

Horizon Scanning in Oncology

Panitumumab (Vectibix[®]) as 1st
line combination therapy for the
treatment of WT KRAS metastatic
colorectal cancer

1st Update 2011



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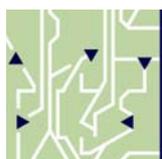
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1 Background

1.1 Drug

Generic/Brand name: Panitumumab/Vectibix®

Panitumumab,
Vectibix®

Developer/Company: Amgen

Description: Panitumumab is a fully human monoclonal antibody. It is designed to specifically attach to the antigen epidermal growth factor receptor (EGFR), which can be found on the surface of certain cells, including tumour cells. By targeting the EGFR, the tumour cells no longer receive the information needed for growth, progression and spreading. Approximately 70-80% of patients with advanced colorectal cancer (CRC) overexpress EGFR [1]. Panitumumab does not work in tumour cells that contain the mutated (MT) KRAS gene, because the growth of these cells is not controlled by signals transmitted by the EGFR. Thus, these cells continue to grow even when EGFR is blocked [2-3]. Consequently, panitumumab was recommended for the treatment of adult patients suffering from metastatic colorectal cancer (mCRC) with non-mutated KRAS genes, that is with a wild-type (WT) KRAS status, by the European Medicines Agency (EMA) [4].

monoclonal antibody
targeting EGFR

... not effective in MT
KRAS gene

Application: 6mg/kg panitumumab are administered via intravenous infusion once every two weeks [4].

6mg/kg once every 2
weeks

1.2 Indication

Panitumumab as 1st-line combination therapy with FOLFOX (oxaliplatin, 5-fluorouracil and folinic acid) for patients with wild-type KRAS metastatic colorectal cancer (WT KRAS mCRC) [1].

panitumumab +
FOLFOX as 1st-line
therapy

1.3 Burden of disease

Colorectal cancer is one of the leading causes of cancer-deaths worldwide. Its primary risk factors are age >50 years, colorectal polyps, family history of colorectal cancer, personal history of cancer, genetic alterations, diets high in fat and low in calcium, folate and fiber and cigarette smoking [5]. Men are still more often affected by mCRC than women. 90% of the patients are diagnosed at an age of >50 years [6]. On average, patients are aged 70 years at the time of diagnosis of mCRC [7]. Initial symptoms in patients with CRC are abdominal pain, change in bowel habit, haematochezia or melena, weakness, anaemia without other gastrointestinal symptoms and weight loss. CRC is either diagnosed due to the presence of one or more of these signs/symptoms or by routine screening [8]. Approximately 20% [7] of patients are initially diagnosed with metastatic disease and 30-40% of CRC patients initially diagnosed with localized disease will develop metastatic disease [9].

CRC one of the leading
causes of cancer death

90% are diagnosed at
an age >50 years ...

... because of symptoms
or by routine screening

20% are initially
diagnosed with mCRC

TNM staging system relevant for choice of therapy and as an important prognostic factor

The TNM (tumour **n**ode **m**etastasis) staging system is the preferred staging system for CRC and is based on the depth of invasion of the bowel wall, extent of regional lymph node involvement, and presence of distant sites of the disease [9]. Based on the determination of the T, N and M these three letters and their accompanying numbers are combined in an overall stage (0-IV). The exact TNM staging is described in more detail elsewhere [10]. Metastatic colorectal cancer is classified as stage IV disease. Five-year survival rate for stage IV colorectal cancer is <10% [8-9]. Overall, pathologic stage of the disease is the most important prognostic factor [9].

EGFR is not a valid prognostic factor for response

MT KRAS is a prognostic factor for non-response

...

... only ~50% of pts with WT KRAS respond to anti-EGFR therapy

Although panitumumab is a monoclonal antibody targeting the EGFR, evidence suggests that EGFR expression is not a valid predictive factor for response to panitumumab as also patients with low or negative EGFR expression benefit from EGFR inhibitors [11]. On the other hand, KRAS testing is strongly recommended prior to initiation of therapy, as only patients with WT KRAS respond to panitumumab therapy [11]. Thus, KRAS testing is essential to identify patients eligible for panitumumab therapy and consequently to spare patients which are unlikely to respond associated toxicities [12-13]. KRAS mutations are found in 30-50% of CRC tumours and are associated with tumours of more advanced stages, increased metastatic potential, poor prognosis and decreased progression-free survival (PFS) and overall survival (OS) [2-3]. Whereas, KRAS status is currently the only predictive factor for response to anti-EGFR therapy, only 50% of patients with WT KRAS respond to anti-EGFR agents [13].

