shown in the below table.

	Panitumumab plus FOLFIRI Median (95% CI), (months)	FOLFIRI Alone Median (95% CI), (months)	Hazard Ratio (95% CI)
Wild-type RAS population			
PFS	6.4 (5.5, 7.4)	4.6 (3.7, 5.6)	0.701 (0.542, 0.907)
OS	16.2 (14.5, 19.7)	13.9 (11.9, 16.0)	0.807 (0.634, 1.027)
Mutant RAS population			
PFS	4.8 (3.7, 5.5)	4.0 (3.6, 5.5)	0.861 (0.705, 1.053)
OS	11.8 (10.4, 13.1)	11.1 (10.2, 12.4)	0.914 (0.759, 1.101)
Wild-type KRAS (exon 2) Mutant RAS population			
PFS	3.7 (2.3, 5.8)	3.7 (2.8, 5.1)	0.892 (0.561, 1.419)

	Panitumumab plus FOLFIRI Median (95% CI), (months)	FOLFIRI Alone Median (95% CI), (months)	Hazard Ratio (95% CI)
OS	11.3 (8.3, 13.1)	9.2 (7.0, 12.9)	0.825 (0.527, 1.293)

In this analysis, BRAF mutation appears to be a negative prognostic factor associated with reduced PFS and OS among patients with wild-type KRAS exon 2 mCRC, regardless of treatment arm. The data also suggest that BRAF mutation did not have additional predictive value for the effect of panitumumab therapy.
Among patients with wild-type RAS mCRC, PFS, OS, and ORR were improved for patients receiving panitumumab plus FOLFIRI compared with those receiving FOLFIRI alone. Patients with additional RAS mutations beyond KRAS exon 2 were unlikely to benefit from the addition of panitumumab to FOLFIRI.

In combination bevacizumab and oxaliplatin or irinotecan-based chemotherapy

In a randomised, open label, controlled clinical trial, chemotherapy (oxaliplatin or irinotecan) and bevacizumab were given with and without panitumumab in the first line treatment of patients with metastatic colorectal cancer (n = 1053 [n = 823 oxaliplatin cohort, n = 230 irinotecan cohort]). Panitumumab treatment was discontinued due to a statistically significant reduction in PFS in patients receiving panitumumab observed in an interim analysis.
The major study objective was comparison of PFS in the oxaliplatin cohort. In the final analysis, the hazard ratio for PFS was 1.27 (95% CI: 1.06, 1.52). Median PFS was 10.0 (95% CI: 8.9, 11.0) and 11.4 (95% CI: 10.5, 11.9) months in the panitumumab and the non-panitumumab arm, respectively. There was an increase in mortality in the panitumumab arm. The hazard ratio for overall survival was 1.43 (95% CI: 1.11, 1.83). Median overall survival was 19.4 (95% CI: 18.4, 20.8) and 24.5 (95% CI: 20.4, 24.5) in the panitumumab arm and the non-panitumumab arm.
An additional analysis of efficacy data by *KRAS* status did not identify a subset of patients who benefited from panitumumab in combination with oxaliplatin- or irinotecan based chemotherapy and bevacizumab. For the wild-type *KRAS* subset of the oxaliplatin cohort, the hazard ratio for PFS was 1.36 with 95% CI: 1.04-1.77. For the mutant *KRAS* subset, the hazard ratio for PFS was 1.25 with 95% CI: 0.91-1.71. A trend for OS favouring the control arm was observed in the wild-type *KRAS* subset of the oxaliplatin cohort (hazard ratio = 1.89; 95% CI: 1.30, 2.75). A trend towards worse survival was also observed with panitumumab in the irinotecan cohort regardless of *KRAS* mutational status. Overall, panitumumab treatment combined with chemotherapy and bevacizumab is associated with an unfavourable benefit-to-risk profile irrespective of tumour *KRAS* mutational status.

Pre-clinical Safety Data

Carcinogenecity

The carcinogenic potential of panitumumab has not been evaluated.

Mutagenicity

The mutagenic potential of panitumumab has not been evaluated *in vitro* or *in vivo*.

