Announcement regarding harshment (safety information) in the Physician Leaflet

הודעה על החמרה (מידע בטיחות) בעלון לרופא

08.03.2015 : תאריך

Name of the product:

Vectibix 20mg/ml שם תכשיר באנגלית:

Registration No's:

מספר רישום: 142923295100

Name of the registration owner:

Amgen Europe B.V. שם בעל הרישום

Current				Proposed					
	varnings and prec	autions for use			varnings and prec	autions for use			
Dermatologic re	eactions and soft tis	sue toxicity		Dermatologic reactions and soft tissue toxicity					
epidermal grow nearly all patien 4.8), the majorit dermatologic re	th factor receptor (its (approximately ty are mild to mode actions that are gra	harmacologic effect of EGFR) inhibitors, are 90%) treated with Veo rate in nature. If a pai de 3 (NCI-CTC/CTC following dose modit	experienced with ctibix (see section tient develops AE) or higher, or	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:					
$\frac{Occurrence}{of skin}$ $\frac{symptom(s):}{\geq grade 3^{1}}$	Administration of Vectibix	Outcome	Dose regulation	$\frac{Occurrence}{of skin}$ $\frac{symptom(s):}{\geq grade 3^{1}}$	Administration of Vectibix	Outcome	Dose regulation		
Initial occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 100% of original dose	Initial occurrence	Hold-Withhold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 100% of original dose		
At the	Hold 1 or 2	Not recovered Improved (< grade	Discontinue Continuing	At the	Hold-Withhold	Not recovered Improved (< grade	Discontinue Continuing		
second occurrence	doses	3) Not recovered	infusion at 80% of original dose Discontinue	second occurrence	1 or 2 doses	3) Not recovered	infusion at 80% of original dose Discontinue		
At the third occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 60% of original dose	At the third occurrence	Hold-Withhold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 60% of original dose		
At the fourth occurrence	Discontinue	Not recovered -	Discontinue -	At the fourth occurrence	Discontinue	Not recovered	Discontinue -		
	equal to grade 3 is	defined as severe or	life-threatening		equal to grade 3 is	defined as severe or	life-threatening		

	4.8 Unde	sirable effec	ts				4.8 Undesi	rable effects				
			Adver	se reactions					Adver	e 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*	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			Infections and infestations	Paronychia ¹	Rash pustular Cellulitis ¹ Urmary tract infection Folliculitis	Eye infection Eyelid infection		
	Blood and lymphatic system disorders	Anaemia	Leukopenia				Blood and lymphatic system	Anaemia	Localised infection Leukopenia			
	Immune system disorders Metabolism and	Hypokalaemia	Hypersensitivity ¹ Hypocalcaemia		Anaphylactic reaction ¹		disorders Immune system disorders		Hypersensitivity ¹		Anaphylactic reaction ¹	
	nutrition disorders	Anorexia Hypomagnesaemia	Dehydration Hyperglycaemia Hypophosphataemia				Metabolism and nutrition disorders	Hypokalaemia Anorexia Hypomagnesaemia	Hypocalcaemia Dehydration Hyperglycaemia			
	Psychiatric disorders Nervous system	Insomnia	Anxiety Headache				Psychiatric disorders	Insomnia	Hypophosphataemia Anxiety			
	disorders Eye disorders	Conjunctivitis	Dizziness Blepharitis	Eyelid irritation	Ulcerative		Nervous system disorders		Headache Dizziness			
kepa,מעוצב:רגיל	Cardiac disorders		Growth of eyelashes Lacrimation increased Ocular hyperaemia Dry eye Eye pruritus Eye irritation Tachycardia	Keratitis ¹	Keratitis ¹		Eye disorders	Conjunctivitis	Blepharitis Growth of eyelashes Lacrimation increased Ocular hyperaemia Dry eye Eye pruritus Eye irritation	Eyelid irritation Keratitis ¹	Ulcerative	
				Cyanosis			Cardiac disorders		Tachycardia	Cyanosis		
	Vascular disorders	-	Deep vein thrombosis Hypotension Hypertension Flushing				Vascular disorders		Deep vein thrombosis Hypotension Hypertension			
	Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Epistaxis	Bronchospasm Nasal dryness		Interstitial lung disease ³	Respiratory, thoracic and mediastinal	Dyspnoea Cough	Flushing Pulmonary embolism Epistaxis	Bronchospasm Nasal dryness		Interstitial lung disease
	Gastrointestinal disorders	Diarrhoea ¹ Nausea Vomiting	Rectal haemorrhage Dry mouth Dyspepsia	Chapped lips			disorders Gastrointestinal disorders	Diarrhoea ¹ Nausea	Rectal haemorrhage Dry mouth	Chapped lips Dry lips		
עיצב:גופן: 6 נק', סמן עיצב:גופן: 11 נק', גופן עבור עברית ושפות אחרות: (Abdominal pain Stomatitis Constipation	Aphthous stomatitis Cheilitis Gastrooesophageal reflux disease					Vomiting Abdominal pain Stomatitis Constipation	Dyspepsia Aphthous stomatitis Cheilitis Gastrooesophageal reflux			
מעוצב:תאריך	Skin and subcutaneous	Dermatitis acneiform	Palmar-plantar erythrodysaesthesia	Angioedema ¹ Hirsutism	Skin Necrosis ¹		Skin and	Dermatitis	disease Palmar-plantar	Angioedema ¹	Skin	
	tissue disorders	Rash ^{1,2} Erythema Pruritus Dry skin Skin fissures Acne Alopecia	syndrome Skin ulcer Scab Hypertrichosis Onychoclasis Nail disorder	Ingrowing nail Onycholysis	Stevens- Johnson syndrome ¹ Toxic epidermal necrolysis ¹		subcutaneous tissue disorders	acneiform Rash ^{1,2} Erythema Pruritus Dry skin Skin fissures Acne	erythrodysaesthesia syndrome Skin ulcer Scab Hypertrichosis Onychoclasis Nail disorder	Hirsutism Ingrowing nail Onycholysis	Necrosis ¹ Stevens- Johnson syndrome ¹ Toxic epidermal necrolysis ¹	
	Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity					Alopecia	<u>Hyperhidrosis</u> Dermatitis		-	

