



Therapeutic Class ReviewSM

Antineoplastics – lapatinib (Tykerb[®])

October 2008

New Product for Review:

lapatinib (Tykerb[®]) [GlaxoSmithKline]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 1

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Executive Summary

- Advanced or metastatic breast cancer is often defined as the presence of disease at distant sites including bone, lung, or liver.
- The American Cancer Society estimates:
 - New cases of Breast Cancer in 2006 were approximately 212,290.
 - Approximately 10% metastatic at diagnosis.
 - Approximately 33% of the rest progresses advanced/metastatic status.
 - Approximately 20% to 30% of invasive breast CA will be HER2+.
- There is an unmet need for the treatment of advanced or metastatic breast cancer due to lack of current options that offer disease cure. The goal of treatment is typically palliative.
- Testing tumor for HER2 is essential. Overexpression leads to a greater risk for disease progression and death.^[2]
- Treatment options for advanced and/or metastatic breast cancer that over-expresses HER2 may include the following therapies:^[1]
 - Endocrine Therapy
 - Chemotherapy – options include anthracyclines, taxanes, and trastuzumab (Herceptin) used alone or in combination.^[1]
 - Trastuzumab (Herceptin) is considered the primary standard of care either alone or in combination with chemotherapy.
 - Oncologists and national practice standards generally recognize trastuzumab (Herceptin) as a primary option before considering lapatinib (Tykerb) because:
 - There are no clinical trials evaluating lapatinib (Tykerb) as initial or primary therapy of advanced and/or metastatic breast cancer.
 - There is experience and familiarity with the efficacy and safety profile of trastuzumab (Herceptin) as an established agent.
 - Potential benefits have been reported in clinical trials for advanced or metastatic breast cancer tumors that over-express HER2.^[18]

- * Modest improvements in overall survival of 4.8 months versus standard chemotherapy alone ($p < 0.001$).
 - * Time to disease progression improved by 2.8 months ($p < 0.001$). (Time to disease progression is defined as the time from randomization to disease progression or death due to breast cancer).
- Lapatinib (Tykerb):
 - Is a new oral chemotherapy drug (approved in March 2007).
 - Is indicated in combination with capecitabine (Xeloda) for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab (Herceptin[®]).
 - Works at the HER2 receptor.
 - Also inhibits EGFR (Epidermal Growth Factor Receptor), though the significance of this activity is unknown.
 - As a small molecule, lapatinib (Tykerb) has significant CNS penetration, in contrast to Herceptin. Therefore, lapatinib (Tykerb) has a potential for benefit in brain metastases.
 - Considerations for evaluating lapatinib (Tykerb) include:
 - Quality of the science.
 - Unmet need in treating advanced/metastatic breast cancer.
 - Likelihood of benefit.
 - Risk of harms.
 - Ongoing clinical trials in the pipeline that may add more information about its benefit.
 - Response to lapatinib (Tykerb) was determined by measuring the time to progression. (Disease progression is determined using radiographic evidence of tumor size changes based on the RECIST criteria.)
 - Time to disease progression is a surrogate marker often used to correlate with survival. However, this association continues to be controversial.^[15]
 - Reliance on this endpoint to determine efficacy of chemotherapy agents may result in:
 - Failure to determine optimally useful therapies.
 - Investment of significant resources on a therapy that does not have a substantive effect on overall survival.
 - Overlooking potentially serious harms that could outweigh any potential benefit.
 - There is the potential for off-label use with lapatinib (Tykerb) as evidenced by recruitment of subjects in more than 60 trials in various cancer types (brain, prostate, esophageal, head and neck, bladder, lung, early breast, etc.).

Evidence

- There is no reliable evidence supporting the efficacy and safety of lapatinib (Tykerb) in combination with capecitabine (Xeloda) in the treatment of advanced or metastatic breast cancer (open label trial).

- It is not known whether treatment with lapatinib (Tykerb) alone or in combination with capecitabine (Xeloda) improves or affects overall survival or quality of life as palliative or a treatment option of last resort.
- There is no data comparing lapatinib (Tykerb) to other recommended treatment options for advanced or metastatic breast cancer over-expressing HER2. Therefore, there is unknown benefit as an option over trastuzumab (Herceptin) or other conventional agents.
- Lapatinib (Tykerb) has not been studied as monotherapy in any treatment setting.

Decision

Lapatinib (Tykerb) is non-preferred/non-formulary because it has uncertain benefit in advanced or metastatic breast cancer.

Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
capecitabine (Xeloda [®]) ⁵	4/30/1998	2011-2013	-Colorectal Cancer -In combination with docetaxel for the tx of pts with metastatic breast cancer after failure of prior anthracycline containing chemotherapy -Monotherapy in metastatic breast cancer resistant to both paclitaxel and an anthracycline.	2,000 mg/m ² /day (administered orally in 2 doses approximately 12 hrs apart) on days 1-14 in a repeating 21 day cycle..	-Various other cancers: gastric, liver, nasopharyngeal, pancreatic, head and neck, pancreatic.
lapatinib (Tykerb [®]) ⁴	03/2007	2019	-In combination with capecitabine (Xeloda) for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.	1,250 mg (5 tablets) given orally once daily on days 1-21 continuously in combination with capecitabine 2,000 mg/m ² /day (administered orally in 2 doses approximately 12 hrs apart) on days 1-14 in a repeating 21 day cycle.	-Breast CA – inflammatory, relapsed or refractory; -Metastatic breast CA – HER2 over-expression, first line, monotherapy -Secondary malignant neoplasm of the brain. -Solid Tumors -Renal Cancer -Bladder Cancer
trastuzumab (Herceptin [®]) ⁶	09/1998	~2018	-Adjuvant tx of pts with HER2 over-expressing, node-positive breast cancer as part of a tx regimen containing doxorubicin, cyclophosphamide, and paclitaxel. -Monotherapy for the tx of pts with metastatic breast cancer in tumors over-expressing HER2 who have received 1 or more chemo regimens for metastatic disease. -In combination with paclitaxel for tx of pts with metastatic breast cancer in tumors over-expressing HER2 and who have not received chemo for their metastatic disease.	-Administered as an IV infusion once every 7 days - First infusion: 4 mg/kg over 90 min; Subsequent infusions: 2 mg/kg over 30 minutes. -For metastatic cancer, administer until tumor progression. -For adjuvant tx administer for 52 weeks (first 12 with paclitaxel).	-Various other cancers: ovarian, endometrial, sarcoma, bladder.

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Based on patents listed in Orange Book as of 04/01/07 or from information gained from the manufacturer.

^c As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology – Breast Cancer. Version 2.2008. 1/28/2008. Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed on 5/5/2008.
2. Slamon DF, Clark GM, Wong SG, Levin WF, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235:177-82.
3. Tykerb[®] (lapatinib) tablets Product Information. GlaxaSmithKline: Research Triangle Park, NC; March 2007.
4. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006;355:2733-43.
5. Xeloda[®] (capecitabine) tablets Product Information. Roche Pharmaceuticals: Nutley, NJ; April 2006.
6. Herceptin[®] (trastuzumab) Product Information. Genentech, Inc.: South San Francisco, CA; November 2006.
7. Moja L, Compagnoni A, Brambilla C, McGowan JL, Nurbhai M, Pistotti V. Trastuzumab containing regimens for metastatic breast cancer. (Protocol) *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD006242. DOI: 10.1002/14651858.CD006242.

8. Carrick S, Parker S, Wilcken N, Gherzi D, Marzo M, Simes J. Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD003372. DOI: 10.1002/14651858.CD003372.pub2.
9. Stebbing J, Slater S, Slevin M. Breast cancer (metastatic). *Clin Evid* 2006;15:1-29.
10. National Cancer Institute (NCI). Breast Cancer (PDQ®): Treatment – Stage IIB, Inoperable IIIC, IV, Recurrent, and Metastatic Breast Cancer.. Available at: <http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/page8> Accessed: 5/5/2008
11. National Institute for Clinical Excellence (NICE). Improving outcomes in breast cancer; manual update. August 2002. Available at: <http://guidance.nice.org.uk/csgbc>.
12. Cancerstaging.org. American Joint Committee on Cancer (AJCC). [updated Jan 12, 2007]. Available from: <http://www.cancerstaging.org/mission/whatis.html>.
13. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.* 2000;92(3):205-16.
14. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. [updated Aug 9, 2006]. Available from: <http://ctep.cancer.gov/reporting/ctc.html>.
15. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *The Oncologist.* 2005;10(suppl 3):20-29.
16. American Cancer Society. Breast cancer facts and figures 2005-2006. Atlanta: American Cancer Society, Inc.
17. BMJ Clinical Evidence. Better use, and understanding, of evidenced-based medicine. ©BMJ Publishing Group Limited 2007. Available from: <http://www.clinicalevidence.com/ceweb/resources/glossary.jsp#H>.
18. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-792.
19. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol.* 2008 Apr 20;26(12):1993-9.
20. Johnston S, Trudeau M, Kaufman B, et al. Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2 (HER-2) in advanced inflammatory breast cancer with lapatinib monotherapy. *J Clin Oncol.* 2008 Mar 1;26(7):1066-72.
21. Agulnik M, Cohen EW, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. *J Clin Oncol.* 2007 Sep 1;25(25):3978-84.
22. Gomez HL, Doval DC, Chavez MA, et al. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. *J Clin Oncol.* 2008 Jun 20;26(18):2999-3005.
23. Burstein HJ, Storniolo AM, Franco S, et. al. A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer. *Ann Oncol.* 2008 Jun;19(6):1068-74.
24. Personal Communication. GlaxoSmithKline Medical Information Response. Received September 16, 2008
25. Ravaud A, Hawkins R, Gardner JP, et. al. Lapatinib versus hormone therapy in patients with advanced renal cell carcinoma: a randomized phase III clinical trial. *J Clin Oncol.* 2008 May 10;26(14):2285-91.