~960 newly diagnosed WT KRAS mCRC in Austria per year

In Austria, 2200 people died of and 4460 (2450 men and 2010 women) patients were newly diagnosed with CRC in 2008 [14]. Applying the estimates mentioned above, approximately 960 patients are newly diagnosed with or progress to WT KRAS mCRC in Austria per year.

1.4 Current treatment options

treatment aims at prolonging OS, maintaining QoL

majority of pts suffer from unresectable disease ...

... treatment approach is palliative and combines different chemotherapeutic and targeted drugs

Surgical resection is a potentially curative therapy of CRC [8], but only few patients with mCRC are eligible for resection in the first place or become resectable after response to chemotherapy and shrinkage of their tumour (“conversion therapy”) [15-16]. Since the majority of mCRC patients suffer from unresectable disease the treatment goal then is palliative, aiming at prolonging OS and maintaining quality of life (QoL) for as long as possible [15]. In the past decade several new chemotherapeutic agents and novel targeted drugs have been approved for the treatment of mCRC and have led to improved outcomes for patients with mCRC and to an increased number of therapeutic options [3].

Even though the majority of patients is asymptomatic at time of diagnosis, there is some evidence that chemotherapy should be initiated immediately after diagnosis rather than delaying therapy until they become symptomatic [15]. The optimal duration of the initial chemotherapy depends on tolerance of and response to chemotherapy, disease bulk and location and symptomatology [15].

Currently, the following five different classes of drugs are available for the treatment of non-operable mCRC:

- Fluoropyrimidines (5-fluorouracil (5-FU)), usually given with leucovorin, capecitabine, tegafur plus uracil
- Irinotecan
- Oxaliplatin
- Cetuximab or panitumumab, two monoclonal antibodies designed to target the EGFR
- Bevacizumab, a monoclonal antibody targeting VEGF [16].

5 different classes of drugs are available

The best way of combining and sequencing these agents has not been established yet, but evidence indicates that exposing mCRC patients to all cytostatic drugs is more important than a specific sequence of administration [16].

optimal sequence and combination of the available drugs not yet established

Although, no trial has yet compared the two EGFR-targeting agents cetuximab and panitumumab directly, cross-trial comparisons and preclinical data suggest that they do not only have a similar mode of action but they also appear to have comparable efficacy profiles [16]. Despite, there is no therapeutic preference of using panitumumab rather than cetuximab in clinical practice, the lower rate of infusion reactions favour the use of panitumumab in regions with a high rate of cetuximab-related infusion reactions [16].

currently no trial compared the targeting agents directly to each other

Generally, a doublet chemotherapy based on either oxaliplatin or irinotecan is recommended as the backbone of initial mCRC therapy. Further, the addition of bevacizumab to either oxaliplatin- or irinotecan-based regimens is recommended, but improved outcomes have to be balanced carefully against the potential for serious treatment-related toxicity. The addition of the EGFR-targeting agents cetuximab and panitumumab to irinotecan-based chemotherapy is only recommended for patients with WT KRAS tumours [16-18]. Due to insufficient evidence on the use of bevacizumab in the second-line setting, its role as a component in a second-line regimens is not yet established [16, 19].

doublet chemotherapy based on oxaliplatin or irinotecan is recommended as backbone of initial mCRC therapy

1.5 Current regulatory status

Panitumumab was initially approved as a single-agent in the third-line therapy of mCRC by the European Medicines Agency (EMA) in December 2007. In March 2011, the Committee for Human Medicinal Products (CHMP) adopted a negative opinion for the extension of indication of panitumumab as first- or second-line therapy in mCRC in combination with chemotherapy. Reasons for this negative opinion were concerns about the clinical relevance of the relatively small increase in PFS, lack of improvement in OS, increased toxicity and the risk of MT KRAS patients being treated with panitumumab if they could not be identified a priori through appropriate tests. After re-examination, the CHMP recommended the extension of indication for first- and second-line treatment of WT KRAS mCRC patients in June 2011 [1]. The final approval by the European Commission is still awaited.

