

Panitumumab for the Treatment of Metastatic Colorectal Cancer

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1. Introduction

According to data by GLOBOCAN, the worldwide incidence of colorectal cancer in 2008 was 1,234,000 (with 663,000 male and 571,000 female cases). The number of deaths due to this disease was 608,000 (320,000 men and 288,000 women). Given these figures, colorectal cancer is the third and second leading cause of mortality among men and women. In the recent year in Hungary with a population around 10 million the annual incidence among males was 4,415, whereas the number of afflicted women was 3,690. Mortality data is similar with deaths among men and women being 2,563 and 2,190 respectively. Therefore, the disease is the second leading cause of death for both genders worldwide and in Hungary as well (Gaudi & Kásler, 2002; Ottó & Kásler, 2005; World Health Organization [WHO] – International Agency for Research on Cancer [IARC], 2008). In international comparison Hungarian colorectal cancer mortality rates for 2008 were the highest in Europe for both men (31.4 per 100,000) and women (16.2 per 100,000). This is in striking contrast to comparable figures of Albanian men (6.2 per 100,000) and women (5.8 per 100,000), with the lowest registered numbers (WHO – IARC, 2008). Both frequencies of the disease and continuously improving treatment results highlight the accentuated place colorectal cancer takes in routine oncology practice and at the same time oblige health care services to provide the best possible treatment for patients.

As a result of organizational efforts in the last decades to improve professional cooperation, leading to the development of new drugs and to a more conscious treatment planning with a closer to optimal use of combinations, metastatic colorectal cancer (mCRC) has become a chronic disease (Haller, 2007; Khan et al., 2008; Khan et al., 2010; Phillips & Currow, 2010; van der Velden et al., 2009; van Kleffen et al., 2004).

Today median survival of CRC-patients from the diagnosis of distant metastases can reach 36 months on overall. Even in disseminated illness the chances of surviving more than five years are above 12% now (Blaser, 2010; Chau & Cunningham, 2009; Goldberg, 2007; Grothey, 2007; Michael & Zalberg, 2000; National Cancer Institute [NCI], n. d.; Sudoyo, n. d.)

In 2004 Grothey and colleagues presented a diagram in the *Journal of clinical oncology* which has been cited countless times ever since. The survival of mCRC patients was plotted on this diagram as a function of the proportion of patients treated with drug combinations considered "basic" (fluoropyrimidine, irinotecan, and oxaliplatin), and multiple linear regression was performed (Grothey et al., 2004) Based on the results it is clear that those the patients that had the greatest chance of survival who had received all three drugs during their treatment. Of course, it is not just "traditional" cytostatic remedies – antimetabolite fluoropyrimidines, the topoisomerase inhibitor irinotecan, and alkalinizing agent oxaliplatin – that influence survival (Takimoto and Calvo, 2005). Based on new results, drugs aimed at biological targets do so, on their own and in different combinations with chemotherapy as well, which we will discuss later in detail.

2. Biological targeted drugs

2.1 Brief description of drugs affecting biological targets

Drugs currently in use in this category can be classified into two major groups.

A well known and characteristic representative of one of these groups is bevacizumab (Avastin®) (European Medicines Agency [EMA], 2011a) inhibiting neoangiogenesis, i.e. this drug slows down the pathological vascularization of tumours and thus inhibits their provision of oxygen and nutrition.

The other group consists of cetuximab (Erbix®) (EMA, 2010) and panitumumab (Vectibix®) (EMA, 2011b), both influencing the effect of "epidermal growth factor receptors" (EGFR) located on the surface of tumours and in this way both interfere with the regulation of cell division and proliferation (Helbling & Borner, 2007; Mayer, 2009; Siena et al., 2009; Willet et al., 2007).

These are all monoclonal antibodies. As a result of advances in manufacturing technology "chimeras" containing more non-human amino acid sequences (cetuximab – "cmab") were followed by "humanized" antibodies like bevacizumab ("beva") with increased proportion of human sequences within the molecule. The ultimate result of this process is the development of monoclonal antibodies containing exclusively human amino acid sequences (panitumumab – "pmab"). The ratio of human and non-human amino acid sequences within a given therapeutic antibody medication is crucial – the presence of the latter usually necessitates the use of saturating doses, while fully human substances can be administered using the same dose from the start of therapy. Human versus non human composition of complex protein molecules administered via infusion is also a key determinant of the frequency of infusion related and other side effects caused by "foreign proteins" (Eng, 2010; de Bono & Rowinsky, 2002; EMA, 2009; EMA, 2011a, b; Hochster, 2006; LoBuglio, 1989; Yang et al., 2001).

2.1.1 Bevacizumab

Generally used in combination with traditional cytostatic drugs, bevacizumab has been approved in Europe for many types of tumors: mCRC, breast cancer, clear cell renal cell

carcinoma, and lung cancer (excluding planocellular or small cell carcinoma-types) (EMA, 2011a). In addition, the U. S. Food and Drug Administration (FDA) has also approved its use in brain tumour recurrences following "traditional" treatment and in advanced brain tumour cases as well (glioblastoma multiforme) (U. S. Food and Drug Administration, 2009).

Beva binds to "vascular endothelial growth factor" (VEGF), one of the most important angiogenesis regulators. By doing this, beva inhibits the binding of VEGF to its receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells. The neutralization of VEGF's biological activity lowers tumour vascularisation, normalizes the tumour's surviving vasculature and inhibits the development of a new vascular system for the tumour. By blocking tumour growth beva thus lowers intra-tumour pressure helping anticancer drug delivery to tumour tissue (Bergers & Benjamin, 2003; Borgstrom et al., 1999; EMA, 2011a; Folkman, 1971, Kim al., 1993).