General disorders and administration site conditions	Fatigue Pyrexia Asthenia	Chest pain Pain Chills	Infusion-related reaction ¹			Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity				
	Mucosal inflammation Oedema peripheral					General disorders and administration site conditions	Fatigue Pyrexia Asthenia	Chest pain Pain Chills	Infusion-related reaction1]
Investigations	Weight decreased	Blood magnesium decreased eactions" below					Mucosal inflammation Oedema peripheral					
	on terms of skin toxicity lar, rash maculo-papula	, skin exfoliation, exfoliative	rash, rash papular, ra	sh pruritic, rash eryt	thematous, rash	Investigations	Weight decreased	Blood magnesium decreased]
	estimated from the avail	able data				² Rash includes commor rash macular, rash macu ³ See Section 4.4 Pulmor	lo-papular, skin lesion	kin exfoliation, exfoliative rash	, rash papular, rash pru	rritic, rash erythem	atous, rash general	ised,

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 <i>KRAS</i> (exon 2) status versus mutant <i>KRAS</i> (exon 2) status. <i>KRAS</i> mutation status was determined by analysis of archived paraffin embedded tumour tissue.	The study was retrospectively analysed by wild-type <i>KRAS</i> (exon 2) status versus mutant <i>KRAS</i> (exon 2) status. <i>KRAS</i> 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.

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Wild-type KRAS	Vectibix	Cetuximab		
(exon 2) population	(n = 499)	(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 (0.8	34, 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 (0.8	83, 1.58)		
CI = confidence interval				
•••••				

(exon 2) population $(n = 499)$ $(n = 500)$ OSMedian (months) (95% $10.4 (9.4, 11.6)$ $10.0 (9.3, 11)$ Hazard ratio (95% CI) $0.97 (0.84, 1.11)$ PFS Median (months) (95% $4.1 (3.2, 4.8)$ $4.4 (3.2, 4.8)$ Hazard ratio (95% CI) $1.00 (0.88, 1.14)$
CI) 10.4 (9.4, 11.6) 10.0 (9.3, 11) Hazard ratio (95% CI) 0.97 (0.84, 1.11) PFS Median (months) (95% 4.1 (3.2, 4.8) 4.4 (3.2, 4.8) Hazard ratio (95% CI) 1.00 (0.88, 1.14)
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	Clinical efficacy in con	nbination with	n chemothera	ру		Clinical efficacy in combination with chemotherapy
מעוצב:אל תשמור עם הבא	First-line combination The efficacy of Vectibi FU), and leucovorin (F trial of 1183 patients w progression-free surviv survival (OS), objective progression (TTP), and analysed by tumour KF •the patients.	Y tion with oxa evaluated in th the primar er key endpo e (ORR), tim esponse. The	liplatin, 5-flu a randomise y endpoint of ints included e to response study was pr	d, controlled the overall b, time to ospectively	Among patients with wild-type <i>RAS</i> 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 <i>RAS</i> mutations beyond <i>KRAS</i> 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. <i>BRAF</i> mutations in exon 15 were found to be prognostic of worse outcome. <i>BRAF</i> mutations were not predictive of the outcome for panitumumab treatment in combination with FOLFOX or FOLFIRI.	
	The efficacy results from the pre-specified final analy wild-type <i>KRAS</i> (exon 2) mCRC and mutant <i>KRAS</i> m the table below. This table also summarises subseque (irinotecan, oxaliplatin, or fluoropyrimidine) and antirole of subsequent anti-EGFR therapy or chemotherap OS treatment effect is unknown.				presented in therapy nerapy. The	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 <i>KRAS</i>
		First-line m wild-type <i>K</i> 2) populatio	RAS (exon	First-line mCRC mutant <i>KRAS</i> (exon 2) population		(exon 2) status which was evaluable in 93% of the patients.
		Vectibix plus FOLFOX (n = 325)	FOLFOX (n = 331)	Vectibix plus FOLFOX (n = 221)	FOLFOX (n = 219)	type <i>KRAS</i> (exon 2) mCRC and mutant <i>KRAS</i> 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
	ORR % (95% CI)	57% (51%,	48% (42%,	40% (33%,	41% (34%,	<mark>effect is unknown.</mark>
	Odds ratio (95% CI) Median duration of response (months) (95% CI)	63%) 1.47 (1.07, 2 10.9 (9.5, 13.3)	53%) 2.04) 8.8 (7.7, 9.6)	47%) 0.98 (0.65, 7.4 (5.9, 8.3)	48%) 1.47) 8.0 (6.7, 9.6)	First-line mCRCFirst-line mCRCwild type KR-1S (exon 2) populationmutant KR-1S (exon 2) population

