Announcement regarding harshment (safety information) in the Physician Leaflet

הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: 08.03.2015

Name of the product:

שם תכשיר באנגלית: Vectibix 20mg/ml

Registration No's:

מספר רישום: 142923295100

Name of the registration owner:

שם בעל הרישום Amgen Europe B.V.

Current

4.4 Special warnings and precautions for use

Dermatologic reactions and soft tissue toxicity

Dermatologic related reactions, a pharmacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients (approximately 90%) treated with Vectibix (see section 4.8), the majority are mild to moderate in nature. If a patient develops dermatologic reactions that are grade 3 (NCI-CTC/CTCAE) or higher, or that are considered intolerable, the following dose modification is recommended:

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

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Proposed

4.4 Special warnings and precautions for use

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

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מעוצב:רגיל,kepa

עיצב:גופן: 6 נק', סמן

עיצב:גופן: 11 נק', גופן עבור עברית ושפות אחרות: 10 נק'

מעוצב:תאריך

4.8 Undesirable effects

	Adverse reactions				
MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1000**	**Frequency not known***
Infections and infestations	Paronychia[1]	Rash pustular Cellulitis[1] Folliculitis Localised infection	Eye infection Eyelid infection		
Blood and lymphatic system disorders	Anaemia	Leukopenia			
Immune system disorders		Hypersensitivity[1]		Anaphylactic reaction[1]	
Metabolism and nutrition disorders	Hypokalaemia Anorexia Hypomagnesaemia	Hypocalcaemia Dehydration Hyperglycaemia Hypophosphataemia			
Psychiatric disorders	Insomnia	Anxiety			
Nervous system disorders		Headache Dizziness			
Eye disorders	Conjunctivitis	Blepharitis Growth of eyelashes Lacrimation increased Ocular hyperaemia Dry eye Eye pruritus Eye irritation	Eyelid irritation Keratitis[1]	Ulcerative Keratitis[1]	
Cardiac disorders		Tachycardia	Cyanosis		
Vascular disorders		Deep vein thrombosis Hypotension Hypertension Flushing			
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Epistaxis	Bronchospasm Nasal dryness		Interstitial lung disease[3]
Gastrointestinal disorders	Diarrhoea[1] Nausea Vomiting	Rectal haemorrhage Dry mouth Dyspepsia	Chapped lips		
	Abdominal pain Stomatitis Constipation	Aphthous stomatitis Cheilitis Gastrooesophageal reflux disease			
Skin and subcutaneous tissue disorders	Dermatitis acneiform Rash[1,2] Erythema Pruritus Dry skin Skin fissures Acne Alopecia	Palmar-plantar erythrodysaesthesia syndrome Skin ulcer Scab Hypertrichosis Onychoclasis Nail disorder	Angioedema[1] Hirsutism Ingrowing nail Onycholysis	Skin Necrosis[1] Stevens-Johnson syndrome[1] Toxic epidermal necrolysis[1]	
Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity			

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Metabolism and nutrition disorders	Hypokalaemia Anorexia Hypomagnesaemia	Hypocalcaemia Dehydration Hyperglycaemia Hypophosphataemia			
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General disorders and administration site conditions	Fatigue Pyrexia Asthenia Mucosal inflammation Oedema peripheral	Chest pain Pain Chills	Infusion-related reaction[1]		
Investigations	Weight decreased	Blood magnesium decreased			

[1] See section "Description of selected adverse reactions" below
[2] Rash includes common terms of skin toxicity, skin exfoliation, exfoliative rash, rash papular, rash pruritic, rash erythematous, rash generalised, rash macular, rash maculo-papular, skin lesion
[3]See Section 4.4 Pulmonary complications
* Frequency cannot be estimated from the available data