One of its main side effects is high blood pressure (usually successfully treated with ACE inhibitors, calcium channel blockers, or diuretics), and this usually does not necessitate ending or suspending the use of the drug. Therapy-resistant chronic hypertension however may mean a treatment contraindication. The frequency of proteinuria can vary considerably. Its severity can range from laboratory value deviations to development of nephritic syndrome. The severity of the detrimental side effect congestive heart failure can also cover quite a wide spectrum. Reduced left ventricle ejection fraction may ensue without any clinical symptoms but can be represented in a life-threatening form too. A wide variety of arterial and venous thromboembolic complications, as well as bleeding of any grade can occur. Bleedings may represent in the gastrointestinal system, primarily as perforations in patients with metastatic colorectal cancer treated with bevacizumab. Inflammatory intestinal diseases render patients especially susceptible to such perforations. Fistulae can also develop in different areas; perforations of the nasal septum are detected rarely. Reversible posterior leukoencephalopathy syndrome is a rare, neurological disorder which can also develop during beva treatment. Differential diagnosis can be challenging in such cases to rule out headaches, mental disorders, and possible cortical blindness frequently caused by cerebral metastases. (Allen et al., 2006; BC Cancer Agency Cancer Management Guidelines, 2006; Benson et al., 2003; EMA, 2011a; Fakih & Lombardo, 2006; Giantonio et al., 2004; Hamilton, 2008; Kilickap et al., 2003; Martel et al., 2006; Pereg & Lishner, 2008; Scappaticci et al., 2007; Traina et al., 2006; van Heeckeren et al., 2007; Widakowich et al., 2007).

2.1.2 Correlation between the therapeutic effect of EGFR inhibitor monoclonal antibodies (cmab and pmab) and K-ras mutation status

Before presenting the mechanism of action of cmab and later that of pmab in details, it is necessary to understand the importance of EGFR status and K-ras mutation. Awareness of EGFR and K-ras mutation status has proven to be essential not only for an apt evaluation and interpretation of clinical trial results, but for adequate patient selection and diagnostics planning as well. A precise determination of both is a prerequisite for an effective treatment in everyday clinical routine. EGFR, a superficial structure of epithelial tumours and also CRC cells is a glycoprotein composed of three subunits. The exodomain receiving the ligand is outside the cell membrane, while the hydrophobic transmembrane domain provides proper cell membrane integration. The cytoplasmic "endodomain" is a catalytic subunit with tyrosine kinase activity. It transmits signals to other proteins by phosphorylating

messenger routes. In a complex mechanism, EGF activation initiates cell division following the reception of an adequate external signal. It also assures survival and inhibits apoptosis. The resulting effect is cell proliferation. While this mechanism is strictly controlled in healthy cells, EGF activation is uncontrolled in a considerable proportion of epithelial tumours. The signal is transmitted to other proteins via the biochemical route of tyrosine kinase by phosphorylation. EGF activation can initiate cell division, proliferation, development of metastases and inhibition of apoptosis. Apparently, this leads to tumour progression (Cohenuram & Saif, 2008; Coutinho & Rocha Lima, 2003; EMA, 2009; EMA 2011b; Harari, 2004; Hamilton, 2008; Herbst & Shin, 2002; (Ritter & Arteaga, 2003; van Cutsem et al., 2009).

EGFR inhibitors (cmab and pmab) are licensed for the treatment of mCRC patients. They bind to the extracellular ligand-binding domain and thus inhibit transmembrane signal transmission and prevent EGF dependent signal transduction within the cell as well. Although the mechanism of action has already been established in theory, EGFR inhibitors yield clinical improvement to not more than approximately 50% of mCRC patients. This observation led to the assumption that a biological factor could have prevented these monoclonal antibodies from being effective in tumours expressing EGFR. The K-ras (“Kirsten rat sarcoma 2 viral oncogene homolog”) gene belongs to the family of RAS proto-oncogenes. The K-ras protein coded by this gene plays a central role in growth-inducing signal transmission routes. By doing so it affects cell reproduction, differentiation and survival. If a mitogenic signal reaches the EGF receptor, the signal is forwarded to the nucleus by the K-ras. It is essential that this close correlation applies only to the “normal” (i.e. non-mutated or “wild type”) K-ras. Mutant types of K-ras escape receptorial regulation and thus they autonomously stimulate cell proliferation.

For this reason K-ras mutation is not a genetic failure with “function loss”, on the contrary, in this case RAS remains in “on” status (i.e. phosphorylation is continuous) and acts independently from EGFR (and other physiological signaling pathways). As a consequence, despite the signals reaching the cell surface being “blocked” by monoclonal antibodies at the receptor level, signaling tracks regulated by EGFR under normal conditions remain (chronically) activated (Amado et al., 2008; Benvenuti et al., 2007; Dahabreh et al., 2011; De Roock et al., 2010; (Engstrom et al., 2011a, b; Esteller et al., 2001; EMA, 2009; EMA 2011b; Hamilton, 2008; Heinemann et al., 2009; Malumbres & Barbacid, 2003; Normanno et al., 2009).

As the estimated incidence of K-ras mutation in CRC is 30-50%, it is expected that in about half to two thirds of patients the regulation of signal effect and signal transmission are preserved and drugs acting via the K-ras route can be used with success. (Amado et al., 2008; Benvenuti et al., 2007; Bardelli & Sien, 2010; Esteller et al., 2001; Garcia-Sáenz et al., 2009; Malumbres & Barbacid, 2003; Nagasaka et al., 2004). In an interesting re-evaluation of their primary study population Hurwitz et al. found that though bev combined with IFL as a first line treatment of mCRC was effective in both K-ras wild type and mutant subgroups, efficacy was by large affected by K-ras status, underlining a mixed predictive and prognostic function of this mutation (Hurwitz et al., 2009).

3. Characteristics, application and side effects of panitumumab

3.1 Characteristics of panitumumab (Vectibix®)

Pmab is a recombinant fully human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese Hamster Ovary, CHO) by recombinant DNA technology. Vectibix has high

affinity and specificity to human EGFR. It inhibits receptor autophosphorylation caused by all known EGFR ligands by attaching to the ligand-binding domain. Binding of pmab to EGFR results in the internalization of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin-8 and vascular endothelial growth factor production (Berardi et al., 2010; EMA, 2011b; Harari, 2004; Helbling & Borner, 2007; Keating, 2010; Martinelli et al., 2007; Peeters et al., 2008; Pikó, 2009; Rakkar, 2007).

3.2 Using Vectibix

The recommended dose of Vectibix is 6 mg/kg of bodyweight once every two weeks both in monotherapy and when combined with cytostatics. Prior to infusion Vectibix should be diluted in 100 mL of 0.9% sodium chloride solution to a final concentration not exceeding 10 mg/mL. Vectibix must be administered as an intravenous infusion via an infusion pump using a low protein binding 0.2 or 0.22 micrometer in-line filter through a peripheral line or indwelling catheter. The recommended infusion time is approximately 60 minutes (Alberta Health Services, 2010; EMA, 2011b). The first dose injected over 60 minutes was well tolerated in clinical trials where Vectibix was combined with cytostatic agents; subsequent treatments were allowed to be given over 30 minutes (Douillard et al., 2010; Peeters et al., 2010). Doses higher than 1,000 mg should be administered as a 150 mL solution over approx. 90 minutes. No incompatibilities have been observed with 0.9% sodium chloride injection in polyvinyl chloride bags or polyolefin bags (EMA, 2011b; Knudson, 2007).