Reproductive toxicology

Fertility

Formal male fertility studies have not been conducted; however, microscopic evaluation of male reproductive organs from cynomolgus monkeys administered Panitumumab *(Vectibix™)* for 26 weeks at doses ranging up to 5-fold the human dose revealed no differences compared to control male monkeys. Fertility studies conducted in female cynomolgus monkeys showed that Panitumumab *(Vectibix™)* may produce secondary effects that could impact the ability of a woman to become pregnant while receiving Panitumumab *(Vectibix™)*.

Pregnancy

Animal studies are insufficient with respect to embryo-foetal development since foetal panitumumab exposure levels were not examined. Panitumumab has been shown to cause foetal abortions and/or foetal deaths in cynomolgus monkeys when administered during the period of organogenesis at doses approximately equivalent to the recommended human dose. No pre- and post-natal development animal studies have been conducted with panitumumab. All patients should be advised regarding the potential risk of panitumumab on pre- and post-natal development prior to initiation of Panitumumab *(Vectibix™)* therapy.

INDICATIONS

Panitumumab *(Vectibix™)* in combination with oxaliplatin-based chemotherapy is indicated for the treatment of patients with wild-type *RAS* metastatic colorectal cancer (mCRC).
Panitumumab *(Vectibix™)* is indicated for the treatment of patients with wild-type RAS metastatic colorectal cancer (mCRC) in combination with irinotecan-based chemotherapy.
Panitumumab *(Vectibix™)* monotherapy is indicated for the treatment of patients with wild-type *RAS* mCRC after failure of standard chemotherapy.

DOSAGE AND ADMINISTRATION

Posology

Panitumumab *(Vectibix™)* treatment should be supervised by a physician experienced in the use of anti-cancer therapy.
RAS mutational status should be determined by an experienced laboratory using a validated test method.

Recommended dose:

6 mg/kg bodyweight given once every 2 weeks
Prior to infusion, Panitumumab *(Vectibix™)* should be diluted in 0.9% sodium chloride to a final concentration not to exceed 10 mg/ml *(for preparation instructions see Instuctions for Use and Handling).*

DOSE MODIFICATIONS – INFUSION 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.
Stop infusion if a severe or life-threatening infusion reaction occurs and depending on the severity and/or persistence of the reaction, consider permanently discontinuing Panitumumab *(Vectibix™)*.

DOSE MODIFICATIONS – DERMATOLOGIC TOXICITY

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

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

MANAGEMENT OF SKIN TOXICITIES

Proactive skin treatment including skin moisturizer, sun screen (SPF > 15 UVA and UVB), topical steroid cream (not stronger than 1% hydrocortisone) and an oral antibiotic, as prescribed by the physician, may be useful in the management of skin toxicities. Patients may be advised to apply moisturiser and sunscreen to face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night. Treatment of skin reactions should be based on severity and may include a moisturiser, sun screen (SPF >15 UVA and UVB), and topical steroid cream (not stronger than 1% hydrocortisone) applied to affected areas, and/or oral antibiotics, as prescribed by the physician.

Method of administration

Panitumumab *(Vectibix™)* must be administered as an intravenous (IV) infusion via an infusion pump, using a low protein binding 0.2 or 0.22 micrometer in-line filter, through a peripheral line or indwelling catheter.

The recommended infusion time is approximately 60 minutes. Doses higher than 1000 mg should be infused over approximately 90 minutes. The infusion line should be flushed with sodium chloride solution before and after Panitumumab *(Vectibix™)* administration to avoid mixing with other medicinal products or IV solutions.

Do not administer Panitumumab *(Vectibix™)* as an IV push or bolus.

For instructions on dilution of the medicinal product before administration *(see Instructions for Use and Handling).*

Populations

Children

There is no experience in children and Panitumumab *(Vectibix™)* should not be used in those patients less than 18 years of age. The safety and effectiveness of Panitumumab *(Vectibix™)* in paediatric patients has not been established.

Elderly

No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Panitumumab *(Vectibix™)* monotherapy. However, an increased number of serious adverse events were reported in elderly patients treated with Panitumumab *(Vectibix™)* in combination with irinotecan or oxaliplatin-based chemotherapy compared to chemotherapy alone.

Renal Impairment

The safety and efficacy of Panitumumab *(Vectibix™)* x have not been studied in patients with renal impairment.

