

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tykerb® (lapatinib ditosylate tablets – Novartis Pharmaceuticals)

TAC APPROVAL DATE: 12/19/2018

OVERVIEW

Tykerb is indicated in combination with capecitabine tablets for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and Herceptin® (trastuzumab intravenous injection).¹ *Limitation of use.* Patients should have disease progression on Herceptin prior to initiation of treatment with Tykerb in combination with capecitabine tablets. Tykerb is also indicated in combination with letrozole tablets for the treatment of postmenopausal women with hormone receptor-positive (HR+) metastatic breast cancer that overexpresses HER2 for whom hormonal therapy is indicated. Tykerb in combination with an aromatase inhibitor (AI) has not been compared to a Herceptin-containing chemotherapy regimen for the treatment of metastatic breast cancer. Tykerb is a kinase inhibitor of the intracellular tyrosine kinase domains of both epidermal growth factor receptor (*EGFR*) and of HER2 (ErbB2) receptors. Tykerb inhibits ErbB-driven tumor cell growth *in vitro* and in various animal models.

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on breast cancer (version 3.2018) recommend Tykerb in combination with Herceptin (without cytotoxic therapy) or capecitabine for HER2-positive (HER2+) recurrent or metastatic Herceptin-exposed disease with symptomatic visceral disease or visceral crisis OR that is hormone receptor-negative or HR+ and endocrine therapy refractory (category 2A).²

Tykerb is also recommended in combination with an AI with or without Herceptin for the treatment of recurrent or Stage IV HR+, HER2+ disease in postmenopausal women.² Premenopausal women with HR+ disease should have ovarian ablation/suppression and follow the guidelines for postmenopausal patients. Men with breast cancer should be treated similarly to postmenopausal women except that using an AI is ineffective without suppression of testicular steroidogenesis (category 2A).

The NCCN clinical practice guidelines on central nervous system (CNS) cancers (version 2.2018) recommend treatments for patients with brain metastases from breast cancer.³⁻⁴ Capecitabine with or without Tykerb is recommended for recurrent disease in patients with limited (one to three) metastatic lesions or treatment for recurrent stable systemic disease in patients with multiple (> three) metastatic lesions if Tykerb is active against the primary tumor (breast).

Safety

Tykerb has a boxed warning regarding hepatotoxicity that may be severe and deaths have been reported. Causality of the deaths is uncertain.¹

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tykerb to recommend use in treatment of patients with HER2 overexpressing breast cancer. All approvals are provided for 3 years in duration unless otherwise noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next

to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; a man is defined as an individual with the biological traits of a man, regardless of the individual's gender identity or expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tykerb is recommended in those who meet the following criteria:

FDA-Approved Indications

- 1. Breast Cancer, Human Epidermal Growth Factor Receptor 2 Positive (HER2+).** Approve for 3 years if the patient meets one of the following criteria (A or B):
 - A)** Patient has advanced or metastatic breast cancer and the following criteria are met (i and ii):
 - i.** Tykerb will be used in combination with capecitabine OR Herceptin; AND
 - ii.** Patient has received prior therapy with Herceptin; OR
 - B)** Patient has hormone receptor-positive (that is, estrogen- and/or progesterone-positive) metastatic breast cancer and the following criteria are met (i and ii):
 - i.** One of the following (a, b, or c) applies:
 - a)** The patient is a postmenopausal woman;* OR
 - b)** The patient is a premenopausal or perimenopausal woman* and is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron® [leuprolide], Trelstar® [triptorelin], Zoladex® (goserelin)), surgical bilateral oophorectomy, or ovarian irradiation; OR
 - c)** The patient is a man* and is receiving a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin)) AND
 - ii.** Tykerb will be used in combination with an aromatase inhibitor (that is, letrozole, anastrozole, or exemestane).

* Refer to the Policy Statement.

Other Uses with Supportive Evidence

- 2. Bone Cancer – Chordoma.** Approve for 3 years if the patient has epidermal growth-factor receptor (EGFR)-positive recurrent disease.

The NCCN guidelines for bone cancer (version 1.2019) and the compendium recommends the use of Tykerb for EGFR-positive recurrent disease.^{3,5}

