National PBM Drug Monograph

Panitumumab (Vectibix)

January 2007

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Indication- Panitumumab is a fully humanized monoclonal antibody FDA approved for the treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy regimens.

Mode of Action- Panitumumab competes with endogenous ligands such as epidermal growth factor and tumor growth factor α (TGF- α) to block stimulation of the EGF receptor. By blocking these chemicals, it is thought that critical signaling cascades are prohibited from occurring which would otherwise result in downstream activation of key signaling pathways involved in the progression of metastatic disease. Some of these processes include: cell growth, survival, motility, proliferation, and transformation.

Dose- There is no loading dose. Panitumumab is administered intravenously at 6mg/kg every 14 days. The manufacturer has provided specific dosage adjustment recommendations in patients who experience intolerable skin and infusion-related adverse events.

Safety- In clinical trials, panitumumab was associated with the following serious adverse events: pulmonary fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation. Common adverse events noted were: skin rash with variable presentation, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea and diarrhea.

Efficacy- Panitumumab was approved for metastatic colorectal cancer (mCRC) on the basis of a pivotal phase III trial in which patients were randomized to either panitumumab with best supportive care or best supportive care alone. The primary endpoint in this trial was progression free survival. Subjects in the panitumumab arm had a hazard ratio of 0.54 (95 confidence interval [CI]: 0.44-0.55; P<0.0001). Subset analyses demonstrated that these findings were irrespective of other patient factors (sex, previous chemotherapeutic regimens, amount of EGFR staining). On the other hand, it is suggested that there is a correlation between the grade of rash and the extent to which a patient may respond to therapy with grades 3 and 4 rash associated with better response rates. On a final note, inclusion criteria within the studies included EGFR staining and intensity; however, correlation analyses did not demonstrate any relationship between extent of EGFR staining and patient response.

Panitumumab is also being studied in the context of metastatic renal cell carcinoma and non-small cell lung cancer. Additionally, clinical trials are currently ongoing or in recruitment to determine the efficacy of this agent in combination with other chemotherapeutics or as a radiosensitizing agent.

Conclusions- Panitumumab monotherapy is associated with an improvement in progression free survival in comparison to best supportive care. The basis of the approval of this agent was a phase III pivotal trial powered for this endpoint as opposed to overall survival. It is unclear what subset of patients would derive the most benefit from this agent as EGFR expression was not demonstrated to correlate with a patient's response rate.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating panitumumab for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Panitumumab is a fully humanized IgG2 monoclonal antibody that binds specifically to the Epidermal Growth Factor Receptor (EGFR). The fully humanized property of this agent is thought to confer less of an antigenic response within the human host compared with its murine or chimeric counterparts.

Pharmacology/Pharmacokinetics[1,2,3,6]

EGFR is expressed in normal epithelial cell lines. The over expression of this receptor within human cancers is the basis of targeted therapies such as panitumumab. The sequence of cell-signaling events begins with endogenous ligand (epidermal growth factor or tumor growth factor alpha) stimulation of the receptor, leading to dimerization reactions within the tyrosine kinase domain of the proteins, and then transmission of the signal to the nucleus which in turn leads to the regulation of the transcription of proteins involved in cellular growth, survival, motility, proliferation, and transformation.

Panitumumab blocks the initial ligand binding step of the reaction consequently preventing other downstream cellular processes from occurring.

Table 1: Pharmacokinetic parameters*

* Based on recommended dose regimen of 6mg/kg intravenous infusion every 14 days as a 1-hour infusion

Parameter	Panitumumab
Elimination	
Mean Clearance (SD)	4.9 ± 1.4ml/kg/day
Half-life (range)	7.5 days (3.6-10.9 days)

Clearance of panitumumab occurs via 2 pathways:

1- Presence of an “EFGR sink” which results in saturation of panitumumab and consequent clearance.

2- Clearance via the reticuloendothelial system as occurs with endogenous immunoglobulin.

FDA Approved Indication(s) and Off-label Uses[1,2]

Panitumumab is FDA approved for the treatment of EGFR-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy regimens.

Off label uses:

In combination with chemotherapy for metastatic colorectal cancer (mCRC) and advanced non-small cell lung cancer (NSCLC). Panitumumab has also been studied in renal cell cancer, prostate cancer, and solid malignancies.

NOTE: Combination of IFL (irinotecan, bolus 5-fluorouracil, and leucovorin) and panitumumab is not recommended due to severe grade 3-4 diarrhea resulting in 1 patient fatality as demonstrated in clinical trials.

Current VA National Formulary Alternatives

Cetuximab is a chimeric monoclonal antibody that is an alternative to panitumumab; however, at the present time this agent is not included in the national formulary. Access is restricted to patients who may receive the most benefit after risks are assessed.

Dosage and Administration[1,2,4]

The recommended dose is a 6mg/kg intravenous infusion over 60 minutes every 14 days. Doses greater than 1000mg should be administered over 90 minutes. No formal studies have been conducted in patients with renal or hepatic impairment.

Preparation and Administration

- ✓ Panitumumab should always be administered by an IV infusion pump via a low-protein-binding 0.22 micron in-line filter.
  - o ***Flush line before and after*** Panitumumab with 0.9% sodium chloride injection.
- ✓ Panitumumab solution should be colorless, but may contain some visible white panitumumab particulate.
  - o ***Do not shake solution.***
- ✓ After withdrawing amount of Panitumumab necessary for a dose of 6 mg/kg, dilute to a total volume of 100 ml with ***0.9% sodium chloride solution, USP.*** For doses greater than 1000 mg, dilute to total volume of 150 ml with 0.9% sodium chloride solution.
  - o The final concentration ***should not exceed 10 mg/ml.***

Stability and Storage Information

- ✓ Store vials in original container under refrigeration (2-8ºC/ 36-46ºF) until ready to use.
  - o ***Do not freeze***
- ✓ Upon opening vial, any ***unused portion of panitumumab must be discarded*** and should not be kept for future use.
- ✓ Duration of storage for diluted panitumumab solution is contingent on temperature at which infusion solution is kept.
  - o ***If kept at room temperature***, the solution should be used within **6 hours of dilution**.
  - o ***If stored at refrigerated temperatures of 2-8ºC/ 36-46ºF,*** the solution should be used within **24 hours of dilution**.