Hepatic Impairment

The safety and efficacy of Panitumumab *(Vectibix™)* have not been studied in patients with hepatic impairment.

CONTRAINDICATIONS

Panitumumab *(Vectibix™)* is contraindicated in patients with a history of life-threatening hypersensitivity reactions to panitumumab or any of the excipients.

For patients with mutant *RAS* mCRC or for whom *RAS* status is unknown, the combination of Panitumumab *(Vectibix™)* with oxaliplatin-based chemotherapy is contraindicated. (*see Warnings and Precautions*).

WARNINGS AND PRECAUTIONS

RAS mutations

In patients with mutant RAS (exons 2,3,4 of KRAS and NRAS) mCRC or for whom RAS status is unknown, Panitumumab *(Vectibix™)* should not be used in combination with oxaliplatin-based chemotherapy.

In other treatment settings (2nd and 3rd line) of mutant RAS mCRC, use of Panitumumab *(Vectibix™)* should be considered with caution.

Dermatologic and and Soft Tissue Toxicity

Skin and subcutaneous tissue disorders, a pharmacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, were frequently reported [93% in patients across the monotherapy mCRC clinical trials (N = 1,052)].

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving Panitumumab *(Vectibix™)* as sunlight can exacerbate any skin reactions that may occur.
For dose modifications related to dermatological toxicity, *see Dosage and Administration, Dose modifications-Dermatological toxicity.*
Patients who develop dermatologic or soft tissue toxicities while receiving Panitumumab *(Vectibix™)* should be monitored for the development of inflammatory or infectious sequelae.
Life threatening and fatal infectious complications including events of necrotizing fasciitis and/or sepsis have been observed in patients treated with Panitumumab (*Vectibix™*).
Rare cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients treated with Panitumumab (*Vectibix™*) in the postmarketing setting.
Withhold or discontinue Panitumumab (Vectibix™) for dermatologic or soft tissue toxicity associated with severe or life threatening inflammatory or infectious complications.
Eye Toxicity
Very rarely, serious cases of keratitis and/or ulcerative keratitis have been reported.
Patients who develop eye toxicities while receiving Panitumumab *(Vectibix™)* should be monitored for evidence of keratitis or ulcerative keratitis.
Infusion Reactions
Infusion reactions, including anaphylactic reactions, bronchospasm, and hypotension, have been reported in clinical trials and postmarketing experience. Across the monotherapy mCRC clinical trials (N = 1,052), severe infusion reactions (NCI-CTC grade 3 and grade 4) occurred with the administration of Panitumumab *(Vectibix™)* in 0.5% of patients.
In the (pooled) irinotecan-based chemotherapy with Panitumumab *(Vectibix™)* (N = 951) and the irinotecan-based chemotherapy alone (N = 594) settings, severe infusion reactions (NCI-CTC grade 3 and grade 4) occurred in 0.1% and 0.2% of patients, respectively. In the oxaliplatin-based chemotherapy with Panitumumab *(Vectibix™)* (N = 585) and the oxaliplatin-based chemotherapy alone (N = 584) settings, severe infusion reactions (NCI-CTC grade 3 and grade 4) occurred in 2.4% of patients in both treatment arms.
From postmarketing experience, serious infusion reactions have been reported in < 1% of patients, very rarely with a fatal outcome (less than 1 in 10,000).
Stop infusion if a severe or life-threatening infusion reaction occurs. Depending on the severity and/or persistence of the reaction, consider permanently discontinuing Panitumumab *(Vectibix™)*.
Other Hypersensitivity Reactions
Hypersensitivity reactions have been reported, including a fatal case of angioedema that occurred more than 24 hours after the infusion. Depending on the severity and/or persistence, of the hypersensitivity reactions; permanently discontinue Panitumumab *(Vectibix™)* (see Contraindications and Adverse Reactions).
Pulmonary Toxicity
Fatal and non-fatal cases of interstitial lung disease (ILD) have been observed in patients treated with EGFR inhibitors including Panitumumab *(Vectibix™)*. In the event of acute onset or worsening of pulmonary symptoms, Panitumumab *(Vectibix™)* therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, Panitumumab *(Vectibix™)* should be permanently discontinued and the patient should be treated appropriately.
In patients with a history of interstitial pneumonitis or pulmonary fibrosis or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with Panitumumab *(Vectibix™)* versus the risk of pulmonary complications must be carefully considered.
Panitumumab *(Vectibix™)* in Combination with Irinotecan, 5-fluorouracil, and Leucovorin (IFL) Chemotherapy
In a single-arm study (N = 19), patients receiving Panitumumab *(Vectibix™)* in combination with irinotecan, 5-fluorouracil, and leucovorin administered as the IFL regimen experienced a high incidence of severe diarrhoea (58%), therefore, administration of Panitumumab *(Vectibix™)* in combination with IFL should be avoided.
Panitumumab *(Vectibix™)* in Combination with Bevacizumab and Oxaliplatin-Containing Chemotherapeutic Regimens or Panitumumab *(Vectibix™)* in Combination with Bevacizumab and Irinotecan-Containing Chemotherapeutic Regimens for First-line Treatment of Metastatic Colorectal Cancer