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Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity			
General disorders and administration site conditions	Fatigue Pyrexia Asthenia Mucosal inflammation Oedema peripheral	Chest pain Pain Chills	Infusion-related reaction[1]		
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5. PHARMACOLOGICAL PROPERTIES	**5. PHARMACOLOGICAL PROPERTIES**
5.1 Pharmacodynamic properties	**5.1 Pharmacodynamic properties**
Clinical efficacy as monotherapy	Clinical efficacy as monotherapy
The efficacy of Vectibix as monotherapy in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in open-label, single-arm trials (384 patients) and in two randomised controlled trials versus best supportive care (463 patients) and versus cetuximab (1010 patients).	The efficacy of Vectibix as monotherapy in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in open-label, single-arm trials (~~384~~ 585 patients) and in two randomised controlled trials versus best supportive care (463 patients) and versus cetuximab (1010 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 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 Vectibix at a dose of 6 mg/kg given once every two weeks.	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 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 Vectibix at a dose of 6 mg/kg given once every two weeks.
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 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 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 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* (exon 2) status versus mutant *KRAS* (exon 2) status. *KRAS* mutation status was determined by analysis of archived paraffin embedded tumour tissue.	The study was retrospectively analysed by wild-type *KRAS* (exon 2) status versus mutant *KRAS* (exon 2) status. ~~*KRAS* mutation status was determined by analysis of archived paraffin embedded tumour tissue.~~
Tumour samples obtained from the primary resection of colorectal cancer	Tumour samples obtained from the primary resection of colorectal cancer were

were analysed for the presence of the seven most common activating mutations in the codon 12 and 13 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. The efficacy results from an analysis adjusting for potential bias from unscheduled assessments are shown in the table below. There was no difference in overall survival (OS) seen in either group.

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The efficacy results for the study are presented in the table below.

Wild-type *KRAS* (exon 2) population	**Vectibix** (n = 499)	**Cetuximab** (n = 500)
OS		
Median (months) (95% CI)	10.4 (9.4, 11.6)	10.0 (9.3, 11.0)
Hazard ratio (95% CI)	0.97 (0.84, 1.11)	
PFS		
Median (months) (95% CI)	4.1 (3.2, 4.8)	4.4 (3.2, 4.8)
Hazard ratio (95% CI)	1.00 (0.88, 1.14)	
ORR		
n (%) (95% CI)	22% (18%, 26%)	20% (16%, 24%)
Odds ratio (95% CI)	1.15 (0.83, 1.58)	

CI = confidence interval

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Median (months) (95% CI)	4.1 (3.2, 4.8)	4.4 (3.2, 4.8)
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~~CI = confidence interval~~

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מעוצב:אל תשמור עם הבא

Clinical efficacy in combination with chemotherapy

First-line combination with FOLFOX

The efficacy of 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* (exon 2) status which was evaluable in 93% of the patients.

The efficacy results from the pre-specified final analysis in patients with wild-type *KRAS* (exon 2) mCRC and mutant *KRAS* mCRC are presented in the table below. This table also summarises subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine) and anti-EGFR therapy. The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS treatment effect is unknown.

	First-line mCRC wild-type *KRAS* (exon 2) population		**First-line mCRC mutant *KRAS* (exon 2) population**	
	Vectibix plus FOLFOX (n = 325)	**FOLFOX (n = 331)**	**Vectibix plus FOLFOX (n = 221)**	**FOLFOX (n = 219)**
ORR				
% (95% CI)	57% (51%, 63%)	48% (42%, 53%)	40% (33%, 47%)	41% (34%, 48%)
Odds ratio (95% CI)	1.47 (1.07, 2.04)		0.98 (0.65,1.47)	
Median duration of response (months) (95% CI)	10.9 (9.5, 13.3)	8.8 (7.7, 9.6)	7.4 (5.9, 8.3)	8.0 (6.7, 9.6)

Clinical efficacy in combination with chemotherapy

Among patients with wild-type *RAS* mCRC, PFS, OS, and ORR were improved for subjects receiving panitumumab plus chemotherapy (FOLFOX or FOLFIRI) compared with those receiving chemotherapy alone. Patients with additional *RAS* mutations beyond *KRAS* exon 2 were unlikely to benefit from the addition of panitumumab to FOLFIRI and a detrimental effect was seen with the addition of panitumumab to FOLFOX in these patients. *BRAF* mutations in exon 15 were found to be prognostic of worse outcome. *BRAF* mutations were not predictive of the outcome for panitumumab treatment in combination with FOLFOX or FOLFIRI.