2007: approved as mono-therapy for 3rd-line and subsequent lines

06/2011: CHMP recommended extension of indication for 1st- and 2nd-line mCRC therapy in combination with FOLFOX and FOLFIRI, respectively

Panitumumab is recommended for the following indications:

- as monotherapy for the treatment of patients with EGFR expressing mCRC with WT KRAS after failure of previous chemotherapy regi-

mens including fluoropyrimidine, oxaliplatin or irinotecan (conditional approval) [20].

- as first-line therapy in combination with FOLFOX (oxaliplatin, 5-fluorouracil and folinic acid) in WT KRAS mCRC [1].
- as second-line therapy in combination with FOLFIRI (irinotecan, 5-fluorouracil and folinic acid) in WT KRAS mCRC patients who have already received fluoropyrimidine-based chemotherapy (excluding irinotecan) [1].

2006: FDA approved panitumumab as 3rd-line monotherapy in mCRC pts

The US Food and Drug Administration (FDA) approved panitumumab as monotherapy in WT KRAS mCRC patients who have progressed on or following fluoropyrimidine, oxaliplatin or irinotecan chemotherapy regimens in September 2006 [21-22].

1.6 Treatment costs

monthly treatment costs additional to chemotherapy: €4,250 - €7,072

Panitumumab is administered as an intravenous infusion (i.v.) once every 2 weeks. The recommend dose is 6mg/kg [4]. In Austria, the price for one vial of 5ml containing 20mg/ml panitumumab is €425.- (manufacturer's price [23]; pharmacy retail price: €707.- [24]). Assuming an average weight of 70kg of patients, 5 vials are needed for one treatment cycle of two weeks. Therefore, estimated monthly treatment costs for panitumumab mono-therapy are €4,250.- (€7,072.-).

costs for KRAS testing prior to EGFR-targeting therapy are additional

Based on the evidence that EGFR-targeting agents are not effective in KRAS-mutated tumours, KRAS testing is required prior to panitumumab containing therapy regimens [1]. Thus, the costs of KRAS testing and panitumumab are additional to the costs of chemotherapy.

2 Evidence

literature search in 4 electronic databases

492 references retrieved, 4 relevant references included

A literature search was conducted in the following electronic databases on the 3rd of August 2011: Cochrane Library, Ovid Medline, CRD Database and EMBASE. Search terms included panitumumab or vectibix combined with metastatic colorectal cancer, metastatic colorectal carcinoma, colorectal cancer, colorectal carcinoma, mCRC. After removing duplicates, 492 references were identified. Of those, only randomized controlled trials reporting results for WT KRAS mCRC patients treated with panitumumab in the first-line setting were included, yielding 4 relevant references reporting results from 2 randomized controlled trials and two meta-analyses [3, 25-27].

In comparison to the initial HSS report [28], OS and safety data of the PRIME trial have been fully published in a paper [25]. In addition, two meta-analyses investigating the treatment effect of panitumumab in the first-, second- or subsequent lines of therapy of mCRC were published [3, 27].