PFS						<mark>Vectibix</mark>	FOLFOX	<mark>Veetibix</mark>	FOL
Median (months)	10.0 (9.3,	8.6 (7.5,	7.4 (6.9,	9.2 (8.1,		<mark>plus</mark>	(n = 331)	<mark>plus</mark>	<mark>(n = 2</mark>
(95% CI)	11.4)	9.5)	8.1)	9.9)		<mark>FOLFOX</mark>		FOLFOX	
Difference in	1.4		-1.8			(n = 325)		(n = 221)	
median (months)					<mark>ORR</mark>				
Hazard ratio (95%	0.80 (0.67,	0.95);	1.27 (1.04	, 1.55);	<mark>9/0</mark>	<mark>57%</mark>	<mark>48%</mark>	<mark>40%</mark>	<mark>41%</mark>
CI); p-value	p = 0.0092		p = 0.0194		<mark>(95%-CI)</mark>	(51%, 63%)	<mark>(42%,</mark>	(33%,	(34%,
Estimated rate at 12	44%	32%	24%	30%			<mark>53%)</mark>	<mark>47%)</mark>	48%)
months (95% CI)	(38%,	(27%,	(18%,	(24%,	<mark>Odds ratio (95% CI)</mark>	<mark>1.47 (1.07, 2</mark>		0.98 (0.65,	
	49%)	38%)	30%)	37%)	Median duration of	10.9 (9.5,	<mark>8.8 (7.7,</mark>	<mark>7.4 (5.9,</mark>	<mark>8.0 (6</mark> .
On-treatment PFS	0.77 (0.63,	0.92);	1.32 (1.05		<mark>response (months)</mark>	<mark>13.3)</mark>	<mark>9.6)</mark>	<mark>8.3)</mark>	<mark>9.6)</mark>
hazard	p = 0.0054		p = 0.0158	3	(95% CI)				
ratio (95% CI) ^a ; p-					PFS				
value					<mark>Median (months)</mark>	<mark>10.0 (9.3,</mark>	<mark>8.6 (7.5,</mark>	<mark>7.4 (6.9,</mark>	<mark>9.2 (8</mark> .
ТТР	1	1	1		<mark>(95%-CI)</mark>	<mark>11.4)</mark>	<mark>9.5)</mark>	<mark>8.1)</mark>	<mark>9.9)</mark>
Median (months)	10.8	9.2 (7.7,	7.5 (7.3,	9.2 (8.0,	<mark>Difference in median</mark>	<mark>1.4</mark>		<mark>-1.8</mark>	
(95% CI)	(9.4,12.5)	10.0)	8.9)	9.7)	(months)				
Hazard ratio (95%	0.76 (0.62,	0.92)	1.24 (0.98	,1.58)	<mark>Hazard ratio (95%</mark>	0.80 (0.67, 0	.95);	1.27 (1.04,	1.55);
CI)					CI); p-value	р — 0.0092		p = 0.0194	
OS	1		1		Estimated rate at 12	<mark>44%</mark>	<mark>32%</mark>	<mark>24%</mark>	<mark>30%</mark>
Median (months)	23.9	19.7	15.5	19.2	months (95% CI)	<mark>(38%, 49%)</mark>	(27%,	(18%,	(24%,
(95% CI)	(20.3,	(17.6,	(13.1,	(16.5,			38%)	<mark>30%)</mark>	<mark>37%)</mark>
	27.7)	22.7)	17.6)	21.7)	On treatment PFS	0.77 (0.63, 0	.92);	1.32 (1.05,	1.65);
Difference in	4.2		-3.7		hazard	<mark>р = 0.0054</mark>		<mark>р = 0.0158</mark>	
median (months)	0.00 (0.75	1.0.0	1 1 - (0		ratio (95% CI) ; p-				
Hazard ratio (95%	0.88 (0.73,	1.06);	1.17 (0.95		value			1	
CI); p-value	p = 0.1710	110/	p = 0.1444		TTP	10.0			
Estimated rate at 24	50%	41%	29%	39%	Median (months)	<mark>10.8</mark> (0.4.12.5)	9.2 (7.7,	7.5 (7.3,	<mark>9.2 (8</mark> 0.7)
months	(44%,	(36%,	(23%,	(32%,	(95% CI)	(). 1,12.2)	10.0)	8.9)	<u></u>
(95% CI)	55%)	47%)	36%)	45%)	Hazard ratio (95% CI)	0.76 (0.62, 0	.92)	1.24 (0.98,	1.58)
					OS		10.5	1.5.5	10.0
					Median (months)	23.9	<mark>19.7</mark>	15.5	<u>19.2</u>
					<mark>(95% CI)</mark>	(20.3, 27.7)	(17.6,	(13.1,	(<u>16.5</u> ,
							<mark>22.7)</mark>	<mark>17.6)</mark>	<mark>21.7)</mark>

Subjects receiving	59%	65%	60%	70%	Difference in mediar	<mark>t 4.2</mark>		<mark>-3.7</mark>	
chemotherapy after					(months)				
the protocol					Hazard ratio (95%	<mark>0.88 (0.73</mark>	, 1.06);	<mark>1.17 (0.95</mark>	<mark>, 1.45);</mark>
treatment phase –					CI); p-value	<mark>р – 0.1710</mark>)	р — 0.144 -	<mark>4</mark>
(%)					Estimated rate at 24	<mark>50%</mark>	<mark>41%</mark>	<mark>29%</mark>	<mark>39%</mark>
Subjects receiving	13%	25%	7%	16%	months	<mark>(44%, 55</mark> %		<mark>(23%,</mark>	<mark>(32%,</mark>
anti-EGFR therapy					<mark>(95%-CI)</mark>		<mark>47%)</mark>	<mark>36%)</mark>	<mark>45%)</mark>
after the protocol					Subjects receiving	<mark>59%</mark>	<mark>65%</mark>	<mark>60%</mark>	<mark>70%</mark>
treatment phase -					chemotherapy after				
(%)					the protocol				
CI = confidence inte					t reatment phase (%	·/			
^a Censoring death ev				ast evaluable	Subjects receiving	<mark>13%</mark>	<mark>25%</mark>	<mark>7%</mark>	<mark>16%</mark>
tumour assessment o	or randomizati	on date, which	hever is later.		anti-EGFR therapy				
					after the protocol	_			
The results of an exp					t reatment phase (%	/			
in subjects with wild	l-type KRAS (exon 2) mCR	C are shown b	below:	CI = confidence interv				
	ECOCID	7 60 1	ECOCA		*Censoring death even				evaluable
	ECOG PS (n =		ECOG 2	PS $(n = 40)$	tumour assessment or	randomization	date, whichev	'er 15 later.	
	Vectibix	FOLFOX	Vectibix	FOLFOX	The results of an expl	protory coverio	to apply sis acc	ording to EC	OG status in
	plus	(n = 311)	plus	(n = 20)	subjects with wild typ				oo status m
	FOLFOX	(11 511)	FOLFOX	(11 20)	subjects with whattyp	e Killib (exon	2) merce are	Shown below.	
	(n = 305)		(n = 20)			ECOC PS	offor 1	FCOC 2	PS(n - 40)
Median PFS	10.8	8.7	4.8	7.5		(n=			10(11 40)
(months)	10.0	0.,		,		Vectibix	FOLEOX	Vectibix	FOLFOX
Difference in	2.	.1		2.7		plus	(n - 311)		$\frac{(n-20)}{(n-20)}$
median (months)	2			,		FOLFOX		FOLFOX	(ii 20)
PFS Hazard ratio	0.1	76	1	.80		$\frac{102101}{(n-305)}$		$\frac{101101}{(n-20)}$	
(95% CI); p-	(0.64, 0.91)); p = 0.1060	Median PFS	10.8	<mark>8.7</mark>	4.8	7.5
(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		, P 0.0022	0.00, 5.07	"r 0.1000		10.0	0.7	T. 0	1.0