3.3. Side effects of panitumumab

3.3.1 Skin toxicity

The common pharmacological effect of EGFR inhibitors can lead to the following: EGFR inhibition in the skin, hair follicles, and periungual tissues can cause abnormal proliferation, migration and differentiation of target cells (i.e. basal keratinocytes), while changes in the skin structure attract inflammatory cells. Clinical symptoms emerge within 10 days following the introduction of pmab therapy and resolve in 28 days after the last injection on average. Skin symptoms are characteristic: papular skin rash, monomorphic pustular lesions, etc. presenting on skin areas exposed to the sun. Although signs may resemble those of acne for the first sight (labeled as "acneiform"), differentiation is easy and essential. Acne may manifest as non-inflammatory lesions on the basis of comedos or as inflammatory papules, pustules, or nodules. On the contrary, rash due to EGFR inhibitors is dominated by pustules. Non-inflammatory comedos are never seen in these cases. Skin rash is more widespread than classical acne as symptoms can often be observed on the upper and lower extremities and trunks of patients simultaneously. In order to prevent nail diseases it is important to avoid mechanical injuries (e.g. caused by tight shoes). Development of paronychia can be stopped by bathing the foot in diluted antiseptic agents and by using topical antiseptic ointments. Feet should not be soaked for a long time to prevent tissues from loosening. In some cases surgery cannot be avoided (Busam et al., 2001; Eaby, n. d.; EMA, 2011b; Moy & Goss, 2007; Pérez-Soler et al., 2005; Segært & van Cutsem, 2005; Winkeljohn, 2008).

Conventional modalities to treat acne should not be used. On the contrary, advices and interventions are usually completely different from those applied during acne therapy. Sun bathing is prohibited, patients should protect themselves from any direct sunlight (hat, long-sleeved clothes, and sun screens are recommended). Dryness of the skin should be treated with neutral emollients. Caution is warranted if topical steroid drugs are used. Such

products are recommended solely to alleviate symptoms. Systemic antihistamines are more useful to cure itching. If rash is accompanied by superinfection, external use of either clindamycin or mupirocin, or internal use of tetracycline are to be considered (Eaby, n. d.; EMA, 2011b; Hoda et al., 2008; Lacouture, 2009; Lacouture et al., 2010; Melosky et al., 2009; Moy & Goss, 2007; Peeters et al., 2008; Pérez-Soler et al., 2005; Pikó, 2009; Potthoff et al., 2011; Saif & Cohenuram, 2006; Winkeljohn, 2008). Efforts to deal with skin toxicities via pre-emptive approach (i.e. applying emollients, hydrating and photoprotective creams, topical steroids and oral doxycyclin) in the STEPP (“Skin Toxicity Evaluation Protocol With Panitumumab”) comparative clinical trial resulted in decreasing the frequency of Grade II or more severe forms already present from 62% to 28%. Quality of life improved significantly whereas the clinical efficacy of panitumumab treatment was unaffected. (Lacouture et al., 2010)



Fig. 1. 66-year-old male patient's acneiform rash after 2nd cycle (4th week) of pmab therapy for CRC with hepatic and pulmonary metastases.



Fig. 2. Similar but more pronounced symptoms are visible on the back of the above patient.



Fig. 3. Clearly visible inflammatory signs (pustules) differentiate EGFR-inhibitor therapy related rash from classical acne.



Fig. 4. Nail lesions (paronychia and overgrowth) developed on 6th week of pmab therapy. The disease did not resolve on conservative therapy, surgical treatment (exploration and drainage) was necessary.

It is important to modify or discontinue pmab administration according to the stage of rash. If the adverse events to (U. S. Department of Health And Human Services, U. S. National Institutes of Health, National Cancer Institute - Common Terminology Criteria for Adverse Events [NCI-CTCAE]) Grade 3 skin lesions emerge Vectibix should be suspended until the lesions resolve to Grade 2 or lower. In this case the product can be used by a 50% dose reduction; the dose can then be increased to the original in 25% increments every two weeks. If the rash persists or the symptoms recur in spite of dose reduction, pmab should be definitively discontinued (Alberta Health Services, 2010; EMA, 2011b; Pikó, 2009; Potthoff et

al., 2011; Widakowich et al., 2007). Nevertheless, skin and nail lesions are usually considered as positive predictive markers of efficacy and clinical response (Amado et al., 2008; Berardi et al., 2010; Busam et al., 2001; Eaby, n. d.; EMA 2011b; Grothey, 2006, 2007; Keating, 2010; Malik et al., 2005; Martinelli et al., 2007; Saif & Cohenuram, 2006; Siena et al., 2009; Widakowich, 2007).

3.3.2 Ophthalmologic complications

Since marketing authorization rare cases of keratitis and ulcerative keratitis has been reported, both representing a consequence of general mechanism of action of EGFR inhibitors (EMA, 2009; Burtneess et al., 2009; Specenier et al., 2007; Thomas & Grandis, 2004; Xu et al., 2009). Retrospective analyses have shown that these complications were not severe in clinical trials, i.e. they did not reach Grade 2-4 (U. S. Department of Health And Human Services et al., 2009), and their incidence was between 0.2% and 0.7%. In clinical use as monotherapy, another case of severe keratitis and three cases of severe ulcerative keratitis have been reported (EMA 2011b). Care must be taken when the patients has a record of keratitis or ulcerative keratitis in his/her medical history. Consultation with an ophthalmologist is necessary in any instances the following symptoms are presented: inflammation of the eye, increased lacrimation, sensitivity to light, blurred vision, pain or redness of the eyes. The diagnosis of keratitis allows the oncologist to weigh the risk/benefit ratio of continuing or stopping Vectibix therapy, in cases of ulcerative keratitis however pmab treatment should be discontinued or suspended (EMA, 2011b; ManageCRC.com. 2011).