2.1 Efficacy and safety - RCTs

Table 1: Efficacy and safety results of phase III RCTs

Reference	Douillard et al. 2010 [25], PRIME trial		Hecht et al. 2009 [26], PACCE trial	
Sponsor	Amgen, Thousand Oaks, CA		Amgen Inc.	
Country	133 institutions in 19 countries		USA, 200 centres	
Design	randomized, open-label, multicentre, phase III trial		randomized, open-label, multicentre, phase IIIB trial	
Hypothesis	Superiority		Superiority	
Number of patients	1,096 (I 546 vs C 550)		1,053 (Ox-CT cohort 823 (I 413 vs C 410) vs Iri-CT cohort (230 (I 115 vs C 115)))	
Number of patients with WT KRAS/MT KRAS	I 217/145 vs C 204/128		NR	
Treatment				
Intervention (I)	6 mg/kg panitumumab iv infusion every 2 weeks on day 1 before FOLFOX4 chemotherapy		1. panitumumab + bevacizumab + Ox-CT (=fluorouracil, leucovorin and oxaliplatin-based chemotherapy) 2. panitumumab + bevacizumab + Iri-CT (=fluorouracil, leucovorin and irinotecan-based chemotherapy)	
Control (C)	FOLFOX 4 (every two weeks): oxaliplatin 85mg/m ² iv infusion (day 1), leucovorin 200mg/m ² (or equivalent) iv infusion followed by fluorouracil 400mg/m ² iv bolus and 600mg/m ² 22-hour continuous infusion on days 1 and 2		1. bevacizumab + Ox-CT (=fluorouracil, leucovorin and oxaliplatin-based chemotherapy) 2. bevacizumab + Iri-CT (=fluorouracil, leucovorin and irinotecan-based chemotherapy)	
Inclusion criteria	untreated mCRC (adenocarcinoma), ECOG PS 0-2		untreated mCRC, ECOG PS 0-1, adequate hematologic, hepatic and renal functions	
Participants characteristics	WT KRAS	MT KRAS	Ox-CT cohort	Iri-CT cohort
Median age years (range)	I 62 (27-85) vs C 61 (24-82)	I 63 (33-83) vs C 61 (27-82)	I 61 (28-88) vs C 62 (22-89)	I 60 (35-84) vs C 59 (23-80)
Male (%)	I 67 vs C 62	I 66 vs C 58	I 56 vs C 58	I 49 vs C 62
ECOG PS 0-1 (%)	I 94 vs C 94	I 96 vs C 95	I 100 vs C 100	I 100 vs C 100
Prior adjuvant therapy	I 16 vs C 17	I 16 vs C 12	I 19 vs C 19	I 33 vs C 31
Colon cancer (%)	I 66 vs C 65	I 68 vs C 73	NR	NR
Rectal cancer (%)	I 34 vs C 35	I 32 vs C 27	NR	NR
WT KRAS (%)	60		39	43
Follow-up	I 13.2 vs C 12.5 months	I 10.8 vs C 12 months	7.5* months	6.5* months
OS				
Median (months)	I 23.9 vs C 19.7	I 15.5 vs C 19.3	I 18.4 vs C not reached*	NR
HR	0.83 (95% CI 0.67 to 1.02; p=0.72)	1.24 (95% CI 0.98 to 1.57; p=0.68)	1.56 (95% CI 1.11 to 2.19)*	NR
Subgroup analysis			WT KRAS: HR=1.89 (95% CI 1.30 to 2.75; p=0.045)** MT KRAS: HR=1.02 (95% CI 0.67 to 1.54)**	WT KRAS: HR=1.28 (95% CI 0.5 to 3.25; p=0.445)** MT KRAS: HR=2.14 (95% CI 0.82 to 5.59)**
PFS	(primary outcome)		(primary outcome)	(secondary outcome)
Median (months)	I 9.6 vs C 8.0	I 7.3 vs C 8.8	I 8.8 vs C 10.5*	I 10.1 vs C 11.9*
HR	0.80 (95% CI 0.66 to 0.97; p=0.02)	1.29 (95% CI 1.04 to 1.62; p=0.02)	1.44 (95% CI 1.13 to 1.85; p=0.004)*	1.57 (95% CI 0.71 to 3.46; p=NR)*
Subgroup analysis			WT KRAS: HR=1.36 (95% CI 1.04 to 1.77)** MT KRAS: HR=1.25 (95% CI 0.91 to 1.71)**	WT KRAS: HR=1.5 (95% CI 0.82 to 2.76)** MT KRAS: HR=1.19 (95% CI 0.65 to 2.21)**