(months)

Median OS

Difference in

median (months)

PFS Hazard ratio

(95% CI); p-value

2.1

<mark>0.76</mark>

(0.64, 0.91); p = 0.0022

20.6

25.8

-2.7

1.80

(0.88, 3.69); p = 0.1060

11.7

7.0

value

Median OS

Difference in

median (months) OS Hazard ratio

(months)

25.8

5.2

0.84

20.6

7.0

11.7

-4.7

1.59

	; p- (0.69	9, 1.02); $p = 0.07$	(0.80, 3.1	6); p = 0.1850	(months)	-					
value					Difference i		<mark>5.2</mark>		<mark>-4.7</mark>		
I = confide	ence interval; PS =	= Performance Sta	tus		median (me	/			_		
1	1	1		VDAC	OS Hazard		<mark>0.84</mark>		<mark>1.59</mark>		
		complete resections to the liver on the live			(95% CI); p		, 1.02); p = 0.0	(0.00, 5.)	16); p = 0.185(
		umumab plus FC			CI = confiden	<mark>ce interval; PS = P</mark> o	erformance Statu	<mark>e</mark>			
	.9) in the FOLF			17.570 (9570	In a post hos	analysis the cor	nulate resection	n rate in wild-type	KPAS subject		
. 0.0, 27.								ine was 27.9% (9:			
Predefined	l retrospective su	ubset analysis of	efficacy and saf	etv bv RAS (ie,	$\frac{40.8}{100}$ in the r	anitumumah plu	s FOLFOX arm	and 17.5% (95%)	CI: 8.8. 29.9)		
		BRAF biomarke			the FOLFOX						
		subset analysis of						fficacy and safety	by RAS (ie,		
		AS (exon 2) mCl			KRAS and N	RAS) and RAS/Bi	RAF biomarker	status			
		type KRAS exon									
		nutations in KRA nd NRAS exon 2				A predefined retrospective subset analysis of 641 patients of the 656 patients $(4 - 1)^{1/2} = (2 - 1)^{1/2}$					
		dons 117/146). 7			with wild-type <i>KRAS</i> (exon 2) mCRC was performed. Patient tumour samples with wild-type <i>KRAS</i> exon 2 (codons 12/13) status were tested for additional <i>RAS</i> mutations in <i>KRAS</i> exon 3 (codons 61) and exon 4 (codons 117/146) and						
RAS mutati	ions in the wild-	type KRAS exon			RAS mutation	ns in KRAS exon	3 (codons 61) a	and exon 4 (codor	ns 117/146) and		
	ions in the wild-				RAS mutation NRAS exon 2	ns in <i>KRAS</i> exon 2 (codons 12/13),	3 (codons 61) a exon 3 (codon	and exon 4 (codor 61), and exon 4 (ns 117/146) and codons 117/140		
RAS mutati approximat Results in p	ions in the wild- tely 16%. patients with wil	type <i>KRAS</i> exon ld-type <i>RAS</i> mCI	2 population wa	as	RAS mutation NRAS exon 2 and BRAF ex	ns in <i>KRAS</i> exon 2 (codons 12/13), xon 15 (codon 60	3 (codons 61) a exon 3 (codon <u>0)</u> . The inciden	and exon 4 (codor	ns 117/146) and codons 117/140 onal <i>RAS</i>		
RAS mutati approximat Results in p	ions in the wild- tely 16%. patients with wil	type KRAS exon	2 population wa	as	RAS mutation NRAS exon 2 and BRAF ex mutations in	ns in <i>KRAS</i> exon 2 (codons 12/13), xon 15 (codon 60 the wild-type <i>KR</i>	3 (codons 61) a exon 3 (codon 0). The inciden AS exon 2 popu	and exon 4 (codor 61), and exon 4 (ice of these additi ulation was appro	ns 117/146) and codons 117/146 onal <i>RAS</i> oximately 16%.		
RAS mutati approximat Results in p	ions in the wild- tely 16%. patients with wil rimary analysis a	type <i>KRAS</i> exon ld-type <i>RAS</i> mCI are presented in t	2 population war RC and mutant <i>I</i> the table below.	as R <i>AS</i> mCRC	RAS mutation NRAS exon 2 and BRAF e: mutations in Results in pa	ns in <i>KRAS</i> exon 2 (codons 12/13), <u>xon 15 (codon 60</u> the wild-type <i>KR</i> ttients with wild-t	3 (codons 61) a exon 3 (codon 0). The inciden AS exon 2 populy ype <i>RAS</i> mCRO	and exon 4 (codor 61), and exon 4 (ace of these additi ulation was appro C and mutant <i>RAS</i>	ns 117/146) and codons 117/146 onal <i>RAS</i> oximately 16%.		
RAS mutati approximat Results in p	ions in the wild- tely 16%. patients with wil rimary analysis a Vectibix	type <i>KRAS</i> exon ld-type <i>RAS</i> mCI are presented in t FOLFOX	2 population war RC and mutant <i>I</i> the table below.	as RAS mCRC Hazard	RAS mutation NRAS exon 2 and BRAF e: mutations in Results in pa	ns in <i>KRAS</i> exon 2 (codons 12/13), xon 15 (codon 60 the wild-type <i>KR</i>	3 (codons 61) a exon 3 (codon 0). The inciden AS exon 2 populy ype <i>RAS</i> mCRO	and exon 4 (codor 61), and exon 4 (ace of these additi ulation was appro C and mutant <i>RAS</i>	ns 117/146) and codons 117/146 onal <i>RAS</i> oximately 16%.		