Dose Modifications

Table 2: Dosage Modifications for Infusion Reactions

Grade 1 or 2	Grade 3 or 4
Decrease infusion rate by 50% for duration of infusion	Immediately and permanently discontinue infusion

Dose Modifications (*contd.*)

Table 3: Dosage Modifications for Severe Dermatologic Reactions

Grade 3/ 4 / Intolerable: Withhold panitumumab. If toxicity does not improve to ≤ grade 2 within 1 month, permanently discontinue panitumumab.	
Improvement to ≤ grade 2 and patient symptomatically improved after withholding no more than 2 doses, resume treatment at 50% of original dose.	
If toxicities recur: permanently discontinue	**If toxicities do not recur**: subsequent doses of panitumumab may be increased by increments of 25% of original dose until recommended 6 mg/ kg dose achieved.

Adverse Events (Safety Data)* [1,2]

*Safety data is from 15 clinical trials in which 1467 patients received panitumumab (monotherapy, n=1293; combination therapy, n=174)

Deaths and Other Serious Adverse Events- Pulmonary fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.

Common Adverse Events- Skin rash with variable presentation, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea and diarrhea.

Other Adverse events- Ocular toxicities occurred in 15% of patients and included: conjunctivitis (4%), ocular hyperemia (3%), increased lacrimation (2%), and eye/ eyelid irritation (1%). Mucosal toxicities also reported included stomatitis (7%) and oral mucositis (6%).

Table 4. Incidence of Adverse Events Occurring in ≥ 5% of Patients with Inter-Group Difference of ≥ 5%--- Safety Results from Phase III Pivotal Trial

	Panitumumab + Best Supportive Care (BSC) (n=229)		BSC alone (n=234)	
Body System	**All Grades %**	**Grades 3-4%**	**All Grades %**	**Grades 3-4%**
Body as a Whole				
Fatigue	26	4	15	3
General Deterioration	11	8	4	3
Digestive				
Abdominal Pain	25	7	17	5
Nausea	23	1	16	<1
Diarrhea	21	2	11	0
Constipation	21	3	9	1
Vomiting	19	2	12	1
Stomatitis	7	0	1	0
Mucosal Inflammation	6	<1	1	0
Metabolic/ Nutritional				
Peripheral Edema	12	1	6	<1
Hypomagnesemia	39	4	2	0
	Panitumumab + Best Supportive Care (BSC) (n=229)		BSC alone (n=234)	

Body System	All Grades %	Grades 3-4%	All Grades %	Grades 3-4%
Respiratory				
Cough	14	<1	7	0
Skin/ Appendages				
All Skin Toxicity	90	16	9	0
Skin	90	14	6	0
Erythema	65	5	1	0
Acne dermatitis	57	7	1	0
Pruritis	57	2	2	0
Skin Exfoliation	25	2	0	0
Rash	22	1	1	0
Skin fissures	20	1	<1	0
Dry skin	10	0	0	0
Acne	13	1	0	0
Nail	29	2	0	0
Other Nail Disorder	9	0	0	0
Hair	9	0	1	0
Growth of eyelashes	6	0	0	0
Eye	15	<1	2	0
Paronychia	25	2	0	0

Tolerability

Warnings: The following adverse events were associated with discontinuation of therapy during clinical trials:

(***Please refer below to Precautions/ Contraindications- Warnings section for detailed descriptions***)

- ✓ Infusion reactions: Severe reactions occurred in 1% of patients. Panitumumab therapy was discontinued in 1 patient (n=1336). Premedication was not given prior to the first or subsequent doses of panitumumab in clinical trials. The routine use of an antihistamine prior to panitumumab administration is not outlined as a recommendation by the sponsor; however, may be an option in circumventing this reaction.
- ✓ Severe skin toxicity: Severe reactions occurred in 16% of patients and resulted in complications such as sepsis, septic death, and abscesses. Dose interruption was required in 11% of patients. Since skin reactions occurred in >80% of patients, patients should be monitored for the development of infections which may necessitate the use of topical or oral antibiotics.
- ✓ Paronychia: Severe reactions occurred in 2% of patients.
- ✓ Pulmonary fibrosis: Severe reactions occurred in < 1% of patients.

Geriatric Use: Based on information obtained from the phase III randomized, controlled, pivotal trial, there were 229 patients with mCRC who received panitumumab. There were 96 (42%) patients who were ≥ 65 years of age. There were no differences noted in safety and efficacy between this patient and younger patients.

FDA Pregnancy Category C: No adequate and well-controlled trials in pregnant women. Animal studies demonstrated that panitumumab was associated with increases in abortifacient effects in pregnant cynomolgus monkeys when administered during gestation days 20-50 at doses 1.25 to 5-fold greater than the recommended human dose.

Lactation: Human IgG is secreted in human breast milk. This information can be used to extrapolate that panitumumab may also be secreted into human milk. The effect of panitumumab on infants is unknown. Women who breast-feed should be advised to discontinue nursing while receiving panitumumab and for 2 months after the last dose.

Impairment of Fertility: No clinical studies regarding the effects of panitumumab on male or female fertility have been conducted.

Male fertility- Preclinical data on male cynomolgus monkeys treated for 26 weeks with up to 5 times the recommended human dose of panitumumab demonstrated no adverse effects.

Female fertility- Preclinical data on female cynomolgus monkeys treated with 1.25-5 times the recommended human dose have demonstrated an increase in menstrual cycle duration. Hormonal changes that were noted included a decrease and delay in peak progesterone and 17β-estradiol levels. Such menstrual aberrations resumed back to normal after panitumumab discontinuation.

