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**NLM Citation:** LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Panitumumab. [Updated 2020 Apr 15].
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/

# Panitumumab

Updated: April 15, 2020.

# OVERVIEW

## Introduction

Panitumumab is a human monoclonal antibody to the epidermal growth factor (EGF) receptor, which is used in the treatment of refractory metastatic colorectal cancer. Panitumumab has been linked to minor serum enzyme elevations during therapy, but has not been implicated in cases of clinically apparent liver injury.

## Background

Panitumumab (pan" i toom' ue mab) is a human monoclonal IgG2 antibody to the epidermal growth factor receptor (EGFR, HER1), which is used to treat EGFR-expressing metastatic colorectal cancer. Panitumumab has been shown to induce objective responses in metastatic colorectal cancer and to improve progression free survival. Effects appear to be greater in patients with the wild type as opposed to mutant KRAS status. Panitumumab was approved for use in the United States in 2006 and was the second monoclonal antibody to EGFR approved for use in metastatic colorectal cancer, the other agent being cetuximab (a chimeric mouse-human monoclonal IgG1 antibody) which has a similar profile of efficacy and safety. Panitumumab is available in liquid solution of 100, 200 and 400 mg in single dose vials (20 mg/mL) under the brand name Vectibix. The recommended regimen is 6 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity. Skin toxicity is the most common side effect, occurring in 90% of patients and being severe in 16% to 19%. Other side effects include fatigue, abdominal pain, nausea, anorexia, diarrhea, electrolyte disturbance, leukopenia and infections. Less common, but potentially severe side effects include infusion reactions, hypersensitivity reactions, severe skin toxicity, severe diarrhea and dehydration, pulmonary embolism and ocular toxicities.

## Hepatotoxicity

The rates of serum aminotransferase elevations during panitumumab therapy have not been reported in any detail from clinical trials, but nor has the absence of such elevations. In the FDA review of panitumumab, ALT elevations above 5 times the upper limit of normal (ULN) were reported to be 6% and not greater than with placebo (5%) and there were no early discontinuations because of liver test abnormalities or hepatic serious adverse events. If present, serum aminotransferase elevations must have been self-limited and resolved even with continuing cyclic therapy. No individual case reports of clinically apparent, acute liver injury with symptoms or jaundice attributed to panitumumab have been published and the product label does not discuss hepatotoxicity.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

## Mechanism of Injury

The cause of the transient enzyme elevations during monoclonal antibody therapies is generally unknown, but may relate to direct effects of the antibody reactivity to cell surface markers that may be over-expressed on cancer cells, but are also present in lower density on normal epithelial cells.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Panitumumab – Vectibix®

**DRUG CLASS**

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

# CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NO. | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Panitumumab | 339177-26-3 | Monoclonal Antibody | Not Available |

# ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2020

Abbreviations: EGFR, epidermal growth factor receptor; TNF, tumor necrosis factor.

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

*(Review of hepatotoxicity of immunosuppressive agents mentions rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the tumor necrosis factor [TNF] alpha antagonists").*

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Pathway-targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1203-36.

*(Textbook of pharmacology and therapeutics).*

Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125147s0000_MedR.pdf

*(FDA website on panitumumab with medical review for efficacy and safety).*

Rowinsky EK, Schwartz GH, Gollob JA, Thompson JA, Vogelzang NJ, Figlin R, Bukowski R, 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;22:3003–15. PubMed PMID: 15210739.

*(Among 88 patients with resistant, metastatic renal cancer treated with one of 4 doses of panitumumab intravenously once weekly, there was scant evidence of benefit and side effects were common, 68-100% of patients developing an acneiform rash, but ALT elevations and hepatotoxicity were not mentioned).*

Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon JL, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25:1658–64. PubMed PMID: 17470858.

*(Among 463 patients with metastatic, refractory colorectal cancer treated with panitumumab every two weeks or best supportive care, progression free survival was prolonged from a median of 7.3 to 8.0 weeks in the monoclonal antibody treated subjects, but overall survival was unchanged; side effects included skin toxicity in almost all patients; no mention of ALT elevations or hepatotoxicity).*

Panitumumab (Vectibix) for metastatic colorectal cancer. Med Lett Drugs Ther. 2007;49(1259):35–6. Erratum in. PubMed PMID: 17450113.

Med Lett Drugs Ther 2007; 49(1262): 48; dosage error in article text.

*(Concise review of the efficacy and safety of panitumumab shortly after its approval for use in the US for metastatic colorectal cancer, mentions the frequency of skin related toxicities, but does not mention ALT elevations or hepatotoxicity).*

Giusti RM, Shastri K, Pilaro AM, Fuchs C, Cordoba-Rodriguez R, Koti K, Rothmann M, et al. U.S. Food and Drug Administration approval: panitumumab for epidermal growth factor receptor-expressing metastatic colorectal carcinoma with progression following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Clin Cancer Res. 2008;14:1296–302. PubMed PMID: 18316547.

*(Analysis of efficacy and safety results that provided the basis for the FDA decision to approve panitumumab for use in metastatic colorectal cancer; combined safety analysis in 1467 patients mentions skin toxicity in 90% [severe in 16%], diarrhea in 21% [severe in 2%], infusion reactions in 4% [severe in 1%], pulmonary fibrosis in 1%; among 117 deaths in panitumumab treated patients, 1 was listed as due to hepatic failure, but no details given and rates of ALT elevations not mentioned).*

Wu M, Rivkin A, Pham T. Panitumumab: human monoclonal antibody against epidermal growth factor receptors for the treatment of metastatic colorectal cancer. Clin Ther. 2008;30:14–30. PubMed PMID: 18343240.