RAS mutati approximat Results in p	ions in the wild- tely 16%. patients with wil rimary analysis a Vectibix plus	type <i>KRAS</i> exon Id-type <i>RAS</i> mCI are presented in t FOLFOX (months)	2 population war RC and mutant <i>I</i> the table below.	as R <i>AS</i> mCRC Hazard ratio	RAS mutation NRAS exon 2 and BRAF e: mutations in Results in pa	ns in <i>KRAS</i> exon 2 (codons 12/13), <u>xon 15 (codon 60</u> the wild-type <i>KR</i> tients with wild-t ysis -are presented	3 (codons 61) a exon 3 (codon 0). The inciden AS exon 2 pop ype RAS mCRO 1 in the table be	and exon 4 (codor 61), and exon 4 (ace of these additi ulation was appro C and mutant <i>RAS</i> clow.	ns 117/146) and codons 117/140 onal <i>RAS</i> eximately 16%. S mCRC from 1		
RAS mutati approximat Results in p	ions in the wild- tely 16%. patients with wil rimary analysis a Vectibix plus FOLFOX	type <i>KRAS</i> exon Id-type <i>RAS</i> mCI are presented in t FOLFOX (months) Median	2 population war RC and mutant <i>I</i> the table below.	as RAS mCRC Hazard	RAS mutation NRAS exon 2 and BRAF e: mutations in Results in pa	ns in <i>KRAS</i> exon 2 (codons 12/13), xon 15 (codon 60 the wild-type <i>KR</i> ttients with wild-t ysic-are presented Vectibix plus	3 (codons 61) a exon 3 (codon 0). The inciden AS exon 2 pop ype RAS mCR0 1 in the table be FOLFOX	and exon 4 (codor 61), and exon 4 (ace of these additi ulation was appro C and mutant <i>RAS</i> clow. Difference	ns 117/146) and codons 117/146 onal <i>RAS</i> eximately 16%. S mCRC from 1 Hazard		
RAS mutati approximat Results in p	ions in the wild- tely 16%. patients with wil rimary analysis a Vectibix plus FOLFOX (months)	type <i>KRAS</i> exon Id-type <i>RAS</i> mCI are presented in t FOLFOX (months)	2 population war RC and mutant <i>I</i> the table below.	as R <i>AS</i> mCRC Hazard ratio	RAS mutation NRAS exon 2 and BRAF e: mutations in Results in pa	ns in <i>KRAS</i> exon 2 (codons 12/13), xon 15 (codon 60 the wild-type <i>KR</i> titients with wild-t ysic-are presented Vectibix plus FOLFOX	3 (codons 61) a exon 3 (codon 0). The inciden AS exon 2 pop ype RAS mCR0 1 in the table be FOLFOX (months)	and exon 4 (codor 61), and exon 4 (ace of these additi ulation was appro C and mutant <i>RAS</i> clow.	ns 117/146) and codons 117/146 onal <i>RAS</i> eximately 16%. S mCRC from 4 Hazard ratio		
RAS mutati approximat Results in p	ions in the wild- tely 16%. patients with wil rimary analysis a Vectibix plus FOLFOX (months) Median	type <i>KRAS</i> exon Id-type <i>RAS</i> mCI are presented in t FOLFOX (months) Median	2 population war RC and mutant <i>I</i> the table below.	as R <i>AS</i> mCRC Hazard ratio	RAS mutation NRAS exon 2 and BRAF e: mutations in Results in pa	ns in <i>KRAS</i> exon 2 (codons 12/13), xon 15 (codon 60) the wild-type <i>KR</i> tients with wild-t ysic-are presented Vectibix plus FOLFOX (months)	3 (codons 61) a exon 3 (codon 0). The inciden AS exon 2 pop ype RAS mCRO 1 in the table be FOLFOX (months) Median	and exon 4 (codor 61), and exon 4 (ace of these additi ulation was appro C and mutant <i>RAS</i> clow. Difference	ns 117/146) and codons 117/146 onal <i>RAS</i> eximately 16%. S mCRC from 1 Hazard		
RAS mutati approximat Results in p from the pr	ions in the wild- tely 16%. patients with wil rimary analysis a Vectibix plus FOLFOX (months) Median (95% CI)	type <i>KRAS</i> exon Id-type <i>RAS</i> mCI are presented in t FOLFOX (months) Median (95% CI)	2 population war RC and mutant <i>I</i> the table below.	as R <i>AS</i> mCRC Hazard ratio	RAS mutation NRAS exon 2 and BRAF e: mutations in Results in pa	ns in <i>KRAS</i> exon 2 (codons 12/13), xon 15 (codon 60) the wild-type <i>KR</i> tients with wild-t ysig-are presented Vectibix plus FOLFOX (months) Median	3 (codons 61) a exon 3 (codon 0). The inciden AS exon 2 pop ype RAS mCR0 1 in the table be FOLFOX (months)	and exon 4 (codor 61), and exon 4 (ace of these additi ulation was appro C and mutant <i>RAS</i> clow. Difference	ns 117/146) and codons 117/146 onal <i>RAS</i> eximately 16%. S mCRC from 4 Hazard ratio		
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Mutant	RAS populatior	1		
PFS	7.3	8.7	-1.4	1.31
	(6.3, 7.9)	(7.6, 9.4)		(1.07, 1.60)
OS	15.6	19.2	-3.6	1.25
	(13.4, 17.9)	(16.7, 21.8)		(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	20.2	5.8	0.78
		(21.7, 30.4)	(17.7, 23.1)		(0.62, 0.99)
	Mutant R	4S population			
	PFS	7.3	8.7	-1.4	1.31
		(6.3, 7.9)	(7.6, 9.4)		(1.07, 1.60)
	OS	15.6	19.2	-3.6	1.25
		(13.4, 17.9)	(16.7, 21.8)		(1.02, 1.55)
e	I = confider	<mark>ice interval</mark>			

