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# Pertuzumab

Updated: June 18, 2015.

## OVERVIEW

### Introduction

Pertuzumab is a humanized monoclonal antibody to the human epidermal growth factor receptor 2 (HER2) which is used in combination with other antineoplastic agents in the therapy of refractory, advanced breast cancer. Pertuzumab has been implicated in rare instances of transient, occasionally marked serum enzyme elevations, but has not been linked to instances of clinically apparent liver injury with jaundice.

### Background

Pertuzumab (per tooz' ue mab) is humanized monoclonal antibody to HER2 which is a growth factor receptor that is overexpressed in 20% to 25% of breast cancers. The interaction of epidermal growth factor (EGF) with HER2 results in rapid cell growth and proliferation via intracellular pathways that include MAP and PI3 kinase. Blockage of this pathway results in cell cycle arrest and cell death. Pertuzumab binds to the dimerization site on the HER2 receptor and prevents pairing of receptors and blocks their intracellular signaling. Because the binding site for pertuzumab is different from that of trastuzumab (another monoclonal antibody to HER2), they can be used together and are believed to have additive antitumor effects. Pertuzumab in combination with trastuzumab and docetaxel has been shown to increase the rate of pathological complete responses in women with advanced HER2 positive breast cancer and it was approved for this indication in 2012. Pertuzumab is available in multiple use vials of 420 mg under the brand name Perjeta. The typical dose is 840 mg intravenously initially, followed by 420 mg every three weeks. Common side effects include diarrhea, nausea, fatigue, rash, abdominal pain and cardiac dysfunction. Rare, but serious side effects include infusion reactions (usually with the initial dose), cardiomyopathy (especially when combined with an anthracycline), pneumonitis and fetal toxicity.

### Hepatotoxicity

In large registration trials of pertuzumab for breast and other cancers, rates of serum enzyme elevations were usually not reported, although elevations in ALT above 5 times the ULN have been reported in studies of pertuzumab combined with carboplatin, docetaxel and trastuzumab or with trastuzumab emtansine. A single instance of acute liver failure was reported in a patient who received pertuzumab, trastuzumab and docetaxel in a clinical trial, but few details were given. In all of these situations, the role of pertuzumab as opposed to the other antineoplastic agents being used was uncertain. Since its approval and wider scale use, there have been no reports of serum ALT elevations or clinically apparent, acute liver injury with jaundice attributed to pertuzumab.

## Mechanism of Injury

Pertuzumab is a human monoclonal antibody and is unlikely to have intrinsic hepatotoxicity, but it may interact with endothelial growth factor receptors present on normal cells and cause injury by its direct cellular effects on epithelial growth factor pathways.

## Outcome and Management

The liver injury attributed to pertuzumab has not been well characterized and there is no information on possible cross sensitivity to the injury among different monoclonal antibodies or therapies directed at epidermal growth factor receptors.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Pertuzumab – Perjeta®

**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 |
|---|---|---|---|
| Pertuzumab | **380610-27-5** | Monoclonal Antibody | Not Available |

# ANNOTATED BIBLIOGRAPHY

References updated: 18 June 2015

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

*(Expert review of hepatotoxicity published in 1999, well before the availability of most monoclonal antibody therapies).*

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 drugs mentions that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").*

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds.

Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

*(Textbook of pharmacology and therapeutics).*

Gianni L, Lladó A, Bianchi G, Cortes J, Kellokumpu-Lehtinen PL, Cameron DA, Miles D, et al. Open-label, phase II, multicenter, randomized study of the efficacy and safety of two dose levels of Pertuzumab, a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010; 28: 1131-7. PubMed PMID: 20124183.

*(Among 78 women with metastatic breast cancer [HER2 negative] treated with one of 2 doses of pertuzumab every 3 weeks, response rates were minimal and side effects were common, including diarrhea [51%], nausea [27%], fatigue [24%], rash [21%], abdominal pain [156%] and cardiac dysfunction [11%]; no mention of ALT elevations or hepatotoxicity).*

Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13: 25-32. PubMed PMID: 22153890.

*(Among 417 women with HER2 positive breast cancer treated with 1 of 4 regimens of pertuzumab, docetaxel and trastuzumab, highest rates of response and side effects occurred with triple therapy, including one death from fulminant hepatitis after a 4th cycle; no mention of rates of ALT elevations ).*

Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, et al.; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012; 366: 109-19. PubMed PMID: 22149875.

*(Among 808 women with metastatic breast cancer [HER2 positive] treated with trastuzumab and docetaxel, the addition of pertuzumab increased progression free survival from 12.4 to 18.5 months and increased side effects of diarrhea [46% to 67%] and febrile neutropenia [8% to 14%]; no mention of hepatotoxicity).*

Pertuzumab (Perjecta) for HER2-positive metastatic breast cancer. Med Lett Drugs Ther 2012; 54 (1395): 59-60. PubMed PMID: 22825690.

*(Concise review of mechanism of action, efficacy and safety of pertuzumab as therapy of metastatic breast cancer [HER2 positive] shortly after its approval for this use in the US; no mention of ALT elevations or hepatotoxicity).*

Pertuzumab (Perjeta) for preoperative use in HER2-positive breast cancer. Med Lett Drugs Ther 2013; 55 (1431): 98-9. PubMed PMID: 24322664.

*(Concise review of mechanism of action, efficacy and safety of pertuzumab as neoadjuvant [preoperative] therapy for HER2 positive breast cancer mentions cardiomyopathy, anaphylaxis and embryotoxicity, but not hepatotoxicity or ALT elevations).*

Miller KD, Diéras V, Harbeck N, Andre F, Mahtani RL, Gianni L, Albain KS, et al. Phase IIa trial of trastuzumab emtansine with pertuzumab for patients with human epidermal growth factor receptor 2-positive, locally advanced, or metastatic breast cancer. J Clin Oncol 2014; 32: 1437-44. PubMed PMID: 24733796.

*(Among 64 women with HER2 positive metastatic breast cancer [HER2 positive] treated with the combination of pertuzumab and trastuzumab emtansine [every 3 weeks], common side effects were fatigue [61%], nausea [50%] and diarrhea [39%] and "hepatic dysfunction" in 38% with ALT levels above 5 times ULN in 9%).*