*(Review of efficacy and safety of panitumumab for metastatic colorectal cancer mentions side effects of skin toxicity, infusion reactions, electrolyte disturbances, pulmonary complications and nail and hair changes, but does not mention ALT elevations or hepatotoxicity).*

Stephenson JJ, Gregory C, Burris H, Larson T, Verma U, Cohn A, Crawford J, et al. An open-label clinical trial evaluating safety and pharmacokinetics of two dosing schedules of panitumumab in patients with solid tumors. Clin Colorectal Cancer. 2009;8:29–37. PubMed PMID: 19203894.

*(Among 86 patients with advanced solid tumors treated with 6 or 9 mg/kg of panitumumab every 2 weeks, all patients had at least one adverse event and therapy was stopped early in 27% of patients, the most frequent side effects being skin rash and gastrointestinal symptoms; no mention of hepatotoxicity).*

Nie F, Shen J, Tong JL, Xu XT, Zhu MM, Ran ZH. Meta-analysis: the efficacy and safety of monoclonal antibody targeted to epidermal growth factor receptor in the treatment of patients with metastatic colorectal cancer. J Dig Dis. 2009;10:247–57. PubMed PMID: 19906103.

*(Systematic review of efficacy and safety of monoclonal antibodies to EGFR in metastatic colorectal cancer summarized 7 randomized trials with 4186 patients using cetuximab or panitumumab, reported similar rates of response and adverse events with the two agents; no mention of ALT elevations or hepatotoxicity).*

Fakih M, Vincent M. Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. Curr Oncol. 2010;17 Suppl 1:S18–30. PubMed PMID: 20680104.

*(Review of frequency, nature and management of adverse effects of monoclonal anti-EGFR [cetuximab and panitumumab] therapy of metastatic colorectal cancer including skin, nail, hair, ocular toxicities, hypomagnesemia, diarrhea, and infusion reactions, but no mention of hepatotoxicity).*

Baumgaertner I, Ratziu V, Vaillant JC, Hannoun L, Poynard T, André T. Bull Cancer. 2010;97(5):559–69. [Hepatotoxicity of metastatic colorectal cancer chemotherapy: systematic review]. PubMed PMID: 20167564.

*(Review of the hepatotoxicity of agents used for metastatic colorectal cancer mentions that the anti-EGFR monoclonal antibodies have not been reported to cause liver injury).*

Stremitzer S, Sebio A, Stintzing S, Lenz HJ. Panitumumab safety for treating colorectal cancer. Expert Opin Drug Saf. 2014;13:843–51. PubMed PMID: 24766434.

*(Review of mechanism of action and safety of panitumumab therapy of metastatic colorectal cancer discusses skin toxicity, hypomagnesemia, diarrhea and infusion reactions [which are less with panitumumab than cetuximab], but not hepatotoxicity or ALT elevations).*

Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, et al. Final results from PRIME: randomized phase 3 study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25:1346–55. PubMed PMID: 24718886.

*(Among 1183 patients with previously untreated metastatic colorectal cancer given panitumumab and FOLFOX4 or FOLFOX4 alone, severe side effects more frequent in the panitumumab exposed patients included skin toxicity [27% vs 2%], diarrhea, hypokalemia, hypomagnesemia, fatigue and mucositis; no mention of hepatotoxicity or ALT elevations).*

Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, André T, et al. Final results from a randomized phase 3 study of FOLFIRI {+/-} panitumumab for second-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25:107–16. PubMed PMID: 24356622.

*(Among 1186 patients with previously treated metastatic colorectal cancer given panitumumab and FOLFIRI or FOLFIRI alone, adverse events that were more frequent with panitumumab therapy included site toxicity, hypokalemia and hypomagnesemia; no mention of ALT elevations or hepatotoxicity).*

Kim TW, Elme A, Kusic Z, Park JO, Udrea AA, Kim SY, Ahn JB, et al. A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer. Br J Cancer. 2016;115:1206–14. PubMed PMID: 27736842.

*(Among 677 patients with metastatic colorectal cancer treated with panitumumab or standard of care alone, overall survival is improved by the combination [10 vs 6.9 months], while adverse event rates were higher [97% vs 61%] particularly for rash [31% vs 1%], acneiform dermatitis [29% vs 0%], hypomagnesemia [28% vs 1%], itching [25% vs 2%]; but no mention of ALT elevations or hepatotoxicity).*

Kamo H, Shinozaki E, Sugase T, Mizunuma N, Taniguchi S, Gotoh T, Chin K, et al. Leukocytoclastic vasculitis with purpura and renal failure induced by the anti-epidermal growth factor receptor antibody panitumumab: a case report. J Med Case Rep. 2019;13:13. PubMed PMID: 30646927.

*(67 year old Japanese man with advanced colon cancer developed rash and renal dysfunction 2 days after a second infusion of panitumumab, liver tests not mentioned).*

Hisaka T, Ishikawa H, Sakai H, Kawahara R, Goto Y, Nomura Y, Yasunaga M, et al. Sinusoidal obstruction syndrome and postoperative complications resulting from preoperative chemotherapy for colorectal cancer liver metastasis. Anticancer Res. 2019;39:4549–54. PubMed PMID: 31366558.

*(Among 90 patients with colorectal cancer and liver metastases treated with preoperative mFOLFOX6 with or without bevacizumab, panitumumab or cetuximab, liver histology at time of resection sinusoidal injury was seen in all groups, but was less severe in those who had received bevacizumab).*