3.3.3 Pulmonary complications

Lung toxicity is a widely known complication of EGFR inhibitor therapies (interstitial lung disease [ILD], interstitial pneumonitis, fibrosis) (Eaby, n. d.; Cohenuram & Saif, 2007; Gandara et al., 2006; Grothey, 2006; Inoue et al., 2003 ; Nagaria et al., 2005 ; Pikó, 2009 ; Saif & Cohenuram, 2006 ; Yoneda et al., 2007).

As patients suffering from the above lung diseases were excluded from pmab clinical trials before randomization, there are no available data on lung complications in these patients during pmab therapy (EMA, 2011b). If patients experience chest symptoms (dyspnea, dry cough, clinical or ECG signs of hypoxia, abnormalities of pulmonary function tests), at least simple (posterior-anterior) chest radiography or a more appropriate chest CT should be performed. If these examinations are indicative of an interstitial pulmonary disease, Vectibix should be discontinued. Depending on the severity of symptoms, symptomatic treatment with corticosteroids or diuretics (NCI-CTCAE Grade 2), oxygen supplementation (Grade 3), or intubation, tracheostomy or assisted respiration (Grade 4) may be necessary (Alberta Health Services, 2010; Peeters et al., 2008; U. S. Department of Health And Human Services et al., 2009).

It is important to differentiate pulmonary changes due to pmab therapy from signs of an underlying malignancy (e.g. well-defined metastases, carcinomatous lymphangiosis). Besides scrutinizing radio-morphologic features, other helpful measures, e.g. obtaining earlier radiographs, considering the dynamics of the process and sharing exact data with the radiologist (about the disease, signs, physical examination results, applied therapy) and further personal consultations may be appropriate as well and would underline the necessity of multidisciplinary oncological team-work.

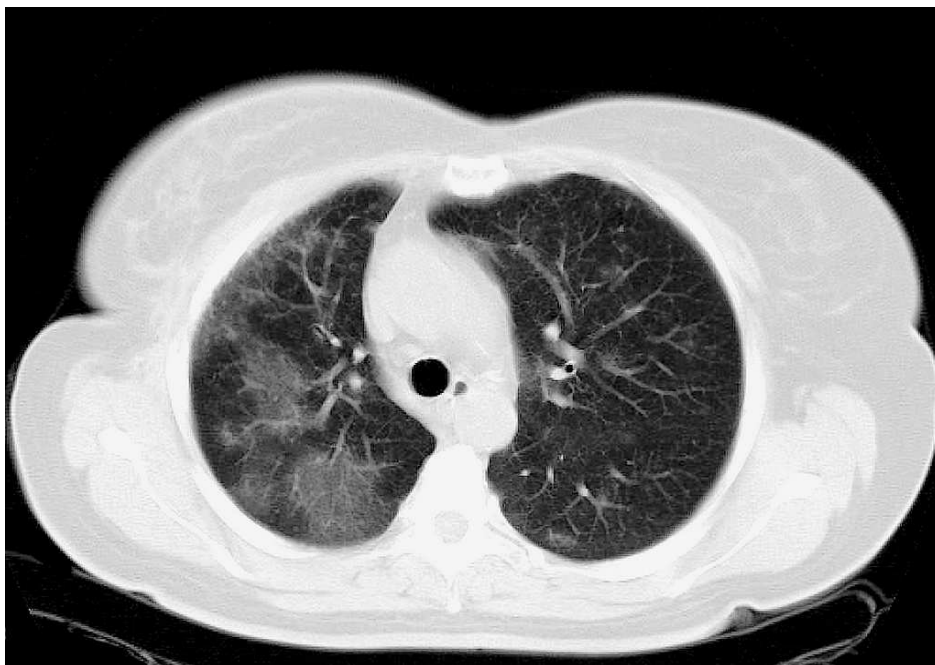


Fig. 5. Chest CT taken before starting planned pmab therapy of a mCRC patient who received therapy earlier in another institution. As the scan revealed pulmonary infiltration we did not administer Vectibix.

3.3.4 Hypomagnesaemia and hypocalcaemia

Symptoms are caused by the renal effects of EGFR inhibitors. Pronounced EGFR expression can be detected in the renal parenchyma (primarily in the ascending limb of loop of Henle, where magnesium and calcium are absorbed). Inhibition of EGFR in the renal tissue causes a decrease in the serum magnesium and calcium concentration. Following the recognition of these phenomenon patients involved in pmab studies have had their serum magnesium levels assessed. In 39% of cases the result proved to be abnormal, most often indicating mild hypomagnesaemia. The “Summary of Product Characteristics” requires regular assessments of serum magnesium and calcium levels before the treatment starts and for at least 8 weeks thereafter. Appropriate substitution is necessary for patients with mild-moderate disturbances, but the treatment may be discontinued in those who do not respond to substitution or present with severe clinical signs. Other electrolyte changes, such as hypokalaemia, have been detected as well. In such cases appropriate electrolyte substitution must be the primary step (Eaby, n. d.; EMA, 2011b; Pérez-Soler et al., 2005; Peeters et al., 2008; Pikó, 2009;; U. S. Department of Health And Human Services et al., 2009).

3.3.5 Diarrhoea

This is also a common side effect of EGFR inhibitors and indicates an injury of the intestinal mucosa similar to what is seen in dermatologic toxicities. Its frequency is not high; about 2% in patients with wild-type K-ras would develop diarrhoea. Its significance and its effect on

the continuability of pmab therapy depend on the severity of symptoms. Apart from lifestyle advices and loperamide administration, one should bear in mind that parenteral fluid replacement and normalization of electrolyte levels is essential in NCI-CTCAE Grade 3 diarrhoea (defecation more than 7 times per day or fecal incontinence, or necessity of hospitalization due to symptoms). If one fails to do so, calcium and magnesium electrolyte disturbances may increase in severity and acute renal failure may also develop (Berlin et al., 2007; Eaby, n. d.; EMA 2011b; Moy & Goss, 2007; Peeters et al., 2008; Pikó, 2009; Tuma, 2006; Widakowich et al., 2007).