First-line combination with FOLFOX

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	~~**First-line mCRC wild-type *KRAS* (exon 2) population**~~	~~**First-line mCRC mutant *KRAS* (exon 2) population**~~

PFS				
Median (months) (95% CI)	10.0 (9.3, 11.4)	8.6 (7.5, 9.5)	7.4 (6.9, 8.1)	9.2 (8.1, 9.9)
Difference in median (months)	1.4		-1.8	
Hazard ratio (95% CI); p-value	0.80 (0.67, 0.95); p = 0.0092		1.27 (1.04, 1.55); p = 0.0194	
Estimated rate at 12 months (95% CI)	44% (38%, 49%)	32% (27%, 38%)	24% (18%, 30%)	30% (24%, 37%)
On-treatment PFS hazard ratio (95% CI)[a]; p-value	0.77 (0.63, 0.92); p = 0.0054		1.32 (1.05, 1.65); p = 0.0158	
TTP				
Median (months) (95% CI)	10.8 (9.4,12.5)	9.2 (7.7, 10.0)	7.5 (7.3, 8.9)	9.2 (8.0, 9.7)
Hazard ratio (95% CI)	0.76 (0.62, 0.92)		1.24 (0.98,1.58)	
OS				
Median (months) (95% CI)	23.9 (20.3, 27.7)	19.7 (17.6, 22.7)	15.5 (13.1, 17.6)	19.2 (16.5, 21.7)
Difference in median (months)	4.2		-3.7	
Hazard ratio (95% CI); p-value	0.88 (0.73, 1.06); p = 0.1710		1.17 (0.95, 1.45); p = 0.1444	
Estimated rate at 24 months (95% CI)	50% (44%, 55%)	41% (36%, 47%)	29% (23%, 36%)	39% (32%, 45%)

	~~Vectibix plus FOLFOX (n = 325)~~	~~FOLFOX (n = 331)~~	~~Vectibix plus FOLFOX (n = 221)~~	~~FOLFOX (n = 219)~~
~~**ORR**~~				
~~% (95% CI)~~	~~57% (51%, 63%)~~	~~48% (42%, 53%)~~	~~40% (33%, 47%)~~	~~41% (34%, 48%)~~
~~Odds ratio (95% CI)~~	~~1.47 (1.07, 2.04)~~		~~0.98 (0.65,1.47)~~	
~~Median duration of response (months) (95% CI)~~	~~10.9 (9.5, 13.3)~~	~~8.8 (7.7, 9.6)~~	~~7.4 (5.9, 8.3)~~	~~8.0 (6.7, 9.6)~~
~~**PFS**~~				
~~Median (months) (95% CI)~~	~~10.0 (9.3, 11.4)~~	~~8.6 (7.5, 9.5)~~	~~7.4 (6.9, 8.1)~~	~~9.2 (8.1, 9.9)~~
~~Difference in median (months)~~	~~1.4~~		~~-1.8~~	
~~Hazard ratio (95% CI); p-value~~	~~0.80 (0.67, 0.95); p = 0.0092~~		~~1.27 (1.04, 1.55); p = 0.0194~~	
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~~On-treatment PFS hazard ratio (95% CI)[a]; p-value~~	~~0.77 (0.63, 0.92); p = 0.0054~~		~~1.32 (1.05, 1.65); p = 0.0158~~	
~~**TTP**~~				
~~Median (months) (95% CI)~~	~~10.8 (9.4,12.5)~~	~~9.2 (7.7, 10.0)~~	~~7.5 (7.3, 8.9)~~	~~9.2 (8.0, 9.7)~~
~~Hazard ratio (95% CI)~~	~~0.76 (0.62, 0.92)~~		~~1.24 (0.98,1.58)~~	
~~**OS**~~				
~~Median (months) (95% CI)~~	~~23.9 (20.3, 27.7)~~	~~19.7 (17.6, 22.7)~~	~~15.5 (13.1, 17.6)~~	~~19.2 (16.5, 21.7)~~

Subjects receiving chemotherapy after the protocol treatment phase – (%)	59%	65%	60%	70%
Subjects receiving anti-EGFR therapy after the protocol treatment phase - (%)	13%	25%	7%	16%

CI = confidence interval

[a] Censoring death events if they occurred > 60 days after the last evaluable tumour assessment or randomization date, whichever is later.