Precautions/Contraindications

Warnings

Table 5: Blackbox Warnings

BLACKBOX WARNINGS
Dermatologic Toxicity: These reactions are associated with EGFR blockade. They were reported in 89% of patients and were severe (NCI-CTC grade 3 or higher) in 12% of patients. Some of the clinical manifestations of the rash included: dermatitis acneiform, rash, skin exfoliation, paronychia, skin fissures. Patients who develop severe dermatologic reactions may develop complications such as sepsis, septic death, and abscesses. Panitumumab should be held or discontinued in patients who develop such sequelae.
Infusion Reactions: Severe infusion reactions occur in approximately 1% of patients. These reactions are characterized by the following: anaphylactic reactions, bronchospasm, fever, chills, and hypotension. No fatalities have occurred with panitumumab secondary to infusion reactions. Dose adjustment or discontinuation of panitumumab is warranted depending on the severity of the reaction.

Pulmonary Fibrosis: This occurred in 1% (n=2/1467) of patients in clinical studies. One of the 2 patients had underlying idiopathic pulmonary fibrosis and died after receiving 4 doses of panitumumab and chemotherapy. The second case involved a patient who developed CT evidence of fibrosis after the 11th dose of panitumumab monotherapy. As a result of the noted fatality, patients with a history or evidence of interstitial pneumonitis or pulmonary fibrosis were excluded from the trials. Patients that develop interstitial lung disease, pneumonitis, or lung infiltrates should be permanently discontinued from panitumumab.

Diarrhea: Panitumumab is associated with diarrhea and when combined with irinotecan, there is an increased incidence and severity of diarrhea. Of note, out of 19 patients receiving panitumumab and IFL therapy, there was a 58% incidence of NCI-CTC grade 3-4 diarrhea resulting in 1 fatality.

Ocular toxicity: Eye-related toxicities occurred in ~15% of patients. Some of the ocular adverse events included: conjunctivitis, ocular hyperemia, increased lacrimation, and eyelid irritation.

Electrolyte Depletion: Based on the phase III pivotal trial, 2% of patients (NCI-CTC grade 3/4) in the panitumumab required oral or IV magnesium supplementation. Hypomagnesemia occurred for ≥ 6 weeks after panitumumab initiation. Hypocalcemia was associated with hypomagnesemia in some patients. Electrolyte monitoring is recommended during panitumumab therapy and for 8 weeks after the completion of therapy.

Precautions

- ✓ Photosensitivity: Patients should wear sunscreen and limit sun exposure while on panitumumab since such exposure may exacerbate skin reactions.
- ✓ EFGR testing: All patients enrolled in clinical trials underwent EGFR testing using the Dako EGFR pharmDx ® test kit. As a result, it is noted in the manufacturer's recommendations that detection of EGFR expression is a prerequisite for panitumumab therapy; although, no specific recommendations regarding interpretation of results are presented. Results of exploratory analyses in the phase III pivotal trial of EGFR expression revealed no correlation between EGFR status and progression free survival (PFS):

Table 6: EGFR Expression and Progression Free Survival Exploratory Analysis[3]

	% cells with Positive Staining		Maximum staining Intensity	
	1-9% p=0.0003	**≥ 10%** p<0.0001	**0,1+, 2+** p<0.0001	**3+** p= 0.0132
Number (%) Progressed				
Panitumumab + Best Supportive Care (BSC)	57(72)	172(87)	182 (82)	47(87)
BSC alone	57(88)	174(90)	190(88)	41(95)
Median Days (95% CI)				
Panitumumab + Best Supportive Care (BSC)	59 (53,80)	56 (55,58)	56(55,61)	56(51,83)
BSC alone	50(42,54)	51(50,54)	51(50,54)	48(36,55)

- ✓ Electrolyte monitoring: As mentioned earlier, patients should be monitored for hypomagnesemia and hypocalcemia for the duration of panitumumab therapy and for 8 weeks beyond the last dose. Appropriate electrolyte supplementation should be delivered as needed.

Contraindications
Hypersensitivity to panitumumab or any of its components.

Look-alike / Sound-alike Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name (Panitumumab): palivizumab, gemtuzumab, adalimumab, alemtuzumab, bevacizumab, daclizumab, ibritumomab, natalizumab, ranizumab, trastuzumab, efalizumab, omalizumab injections.

LA/SA for trade name (Vectibix): Ventavis inhalation solution, Cerebyx injection, Vepesid injection, Varivax injection.

Drug Interactions[1,3]

There are no formal evaluations regarding drug-food, drug-lab, or drug disease interactions that are currently available.

Drug-Disease Interactions

- ✓ Pulmonary fibrosis was reported in < 1% (2/1467) of patients in all clinical trials. There were 2 fatalities that occurred in patients on combination therapy including panitumumab. Following the first fatality, patients with a history/ evidence of interstitial pneumonitis or pulmonary fibrosis were excluded from future studies.

Drug-Drug Interactions

- ✓ No formal evaluation relating to drug-drug interactions with panitumumab have been conducted. Of note, however, the combination of IFL and panitumumab is not recommended because of a 58% incidence in severe life-threatening diarrhea (NCI-CTC grade 3-4) resulting in 1 patient fatality (5%) as documented in one clinical trial.
- ✓ Prior to patient administration of panitumumab, it is recommended to flush the line before and after administration with 0.9% sodium chloride injection, USP to avoid mixing with other drug products or IV solutions. Panitumumab should not be mixed with, or administered as an infusion with, other medicinal products.

Efficacy Measures[2, 6, 7]

Primary Outcome:

Progression-free survival (PFS) time in EGFR positive mCRC patients receiving panitumumab monotherapy versus best supportive care.

Secondary outcomes:

Overall survival (OS)	Disease control rate	Objective Response
Time to response	Duration of response	Safety

Clinical Trials[2, 3,6,7,8]

Pivotal Trial

Panitumumab was approved on the basis of a single phase III pivotal trial for pts with mCRC. Patients were assigned to 1 of 2 treatment groups: panitumumab 6mg/kg IV Q 14 days (n=231) + Best supportive care (BSC) versus BSC alone (n=232). Patients in the BSC arm were allowed to crossover once they demonstrated radiographic progression. The primary endpoint in this study was Progression Free Survival. Study findings indicated that there was a statistically significant

increase in mean PFS (versus median PFS). Among the secondary endpoints, the response rate was noted at 8% in the panitumumab group. More importantly, there was no statistically significant difference in overall survival between both treatment arms.