3.3.6 General symptoms and infusion complications

Generally speaking, this term actually stands for adverse events (fever, chills and suffocation) which develop when a “foreign” protein is administered. Infusion complications emerge within 24 hours after administration. In most cases, premedication is needed to prevent general symptoms and infusion complications if human-animal chimeric or humanized monoclonal antibodies are used. As pmab is fully human, this is unnecessary when applying Vectibix. Nevertheless, infusion reactions might emerge during administration of fully human amino acid sequences despite using adequate protein filters to avoid complications. Several authors have reported however, that treatment with pmab may still be a viable and beneficial option for patients who suffered infusion reaction while being treated with the “chimeric” monoclonal antibody cetuximab (Cartwright & Genter, 2008; Chung, 2008; EMA, 2011b; Grothey, 2006; Helbling & Borner, 2007; Heun & Holen, 2007; Langerak et al., 2009; Lenz, 2007; Nielsen et al., 2009; O’Neil et al., 2007; Power et al., 2010; Saif et al., 2008).

Across all clinical studies, infusion-related reactions were reported in 3% of Vectibix-treated patients; of which < 1% were severe (NCI-CTC grade 3 or 4), i.e. required acute hospitalization or prolongation of hospitalization or was life-threatening. In the post-marketing setting serious infusion reactions have been reported, including rare reports of fatal outcome. If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion, Vectibix should be permanently discontinued (U. S. Department of Health And Human Services et al., 2009).

4. Results of clinical studies with panitumumab

4.1 Phase 1 studies

At the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2002 Figlin and co-workers demonstrated the effect of a newly developed monoclonal antibody (called “ABX-EGF” in the presentation) on different tumors they evaluated in a phase 1 study (Figlin et al., 2002). The applied doses ranged from 0.01 mg/kg to 2.5 mg/kg. They found that the above therapy resulted in significantly long survival in certain cases. One patient with oesophageal cancer had stable disease for 7 months and minor response was reached in a patient with prostate cancer. No antibodies produced against ABX-EGF were detected, and its main side effect was rash.

In 2004, Rowinsky and co-workers published their results from a Phase 1 study with ABX-EGF (the agent later named pmab) used in renal cell carcinoma (Rowinsky et al., 2004). The highest dose used in this study was 2.5 mg per week. Although this dose could produce the highest rate of objective tumour response, the relationship between time to progression (median values were between 53 and 165 days) and the applied dose was unclear. It was

found that the most common side effects were dermatological symptoms (rash), already known in case of EGFR inhibitors. Presentation and severity of these symptoms were dose dependent and closely correlated with treatment results, while low haemoglobin and high alkaline phosphatase levels had a negative predictive value. No antibodies against ABX-EGF have been detected in this study.

4.2 Phase 2 studies

Based on the analysis of early Phase 1 study results subsequent studies with pmab were conducted in mCRC patients.

In 2004 and 2005 results of a phase 2 study with pmab monotherapy, involving CRC patients relapsing following a subsequent irinotecan and oxaliplatin therapy, were published (Hecht et al., 2004; Malik et al., 2005). Data of 148 patients were evaluable in the analysis. Median progression-free survival (PFS) was 3.4 (2.0-4.0) months and overall survival (OS) was 9.4 months (6.0-10.6). Results did not differ in EGFR positive or negative patients.

Berlin and co-workers (Berlin et al., 2004) and Hecht and co-workers (Hecht et al., 2006b) used pmab with combinations containing irinotecan (IFL or FOLFIRI) in Phase 2 studies. The main adverse effects were dermatological symptoms and diarrhoea. In the IFL arm partial remission fulfilling the "Response Evaluation Criteria in Solid Tumors" (RECIST) was seen in 48% of patients and stable disease could be reached in 26% that equated to a tumour control in 74% of cases (Jaffe, 2006; Padhan & Ollivier, 2001; Therasse et al., 2000). Median PFS and OS were 5.6 and 17 months, respectively. When pmab was used in combination with FOLFIRI rates of remission, stable disease and total tumour control were 33%, 46%, and 79%, respectively. Progression-free survival was 10.9 months, but overall survival results could not have been calculated (overlapping results of the study had been published by other authors in various forums).

Patients were later divided into groups with negative or "low" (1 to 10%) (Hecht et al., 2006a), and "high" (above 10%) EGFR-expression (Berlin et al., 2006). No significant differences were found: at low EGFR levels 48% response rate and the rate 7.9 weeks median PFS were detected, while in patients with high EGFR levels 42% tumour response rate and 12-14 weeks PFS was seen. The adverse effect profile was similar. Grade 3/4 adverse events were presented in 19-24% (dermatological symptoms prevailed), and the rate of hypomagnesaemia was similar (8 and 12%).

4.3 Phase 3 study and analysis of further results

Van Cutsem et co-workers were the first to publish a comparison of Vectibix and "best supportive care" (BSC): they treated a total of 463 patients with EGFR expressing mCRC, after failure of irinotecan- and oxaliplatin-containing therapies (van Cutsem et al., 2007). Patients were given either pmab (6 mg/kg every two weeks, without premedication) in combination (with symptomatic treatment) or BSC alone, in 1:1 ratio. Patients in the BSC group could have been switched to the active arm in case of progression. Thirty-five percent of patients had been on adjuvant chemotherapy earlier, and all of them had had at least two treatment options due to metastatic disease. Thirty-seven percent of the patients had a disease progression after the third line of drug therapy. Treatment efficacy was assessed after week 8, 12, 16, 24, 32, and 40, and every 3 months thereafter according to the RECIST (Jaffe, 2006; Padhan & Ollivier, 2001; Therasse et al., 2000).

The following chart represents the results of this study and shows the benefits of Vectibix compared to supportive care:

Studied parameters	pmab + BSC (232 patients)	BSC alone (231 patients)
PFS rate at week 24	18%	5%
PFS rate at week 32	10%	34%
Response rate (RR)	8%	0%
Stable disease (SD)	28%	10%
Overall response rate (ORR)	36%	10%
Median duration of response	17 weeks	NA

Table 1. Results of progression-free survival (PFS), response rate, stable disease, overall response rate treated with pmab + BSC vs. BSC alone (adapted from: van Cutsem et al., 2007)

In terms of all parameters (age, sex, site of primary tumour, ECOG performance status, former lines of chemotherapy applied, number of organs with metastases and degree of EGFR positivity), subgroup analyses unanimously showed that the active treatment arm (pmab) was superior to BSC. Degree of risk reduction was 46%, which was statistically significant ($p < 0.000000001$). It is remarkable that among the 174 patients who were crossed over from BSC arm to the active (pmab) arm due to progression partial response (PR) could be reached in 9% and SD in 32% of cases, in spite of a more progressed disease (Cohenuram & Saif, 2007).