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

	ECOG PS of 0 or 1 (n = 616)		**ECOG 2 PS (n = 40)**	
	Vectibix plus FOLFOX (n = 305)	**FOLFOX (n = 311)**	**Vectibix plus FOLFOX (n = 20)**	**FOLFOX (n = 20)**
Median PFS (months)	10.8	8.7	4.8	7.5
Difference in median (months)	2.1		-2.7	
PFS Hazard ratio (95% CI); p-value	0.76 (0.64, 0.91); p = 0.0022		1.80 (0.88, 3.69); p = 0.1060	
Median OS (months)	25.8	20.6	7.0	11.7
Difference in median (months)	5.2		-4.7	
OS Hazard ratio	0.84		1.59	
~~Difference in median (months)~~	~~4.2~~		~~-3.7~~	
~~Hazard ratio (95% CI); p-value~~	~~0.88 (0.73, 1.06); p = 0.1710~~		~~1.17 (0.95, 1.45); p = 0.1444~~	
~~Estimated rate at 24 months (95% CI)~~	~~50% (44%, 55%)~~	~~41% (36%, 47%)~~	~~29% (23%, 36%)~~	~~39% (32%, 45%)~~
~~Subjects receiving chemotherapy after the protocol treatment phase – (%)~~	~~59%~~	~~65%~~	~~60%~~	~~70%~~
~~Subjects receiving anti-EGFR therapy after the protocol treatment phase – (%)~~	~~13%~~	~~25%~~	~~7%~~	~~16%~~

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~~Median PFS (months)~~	~~10.8~~	~~8.7~~	~~4.8~~	~~7.5~~
~~Difference in median (months)~~	~~2.1~~		~~-2.7~~	
~~PFS Hazard ratio (95% CI); p-value~~	~~0.76 (0.64, 0.91); p = 0.0022~~		~~1.80 (0.88, 3.69); p = 0.1060~~	
~~Median OS~~	~~25.8~~	~~20.6~~	~~7.0~~	~~11.7~~

(95% CI); p-value	(0.69, 1.02); p = 0.0735	(0.80, 3.16); p = 0.1850

CI = confidence interval; PS = Performance Status

In a post-hoc analysis, the complete resection rate in wild-type KRAS subjects who had metastases to the liver only at baseline was 27.9% (95% CI: 17.2, 40.8) in the panitumumab plus FOLFOX arm and 17.5% (95% CI: 8.8, 29.9) in the FOLFOX alone arm.

Predefined retrospective subset analysis of efficacy and safety by RAS (ie, 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. Patient tumour samples with wild-type *KRAS* exon 2 (codons 12/13) status were tested for additional *RAS* mutations in *KRAS* exon 3 (codons 61) and exon 4 (codons 117/146) and *NRAS* exon 2 (codons 12/13), exon 3 (codon 61), and exon 4 (codons 117/146). The incidence of these additional *RAS* mutations in the wild-type *KRAS* exon 2 population was approximately 16%.

Results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC from the primary analysis are presented in the table below.

	Vectibix plus FOLFOX (months) Median (95% CI)	**FOLFOX (months) Median (95% CI)**	**Difference (months)**	**Hazard ratio (95% CI)**
Wild-type *RAS* population				
PFS	10.1 (9.3, 12.0)	7.9 (7.2, 9.3)	2.2	0.72 (0.58, 0.90)
OS	26.0 (21.7, 30.4)	20.2 (17.7, 23.1)	5.8	0.78 (0.62, 0.99)

~~(months)~~

~~Difference in median (months)~~ ~~5.2~~ ~~4.7~~

~~OS Hazard ratio (95% CI); p-value~~ ~~0.84 (0.69, 1.02); p = 0.0735~~ ~~1.59 (0.80, 3.16); p = 0.1850~~

~~CI = confidence interval; PS = Performance Status~~

~~In a post-hoc analysis, the complete resection rate in wild-type KRAS subjects who had metastases to the liver only at baseline was 27.9% (95% CI: 17.2, 40.8) in the panitumumab plus FOLFOX arm and 17.5% (95% CI: 8.8, 29.9) in the FOLFOX alone arm.~~

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Results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC ~~from the primary analysis~~ are presented in the table below.

	Vectibix plus FOLFOX (months) Median (95% CI)	**FOLFOX (months) Median (95% CI)**	**Difference (months)**	**Hazard ratio (95% CI)**
Wild-type *RAS* population				
PFS	10.1 (9.3, 12.0)	7.9 (7.2, 9.3)	2.2	0.72 (0.58, 0.90)

Mutant *RAS* population				
PFS	7.3 (6.3, 7.9)	8.7 (7.6, 9.4)	-1.4	1.31 (1.07, 1.60)
OS	15.6 (13.4, 17.9)	19.2 (16.7, 21.8)	-3.6	1.25 (1.02, 1.55)

CI = confidence interval

Additional mutations in *KRAS* and *NRAS* at exon 3 (codon 59) were subsequently identified (n = 7). An exploratory analysis showed similar results to those in the previous table.