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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 wildtype *KRAS* (exon 2) population was approximately 8%. Efficacy results in

treatment effect	1s unknown.				patients with wild-type <i>RAS</i> mCRC and mutant <i>RAS</i> mCRC are show below table.
					Vectibix plusFOLFIRIHazaFOLFIRI(months)(95)(months)Median (95%)
	Second-line mCRC wild-type <i>KRAS</i> (exon 2) population		Second-line mCRC mutant KRAS (exon 2) population		Median (95% Cl)
	Vectibix plus FOLFIRI (n = 303)	FOLFIRI (n = 294)	Vectibix plus FOLFIRI (n = 238)	FOLFIRI (n = 248)	CD Wild-type <i>RAS</i> population
ORR	(11 – 303)				
% (95% CI) Odds ratio (95% CI)	36% (31%, 42%) 5.50 (3.32, 8.87)	10 % (7%, 14%)	13% (9%, 18%) 0.93 (0.53, 1.63)	15% (11%, 20%)	PFS 6.4 4.6 0. (5.5, 7.4) (3.7, 5.6) (0.54
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)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
PFS Median (months) (95%	6.7 (5.8, 7.4)	4.9 (3.8, 5.5)	5.3 (4.2, 5.7)	5.4 (4.0, 5.6)	Mutant RAS population
CI) Difference in median (months)	1.8	/	-0.1		PFS 4.8 4.0 0
(months) Hazard ratio (95% CI); p- value	0.82 (0.69, 0.97); p = 0.0231		0.95 (0.78, 1.14); p = 0.5611		(3.7, 5.5) (3.6, 5.5) (0.7)
Estimated rate at six months (95% CI)	54% (48%, 60%)	39% (33%, 44%)	40% (34%, 47%)	38% (32%, 44%)	OS <u>11.8</u> <u>11.1</u> (10.4, 13.1) (10.2, 12.4) (0.76
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	I	The efficacy results in patients with wild type KR4S mCRC and mut
ТТР					mCRC are presented in the table below. Eighteen (18) % (n = 115) c
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)	mCRC are presented in the table below. Eighteen (18) % (n = 115) o with wild type <i>KRAS</i> mCRC had been exposed to prior bevacizumal PFS and Response Rate were similar regardless of prior bevacizuma
Hazard ratio (95% CI)	0.72 (0.59, 0.88)		0.89 (0.71, 1.11)		rrs and Kesponse Kate were similar regardless of prior bevacizuma
OS	1				
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)	The table below also summarises subsequent chemotherapy (irinotec oxaliplatin, or fluoropyrimidine) and anti-EGFR therapy. The role of
Difference in median (months) Hazard ratio (95% CI); p-	2.0 0.7 0.92 (0.78, 1.10); p = 0.3660 0.93 (0.77, 1.13); p = 0.4815		5	subsequent anti-EGFR therapy or chemotherapy on the estimated OS	
value					effect is unknown.
Estimated rate at 12 months (95% CI)	59% (53%, 64%)	53% (47%, 59%)	49% (42%, 55%)	45% (39%, 51%)	Second-line.mCRC Second-line.mCRC
Estimated rate at 18 months (95% CI)	40% (34%, 45%)	33% (27%, 39%)	26% (21%, 32%)	24% (19%, 29%)	Second and and the study of the second and and a second and a second and a second and a second a
Subjects receiving	53%	50%	48%	55%	(n=303)
chemotherapy after the protocol treatment phase - (%)					ORR

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Subjects receiving anti- EGFR therapy after the protocol treatment phase - (%)	13%	34%	9%
CI = confidence interval			