This study once again proved the correlation between side effects and efficacy, i.e. assessment of the results showed that skin symptoms are of good predictive value. These findings underline the fact that rash is one of the most important predictive factors of efficacy.

In the study designed to compare pmab and BSC, Siena and co-workers re-assessed response and survival data, and divided the group of responders into subgroups of patients with remission and those with stable disease. Differences between each group were statistically confirmed (Siena et al., 2007). Curves demonstrating treatment efficacy were also different, survival curve of patients with disease progression and that of those with no progression after 8 weeks of pmab therapy (equivalent with 4 treatment cycles) were compared. Based on these data the authors presumed with good reason that there must be another factor apart from the detectable EGFR expression (an inclusion criterion for all patients) that has an impact on treatment results.

The presumed factor was later proved to be the K-ras mutation status. Differences in treatment results could be explained by the presence of "normal" (wild type) or "abnormal" (mutated) K-ras genes. Amado and co-workers determined the frequency of mutations in the already known patient population (Amado et al., 2008). Although not all, 427 samples of the 463 patients were suitable for subsequent central laboratory evaluations and were eventually analyzed. Analyses showed mutations in 184 patients and "wild type" K-ras in 243 patients. Data analyses showed that no correlation can be detected between K-ras mutation and EGFR status (the latter determined by immunohistochemistry), neither by expression nor by the intensity of membrane staining.

Analyses of clinical results showed that (in accordance with the biological role of K-ras described earlier) tumour progression in mutation carriers is independent from the regulation of stimuli reaching the EGFR. Consequently, in these patients the EGFR inhibitor pmab is less effective and does not provide better results than BSC.

	pmab + BSC		BSC	
	wild type K-ras	mutant K-ras	wild type K-ras	mutant K-ras
Number of patients	124	84	119	100
Median PFS (weeks)	16	8	8	8
Median OS (months)	8,1	7,6	4,9	4,4

Table 2. Progression-free survival (PFS) and overall survival (OS) of pmab + BSC vs. BSC treated patients by K-ras status. (Source: Amado et al., 2008)

Side effects were more frequent and severe in the K-ras mutant subgroup that, apart from inefficacy, may lead to a worse tolerability and possibly higher treatment risks. Considering both efficacy results and side effects, it was proven that pmab should only be used in patients with the wild type K-ras.

4.4 Vectibix summaries of product characteristics: A reinforcement of treatment criteria and results of the clinical trials

Based on the consideration that the approval had been based on a clinical trial including pre-treated EGFR positive patients whose treatment was shown to be effective only in those with the K-ras wild type, the European Medicines Agency (EMA) summarizes treatment criteria in all of the Summaries of Product Characteristics congruently. „Vectibix is indicated as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens” (EMA, 2011b). The U. S. Food and Drug Administration (FDA) defines the same criteria in more detail: „Vectibix is an epidermal growth factor receptor antagonist indicated as a single agent for the treatment of metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens. Approval is based on progression-free survival; no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix. Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix is not recommended for the treatment of colorectal cancer with these mutations” (U. S. Food and Drug Administration, 2009).

5. Combining panitumumab with cytostatic agents

The Summary of Product Characteristics of other anti-mCRC targeted biologic therapies states that these agents can be used either only in combination with “traditional” anti-tumour chemotherapies (e.g. beva), or both in combination and as a stand-alone therapy (e.g. cmab). In contrast, pmab could only have been used as a monotherapy and in patients who have already had a definite cytostatic pre-treatment. Supposing that such timing of treatments does not provide optimal circumstances for the efficacy of monoclonal antibodies, possible combinations of Vectibix and cytostatic agents have been evaluated in clinical studies.

5.1 Combination of pmab and chemotherapy as a first-line treatment

Following completion of a study involving 1183 patients titled “Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to determine

Efficacy" (PRIME), Douillard and co-workers presented results of the application of pmab with FOLFOX4 (5-fluorouracil, leucovorin and oxaliplatin) versus FOLFOX4 alone as the first-line treatment in mCRC patients in open label, randomized, multicenter, Phase 3 trial (Douillard et al., 2010). Eligible patients were individuals older than 18 years who did not receive chemotherapy for their metastatic disease. 5-fluorouracil was allowed in adjuvant chemotherapy in case the disease recurred within 6 months after discontinuing the adjuvant therapy, but oxaliplatin was not allowed under any circumstances.

Pmab was administered every two weeks in a dose of 6 mg/kg by intravenous infusion over one hour on the day before FOLFOX4 chemotherapy was scheduled. If patients tolerated the first pmab infusion, the consecutive doses could have been administered over 30 minutes. FOLFOX4 was administered every two weeks: on day 1 oxaliplatin was administered at 85 mg/m² and leucovorin at 200 mg/m² (or equivalent dose) via infusion. On days 1 and 2 this was followed by fluorouracil at 400 mg/m² by intravenous bolus and fluorouracil at 600 mg/m² by a continuous 22-hour infusion. This treatment was continued until disease progression (adjudicated by an independent committee) or the occurrence of unacceptable side effects.

In terms of evaluation the study had four arms, as groups of K-ras mutant and wild-type patients were distinguished following previous laboratory assessment both in the FOLFOX4 alone and the pmab + FOLFOX4 arm.

The administration of the monoclonal antibody Vectibix to patients with wild-type K-ras increased PFS significantly from 8.0 to 9.6 months, while increase in overall survival (23.9 months as compared to 19.7 months) was clinically considerable and relevant nevertheless statistically non-significant, compared to FOLFOX4 alone arm. In K-ras mutated cases however, Vectibix with FOLFOX4 versus FOLFOX4 alone decreased the median PFS (7.3 vs. 8.8 months) and OS (15.5 vs. 19.3 months).

By a glance on the table summarizing side effects one can realize that apart from typical side effects of EGFR inhibitors in the Vectibix group no significant differences were revealed.

Antibodies against pmab were found in blood samples of 3.0% of patients (samples were drawn during treatment). After discontinuation, neutralizing antibodies were found in another 0.4% of patients.