Table 6: Pivotal Trial Results

	Panitumumab + BSC	**BSC**	
Outcome	N = 231	N = 232	
PFS* (mean)**	13.7 weeks	8.6 weeks	**P<0.0001**
OS	119 (51.5%) dead	131 (56.5%) dead	**P=0.6041**
Median survival days	193 95% CI (174, 233)	184 95% CI (148, 228)	"
ORR	19 (8%); 95% CI 8.2 (4.5, 12.7)	0	**P<0.0001**
Duration of Response	Median Time= 17 weeks, 95% CI (16.4, 25.3)	N/A	"
TTR Mean (SD)	8.9 (2.7) weeks	N/A	
TTD Median time (95% CI)	8 (7.9-8.7) weeks	7.3 (7.1-7.7) weeks	

Hecht J et al. ASCO 2006	Panitumumab
	N=23
PR n (%)	3(13)
SD n (%)	7(30)
TTR n (%)	7-11.6
Duration of response (weeks)	≥ 16 weeks
Survival-median PFS Weeks (95% CI)	13.3(7.1-22.9)

*****No statistically significant difference in median PFS.**

Approximately, 75% of patients in the BSC arm crossed over to the panitumumab arm (median crossover time= 7 week). Patients in this arm had a partial response rate of 9%. The sponsor suggests that the large proportion of patients in the crossover group may have confounded the study results and contributed to the lack of a statistical difference in overall survival.

Table 7: Pivotal Trial Results- Crossover Phase

	Panitumumab +BSC
Results	N = 174
CR n(%)	1 (1)
PR n(%)	16 (9)
SD n(%)	55(32)
Disease Control	72(42)

Supporting Trials

Additional supporting trials include 3- open-label, single-arm Phase II studies conducted to demonstrate whether there was a correlation between extent of EGFR expression and overall response rate (primary endpoint). The results are provided below and demonstrate a response rate noted within each study irrespective of the extent of EGFR expression.

Table 8: Results from Phase II Study- EGFR < 10% tumor cells stained for EGFR

Table 9: Results from Phase II Study- ≥ 10% tumor cells stained for EGFR

Table 10: Results from Phase II Study- With EGFR Positive tumors

Berlin J et al. ASCO 2006	Panitumumab
	N=39
PR n (%)	3(8)
SD n (%)	8(21)
TTR n (%)	7.7-11.1
Duration of response (weeks)	4.1-14 weeks
Survival- median PFS Weeks (95% CI)	7.6(7.6-8.6)

Malik et al. ASCO 2005	Panitumumab
	N=148
ORR (%)	9%
Median OS (weeks)	37.6
Median duration of response (weeks)	18.1
Survival- median PFS Weeks (95% CI)	13.6

Combination Regimens

This section contains interim results from study conducted with panitumumab in combination with bolus 5-FU (IFL). If patients experienced unacceptable toxicities with IFL, they were switched to the infusional 5-FU therapy (FOLFIRI). Abstract efficacy results are presented in the table below. The primary outcome measure was a safety measure: incidence of grades 3 or 4 diarrhea. Of note, there was a 58% incidence of this adverse event in the IFL group resulting in 4 discontinuations of therapy versus a 25% incidence in the FOLFIRI group.

Table 11: Secondary Endpoints for Panitumumab in combination with Fluoropyrimidine Based Chemotherapy

Hecht et al., ASCO GI 2006	**Panitumumab+ IFL**	**Panitumumab + FOLFIRI**
	N=19	**N=24**
ORR (%)	47	33
Survival- median PFS (months)	5.6	10.9
Disease Control (%)	74	79

Acquisition Costs[2]

Panitumumab was approved by the FDA in September 2006. It has been marketed since this October 2006. Below is a table with FSS pricing information based on an average, healthy male weight of 70kg.

Panitumumab available in following vials (all single use):

100 mg/ 5 ml - $ 595.37; **200 mg/ 10 ml**- $1191.15; **400 mg/ 20 m**l- $ 2381.90

Table 12: Panitumumab FSS Pricing Information

Drug	Dose	Cost/ 2Week/ Patient ($)	Cost/ 4 weeks/ Patient ($)
Panitumumab Maintenance Dose	6 mg/ kg (420 mg) (5 vials)	2976.85	**5953.70**

Cetuximab available as single strength vial (single use):

100mg/5ml vial- $359.29

Table 13: Cetuximab FSS Pricing Information

Drug	Dose	Cost/ 2Week/ Patient ($)	Cost/ 4 weeks/ Patient ($)
Cetuximab Loading	400 mg/m^2 (8 vials)	2,874.32	
Cetuximab	250 mg/ m^2/ week (5 vials)	1,796.45	**7,185.80 (for 4 weeks including LD = 8263.67)**

Cost Analysis[2]

Presently, there are no formal pharmacoeconomic evaluations of panitumumab in metastatic colorectal cancer. A Budget Impact Analysis for a managed care model consisting of 10 million covered lives is available by the sponsor. Using SEER age-adjusted data, it was estimated that 3400 members would be diagnosed with mCRC. Intrinsiq data was used to identify approximately 9% (27) of patients who would potentially be treated with cetuximab monotherapy. This information was used to extrapolate the cost savings associated with panitumumab. The conclusions suggested a 20% annual cost savings (drug acquisition and administration costs) if the 27 patients were switched to panitumumab.

This cost analysis suggests a cost-savings potential associated with the use of panitumumab when compared to the alternative, cetuximab. The extent to which such a cost-savings would apply within the VA system is contingent on the following variables: number of patients who have received cetuximab and cost differential of both agents based on FSS pricing.