A randomised, open-label, multicenter study of 1,053 patients evaluated the efficacy of bevacizumab and oxaliplatin- or irinotecan-containing chemotherapeutic regimens with and without Panitumumab *(Vectibix™)* in the first-line treatment of metastatic colorectal cancer.
Across both chemotherapy treatment groups, more toxicity was seen in the panitumumab group, manifesting as a greater incidence of grade 3 and higher adverse events, a greater incidence of serious adverse events, and more overall deaths relative to the control group. Similar safety trends were seen for the oxaliplatin and irinotecan treatment groups separately.
Serious adverse events were experienced by 59% in the panitumumab group versus 37% in the Control group, with higher incidences in the panitumumab group of dehydration, diarrhoea, pulmonary embolism, nausea, and vomiting. Serious infections overall displayed a treatment difference (15% versus 9%); however, no one specific type of infection occurred at a high frequency. Nineteen percent of patients receiving panitumumab experienced a serious event that was considered related to panitumumab, the most common of which were diarrhoea, dehydration, and vomiting.
This study did not demonstrate an improvement in progression-free survival (the primary endpoint) by the addition of panitumumab to bevacizumab and oxaliplatin based chemotherapy. The addition of Panitumumab *(Vectibix™)* to the combination of bevacizumab and chemotherapy in first-line metastatic colorectal cancer is not indicated.
Panitumumab *(Vectibix™)* in combination with oxaliplatin-based chemotherapy in patients with mutant *RAS* mCRC or for whom *RAS* status is unknown
Panitumumab *(Vectibix™)* should not be administered in combination with oxaliplatin-containing chemotherapy to patients with mutant *RAS* mCRC or for whom *RAS* status is unknown. In the primary analysis of a phase 3 study (N = 1,183, 656 patients with wild-type *KRAS* (exon 2) and 440 patients with mutant *KRAS* mCRC) evaluating panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) compared with FOLFOX alone as first-line therapy for mCRC, a significant shortening of progression-free survival (PFS) was observed in patients with mutant *KRAS* mCRC who received panitumumab and

FOLFOX (N = 221) versus FOLFOX alone (N = 219). A trend toward shortened overall survival (OS) time was also observed in the mutant *KRAS* mCRC population.
A predefined retrospective subset analysis of 641 patients of the 656 patients with wild-type KRAS (exon 2) mCRC from the phase 3 study identified additional RAS (KRAS [exons 3 and 4] or NRAS [exons 2, 3, 4]) mutations in 16% (n=108) of patients. A shortening of PFS and OS was observed in patients with mutant RAS mCRC who received panitumumab and FOLFOX (n = 51) versus FOLFOX alone (n= 57).

Acute Renal Failure

Acute renal failure has been observed in patients who develop severe diarrhoea and dehydration.

Patients with ECOG 2 Performance Status Treated with Panitumumab *(Vectibix™)* in Combination with Chemotherapy

In a phase 3 study (N = 1,183; 656 patients with wild-type *KRAS* and 440 patients with mutant *KRAS* mCRC) evaluating panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) compared to FOLFOX alone as first-line therapy, patients with ECOG 2 (Eastern Cooperative Oncology Group) performance status (n = 40) were observed to have increased toxicity and significant shortening of progression-free survival (PFS) relative to ECOG 0 or 1 performance status (n = 616). For patients with ECOG 2 performance status, assessment of risk-benefit is recommended prior to initiation of Panitumumab *(Vectibix™)* in combination with chemotherapy for treatment of mCRC.

