Cetuximab

Cetuximab (INN) is an epidermal growth factor receptor (EGFR) inhibitor used for the treatment of metastatic colorectal cancer, metastatic non-small cell lung cancer and head and neck cancer. Cetuximab is a chimeric (mouse/human) monoclonal antibody given by intravenous infusion that is distributed under the trade name **Erbitux** in the U.S. and Canada by the drug company Bristol-Myers Squibb and outside the U.S. and Canada by the drug company Merck KGaA. In Japan, Merck KGaA, Bristol-Myers Squibb and Eli Lilly have a co-distribution.

In July 2009, the FDA approved cetuximab (Erbitux) for treatment of colon cancer with wild-type KRAS, since it had little or no effect in colorectal tumors harboring a KRAS mutation (this also applied to the EGFR antibody panitumumab)[1] This was the first genetic test to guide treatment of cancer.[2] In July 2012, the FDA approved a real time PCR companion diagnostic test for KRAS, the therascreen KRAS test.[3]

1 Medical uses

Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer (mCRC), in combination with chemotherapy, and as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. The positive opinion from the European regulatory agency, the Committee for Medicinal Products for Human Use (CHMP), was received for mCRC 1st line use in May 2008.

Cetuximab (Erbitux) is indicated for the treatment of patients with squamous cell carcinoma of the head and neck in combination with platinum-based chemotherapy for the 1st line treatment of recurrent and/or metastatic disease and in combination with radiation therapy for locally advanced disease. The positive CHMP opinion for this indication was received in October 2008.

A diagnostic immunohistochemistry assay (EGFR pharmDx) can be used to detect EGFR expression in the tumor material. Approximately 75% of patients with metastatic colorectal cancer have an EGFR-expressing tumor and are therefore considered eligible for treatment with cetuximab or panitumumab, according to FDA guidelines. Unfortunately, there is evidence that immunohistochemical EGFR receptor testing does not predict response to either cetuximab or panitumumab, so that this has been called a "misleading biomarker" that has nevertheless caused insurers and even health systems to deny payment for EGFR antibody treatment for patients who lack a positive tumor EGFR histochemical test.[2]

1.1 Colorectal cancer

Cetuximab is indicated for the treatment of patients with EGFR expressing, KRAS wild-type metastatic colorectal cancer in combination with chemotherapy or as a single agent in patients who have failed in oxaliplatin- or irinotecan- base therapy and who are intolerant to irinotecan. While there remains some scientific controversy on this, assessment for EGFR expression is required for use in colorectal cancer, but not in head & neck cancer.

1.2 Head and neck cancer

Cetuximab was approved by the FDA in March 2006 for use in combination with radiation therapy for treating squamous cell carcinoma of the head and neck (SCCHN) or as a single agent in patients who have had prior platinum-based therapy.[4]

2 Side effects

One of the more serious side effects of cetuximab therapy is the incidence of acne-like rash. This rash rarely leads to dose reductions or termination of therapy. It is generally reversible.[5]

Further severe infusion reactions include but are not limited to: fevers, chills, rigors, urticaria, pruritis, rash, hypotension, N/V, HA, bronchospasm, dyspnea, wheezing, angioedema, dizziness, anaphylaxis, and cardiac arrest. Therefore, pretreatment with diphenhydramine 30-60 min. before administration is standard of care. Other common side effects include photosensitivity, hypomagnesemia due to magnesium wasting, and less commonly pulmonary and cardiac toxicity. [6]

3 Mechanism of action

When growth factors bind to their receptors on the surface of the cell, the receptors give a signal that causes cells to

divide. Some cancers are caused by mutated receptors that give a signal to divide even without growth factor. That causes the cells to divide uncontrollably. Cetuximab binds to such receptors and turns off that signal.

The EGFR sends a signal down a pathway (see MAPK) that includes another protein, KRAS (also spelled *K-ras*). In some cancers, the EGFR is mutated, and is present to a larger or smaller degree. In these cancers, the KRAS protein may either be "wild type" or mutated. If mutated, KRAS sends a signal to divide uncontrollably, even if EGFR has been blocked by cetuximab.