Conclusions[8,9,10,11,14]

Overview:

Metastatic colorectal cancer is a serious condition that is only associated with an approximately 10% 5-year survival compared to a nearly 90% 5-year survival in patients with localized disease. [8] Currently, first line therapies for patients with mCRC consist of a fluoropyrimidine in conjunction with leucovorin, oxaliplatin or irinotecan, and bevacizumab based regimens. Examples of such regimens include FOLFOX[1], FOLFIRI[2], CAPOX[3], and IFL[4] in conjunction with bevacizumab. [9,10]

The National Comprehensive Care Network (NCCN) has published a set of guidelines that suggests the use of these regimens contingent on patient specific parameters including performance status and any contraindications to medication therapy. [10] Treatment failure to first-line therapies as dictated by radiographic progression and clinical status progresses to initiation of the alternative first-line therapy with the exception of IFL and bevacizumab, neither of which are listed as second-line therapies. Additionally, it is important to note that according to the NCCN algorithm, another potential 2nd line alternative is irinotecan and cetuximab combination therapy. Finally, the 3rd line agents listed include FOLFOX, irinotecan and cetuximab, or cetuximab alone in patients who have not received either therapy previously, as well as best supportive care. Whenever cetuximab is used alone, panitumumab may be substituted.

In gleaning over the current treatment options available to patients with mCRC, one may note that 2 types of agents exist: namely chemotherapeutics and targeted therapies. Cetuximab is an epidermal growth factor receptor inhibitor. Similar to panitumumab, this agent prevents endogenous EGF and TGF-α from binding to the receptor. It is worth underscoring the point that similar to cetuximab, panitumumab is also an EGFR inhibitor. Furthermore, these 2 agents have the potential of targeting the same patient population Outlined below is information comparing and contrasting both agents as related to the efficacy, safety, cost, and other properties of both drugs.

Table 14: Comparison of Panitumumab versus Cetuximab for Safety, Efficacy, and Cost Factors

Drug	Safety	Efficacy	Cost (FSS pricing)
	Infusion reactions- Severe infusion reactions occur in approximately 1% of patients Pulmonary toxicity- Occurred in 26% of patients on panitumumab compared with 20% of patients receiving BSC alone. Dermatologic toxicity- reported in 89% of patients and were severe (NCI-CTC grade 3 or higher) in 12% of patients. Diarrhea/ dehydration- Occurred in 21% of patients on panitumumab versus 11% in	Indicated in advanced mCRC after failure of fluoropyrimidine, oxaliplatin, and irinotecan based therapies. Accelerated approval on the basis of mean PFS = 13.7 weeks versus 8.6 weeks (BSC)- statistically significant difference of 37 days (P<.0001). Associated with partial response rate = 8% compared with 0% (BSC).	$5953.70

[1] Infusional Fluorouracil + leucovorin/ oxaliplatin

[2] Infusional Fluorouracil + leucovorin/ irinotecan

[3] Capecitabine + oxaliplatin

[4] Bolus Fluorouracil + leucovorin/ irinotecan

	BSC arm. Hypomagnesemia- Noted in 6% of patients who received panitumumab monotherapy (n=920).	**No demonstrated increase in overall survival.**	
Cetuximab	Infusion reactions- 90% of severe reactions occur with first infusion; cardiopulmonary arrest, which occurred in 2% of patients with squamous cell carcinoma of the head and neck, who received radiation therapy in conjunction with cetuximab. Pulmonary toxicity- < 0.5% of patients with advanced mCRC Dermatologic toxicity- 90% incidence including acneiform rash and inflammatory/ infectious sequelae Diarrhea/ dehydration occurred in 5% and 6% respectively. Hypomagnesemia identified in patients with squamous cell carcinoma of head and neck. Noted in 13% of patients concurrently on cisplatin versus 0% of patients on cisplatin alone.	Indicated in advanced mCRC as single agent for patients intolerant to irinotecan-based therapies or in combination with irinotecan. Respective partial response rates: **Combination therapy**- 23%, 95% CI (17.5-29.1) 4.1 month time to progression of disease **Monotherapy**- 11%, 95% CI (5.7-18.1) 1.5 month time to progression of disease P=0.007 **No demonstrated increase in overall survival.** *[Also indicated as radiosensitizer in local/ regionally advanced squamous cell carcinoma of the head and neck (SCCHN) and as single agent in metastatic/ recurrent disease]*	$7,185.80 (For 4 weeks including LD =

Clinical efficacy: [2,3,5,6,13,14]

The FDA approved panitumumab on the basis of a single-phase III clinical trial comparing it to best supportive care alone. The primary endpoint for this trial was progression free survival. The secondary endpoints included: tumor response, overall survival, and response rate. Results of the study demonstrated a prolongation in the mean progression free survival in the panitumumab arm with a hazard ratio of 0.54 (95 confidence interval [CI]: 0.44-0.55; P<0.0001). Information from the FDA clinical review document, however, stated that data from the sponsor demonstrated no statistical in median progression free survival which is how this parameter is usually parameter. Additionally, there was no significant difference between both groups with respect to overall survival; although, as mentioned by the author, the crossover design of this study makes it difficult to realize any overall survival benefit. Other findings in this study included a trend such that patients with more severe forms of dermatologic toxicity were found to have better response rates. EGFR expression was an inclusion criterion in various trials; however, correlation analyses

revealed no relationship between extent of EGFR expression and a patient's predicted response to panitumumab.

Cetuximab is currently approved as a single agent for patients who are intolerant to irinotecan-based therapies or as combination with irinotecan for the treatment of EGFR expressing mCRC. The basis of this agent's effectiveness was response rate with cetuximab combination therapy associated with a 23% response rate and a mean 4.1-month time to progression. Cetuximab monotherapy was only associated with an 11% response rate and a mean 1.5 month time to progression. Of note, neither panitumumab nor cetuximab have demonstrated an improvement in overall survival or disease-related symptoms. Furthermore, it is questionable as to what extent the statistically significant response rates translate into meaningful clinical response. Finally, it is unclear as to what population of patients will derive benefit from either panitumumab or cetuximab in light of the lack of a correlation between EGFR expression and response rates.