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

32%

First-line combination with bevacizumab and oxaliplatin or irinotecanbased 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	<mark>7.6 (6.5, 9.4)</mark>	<mark>6.6 (5.7, 10.9)</mark>	<mark>5.8 (5.5, 7.4)</mark>	<mark>5.3 (4.6, 7.9)</mark>	
response (months) (95%					
CD PES					
Median (months) (95%	67(5874)	40(3855)	53(42 57)	54(40,56)	
Median (months) (95% CD	0.7 (5.8, 7.4)	4.У (э.8, э.э)	5.3 (4.2, 5./)	3.4 (4.0, 3.6)	
Difference in median	1.9		-0.4		
Lutterence in median (months)	110		- 0.1		
Hazard ratio (95% CI): n-	0.82(0.69, 0.97) = 0.02	12.1	$\frac{0.95(0.78 + 1.14)}{0.95(0.78 + 1.14)} = 0.5611$		
value	0.62 (0.09, 0.97), p= 0.02		0.95 (0.78, 1.14); p = 0.5011		
Estimated rate at six	5.40%	200%	40%	2.80%	
months (95% CD	(48%_60%)	(330/ 440/)	(34% 47%)	(32% 44%)	
montais (7270 CI)	(1070, 0070)	(3370, 1170)		(
On-treatment PFS hazard	<mark>0.73 (0.60, 0.88); p = 0.00</mark>	H.	0.89 (0.72, 1.10); p = 0.2951		
ratio (95%CI)*; p-value					
TTP					
Median (months) (95%	7.3 (6.0, 7.5)	5.3 (3.9, 5.7)	5.5 (4.5, 5.7)	5.5 (4.8, 5.7)	
CI)					
Hazard ratio (95% CI)	0.72 (0.59, 0.88)		0.89 (0.71 1.11)		
Hazard ratio (95% CI)	0.72 (0.59, 0.88)		0.89 (0.71, 1.11)		
Hazard ratio (95% CI) <mark>OS</mark>	0.72 (0.59, 0.88)	I	0.89 (0.71, 1.11)	1	
<mark>OS</mark> Median (months)	14.5	12.5		41.1	
<mark>OS</mark> Median (months) (95% CI)	14.5 (13.0, 16.1)	12.5 (11.2, 14.2)	11.8 (10.4, 13.3)	<mark>++.4</mark> (10.3, 12.4)	
<mark>OS</mark> Median (months) (<u>95% CI)</u> Difference in median	14.5				
05 Median (months) (05%, C1) Difference in median (months)	14.5 (12.0, 16.1) 2.6	(<u>11.2, 14.2)</u>	1158 (107,13.3) 0.7		
OS Median (months) (95%-CI) Difference in median (months) Huzard ratio (95%-CI): p-	14.5 (13.0, 16.1)	(<u>11.2, 14.2)</u>	11.8 (10.4, 13.3)		
OS Median (monthe) (95%-C1) Difference in median (monthe) Hazard ratio (95%-C1); p- volue	14:3 (13.0, 16.1) 2.6 9.92 (0.78, 1.10); p= 0.30	(11.2, 14.2) 60	44.5 (10.4.13.3) 0.93 (0.77, 1.13), p==0.4815	(10.3, 12.4)	
OS Median (months) (95%-Cl) Difference in median (months) Harard ratio (95%-Cl); p- value Estimated ratio (95%-Cl); p-	14-5 (13.0,16.1) 2-6 0.92 (0.78, 1.10); p=0.36 8098	(11.2, 14.2)	11.4 (10.4, 13.3) 12.3 (10.1, 13.3), p=0.4815 49%	(10.3, 12.4)	
OS Median (montho) (0552-C1) Ofference in median montho) Hazard-ratio (95%-C1)- pr value Estimated values (12) mappin	14:3 (13.0, 16.1) 2.6 9.92 (0.78, 1.10); p= 0.30	(11.2, 14.2) 60	44.5 (10.4.13.3) 0.93 (0.77, 1.13), p==0.4815	(10.3, 12.4)	
OS Mediane (mortilies) (0556-C13) Differences in modian (monthly) Harard ratio (05% C13- ps voltes) Estimated rate of 12 (0556-C13)	14.5 (13.0.16.1) 23. 0.92(0.78.1.10); p=0.36 592 (332,.6056)	41-2-44-2 66 5384 (47%, 59%)	11-8 (10.4, 13.3) 193 1932 (0.72, 1.13): p=0.4815 1935 1429a, 5555	(10.3, 12.4) 45% (39%, 51%)	
OS Median-(montho) (435-c1) Oriference in-modulin ementhol Harandratato-(95%-C3)-cpi volisi Estimated-rate-or-12 anoshite (435-c1) Estimated-rate-or-12 Estimated-rate-or-12 Estimated-rate-or-13	14-2 13-0-16-3 2-6 0.92 (0.78.3-10); p= 0.76 59% 4,59%	(11-2-14-2) (11-2-	11.4 (10.4,10.5) (10.4,10.5) (10.5,10.7,1.13);p=0.4015 (10.5,10.7,1.13);p=0.4015 (10.5,10.7,1.13);p=0.4015 (10.5,10.7,1.13);p=0.4015 (10.5,10.7,1.13);p=0.4015	4500 (30%, 51%) 24%	
OS Mediana (mantho) (555-C1) Officercore in median imontho! Harard (mite (956-C1)-p) exists Fairmated-nate-at-12 monthol (555-C1) Estimated rate-at-12 estimated rate	14.5 (13.0.16.1) 23. 0.92(0.78.1.10); p=0.36 592 (332,.6056)	41-2-44-2 66 5384 (47%, 59%)	11-8 (10.4, 13.3) 193 1932 (0.72, 1.13): p=0.4815 1935 1429a, 5555	(10.3, 12.4) 45% (39%, 51%)	
OS Modian-(monthe) (dife_c1] Ofference in modulin criminity Harmfrattine/05%-Cilicept weight Commentine (dife_c1] Enrimmed instead - 12 monthe (dife_c1] Enrimmed instead - 13 monthe (dife_c1] (diffe_c1] (diffe	14,5 14,6 13,0,0,0,1 2-0 0,92,0,25,1,10,9,9=0.36 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1	(11-2-14.2) 5394 (4794, 5994) 3284 (2794, 3994)	31.0 31.0 140,1,1,3,1 0.7 0.93 (0.77,3,1,3)-p=0.4615 40% 140,0,1,555 30% 140,0,1,555 30%	40.3, 42.43 45% (39%, 51%) 24% 24%	
OS Median - months (355-c.7) Ofference in median (combain Haward ratio (05%-C1)-pe value Estimated-ratio-at-1-2 months (05%-C1)- Estimated-ratio-at-1-2 months (05%-C1)- Subjects receiving	14-2 13-0-16-3 2-6 0.92 (0.78.3-10); p= 0.76 59% 4,59%	(11-2-14-2) (11-2-	11.4 (10.4,10.5) (10.4,10.5) (10.5,10.7,1.13);p=0.4015 (10.5,10.7,1.13);p=0.4015 (10.5,10.7,1.13);p=0.4015 (10.5,10.7,1.13);p=0.4015 (10.5,10.7,1.13);p=0.4015	4500 (30%, 51%) 24%	