In these analyses, *BRAF* mutations in exon 15 were found to be prognostic of worse outcome but not predictive of negative outcome for panitumumab treatment.

Second-line combination with FOLFIRI

The efficacy of 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* (exon 2) status which was evaluable in 91% of the patients.

The efficacy results in patients with wild-type *KRAS* mCRC and mutant *KRAS* mCRC are presented in the table below. Eighteen (18) % (n = 115) of patients with wild-type *KRAS* mCRC had been exposed to prior bevacizumab treatment. PFS and Response Rate were similar regardless of prior bevacizumab treatment.

The table below also summarises subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine) and anti-EGFR therapy. The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS

OS	26.0 (21.7, 30.4)	20.2 (17.7, 23.1)	5.8	0.78 (0.62, 0.99)
Mutant *RAS* population				
PFS	7.3 (6.3, 7.9)	8.7 (7.6, 9.4)	-1.4	1.31 (1.07, 1.60)
OS	15.6 (13.4, 17.9)	19.2 (16.7, 21.8)	-3.6	1.25 (1.02, 1.55)

~~CI = confidence interval~~

Additional mutations in *KRAS* and *NRAS* at exon 3 (codon 59) were subsequently identified (n = 7). An exploratory analysis showed similar results to those in the previous table.

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A predefined retrospective subset analysis of 586 patients of the 597 patients with wild-type *KRAS* (exon 2) mCRC was performed, where tumour samples from these patients were tested for additional *RAS* and *BRAF* mutations as previously described. The *RAS/BRAF* ascertainment was 85% (1014 of 1186 randomized patients). 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 in

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treatment effect is unknown.

	Second-line mCRC wild-type *KRAS* (exon 2) population		Second-line mCRC mutant *KRAS* (exon 2) population	
	Vectibix plus FOLFIRI (n = 303)	FOLFIRI (n = 294)	Vectibix plus FOLFIRI (n = 238)	FOLFIRI (n = 248)
ORR				
% (95% CI)	36% (31%, 42%)	10 % (7%, 14%)	13% (9%, 18%)	15% (11%, 20%)
Odds ratio (95% CI)	5.50 (3.32, 8.87)		0.93 (0.53, 1.63)	
Median duration of response (months) (95% CI)	7.6 (6.5, 9.4)	6.6 (5.7, 10.9)	5.8 (5.5, 7.4)	5.3 (4.6, 7.9)
PFS				
Median (months) (95% CI)	6.7 (5.8, 7.4)	4.9 (3.8, 5.5)	5.3 (4.2, 5.7)	5.4 (4.0, 5.6)
Difference in median (months)	1.8		-0.1	
Hazard ratio (95% CI); p-value	0.82 (0.69, 0.97); p = 0.0231		0.95 (0.78, 1.14); p = 0.5611	
Estimated rate at six months (95% CI)	54% (48%, 60%)	39% (33%, 44%)	40% (34%, 47%)	38% (32%, 44%)
On-treatment PFS hazard ratio (95%CI) [a]; p-value	0.73 (0.60, 0.88); p = 0.001		0.89 (0.72, 1.10); p = 0.2951	
TTP				
Median (months) (95% CI)	7.3 (6.0, 7.5)	5.3 (3.9, 5.7)	5.5 (4.5, 5.7)	5.5 (4.8, 5.7)
Hazard ratio (95% CI)	0.72 (0.59, 0.88)		0.89 (0.71, 1.11)	
OS				
Median (months) (95% CI)	14.5 (13.0, 16.1)	12.5 (11.2, 14.2)	11.8 (10.4, 13.3)	11.1 (10.3, 12.4)
Difference in median (months)	2.0		0.7	
Hazard ratio (95% CI); p-value	0.92 (0.78, 1.10); p = 0.3660		0.93 (0.77, 1.13); p = 0.4815	
Estimated rate at 12 months (95% CI)	59% (53%, 64%)	53% (47%, 59%)	49% (42%, 55%)	45% (39%, 51%)
Estimated rate at 18 months (95% CI)	40% (34%, 45%)	33% (27%, 39%)	26% (21%, 32%)	24% (19%, 29%)
Subjects receiving chemotherapy after the protocol treatment phase – (%)	53%	50%	48%	55%

patients with wild-type *RAS* mCRC and mutant *RAS* mCRC are shown in the below table.