Panitumumab is also being studied in the context of metastatic renal cell carcinoma and non-small cell lung cancer. Additionally, clinical trials are currently ongoing or in recruitment to determine the efficacy of this agent in combination with other chemotherapeutics or as a radiosensitizing agent. Cetuximab is also approved in combination with radiation therapy for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck or as monotherapy in patients whom prior platinum based therapy has failed.

Safety: [1,2,5,6,13,14]

Panitumumab is a fully humanized monoclonal antibody. Compared with its murine and chimeric counterparts, the theoretical advantage conferred by this agent is that it is thought to elicit less of an antigenic response within the human host. Subsequently, this is thought to decrease the chance of developing fatal allergic reactions. As such, within clinical trials, no human anti-human antibodies were detected within subjects. Overall, however, it is noted that approximately 1% of patients exposed to panitumumab experienced a severe infusion reaction. In comparison to panitumumab, cetuximab is a chimeric monoclonal antibody, which is also associated with severe infusion reactions that occurred in approximately 3% of patients. This reaction occurs after administration of the first dose within 90% of patients in light of antihistamine premedication. Unlike panitumumab, cetuximab is associated with infusion-related fatalities (< 1/1000).

Panitumumab and cetuximab have blackbox warnings for dermatologic and infusion reactions. Based on clinical trials, it is noted that dermatologic toxicities were reported in 89% of patients on panitumumab and cetuximab. Among these patients, 12% of those on panitumumab experienced a severe reaction (grade 3 or 4) while 3% of those on cetuximab experienced severe reactions. Terminal consequences of severe cases include development of sepsis and other infectious complications. Other serious side effects noted with both agents include: pulmonary fibrosis; increased incidence of diarrhea especially within irinotecan containing regimens; hypomagnesemia. Overall, both agents appear to have similar adverse event profiles with the exception of cardiopulmonary arrest, which occurred in 2% of patients with squamous cell carcinoma of the head and neck, who received radiation therapy in conjunction with cetuximab.

Quality of Life: [2]

Currently, there is no published quality of life (QoL) data for panitumumab. Peeters and colleagues presented exploratory QoL data comparing panitumumab and best supportive care versus best supportive care in patients with mCRC. Demographics between both treatment groups were similar. Notably, the majority of patients within both groups had an ECOG performance status of 0-1 consistent with a relatively healthier group of patients. Overall health status was assessed using the NCCN/FACT Colorectal Cancer Symptom Index (FCSI) and the EQ-5D. Patient follow-up consisted of questionnaires at baseline and monthly intervals until disease progression or study withdrawal. Patient reported outcomes were assessed via CRC symptoms and overall health status. Several statistical methods were used; however, only one method demonstrated a statistically significant difference in patient reported outcomes favoring

the panitumumab arm. Of note, this difference was marginal. Also, > 50% of data was missing after 8 weeks making the data difficult to interpret.

Cost: [2]

The cost of panitumumab is approximately 20% less than cetuximab. Budget impact analyses performed by the sponsor suggest a similar pricing incentive with this agent. Compared to conventional chemotherapies; however, both targeted therapies increase costs to up to double the costs of regimens such as FOLFOX-4 without any known improvement in overall survival. Compared with cetuximab, panitumumab is associated with decreased administration costs as it is given every 14 days as opposed to every 7 days and there exists no premedication requirement for this agent.

Recommendations[11]

Place in therapy: On the basis of the pivotal trial, panitumumab is considered a 3rd line option in patients with metastatic colorectal cancer who progress on current standard of care regimens comprised of a fluoropyrimidine, oxaliplatin, and/ or irinotecan. The primary endpoint in this study was progression-free survival for which there was a statistically significant difference compared to best supportive care; however, as mentioned earlier, median PFS did not reveal a significant difference between both treatments. It was mean PFS that demonstrated a difference between both groups. Secondary endpoints included overall survival, response rate, and median duration of response. There was no difference in overall survival. Median duration of response was 17 weeks (95% CI: 16-25 weeks). The clinical utility of these results is unclear. Furthermore, there is no overall survival benefit and marginal quality of life benefit that has been attributed to this therapy of which such findings would make it a more beneficial option.

It is unclear as to what population of patients may derive the most benefit from this agent or cetuximab, as there was no correlation with EGFR expression; yet, this was inclusion criteria for the studies to date conducted with both agents. Furthermore, detection of such molecular targets remains to be proven as an adequate predictor of medication response given the infancy of this new area.

Formulary Recommendation: At this time, panitumumab should not be added to the national formulary, but should be made available to patients after an adequate risk: benefit assessment is made.

References:

1. Vectibix (panitumumab) Product Package Insert. Amgen, Thousand Oaks, California;2006.
2. Vectibix (panitumumab) Formulary Submission Dossier. Amgen;November 2006.
3. Giusti, RM. Panitumumab FDA Clinical Review Document. 2006 Sept:1-126.
4. Harari PM. Epidermal growth factor receptor inhibition strategies in oncology. Endocrine-Related Cancer 2004;11:689-708.
5. Gibson TB, Ranganathan A, Grothey A. Randomized phase III trial results of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, in metastatic colorectal cancer. Clin Colorectal Cancer. 2006 May;6(1):29-31.
6. Saif MW, Cohenuram M. Role of panitumumab in the management of metastatic colorectal cancer. Clin Colorectal Cancer 2006 July 6(2):118-124.
7. Wainberg Z, Hecht JR. Panitumumab in colon cancer: a review and summary of ongoing trials. Expert Opin Biol Ther. 2006 Nov;6(11):1229-35.
8. Rowinsky EK, Schwartz GH, Gollob JA, et al. Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. *J Clin Oncol*. 2004;22:3003-3015.
9. Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2006). © 2006 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed

[October 10, 2006]. To view the most recent and complete version of the guideline, go online to www.nccn.org.
10. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005;352:476-87.
11. Venook A. Critical evaluation of current treatments in Metastatic colorectal cancer. Oncologist 2005;10:250-261.
12. Ries LAG, Harkins D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Eisner MP, Horner MJ, Howlader N, Hayat M, Hankey BF, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2003, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2003/, based on November 2005 SEER data submission, posted to the SEER web site, 2006.
13. Erbitux (cetuximab) Product package insert. New York, NY: ImClone Systems Inc., 2006.
14. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Sanotori A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. NEJM 2004;351:337-45.