Cetuximab binds to EGFR and turns off the uncontrolled growth in cancers with EGFR mutations (although in practice, studies have shown that the effect of cetuximab does not actually depend on the amount of EGFR receptor protein found on the cancer cells). However, if the KRAS protein is mutated, cetuximab has been found not to work, because the mutated KRAS gene downstream is causing the problem by continuously sending a growth signal (the KRAS protein) and this mutated gene now does not respond to the EGFR.

Therefore, before cetuximab is used, the standard of care is that the KRAS gene in the cancer cells is tested for mutation. If KRAS is normal (*wild type*), cetuximab might work. But if KRAS is mutated, indications are that cetuximab (and also panitumumab) will not work, because the mutated KRAS gene continuously sends a KRAS protein signal to divide, even when cetuximab has turned the earlier EGFR signal off.

4 KRAS Testing

The KRAS gene encodes a small G protein on the EGFR pathway. Cetuximab and other EGFR inhibitors only work on tumors in which KRAS is not mutated.[7][8][8]

KRAS mutational analysis is commercially available from a number of laboratories.

In July 2009, the US Food and Drug Administration (FDA) updated the labels of two anti-EGFR monoclonal antibody drugs (panitumumab (Vectibix) and cetuximab (Erbitux)) indicated for treatment of metastatic colorectal cancer to include information about KRAS mutations.[1]

Studies have indicated that detection of KRAS gene mutations helps physicians identify patients that are unlikely to respond to treatment with targeted EGFR inhibitors, including cetuximab and panitumumab. Accordingly, genetic testing to confirm the absence of KRAS mutations (and so the presence of the KRAS wild-type gene), is now clinically routine before the start of treatment with EGFR inhibitors. mCRC patients with wild-type KRAS tumors have been shown to benefit from a response rate of over 60% and a decreased risk for progression of over 40% when treated with Erbitux as 1st-line therapy. Around 65% of mCRC patients have the KRAS wild-type gene.

5 History

Michael Sela and co-workers published observations on EGFR inhibition in 1988.[9] Yeda Research, on behalf of the Weizmann Institute of Science in Israel,[10] challenged the Aventis-owned patent,[11] licensed by Imclone, for the use of anti-epidermal growth factor receptor antibodies in combination with chemotherapy, to slow the growth of certain tumors which was filed in 1989 by Rhone-Poulenc-Rorer.[12] The court ruled that Yeda is sole owner of the patent in the U.S., while Yeda and Sanofi-Aventis co-own the patent's foreign counterparts.[13][14][15]

6 Society and culture

6.1 Manufacture

- Eli Lilly and Company is responsible for the manufacture and supply of Erbitux in bulk-form active pharmaceutical ingredient (API) for clinical and commercial use in the U.S. and Canada, and Bristol-Myers Squibb purchases the API for commercial use from Eli Lilly.
- Merck KGaA manufactures Erbitux for supply in its territory (outside the U.S. and Canada) as well as for Japan.[16]

6.2 Distribution

- Erbitux is marketed in the U.S. and Canada by Bristol-Myers Squibb. Eli Lilly has the option to co-promote Erbitux in the U.S. and Canada. Eli Lilly receives royalties from Bristol-Myers Squibb.
- Outside the U.S. and Canada, Erbitux is commercialized by Merck KGaA. Eli Lilly receives royalties from Merck KGaA.
- A separate agreement grants co-exclusive rights among Merck, Bristol-Myers Squibb and Eli Lilly in Japan and expires in 2032.[16]

6.3 Sales

Cetuximab is given by intravenous therapy and costs up to $30,000 for eight weeks of treatment per patient.[17]

Merck KGaA had 887 million euros ($1.15 billion) in Erbitux sales in 2012, from head and neck as well as bowel cancer, while Bristol-Myers Squibb generated $702 million in sales from the drug.[18]

Erbitux was the eighth best-selling cancer drug of 2013, with sales of $1.87 billion.[19]