	Vectibix plus FOLFIRI (months) Median (95% CI)	FOLFIRI (months) Median (95% CI)	Hazard ratio (95% CI)
Wild-type *RAS* population			
PFS	6.4 (5.5, 7.4)	4.6 (3.7, 5.6)	0.701 (0.54, 0.91)
OS	16.2 (14.5, 19.7)	13.9 (11.9, 16.0)	0.81 (0.63, 1.02)
Mutant *RAS* population			
PFS	4.8 (3.7, 5.5)	4.0 (3.6, 5.5)	0.86 (0.70, 1.05)
OS	11.8 (10.4, 13.1)	11.1 (10.2, 12.4)	0.91 (0.76, 1.10)

~~The efficacy results in patients with wild-type *KRAS* mCRC and mutant *KRAS* mCRC are presented in the table below. Eighteen (18) % (n = 115) of patients with wild-type *KRAS* mCRC had been exposed to prior bevacizumab treatment. PFS and Response Rate were similar regardless of prior bevacizumab treatment.~~

~~The table below also summarises subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine) and anti-EGFR therapy. The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS treatment effect is unknown.~~

	~~Second-line mCRC wild-type *KRAS* (exon 2) population~~		~~Second-line mCRC mutant *KRAS* (exon 2) population~~	
	~~Vectibix plus FOLFIRI (n = 303)~~	~~FOLFIRI (n = 294)~~	~~Vectibix plus FOLFIRI (n = 238)~~	~~FOLFIRI (n = 248)~~
~~**ORR**~~				
~~% (95% CI)~~	~~36% (31%, 42%)~~	~~10 % (7%, 14%)~~	~~13% (9%, 18%)~~	~~15% (11%, 20%)~~
~~Odds ratio (95% CI)~~	~~5.50 (3.32, 8.87)~~		~~0.93 (0.53, 1.63)~~	

Subjects receiving anti-EGFR therapy after the protocol treatment phase - (%)	13%	34%	9%	32%

CI = confidence interval
[a] Censoring death events if they occurred > 60 days after the last evaluable tumour assessment or randomisation date, whichever is later.

First-line combination with 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* (exon 2) 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

~~Median duration of response (months) (95% CI)~~	~~7.6 (6.5, 9.4)~~	~~6.6 (5.7, 10.9)~~	~~5.8 (5.5, 7.4)~~	~~5.3 (4.6, 7.9)~~
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~~Hazard ratio (95% CI); p-value~~	~~0.82 (0.69, 0.97); p = 0.0231~~		~~0.95 (0.78, 1.14); p = 0.5611~~	
~~Estimated rate at six months (95% CI)~~	~~54% (48%, 60%)~~	~~39% (33%, 44%)~~	~~40% (34%, 47%)~~	~~38% (32%, 44%)~~
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~~TTP~~				
~~Median (months) (95% CI)~~	~~7.3 (6.0, 7.5)~~	~~5.3 (3.9, 5.7)~~	~~5.5 (4.5, 5.7)~~	~~5.5 (4.8, 5.7)~~
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~~Subjects receiving chemotherapy after the protocol treatment phase - (%)~~	~~53%~~	~~50%~~	~~48%~~	~~55%~~
~~Subjects receiving anti-EGFR therapy after the protocol treatment phase - (%)~~	~~13%~~	~~34%~~	~~9%~~	~~32%~~

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bevacizumab is associated with an unfavourable benefit-to-risk profile irrespective of tumour *KRAS* mutational status. This medicinal product has been authorised under a “conditional approval” scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency (EMA) will review new information on this medicinal product at least every year and this SPC will be updated as necessary.	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* (exon 2) 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. ~~This medicinal product has been authorised under a “conditional approval” scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency (EMA) will review new information on this medicinal product at least every year and this SPC will be updated as necessary.~~

מעוצב:אל תשנה רווח בין טקסט לטיני לאסיאתי, אל תשנה רווח בין טקסט אסיאתי למספרים

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.