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Table 15: [2, 3,6,7,8] **Summary of pivotal trials, supporting trials, and trials supporting off-label use of panitumumab in metastatic renal cell carcinoma and non-small cell carcinoma.**

BSC= best supportive care; OR= objective response rate; RR=response rate; OS= overall survival; PFS= progression free survival; TTR= time to recurrence; TTP= time to disease progression; MCT= multicenter;RCT- randomized controlled trial IHC- immunohistochemistry, PRO-patient reported outcome, ITT- intent to treat.

Citation Design Setting Analysis Type Objectives	Eligibility Criteria	Interventions Follow-Up (if available)	Patient Population Profile	Efficacy Results	Safety Results
PIVOTAL TRIAL Citation [2,3] Phase III, MC, RCT in pts with mCRC All outside of US (Europe, Canada, Australia, and New Zealand) ITT (primary analysis of efficacy endpoints) <u>Primary:</u> PFS based on modified RECIST criteria stratified by ECOG PS and region (ITT) <u>Secondary:</u> Survival time, OR, duration of response, TTR, time to disease progression, time to treatment failure, duration of stable disease, PRO outcome, safety outcomes, **PIVOTAL TRIAL**	Age ≥ 18 y/o with histologically proven mCRC -ECOG score of 0-2 -Failure to standard chemotherapy (fluoropyrimidine, irinotecan, and oxaliplatin therapies) -EGFR staining ≥ 1% by IHC - No longer than 6 months since progression on previous chemotherapy and study start date. - Failure to 2/3 chemotherapies -Single dimension measurable disease, ≥ 20 mm - Adequate	Panitumumab Intravenous 6mg/kg Q 14 days + BSC <u>VERSUS</u> BSC (after progression, these patients were randomized to active treatment group): antibiotics, analgesics, palliative radiation for bone metastases, corticosteroids, transfusions, psychotherapy, growth factors, symptomatic therapy Tumor response at 8,12, 16, 24, 32, 40, 48 weeks and every 12 weeks Survival- every 3 months for up to 48 months	**Baseline characteristics-** ***Similar distribution in both treatment arms for gender, age, race*** Male- 63% Caucasian- 99% Age- Median (range) 62 (27, 83); ≥ 65 y/o- 187 (40%) *****Lower ECOG and more liver metastasis in panitumumab group*** Baseline: Panitumumab N = 231; BSC N = 232 Liver Mets: 178(77%); 194(84%) ECOG (2-3): 30 (13%); 37 (16%)	**Outcome**: **Panitumumab** N = 231; **BSC** N = 232 **PFS*** (mean)**: 13.7 weeks; 8.6 weeks; **P<0.0001** **OS**: 119 (51.5%) dead; 131 (56.5%) dead; **P=0.6041** **Median survival days**: 193 95% CI (174, 233); 184 95% CI (148, 228); " **ORR**: 19 (8%); 95% CI 8.2 (4.5, 12.7); 0; **P<0.0001** **Duration of Response**: Median Time= 17 weeks, 95% CI (16.4, 25.3); N/A; " **TTR Mean (SD)**: 8.9 (2.7) weeks; N/A **TTD Median time (95% CI)**: 8 (7.9-8.7) weeks; 7.3 (7.1-7.7) weeks ***No statistically significant difference in median PFS. **<u>EGFR correlation: refer to Table 6 above</u>**	<u>Refer to Table 4 above</u>

Citation Design Setting Analysis Type Objectives	Eligibility Criteria	Interventions Follow-Up (if available)	Patient Population Profile	Efficacy Results	Safety Results
(contd.) anti-panitumumab antibodies	heme/ renal/hepatic hepatic function			**CROSSOVER STUDY RESULTS** Panitumumab +BSC N = 174 CR n(%) 1 (1) PR n(%) 16 (9) SD n(%) 55(32) Disease Control 72(42)	
Hecht J et al.; ASCO 2006 MCT, Open-label, single-arm Phase II study Primary endpoint: ORR through Week 16 Secondary endpoint: TTR, PFS, safety data	1. mCRC AND 1-9% OR < 1% tumor cells stained for EGFR 2. progression on fluoro-pyrimidine, irinotecan/ Oxaliplatin/ both 3. Disease progression ≤ 6 months of study entry	Panitumumab Intravenous 6mg/kg Q 14 days	N=23 Male = 70% Median Age= 60 (41-82) Race= 83% Caucasian ECOG ≤ 1=100% EGFR (-)=48%	***Interim results*** Panitumumab **N=23** PR n (%) 3(13) SD n (%) 7(30) TTR n (%) 7-11.6 Duration of response (weeks) ≥ 16 weeks Survival-median PFS Weeks (95% CI) 13.3(7.1-22.9)	Skin toxicity: 93% (15% were grade 3 and no grade 4.) Infusion reactions 5%
Berlin J et al.; ASCO 2006 MCT, Open-label, single-arm Phase II study Primary endpoint: ORR Secondary endpoint: TTR, PFS, safety data	1. mCRC AND ≥ 10% tumor cells stained for EGFR 2. progression on fluoropyrimidine, irinotecan/ Oxaliplatin/ both 3. Disease progression ≤ 6 months of study entry	Panitumumab Intravenous 6mg/kg Q 14 days	N=39 Male = 59% Median Age= 60 (41-82) Race= 82% Caucasian ECOG ≤ 1=95% 10-20% EGFR expression= 67% EGFR expression ≥ 21%= 31%	***Interim results*** Panitumumab **N=39** PR n (%) 3(8) SD n (%) 8(21) TTR n (%) 7.7-11.1 Duration of response (weeks) 4.1-14 weeks Survival-median PFS Weeks (95% CI) 7.6(7.6-8.6)	Skin toxicity 97% (21% were grade 3 and no grade 4.) Infusion reactions n=1