A forest plot subgroup analysis with overlapping confidence intervals showed that pmab addition was generally beneficial in terms of improving progression-free survival. Treatment without pmab showed a tendency to be more beneficial in those with bad performance status (ECOG 2). Pmab seemed to be more beneficial in those with hepatic metastases, however in patients with dissemination in multiple organs and in cases presenting exclusively hepatic metastases no significant differences between the arms were shown. Subgroup analyses of overall survival revealed similar results, notably, poorer general condition (ECOG 2) seemed to be again more disadvantageous for Vectibix treated patients, age and gender showed marked but somewhat weaker interference than is PFS.

The authors claimed that adding pmab to FOLFOX4 increased PFS significantly in previously untreated mCRC patients with wild-type K-ras. Another clinically important feature of pmab is that severe infusion reactions are rare, and the standard 2-week protocol of Vectibix enables treating physicians to synchronize administration with chemotherapy schedules and decreases the number of visits to the minimum. As no premedication is required and no observation is necessary following treatment, the short outpatient therapy is advantageous for patients and caregivers as well.

An important aspect, also relevant for routine clinical practice, was investigated by Siena and co-workers in their subgroup analysis of the above study detailed in ASCO Annual Meeting 2011 (Siena et al., 2011). Patients with good performance status (ECOG 0-1) obviously profited from the addition of pmab to FOLFOX4 as PFS increased in these cases from 8.0 (7.5-9.3) to 10.4 months (9.3-11.3), OS from 20.7 (18.2-23.2) to 25.8 months (21.7-not estimable); whereas at ECOG2 (ambulatory and capable of all self-care but unable to carry out any work activities up and about more than 50% of waking hours) patients the addition a pmab decreased PFS from 7.6 (5.3-11.1) to 4.8 months (2.7-5.3), OS from 11.7 (8.0-15.7) to 7.0 (4.6-11.7) months. An adequate determination of performance status may serve as a simple and statistically convincing tool to predict the value of the addition of pmab to FOLFOX4 in the first line treatment of mCRC.

Notably, besides performance status, quality of life may be a further parameter worth evaluating when analysing treatment results. Primary results from a phase II study involving 142 patients evaluating the combination a pmab and FOLFIRI as a first line chemotherapy in mCRC were published by Kohne and co-workers in 2010 (Kohne et al., 2010). Results showed 48% response rate (RR) for wild type and 29% RR for mutant K-ras patients, with no differences in side effects. Results of a secondary analysis of initial quality of life measures were published during ASCO Annual Meeting 2011 (Karthaus et al., 2011). The results demonstrated that those patients with better quality of life had better tumour responses as well by week 8 and 24 of the combination therapy. It does not seem to be an overstatement that the combination of pmab with cytostatics in the first line treatment of CRC is a promising option for patients in better clinical (performance and quality of life) status.

5.2 Combination of pmab and chemotherapy as a second-line treatment

Peeters and co-workers compared the efficacy of pmab and FOLFIRI to FOLFIRI alone as the second-line treatment of mCRC patients in a phase 3, equally randomized trial (Peeters et al., 2010). The study was originally designed to compare the therapeutic effect in the entire population, but due to convincing external data it was modified before the efficacy assessments so that prospective assessments would be carried out as per the K-ras status of the tumour.

A total number of 1186 patients were treated after randomization. Five hundred-ninety-two (50%) patients were given pmab and FOLFIRI, and 595 (50%) were given FOLFIRI alone. The K-ras status of 1083 patients (91%) was known (based on central laboratory tests): 597 patients (55%) had wild-type K-ras tumour and 486 (45%) had K-ras mutant metastatic colon cancer.

The eligible patients were older than 18 years and their ECOG performance status was 0, 1 or 2. Only one earlier chemotherapeutic scheme, i.e. first-line fluoropyrimidine-based chemotherapy was allowed for the treatment of mCRC. A radiologically verified progression by RECIST was required during the course of treatment or within 6 months. Known EGFR expression or K-ras status were not required for enrolment. Patients previously treated with irinotecan or anti-EGFR therapy were excluded from the study (Jaffe, 2006), (Padhan & Ollivier, 2001), (Therasse et al., 2000).

Pmab (at 6 mg/kg) was administered over 60 minutes by infusion before chemotherapy; if patients tolerated the first dose, the following infusions were administered over 30 minutes. Every patient was given FOLFIRI: 180 mg/m² irinotecan and 400 mg/m² raceme leucovorin

(or 200 mg/m² l-leucovorin) by intravenous infusion on day 1 and 400 mg/m² fluorouracil by intravenous bolus on day 1, followed by 2400 mg/m² by continuous infusion on days 1 and 2. Patients were given chemotherapy with pmab or without pmab until the onset of progression or intolerance as per RECIST (confirmed by independent investigators) (Jaffe, 2006), (Padhan & Ollivier, 2001), (Therasse et al., 2000).

In terms of evaluation the study had four arms, groups of K-ras mutant and wild-type patients (as previously assessed) were distinguished both in the FOLFIRI (alone) and the pmab + FOLFIRI arm.

PFS improved significantly in the subgroup of wild-type K-ras patients if pmab was added to chemotherapy; the median PFS was 5.9 and 3.9 months in the pmab + FOLFIRI and the FOLFIRI alone group, respectively. A non-significant increase in OS was also observed, median OS was 14.5 and 12.5 months, the response rate improved from 10% to 35% with added pmab. Theoretical assumptions and earlier clinical experiences were confirmed by the fact that no difference was seen in terms of efficacy in patients with K-ras mutant tumors compared to chemotherapy alone.

Antibodies produced against pmab following therapy were found (by central laboratory) in less than 1% (4 out of 501) of patients. None of these antibodies had a neutralizing effect.

Subgroup analysis suggests that pmab was advantageous in every subgroup in terms of improved PFS with a similar age and gender tendency as seen in the "PRIME" study. In terms of OS, combination arm seemed equivocal with chemotherapy alone in patients previously treated with oxaliplatin, beside those overlapping confidence intervals and summary measures favouring panitumumab reinforced a positive tendency of improving OS.

The authors claimed that the study confirmed the efficacy of pmab with FOLFIRI in K-ras wild-type mCRC patients who were treated previously. PFS improved in a statistically significant manner in this group, which underlines the fact that K-ras status of the tumour can be considered as a predictive biomarker. With a Q2W administration, pmab was comfortably combined with FOLFIRI given at a similar dosing frequency. The toxicity profile was not different from that of EGFR inhibitors and chemotherapy combinations, toxicities could have been managed well.