Electrolyte Disturbances/Monitoring

Progressively decreasing serum magnesium levels leading to severe hypomagnesemia have been observed in some patients. Patients should be monitored for hypomagnesemia and accompanying hypocalcemia prior to initiating Panitumumab *(Vectibix™)* treatment, and periodically during Panitumumab *(Vectibix™)* treatment and for up to 8 weeks after the completion of treatment. Magnesium repletion is recommended, as appropriate.
Other electrolyte disturbances, including hypokalemia, have also been observed. Repletion of these electrolytes is also recommended, as appropriate.

RAS Tumor Genetic Marker Testing

Evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with Panitumumab *(Vectibix™)*. Mutational status should be determined by an experienced laboratory using validated test methods for detection of KRAS (exons 2, 3, and 4) and NRAS 9exons, 2, 3, and 4) mutations.

Effects on Ability to Drive and Use Machines

No studies on the effect on the ability to drive or use heavy machinery have been performed in patients receiving panitumumab. If patients experience treatment-related symptoms affecting their vision and/or ability to concentrate and react, it is recommended that they do not drive or use machines until the side effect subsides.

DRUG INTERACTIONS

Data from a drug-drug interaction study involving Panitumumab *(Vectibix™)* and irinotecan in patients with mCRC indicate that the pharmacokinetics of irinotecan and its active metabolite, SN-38, are not altered when the drugs are co-administered.
Results from a cross-study comparison indicated that irinotecan-containing regimens (IFL or FOLFIRI) have no effect on the pharmacokinetics of panitumumab.

PREGNANCY AND LACTATION

Fertility

Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys (see Preclinical Safety Data). Panitumumab may impact the ability of a woman to become pregnant.

Pregnancy

There are no adequate studies in pregnant women.
Studies in animals have shown reproductive toxicity (see Preclinical safety data). The potential risk for humans is unknown. EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Therefore, Panitumumab *(Vectibix™)* has the potential to cause foetal harm when administered to pregnant women.
Human IgG is known to cross the placental barrier, and panitumumab may therefore be transmitted from the mother to the developing foetus. In women of childbearing potential, contraceptive measures must be used during treatment with Panitumumab *(Vectibix™)*, and for 2 months following the last dose of Panitumumab *(Vectibix™)*.
If the patient becomes pregnant while receiving Panitumumab *(Vectibix™)*, she should be apprised of the potential risk for loss of the pregnancy or potential hazard to the fetus.
Women who become pregnant during Panitumumab (Vectibix™) treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should contact their local GSK representative to enrol.

Lactation

It is unknown whether panitumumab is excreted in human milk. Because human IgG is secreted into human milk, Panitumumab *(Vectibix™)* might also be secreted. The potential for absorption and harm to the infant after ingestion is unknown.
It is recommended that women discontinue nursing when during treatment with Panitumumab *(Vectibix™)* and for 2 months after the last dose of Panitumumab *(Vectibix™)*.

ADVERSE EFFECTS

Summary of safety profile

Based on an analysis of all mCRC clinical trial patients receiving Panitumumab *(Vectibix™)* monotherapy and in combination with chemotherapy (n = 2588), the most commonly reported adverse reactions are skin reactions occurring in 93% of patients. These reactions are related to the pharmacologic effects of Panitumumab *(Vectibix™)*, and the majority are mild to moderate in nature with 25% severe (grade 3 NCI-CTC) and < 1% life threatening (grade 4 NCI-CTC). For clinical management of skin reactions, including dose modification recommendations (see Warnings and Precautions).

Commonly reported adverse reactions occurring in ≥ 20% of patients were gastrointestinal disorders [diarrhoea (50%), nausea (41%), vomiting (27%), constipation (23%) and abdominal pain (23%)]; general disorders [fatigue (37%), pyrexia (20%)]; metabolism and nutrition disorders [anorexia (27%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (45%), dermatitis acneiform (39%), pruritus (35%), erythema (30%) and dry skin (22%)].