ORR (%)	I 55 vs C 48	I 40 vs C 40				I 46 vs C 48 OR=0.92 (95% CI 0.7 to 1.22)**	I 43 vs C 40 OR=1.11 (95% CI 0.65 to 1.9)**			
PR (%)	NR	NR				I 46 vs C 47**	I 43 vs C 40**			
Subgroup analysis						WT KRAS: I 50 vs C 56** MT KRAS: I 47 vs C 44**	WT KRAS: I 54 vs C 48** MT KRAS: I 30 vs C 38**			
Adverse events (AEs)										
Any grade (%)		WT KRAS		MT KRAS			Ox-CT		Iri-CT	
		I	C	I	C		I	C	I	C
	Patients with any event	NR	NR	NR	NR	Skin toxicity	95	30	95	26
	Neutropenia	NR	NR	NR	NR	Diarrhoea	74	66	83	79
	Skin toxicity	NR	NR	NR	NR	Nausea/vomiting	71	75	79	74
	Diarrhoea	NR	NR	NR	NR	Infections	57	48	58	37
	Neurologic toxicities	NR	NR	NR	NR	Neutropenia	36	43	34	33
	Hypokalemia	NR	NR	NR	NR	Dehydration	33	17	29	20
	Fatigue	NR	NR	NR	NR	Hypomagnesemia	28	2	31	4
	Mucositis	NR	NR	NR	NR	Neuropathy	21	28	-	-
	Hypomagnesaemia	NR	NR	NR	NR	Hypertension	18	21	14	20
	Paronychia	NR	NR	NR	NR	Paronychia	9	0	14	0
	Pulmonary embolism	NR	NR	NR	NR	Deep venous thrombosis	7	8	13	6
	Febrile neutropenia	NR	NR	NR	NR	Pulmonary embolism	7	4	12	5
	Infusion-related reaction	NR	NR	NR	NR	Gastrointestinal perforations	<1	0	-	-
Grade ≥3 (%)		WT KRAS		MT KRAS			Ox-CT		Iri-CT	
		I	C	I	C		I	C	I	C
	Patients with any event	84	69	80	73	Skin toxicity	36	1	38	0
	Neutropenia	42	41	37	47	Diarrhoea	24	13	28	9
	Skin toxicity	36	2	30	1	Nausea/vomiting	13	7	13	8
	Diarrhoea	18	9	20	10	Infections	18	10	14	9
	Neurologic toxicities	16	16	17	17	Neutropenia	24	24	17	21
	Hypokalemia	10	5	9	4	Dehydration	17	6	14	6
	Fatigue	9	3	7	5	Hypomagnesemia	4	0	5	1
	Mucositis	9	<1	6	3	Neuropathy	4	7	-	-
	Hypomagnesaemia	6	<1	6	<1	Hypertension	4	5	2	3
	Paronychia	3	0	2	0	Paronychia	1	0	4	0
	Pulmonary embolism	3	2	3	4	Deep venous thrombosis	7	8	13	0
	Febrile neutropenia	2	2	3	3	Pulmonary embolism	6	4	11	5
	Infusion-related reaction	<1	-	0	-	Gastrointestinal perforations	0	0	-	-
Fatal AEs (%)		5	6	8	3		NR	NR	NR	NR
Treatment related deaths (number of pts)		4	4	2	1		5	NR	2	NR
Notes	EGFR expression and KRAS status were not required at entry					Because of decreased PFS and increased toxicity in the panitumumab-arm, panitumumab treatment was discontinued in March 2007 based on results of the planned interim analysis (October 2006). The trial continued without panitumumab treatment. No further protocol-pre-specified hypothesis testing was conducted. The reported results are from the planned interim analysis (October 2006) and a descriptive analysis of the efficacy and safety data available in March 2007.				

*Planned interim analysis of safety and efficacy at approximately 50% progression or death events in the Ox-CT cohort; data cutoff on October 30, 2006.

**Analysis of the descriptive update of the primary analysis, May 2007 (panitumumab was discontinued by the sponsor in March 2007)

Abbreviations: ECOG PS – Eastern Cooperative Oncology Group Performance Status, OS – overall survival, PFS – progression free survival, ORR – objective response rate, PR – partial response, NR – not reported, 95% CI – 95% confidence interval, WT – wild-type, MT – mutant

PRIME trial [25]