Considering that, in Hungary bevacizumab is reimbursed only as a first line treatment by the state health fund - even though its use is not confined to a given line in mCRC by the effective Summaries of Product Characteristics (EMA, 2011a). Peeters and co-workers published data of critical relevance in ASCO Annual Meeting 2010 in this aspect (Peeters et al., 2010). The authors evaluated K-ras wild type patients from the above study previously treated with bevacizumab. According to the results, PFS was not different in bev pre-treated patients compared to the overall K-ras wild type study population (5.8 and 3.7 months vs. 5.9 and 3.9 months for pmab + FOLFIRI and FOLFIRI arms). In striking contrast OS improved when bev treatment preceded the pmab + FOLFIRI combination in second line from 14.5 months to 15.7 months.

6. Panitumumab in current therapeutic guidelines

6.1 Pmab in U. S. guidelines

From among clinical recommendations issued in the United States the first to review is the National Comprehensive Cancer Network's (NCCN) guidelines referring to the diagnosis and treatment of colon (Version 3.2011) and rectal carcinoma (Version 4.2011) (Engstrom et

al., 2011a, b). As the results of clinical studies with pmab concern distant metastatic diseases only, there is no significant difference between the two compilations. Like other agents affecting biological targets pmab is not allowed in any adjuvant indication except for clinical trials. Pmab is recommended in monotherapy or in combination with FOLFIRI in diseases with distant metastases whether or not resection of the primary malignancy was performed. It is considered reasonable to remove the primary malignancy (which has not been removed earlier) and the distant metastases in one or more surgeries following a 2- to 3-month treatment. (It is strongly highlighted in the recommendation, that K-ras evaluation must be performed and that the product should be administered only in patients with the wild type K-ras.) In non-resectable synchronous or metachronous distant metastases FOLFIRI \pm pmab is an alternative of FOLFIRI \pm bevacizumab or cetuximab as a first-line therapy at least 12 months after the administration of adjuvant FOLFOX.

In patients eligible for intensive treatment, pmab \pm FOLFOX is considered as the first-line therapy of metastatic diseases (among other combinations), while pmab \pm FOLFIRI acts as a second-line therapy. Monoclonal antibody panitumumab is indicated as monotherapy in case the patient has decreased chemotherapy tolerance. Biological targeted agents such as pmab (depending on the previously administered agents) can be administered following a new progression (i.e. as a third treatment possibility), mostly in patients who do not tolerate irinotecan. Vectibix is recommended as a monotherapy by NCCN in patients who are ineligible for intensive therapy.

6.2 Pmab in european guidelines

The European Society for Medical Oncology (ESMO) released guidelines in 2010. Pmab is not mentioned in the publications referring to the diagnosis, adjuvant therapy and follow-up of CRC (Labianca et al., 2010). This is compliant with the European Summary of Product Characteristics, which limits treatment possibilities much rigorously than the guidelines in the United States do. In guidelines detailing the treatment of advanced disease authors state (van Cutsem et al., 2010) that anti-EGFR antibodies pmab and cmab are effective as monotherapy for patients with chemorefractory mCRC, and wild-type state of K-ras is necessary to reach therapeutic effect. In comparison with BSC, pmab is considered beneficial in terms of PFS; this effect is not reflected in terms of overall survival (OS) due to the "cross-over" design of trials. Pmab and polychemotherapy (FOLFOX4 as a first-line, and FOLFIRI as a second-line therapy) but the absence of significant improvement in OS is emphasized. Evidence level of all recommendations for pmab therapy is IB.

7. Summary

Being a fully human monoclonal antibody not requiring a special pre-treatment or saturation dosage, pmab belongs to a new group of biological targeted agents used in the treatment of metastatic colon or rectal cancer. Pmab binds to EGF receptors, and the post-study pathologic evaluation of monotherapy registration trial samples provided convincing evidence of the crucial role K-ras status played in clinical efficacy: median progression-free survival was 16 weeks in the wild-type (vs. 8 weeks with best supportive care) patients group. Although pmab was practically ineffective in patients with mutant K-ras, side effects were more frequent and severe. According to effective Summaries of Product Characteristics the product can be applied in Europe as monotherapy in EGFR positive and K-ras wild-type

mCRC patients after fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapeutic protocols had failed.

Based on clinical study results published in 2011, the addition of panitumumab to FOLFOX4 polychemotherapy as a first-line treatment in wild-type K-ras resulted in a significant increase in progression-free survival (PFS) (8.0 to 9.6 months), while increase in overall survival (OS) (19.7 to 23.9 vs. FOLFOX4 alone) was clinically considerable but non-significant. In K-ras mutant cases however, Vectibix with FOLFOX4 versus FOLFOX4 alone decreased the median PFS (8.8 to 7.3 months) and OS (19.3 to 15.5 months). PFS improved significantly in the group of wild-type K-ras patients if pmab was added to the FOLFIRI protocol as a second-line treatment; median PFS was 5.9 and 3.9 months in the pmab + FOLFIRI and the FOLFIRI alone groups, respectively. A non-significant increase in OS was also observed; median OS was 14.5 and 12.5 months, and response rate significantly improved from 10% to 35% with added pmab. In mutant K-ras, PFS was 5.0 months with added monoclonal antibodies and 4.9 months with FOLFIRI alone, while OS was 11.8 and 11.1 months, respectively, i.e. no difference could have been statistically confirmed. Following a positive EMA's Committee for Medicinal Products for Human Use (CHMP) opinion in the middle of 2011, both the FOLFOX4 (1st line) and the FOLFIRI (2nd line) combinations will be likely authorized in the EU for the treatment of mCRC.

The side effect profile matches other EGFR inhibitors (the spectrum as a whole being utterly different from that of conventional cytostatics), with dermatologic symptoms (rash), nail diseases, lung infiltration, diarrhoea and electrolyte disturbances of renal origin may develop. Infusion complications are not common. Panitumumab therapy is safe in cases where followed-up carefully, this may mean temporary suspension of treatment, dose reduction or therapy discontinuation if justified by above detailed side effect related signs and symptoms.

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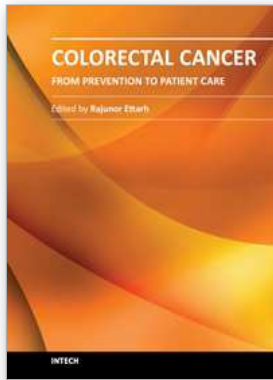
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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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