Tabulated summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical studies in patients with mCRC who received panitumumab as a single agent or in combination with chemotherapy (n = 2588). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1000)**
Blood and lymphatic system disorders	Anaemia	Leukopenia		
Cardiac disorders		Tachycardia	Cyanosis	
Eye disorders	Conjunctivitis	Blepharitis Dry eye Eye irritation Eye pruritus Growth of eyelashes Lacrimation increased Ocular hyperaemia	Eyelid irritation	
Gastrointestinal disorders	Diarrhoea Vomiting Abdominal pain Nausea Constipation Stomatitis	Rectal haemorrhage Dry mouth Dyspepsia Aphthous stomatitis Cheilitis Gastrooesophageal reflux disease Lip dry	Chapped lips	
General disorders and administration site conditions	Pyrexia Asthenia Fatigue Mucosal inflammation Oedema peripheral	Chest pain Pain Chills	Infusion related reaction	
Immune system disorders		Hypersensitivity		Anaphylactic reaction
Infections and infestations	Paronychia	Urinary tract infection Cellulitis Folliculitis Localised infection Rash pustular	Eye infection Eyelid infection	
Investigations	Weight decreased	Blood magnesium decreased		
Metabolism and nutrition disorders	Hypokalaemia Anorexia Hypomagnesaemia	Dehydration Hypocalcaemia Hyperglycaemia Hypophosphataemia		
Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity		
Nervous system disorders		Cholinergic syndrome Dizziness Headache		
Psychiatric disorders	Insomnia	Anxiety		
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Epistaxis	Bronchospasm Nasal dryness	

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1000)**
Skin and subcutaneous tissue disorders	Rash Dermatitis acneiform Acne Erythema Skin fissures Pruritus Alopecia Dry skin	Skin toxicity Dermatitis Skin exfoliation Rash pruritic Exfoliative rash Hypertrichosis Nail disorder Onychoclasis Palmar-plantar erythrodysaesthesia syndrome Hyperhidrosis Rash erythematous Rash generalised Rash macular Rash maculo-papular Rash papular Scab Skin lesion Skin ulcer	Angioedema Hirsutism Ingrowing nail Onycholysis	
Vascular disorders		Deep vein thrombosis Hypotension Hypertension Flushing		

The safety profile of Panitumumab *(Vectibix™)* in combination with chemotherapy consisted of the reported adverse reactions of Panitumumab *(Vectibix™)* (as a monotherapy) and the toxicities of the background chemotherapy regimen. No new toxicities or worsening of previously recognised toxicities beyond the expected additive effects were observed. Skin reactions were the most frequently occurring adverse reactions in patients receiving panitumumab in combination with chemotherapy. Other toxicities that were observed with a greater frequency relative to monotherapy included hypomagnesaemia, diarrhoea, and stomatitis. These toxicities infrequently led to discontinuation of Panitumumab *(Vectibix™)* or of chemotherapy

Description of selected adverse reactions

Gastrointestinal disorders

Diarrhoea when reported was mainly mild or moderate in severity. Severe diarrhoea (NCI-CTC grade 3 and 4) was reported in 2% of patients treated with Panitumumab *(Vectibix™)* as a monotherapy and in 17% of patients treated with Panitumumab *(Vectibix™)* in combination with chemotherapy.

There have been reports of acute renal failure in patients who develop diarrhoea and dehydration (see section Warnings and precautions).

Infusion related reactions

In the setting of infusion-related reactions occurring within 24 hours of infusion, adverse reactions including abdominal pain, anaphylactic reactions, angioedema, back pain, bronchospasm, cardiorespiratory arrest, chest pain, chills, cyanosis, dyspnoea, flushing, hypertension, hypotension, pyrexia, tachycardia and vomiting have been reported in clinical trials and in the post-marketing setting. Across all monotherapy mCRC clinical trials infusion-related reactions occurring within 24 hours of any infusion were reported in 3% of Panitumumab *(Vectibix™)*-treated patients, of which 0.5% were severe (NCI-CTC grade 3 and 4). In clinical studies with irinotecan-based chemotherapy, severe infusion reactions (NCI-CTC grade 3 and 4) occurred in 0.1% of patients administered Panitumumab *(Vectibix™)* in combination with irinotecan-based chemotherapy (n = 951) and in 0.2% of patients administered only irinotecan-based chemotherapy (n = 594). In clinical studies with oxaliplatin-based chemotherapy, severe infusion reactions (NCI-CTC grade 3 and 4) occurred in 2.4% of patients administered Panitumumab *(Vectibix™)* in combination with oxaliplatin-based chemotherapy (n = 585) and 2.4% of patients administered only oxaliplatin-based chemotherapy (n = 584). In the post-marketing setting, serious infusion reactions have been reported, including rare reports with a fatal outcome.