6.4 Biosimilars

Erbitux had 2013 worldwide sales of US$1.9 billion making it a lucrative target for biosimilars developers. Additionally the patent protection for Erbitux in Europe expired in June 2014, and in the U.S. and in Japan the protection will expire in 2016.[20] However biosimilars of Erbitux are not expected until 2018.[21]

As of 2014 biosimilars of cetuximab were in development by several companies.[22][23]

7 Research

The efficacy of cetuximab was explored in a clinical trial of advanced gastric cancer published in 2013; cetuximab showed no survival benefit.[24]

8 References

[1] "Class Labeling Changes to anti-EGFR monoclonal antibodies, cetuximab (Erbitux) and panitumumab (Vectibix): KRAS Mutations". U.S. Food and Drug Administration. 2010-01-11.

[2] Messersmith WA, Ahnen DJ (October 2008). "Targeting EGFR in colorectal cancer". *N. Engl. J. Med.* **359** (17): 1834–6. doi:10.1056/NEJMe0806778. PMID 18946069.

[3] "Therascreen KRAS RGQ PCR Kit – P110030". *Device Approvals and Clearances*. U.S. Food and Drug Administration. 2012-07-06.

[4] "Cetuximab Beneficial in Head and Neck Cancer - National Cancer Institute". Cancer.gov. Retrieved 2013-04-13.

[5] Nguyen A, Hoang V, Laquer V, Kelly KM (December 2009). "Angiogenesis in cutaneous disease: part I". *J. Am. Acad. Dermatol.* **61** (6): 921–42; quiz 943–4. doi:10.1016/j.jaad.2009.05.052. PMID 19925924.

[6] 8. Micromedex Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically

[7] Van Cutsem E, et al. (April 2009). "Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer". *N. Engl. J. Med.* **360** (14): 1408–17. doi:10.1056/NEJMoa0805019. PMID 19339720.

[8] Bokemeyer C, Van Cutsem E, Rougier P, Ciardiello F, Heeger S, Schlichting M, Celik I, Köhne CH (July 2012). "Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials". *Eur. J. Cancer.* **48** (10): 1466–75. doi:10.1016/j.ejca.2012.02.057. PMID 22446022.

[9] Aboud-Pirak E, Hurwitz E, Pirak ME, Bellot F, Schlessinger J, Sela M (1988-12-21). "Efficacy of antibodies to epidermal growth factor receptor against KB carcinoma in vitro and in nude mice". *J. Natl. Cancer Inst.* **80** (20): 1605–11. doi:10.1093/jnci/80.20.1605. PMID 3193478.

[10] "Yeda Research and Development Company Ltd". Technology Transfer Company of the Weizmann Institute of Science

[11] Groombridge N, Gearing BP (February 2008). "Practical lessons from a "made for TV" patent litigation: The trial of Yeda Research & Development Co. Ltd. v. ImClone Systems Inc. and Aventis Pharmaceuticals Inc." (PDF). *The Federal Lawyer*: 51–55.

[12] US patent 6217866, Sela M, Pirak E, Hurwitz E, "Monoclonal antibodies specific to human epidermal growth factor receptor and therapeutic methods employing same", published 2001-04-17, assigned to Yeda Research & Development

[13] "Court ruling on Yeda vs Aventis/Imclone case" (PDF).

[14] "Archived copy". Archived from the original on 2015-11-20. Retrieved 2015-08-30.

[15] "ImClone goes up against patent dispute". USA Today. 2006-09-14.

[16] Eli Lilly and Company Form 10-K Annual Report 2013

[17] Schrag D (July 2004). "The price tag on progress--chemotherapy for colorectal cancer". *N. Engl. J. Med.* **351** (4): 317–9. doi:10.1056/NEJMp048143. PMID 15269308.