OS Martina remention (ASS) CI Otherence in massion encontrol Harrard ratio-(25% CI)-per voltor Encontrol rate-on-12 massion Encontrol rate-on-12 massion Encontrol rate-on-12 Statistics respectively Subjects respectively Subjects respectively	14,5 14,6 13,0,0,0,1 2-0 0,92,0,25,1,10,9,9=0.36 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1	(11-2-14.2) 5394 (4794, 5994) 3284 (2794, 3994)	31.4 1 140,1,1,33 0.4 0.93 (0.73,3,13)-p=0.4615 40% 140,0,1,535 30% 140,0,1,535 30%	40.3, 42.43 45% (39%, 51%) 24% 24%	
OS Mediana (mantha) (0.5%, C3) Oliferance in median (montha) Homed rule (0.5%, C3), pi eating eating eating (0.5%, C3) Subjects reserving elementsherpy-after his system (1) Subjects reserving elementsherpy-after his system (1)	14,5 14,6 13,0,0,0,1 2-0 0,92,0,25,1,10,9,9=0.36 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1 6,50,2,0,10,1	(11-2-14.2) 5394 (4794, 5994) 3284 (2794, 3994)	31.4 1 140,1,1,33 0.4 0.93 (0.73,3,13)-p=0.4615 40% 140,0,1,535 30% 140,0,1,535 30%	40.3, 42.43 45% (39%, 51%) 24% 24%	
OS Martina remented ASSI-CL Otherence in machine internities Harrard ratio-25% Cl)- pil Velko Commission and Close Commission and Close Commission and Close Commission and Close Commission and Close Commission and Close Subjects resolution Commission and Close Commission and Close Commission and Close Commission and Close Commission and Close Commission and Close Close and Close Close and Close Close and Close and Close and Close Close and Close and Close and Close and Close and Close Close and Close and Close and Close and Close and Close and Close Close and Close	14.5 13.0.1.0.1 2.6 0.922 (0.75.1.10); p= 0.24 5.330; 64554 400; 64556 840; 64556 840; 64556	441-02-14-23 441 5256 42294, 50562 42294, 50562 42294, 50562 422954, 50562 5056	11.2 11.2 <td< td=""><td>40.3,12.44 40.3,12.44 40.5 (2004,510,5 1004,2004,5 5554 5554</td></td<>	40.3,12.44 40.3,12.44 40.5 (2004,510,5 1004,2004,5 5554 5554	
S Modum (months) Mo	14,5 14,6 13,0,0,0,1 2,6 0,92,0,25,1,10,9,9,-0,26 6,50,2,45,2 6,50,2,45,2 4,99,49,0,6	(11-2-14.2) 5394 (4794, 5994) 3284 (2794, 3994)	31.4 1 140,1,1,33 0.4 0.93 (0.73,3,13)-p=0.4615 40% 140,0,1,535 30% 140,0,1,535 30%	40.3, 42.43 45% (39%, 51%) 24% 24%	
OS Marilian Grounthil USSL-CI2 Ofference in speciar droothic Passe CD-pr vited Entimated rate at 12 months OSSL-CI2 Entimated rate at 12 months OSSL-CI3 Entimated rate at 12 Subjects receiving anti- protocol treatment plane etba	14.5 13.0.1.0.1 2.6 0.922 (0.75.1.10); p= 0.24 5.330; 64554 400; 64556 840; 64556 840; 64556	441-02-14-23 441 5256 42294, 50562 42294, 50562 42294, 50562 422954, 50562 5056	11.2 11.2 <td< td=""><td>40.3,12.44 40.3,12.44 40.5 (2004,510,5 10,0</td></td<>	40.3,12.44 40.3,12.44 40.5 (2004,510,5 10,0	
OS Modian-(months) OSS-421 Difference in modian (months) Heared-ratio-(OSS-61)-pi with Control Contro	14.5 13.0.1.0.1 2.6 0.922 (0.75.1.10); p= 0.24 5.330; 64554 400; 64556 840; 64556 840; 64556	441-02-14-23 441 5256 42294, 50562 42294, 50562 42294, 50562 422954, 50562 5056	11.2 11.2 <td< td=""><td>40.3,12.44 40.3,12.44 40.5 (2004,510,5 10,0</td></td<>	40.3,12.44 40.3,12.44 40.5 (2004,510,5 10,0	
ON Miniam conserved Mi	14.5 13.0.1.0.1 2.6 0.922 (0.75.1.10); p= 0.24 5.330; 64554 400; 64556 840; 64556 840; 64556	441-02-14-23 441 5256 42294, 50562 42294, 50562 42294, 50562 422954, 50562 5056	11.2 11.2 <td< td=""><td>40.3,12.44 40.3,12.44 40.5 (2004,510,5 10,0</td></td<>	40.3,12.44 40.3,12.44 40.5 (2004,510,5 10,0	

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

bevacizumab is associated with an unfavourable benefit-to-risk profile irrespective of tumour <i>KRAS</i> mutational status.	receiving panitumumab observed in an interim analysis.
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.	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.
	An additional analysis of efficacy data by <i>KRAS</i> (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 <i>KRAS</i> subset of the oxaliplatin cohort, the hazard ratio for PFS was 1.36 with 95% CI: 1.04-1.77. For the mutant <i>KRAS</i> 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 <i>KRAS</i> 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 <i>KRAS</i> mutational status. Overall, panitumumab treatment combined with chemotherapy and bevacizumab is associated with an unfavourable benefit-to-risk profile irrespective of tumour <i>KRAS</i> 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 (FMA) will review new information on this

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.