The PRIME trial was initially designed to compare the treatment effect of adding panitumumab to first-line FOLFOX compared to FOLFOX alone in all randomly assigned patients, regardless of their KRAS status. Due to evolving evidence that a mutational KRAS status is a negative predictive factor of the efficacy of panitumumab and cetuximab, the study was amended to compare PFS and OS according to the KRAS status of patients before any efficacy analyses were conducted. To ensure adequate power for PFS in the WT KRAS stratum, the required sample size was increased from 900 to 1,150. KRAS status was analysed in 93% of the 1,183 patients finally enrolled. Of these, 60% had WT KRAS and 40% had MT KRAS tumours. The effect analysis by KRAS status showed a statistically significant prolongation of median OS (HR = 0.57 (95% CI 0.46 to 0.71; p<0.001) in the WT stratum compared to the MT stratum in the panitumumab + FOLFOX arm. Within the control arm the HR for OS was 0.87 (95% CI 0.7 to 1.08; p=0.21) for the WT stratum versus the MT stratum. The objective response rate (ORR) was numerically higher in the intervention arm of the WT KRAS stratum compared to the control arm, but not statistically significant. By which extent ORR was achieved by partial or complete response is not reported in the publication Patient characteristics were well balanced between the intervention and control groups [29]. As expected, AEs were more frequent and more severe in the intervention arm regardless of KRAS status due to the addition of panitumumab to chemotherapy. Skin-related toxicities occurred also more frequently and more severely in the panitumumab + FOLFOX arm (94%) compared to the FOLFOX arm (31%). PRIME and previous studies with EGFR monoclonal antibodies demonstrated an association between skin-related toxicities and the efficacy of EGFR-targeting monoclonal antibodies. 51% of patients in the WT KRAS stratum and 61% of patients in the MT KRAS stratum discontinued chemotherapy, mainly due to disease progression.

study amendment to compare PFS and OS according to KRAS status

**KRAS analysis in 93%
60% had WT KRAS
status**

**HR for OS (WT KRAS vs.
MT KRAS): 0.57**

**AEs were more frequent
and more severe in the
intervention arm,
regardless of KRAS
status**

PACCE trial [26]

The underlying rationale of the PACCE trial was that the dual-pathway inhibition by combining two targeted agents with chemotherapy leads to an increase in antitumour activity. Results of a planned interim analysis showed that the addition of panitumumab to bevacizumab + chemotherapy led to decreased PFS and increased toxicity in the intervention arm. Thus, the administration of panitumumab was stopped in March 2007 and the trial continued per protocol, but without panitumumab. The updated descriptive analysis was conducted with data as of May 30, 2007. KRAS status was evaluated in 82% of patients of which 40% had mutations. PFS favoured the control arm in both chemotherapy cohorts regardless of KRAS status. Overall response rates were generally comparable between treatment arms. Only two patients in the control arm of the Ox-CT cohort reached complete response, 43-47% of patients in all other groups had partial responses. In both chemotherapy cohorts AEs were more frequent and more serious in the panitumumab arm than in the control arm with 90% and 77% in the Ox-CT cohort, respectively and 90% versus 63% in the Iri-CT cohort, respectively. It is estimated, that about 19% had a panitumumab-related serious AE. According to the investigator assessment, 7 (1%) deaths were panitumumab-related – 5 in the Ox-CT cohort and 2 in the Iri-CT cohort.

**underlying rationale:
dual-pathway inhibition
leads to increased anti-
tumor activity ...**

**... which was found to
decrease PFS and
increase toxicity**

2.2 Efficacy and safety - further studies

meta-analysis on the effect of EGFR-targeting agents in mCRC treatment

EGFR inhibitors are more effective in 2nd- and further lines of therapy than in the 1st-line setting

meta-analysis on the effect of panitumumab in mCRC treatment

panitumumab is more effective in 2nd- or further lines of mCRC therapy than in 1st-line therapy

Petrelli et al. [27] conducted a meta-analysis to investigate whether panitumumab and cetuximab in combination with chemotherapy are superior in terms of relative risk (RR) of response, PFS and OS in WT KRAS mCRC patients to chemotherapy alone. All in all, they included results of 7 randomized controlled trials (RCTs) that analysed the treatment effect in WT KRAS mCRC patients. The main finding of this analysis was that both EGFR-targeting agents seemed to be more effective in second- or further lines of therapy than in the first-line setting. When treated with one of these two agents the chances of obtaining a response is 10-fold higher in second- or further lines of therapy compared to first-line therapy and even 30-fold higher compared to best supportive care alone (RR=33.84; p=0.0005). Whereas both drugs increased the RR of obtaining response and reduced the risk of progression in WT KRAS mCRC patients, the results were more robust in patients treated with panitumumab [27].