Citation Design Setting Analysis Type Objectives	Eligibility Criteria	Interventions Follow-Up (if available)	Patient Population Profile	Efficacy Results	Safety Results
Malik I et al., 2005 MCT, Open-label, single-arm Phase II study Primary endpoint: ORR through week 16 Secondary endpoint: Duration of response, SD, duration of PFS, duration of OS, effect of EGFR expression on ORR, safety data	1. mCRC and overexpressed EGFR 2. progression on fluoropyrimidine, irinotecan/ Oxaliplatin/ both 3. No prior systemic chemotherapy/ radiotherapy within 30 days of first dose of panitumumab 4. No untreated brain metastases 5. No renal, hematologic, or hepatic impairment.	Panitumumab 2.5 mg/kg Intravenous every 7 days over 1 hour in 8-week cycles	N=148 -No additional info provided-	***Interim Results*** Panitumumab **N=148** ORR (%) 9% Median OS (weeks) 37.6 Median duration of response (weeks) 18.1 Survival- median PFS Weeks (95% CI) 13.6	Skin toxicity 95% (7% - grade 3 and no grade 4.) Infusion reactions n=1

Citation Design Setting Analysis Type Objectives	Eligibility Criteria	Interventions Follow-Up (if available)	Patient Population Profile	Efficacy Results	Safety Results
Hecht J et al., ASCO GI 2006 MCT, single arm, open-label, phase II study conducted in 2 parts: 1. panitumumab + IFL 2. panitumumab + FOLFIRI (if patient experienced unacceptable toxicity with IFL or change in standard of care) <u>Primary:</u> safety outcome as measured by incidence of grades 3 or 4 diarrhea <u>Secondary:</u> RR, PFS time, OS, additional safety measures, panitumumab pharmacokinetics in combination with IFL	1. mCRC 2. EGFR expression of 2+ or 3+ in ≥ 10% of tumor cells, ECOG score of 0 or 1 3. No previous treatment for mCRC 4. no history of adjuvant therapy for colorectal cancer 5. no history of active disease within 1 year	Panitumumab 2.5 mg/kg Intravenous every 7 days over 1 hour in 6-week cycles IFL: irinotecan 125mg/m2, leucovorin 20mg/m2, and 5-FU 500mg/m2 on Days 1,8,15,22 FOLFIRI	N/A	**Panitumumab+ IFL N=19** / **Panitumumab + FOLFIRI N=24** **ORR (%)** 47 / 33 **Survival-median PFS (months)** 5.6 / 10.9 **Disease Control (%)** 74 / 79	<u>Grade ¾ Diarrhea:</u> 58% in IFL group (4 D/C secondary to diarrhea) and 25% in FOLFIRI group <u>Skin toxicity:</u> 100% in both groups

Citation Design Setting Analysis Type Objectives	Eligibility Criteria	Interventions Follow-Up (if available)	Patient Population Profile	Efficacy Results	Safety Results
Metastatic NSCLC trial Crawford J et al. ECCO 2005 MCT, open-label phase II study 2-arm trial Primary endpoint: median time to disease progression (TTP) Secondary endpoints: median survival time, objective disease response rate, incidence of adverse events, and incidence of infusion reactions.	1. pathologic diagnosis of NSCLC (bidimensionally measurable) 2. stage IV/ Stage IIb diseased with pericardial or pleural effusion 3. EGFR expression of 1+, 2+, 3+, in at least 10% of cells. 4. Exclusions: -previously received cancer therapy for NSCLC other than radiation, surgery, steroids. -uncontrolled brain metastases within a week of study start - Inadequate hematologic, renal, or hepatic function.	Treatment: Paclitaxel 200 mg/m^2 and carboplatin (AUC of 6 mg/min/ml every 3 weeks up to 6 cycles Group 1: Above treatment + panitumumab 2.5 mg/ kg every week Group 2: Above treatment only (PC arm)	N/A	**Panitumumab** / **Placebo** **Median TTP (p=0.55)**: 4.2 months (95%CI, 3.1-5.4) / 5.3 months (95% CI: 3.6-5.6) **Survival-median PFS – (O=0.80) (months)**: 8.5 months (95%CI, 7.1-12) / 8.0 months (95% CI: 6.7-11.8) **Disease Response**: PR: 15%, SD-56% / PR: 11%, SD-67%	Skin toxicity 12% with grade 3 or 4 rash. Grade 3/4 diarrhea and dyspnea- More common in panitu-mumab group.

Citation Design Setting Analysis Type Objectives	Eligibility Criteria	Interventions Follow-Up (if available)	Patient Population Profile	Efficacy Results	Safety Results
Metastatic Renal Cell Carcinoma trial Rowinsky EK, et al. *J Clin Oncol 22:3003-3015.* MCT, dose-escalating trial Primary endpoint: Tumor response Secondary endpoints: 1.PFS 2. Immunogenicity 3. Safety parameters 4. Pharmacokinetic (PK)/ Pharmacodynamic (PD) data	1.Contra-indication to IL-2/ IFN-α therapy **OR** Histologically confirmed mCRC who failed IL-2/ IFN-α therapy Exclusion: -EGFR inhibitor therapy. - CV compromise (myocardial infarction within 1 year of study, hx of anthracycline/ related agent use). - Received chemo/ RT (adjuvant or for metastatic disease). -prior anticancer treatment/ investigational treatment within 30 days. -symptomatic brain metastases or peritumoral edema -Corticosteroids	Panitumumab 1.0, 1.5, 2.0, and 2.5 mg/ kg weekly *8-week courses until disease progression*	N=95 Males=88(73%) No additional information	**N=88/95 patients received panitumumab** **Panitumumab** **Response Types (N, %)** Major 3(3.4) Minor 2(2.3) Stable Disease 44(50%) **Median PFS** 100 days (95% CI: 58-140)	Skin toxicity- 68-100% of patients in dose-related fashion Serious ADR n=5(5%): dyspnea, diarrhea, DVT, vomiting, rigors

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