A case of fatal angioedema occurred in a patient with recurrent and metastatic squamous cell carcinoma of the head and neck treated with Panitumumab *(Vectibix™)* in a clinical trial. The fatal event occurred after re-exposure following a prior episode of angioedema; both episodes occurred greater than 24 hours after administration (see sections 4.3 and 4.4). Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported in the post-marketing setting.

For clinical management of infusion-related reactions, see section Warnings and precautions

Skin and subcutaneous tissue disorders
Skin rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities. Subsequent to the development of severe skin and subcutaneous reactions, infectious complications including sepsis, in rare cases leading to death, cellulitis and local abscesses requiring incisions and drainage were reported. The median time to first symptom of dermatologic reaction was 10 days, and the median time to resolution after the last dose of Panitumumab *(Vectibix™)* was 28 days.
Paronychial inflammation was associated with swelling of the lateral nail folds of the toes and fingers.
Dermatological reactions (including nail effects), observed in patients treated with Panitumumab *(Vectibix™)* or other EGFR inhibitors, are known to be associated with the pharmacologic effects of therapy.
Across all clinical trials, skin reactions occurred in 93% of patients receiving Panitumumab *(Vectibix™)* as monotherapy or in combination with chemotherapy (n = 2588). These events consisted predominantly of rash and dermatitis acneiform and were mostly mild to moderate in severity. Severe (NCI-CTC grade 3) skin reactions were reported in 34% and life-threatening (NCI-CTC grade 4) skin reactions in < 1% of patients who received Panitumumab *(Vectibix™)* in combination with chemotherapy (n = 1536).
For clinical management of dermatological reactions, including dose modification recommendations, see section Warnings and precautions.

Post-Marketing Data
Skin necrosis has been reported very rarely.
Serious cases of keratitis/ulcerative keratitis have been reported very rarely.
Stevens-Johnson syndrome.
Toxic epidermal necrolysis.

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

STORAGE CONDITIONS
Store between 2°C – 8°C. Do not freeze.
Keep the vial in the outer carton in order to protect from direct light.
Do not shake.
Panitumumab *(Vectibix™)* does not contain any antimicrobial preservative or bacteriostatic agent. The product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should be no longer than 24 hours at 2°C to 8°C.

INSTRUCTIONS FOR USE AND HANDLING
- Panitumumab *(Vectibix™)* must be administered using a low-protein binding 0.2 or 0.22 micrometer in-line filter.
- DO NOT ADMINISTER Panitumumab *(Vectibix™)* AS AN IV PUSH OR BOLUS.
- Do not administer Panitumumab *(Vectibix™)* if discolouration is observed.
- Panitumumab *(Vectibix™)* MUST BE ADMINISTERED BY IV INFUSION PUMP:
  - Withdraw the necessary amount of Panitumumab *(Vectibix™)* for a dose of 6 mg/kg or 2.5 mg/kg as appropriate.
  - Dilute in 100 ml of 0.9% sodium chloride USP. Final concentration should not exceed 10 mg/ml.
  - Diluted solution should be mixed by gentle inversion. **DO NOT SHAKE.**
  - Infuse over approximately 60 minutes through a peripheral line or indwelling catheter*. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes
  - Flush line before and after Panitumumab *(Vectibix™)* administration with 0.9% sodium chloride USP to avoid mixing with other drug products or IV solutions.

* If a patient's actual body weight requires a volume greater than 150 ml infusion, Panitumumab *(Vectibix™)* may be administered over approximately 90 minutes.

AVAILABILITY
Panitumumab *(Vectibix™)* 20mg/mL Concentrate for solution for intravenous infusion: Single-use Type 1 5mL glass vial with elastomeric rubber stopper and aluminum seal with flip-off cap. By 1's.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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