The meta-analysis published by *Ibrahim et al.* [3] aimed at quantifying the benefit and safety of panitumumab in WT KRAS mCRC patients. Four RCTs were included in the analysis – two in the first-line setting (PRIME and PACCE), one in the second-line treatment of mCRC patients and one after failure of several prior interventions. Confirming the findings of *Petrelli et al.* [27], this meta-analysis demonstrated that the positive treatment effect of panitumumab was more pronounced and statistically significant in second- or subsequent lines of therapy in WT KRAS mCRC patients, but no statistical significance in PFS and OS was found in the first-line setting. The findings in the first-line setting might result from the fact, that two studies were included of which one (the PACCE trial) was halted after the first interim analysis due to a decrease in PFS and an increase in AEs caused by the combination of two monoclonal antibodies targeting different receptors. Overall, survival results might have been confounded by an unbalanced cross-over reported in three of the included trials [3].

3 Commentary

**June 2011: positive opinion for 1st- and 2nd-line therapy
contraindication: MT KRAS**

After an initial refusal of market authorization for first-line panitumumab in March 2011, the CHMP adopted a positive opinion for the extension of indication of panitumumab for the first -line treatment but only for *WT KRAS* mCRC patients in combination with FOLFOX in June 2011; MT KRAS was listed as a contraindication [1]. The final decision of approval is still pending.

Limiting panitumumab to patients without KRAS mutations and only in combination with FOLFOX can be explained by two phase III RCTs (see Table 1): the PRIME trial compared panitumumab + FOLFOX with FOLFOX alone and led to a 20% risk reduction of progression or death in patients with WT KRAS [25], whereas patients in the intervention group of the PACCE trial had worse efficacy outcomes and higher toxicities than the control group without panitumumab - regardless of their KRAS status. These findings underpinned that dual-pathway inhibition with different types of targeted agents is inferior to combining the VEGF-inhibitor bevacic-

zumab with chemotherapy (either FOLFIRI or FOLFOX) and is thus not recommended for mCRC treatment [26]. Other results favouring the addition of panitumumab to chemotherapy found in the PRIME trial were numerically higher, but not statistically significant, median OS and ORR in the panitumumab + FOLFOX group compared to the FOLFOX group alone in the WT KRAS stratum. AEs were more frequent and more severe in the intervention group. Even though skin toxicities occurred more frequently and more severely in the panitumumab group, these side-effects are being discussed as potential predictive factors for the effectiveness of EGFR-inhibitors [25].

Even though MT KRAS is predictive for non-response to EGFR-inhibitors, only ~50% of patients with WT KRAS respond to EGFR-inhibitors. Thus, further factors for predicting response to EGFR-therapy are needed in order to avoid EGFR-therapy and its side-effects in patients who do not have the potential to benefit [3, 27]. Some preliminary evidence indicates that determination of BRAF mutations might offer a means of further selecting eligible patients, because some studies suggest that only patients with mCRC WT KRAS *and without* BRAF mutations benefit from EGFR-inhibition [30-31]. Though, due to inconsistent results the role of BRAF status in the treatment management of mCRC has not been fully established yet [32].

Besides the positive opinion for first-line therapy, the CHMP also recommended to approve panitumumab in combination with FOLFIRI as second-line therapy based on improvements in PFS for patients with WT KRAS (HR=0.73) [33]. Two meta-analyses also imply that panitumumab is more effective in the second- or in subsequent-lines of therapy than in the first-line setting [3, 27] (but one meta-analysis [3] also included results of the PACCE trial).

To sum up, these findings highlight the fact that despite the availability of several different treatment options for mCRC further research is required to find the optimal sequence of the available agents, the ideal combination with chemotherapy and the optimal duration of treatment [12, 27].

KRAS status predictive for (non-)response

only ~50% of WT KRAS patients respond to EGFR-inhibitors

predictive role of BRAF status not yet clear

panitumumab also approved for 2nd-line mCRC therapy in combination with FOLFIRI

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