[18] Merck KGaA's Erbitux beats Avastin in bowel cancer trial, Reuters, Jun 1 2013

[19] Top 10 best-selling cancer drugs of 2013; May 29, 2014

[20] Bristol-Myers Squibb Company 2013 Form 10-K

[21] Merck Serono Investor & Analyst Day 2014 - Belen Garijo's presentation - Slide 41 - 18 Sept 2014

[22] Generics and Biosimilars Initiative (GaBI) - Biosimilars of cetuximab - 14/08/2014

[23] Torrent Pharma, Reliance Life sign licensing agreement for biosimilars

[24] Li K, Li J. Current Molecular Targeted Therapy in Advanced Gastric Cancer: A Comprehensive Review of Therapeutic Mechanism, Clinical Trials, and Practical Application. Gastroenterol Res Pract. 2016;2016:4105615. Review. PMID 26880889

9 External links

- FDA Erbitux (cetuximab) Information Page
- Erbitux site from Bristol-Myers Squibb, ImClone Systems, and Merck KGaA

10 Text and image sources, contributors, and licenses

10.1 Text

- **Cetuximab** *Source:* https://en.wikipedia.org/wiki/Cetuximab?oldid=750277876 *Contributors:* Selket, Pretzelpaws, Jfdwolff, Chowbok, Mfv2, Surfingslovak, GreenReaper, Skorpionas, El C, Dalf, Cmdrjameson, Arcadian, Haham hanuka, Axl, Adarshpandit, GJeffery, Japanese Searobin, Alvis, DePiep, Rjwilmsi, FlaBot, Chase me ladies, I'm the Cavalry, Andrew73, SmackBot, Edgar181, Chris the speller, George Church, Sbharris, Flyguy649, Prisonnet, Beetstra, Patho~enwiki, Cydebot, Vargob, RXPhd, Andy Rosenthal, Tjmayerinsf, WarFighter, LinkinPark, Ph.eyes, Reesoff, Rami R, STBot, StephP, Greg.s.green, Nbauman, Boghog, Rod57, Mvramesh99, My Core Competency is Competency, Bassomatic, BlakeCS, Healthvalue, Hofland, Doc James, Ronsword, Squelle, Andrewlkho, Stillwaterising, ClueBot, Carlo Banez, Perkeleperkele, DumZiBoT, BobMullin, Jytdog, Addbot, DOI bot, SamatBot, Johnfravolda, Ben Ben, Luckas-bot, Yobot, CheMoBot, Bisbee2009, Anypodetos, Leapy99, AnomieBOT, CultureSky, Citation bot, Abigor, Stonesoupma, TrueGlue, FrescoBot, Redrose64, MondalorBot, Patentpedant, BogBot, Trappist the monk, Lotje, Ciardiello, Galahadin, ZxxZxxZ, ZéroBot, H3llBot, Hazard-Bot, Peryeat, EdoBot, Kognos, The chemistds, FeatherPluma, Louisajb, ClueBot NG, Pashihiko, HenryScow, Whoooshing, BG19bot, Fuse809, Cyberbot II, Fernando O Lopes, Rt34rt34, Parewaobol, Mogism, Monkbot, Humpath, Medgirl131, Kimsamuel, LamasUI, InternetArchiveBot and Anonymous: 64

10.2 Images

- **File:Ambox_important.svg** *Source:* https://upload.wikimedia.org/wikipedia/commons/b/b4/Ambox_important.svg *License:* Public domain *Contributors:* Own work, based off of Image:Ambox scales.svg *Original artist:* Dsmurat (talk · contribs)
- **File:Rod_of_Asclepius2.svg** *Source:* https://upload.wikimedia.org/wikipedia/commons/e/e3/Rod_of_Asclepius2.svg *License:* CC BY-SA 3.0 *Contributors:* This file was derived from: Rod of asclepius.png
  Original artist:
- Original: CatherinMunro
- **File:X_mark.svg** *Source:* https://upload.wikimedia.org/wikipedia/commons/a/a2/X_mark.svg *License:* Public domain *Contributors:* Own work *Original artist:* User:Gmaxwell
- **File:Yes_check.svg** *Source:* https://upload.wikimedia.org/wikipedia/en/f/fb/Yes_check.svg *License:* PD *Contributors:* ? *Original artist:* ?

10.3 Content license

- Creative Commons Attribution-Share Alike 3.0