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tykerb has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Adenoid/Non-Adenoid Cystic Carcinoma of the Salivary Glands.** In one Phase II study (n = 62) no responses were observed in Tykerb-treated patients with progressive, recurrent, or metastatic adenoid cystic carcinoma (ACC) and non-ACC malignant salivary gland tumors.⁶
 - 2. Biliary Cancer.** In one Phase II study (n = 9) in patients with biliary cancer, Tykerb failed to demonstrate activity as a single agent.⁷ The study was terminated early due to futility. In another Phase II study (n = 17) in patients with biliary tree cancer, Tykerb failed to demonstrate activity.⁸
 - 3. Cervical Cancer.** In one Phase II study (n = 228), Tykerb plus Votrient® (pazopanib tablets) was compared with Tykerb monotherapy or Votrient monotherapy in patients with advanced and recurrent cervical cancer.⁹ At the interim analysis, the futility boundary was crossed for combination therapy vs. Tykerb monotherapy, and the combination arm was discontinued. The median PFS was shorter among Tykerb-treated patients vs. Votrient-treated patients (17.1 weeks vs. 18.1 weeks, respectively; HR 0.66; 90% CI: 0.48, 0.91; P < 0.013). On the clinical cutoff date, median OS was 11.6 weeks greater with Votrient vs. Tykerb (50.7 weeks vs. 39.1 weeks; HR: 0.67; 90% CI: 0.46, 0.99; P = 0.045). Patients were not preselected on the basis of EGFR or HER2 amplification.
 - 4. Gastric, Esophageal, or Gastroesophageal Adenocarcinoma Cancer.** In one Phase II study (n = 47), Tykerb demonstrated modest activity in patients with treatment-naïve advanced/metastatic gastric cancer.¹⁰ A total of four patients had a confirmed partial response, one patient had an unconfirmed partial response, and 10 patients had stable disease. An exploratory analysis revealed gene expression of HER2, interleukin (IL)-8 and genomic polymorphisms IL-8, and vascular endothelial growth factor (VEGF) correlated with OS. In one Phase III, open-label trial conducted in China, Japan, South Korea, and Taiwan, Asian patients (n = 261) with HER2+ advanced gastric cancer were randomized to Tykerb 1,500 mg per day plus paclitaxel 80 mg/m² on Days 1, 8, and 15 of a 28-day cycle or to paclitaxel alone.¹¹ Patients had disease progression after prior therapy. The primary endpoint was OS. Median OS was 11.0 months in patients receiving Tykerb plus paclitaxel vs. 8.9 months with paclitaxel alone (P = 0.1044). There was no significant difference between Tykerb plus paclitaxel or paclitaxel alone in median PFS (5.4 vs. 4.4 months) or time to progression (5.5 vs. 4.4 months), respectively. Overall response rate (ORR) was higher with Tykerb plus paclitaxel vs. paclitaxel alone (27% vs. 9%, respectively; 95% CI: 1.80, 8.87; P < 0.001). In one Phase III trial in patients (n = 545) with previously untreated HER2+ advanced gastroesophageal adenocarcinoma were randomized to receive CapeOx (capecitabine plus oxaliplatin) with either Tykerb or placebo.¹² Median OS was 12.2 months (95% CI: 10.6, 14.2) and 10.5 months (95% CI: 9.0, 11.3) for Tykerb and placebo, respectively (HR 0.91; 95% CI: 0.73, 1.12). Preplanned exploratory analysis showed OS in the Tykerb was prolonged in Asian and younger patients.
 - 5. Glioblastoma Multiforme.** In one Phase II study (n = 17), Tykerb did not demonstrate significant activity in patients with recurrent glioblastoma multiforme.¹³ Four patients had stable disease and 13 patients progressed.
 - 6. Head and Neck, Squamous Cell Carcinoma.** In one Phase III study in 688 patients with SCCHN, adding Tykerb to chemoradiotherapy and as maintenance monotherapy was not more effective than placebo in improving disease-free survival or OS.¹⁴
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7. **Hepatocellular Carcinoma.** In one Phase II study (n = 26), no objective responses were observed in Tykerb-treated patients with advanced hepatocellular carcinoma.¹⁸ In all, 40% of patients (n = 10/25) had stable disease as their best response including 23% of patients (n = 6/25) with stable disease lasting more than 120 days. The median PFS was 1.9 months and median OS was 12.6 months. Tykerb appeared to benefit only a subgroup of patients for whom predictive molecular or clinical characteristics are not yet fully defined. In another Phase II study in patients (n = 40) with hepatocellular cancer, therapy with Tykerb did not meet the predefined efficacy rate (only 5% of patients experienced a response).⁹
 8. **Non-Small Cell Lung Cancer (NSCLC).** In one Phase II study (n = 75), Tykerb monotherapy did not induce a significant number of tumor regressions in patients with recurrent or metastatic NSCLC previously treated with a maximum of one prior systemic therapy (chemotherapy or biologic therapy).¹⁹
 9. **Ovarian or Peritoneal Carcinoma.** In one Phase II study (n = 25), Tykerb demonstrated minimal activity in patients with recurrent or persistent epithelial ovarian cancer or primary peritoneal carcinoma.²⁰ In one Phase II study (n = 18), the combination of Tykerb plus topotecan for the treatment of platinum refractory/resistant epithelial ovarian cancer lacked sufficient activity to warrant further investigation.²¹ A total of four patients experienced clinical benefit: one patient with partial response and three patients with stable disease. The trial was stopped after the first stage due to insufficient activity.
 10. **Prostate Cancer.** In one Phase II study (n = 23), Tykerb failed to demonstrate significant antitumor activity in patients with early stage, hormonally untreated recurrent or metastatic prostate cancer.²²
 11. **Renal Cell Carcinoma (RCC).** In one Phase III study in patients (n = 416) with advanced RCC who experienced disease progression through first-line cytokine therapy, Tykerb and hormone therapy (megestrol acetate or tamoxifen, selected by the investigator) demonstrated comparable efficacy: the median time to progression was 15.3 weeks and 15.4 weeks for Tykerb and hormone therapy, respectively (HR 0.94; P = 0.60).²³ The median OS was 46.9 weeks and 43.1 weeks for Tykerb and hormone therapy, respectively (HR 0.88; P = 0.29).
 12. **Urothelial Carcinoma.** In one Phase III trial, 232 patients with HER1/HER2 metastatic urothelial bladder cancer who did not have progressive disease during chemotherapy were randomized to receive Tykerb or placebo after completing first-line or initial chemotherapy.²⁶ Median PFS, the primary endpoint, for Tykerb and placebo was 4.5 months (95% CI: 2.8, 5.4) and 5.1 months (95% CI: 3.0, 5.8), respectively (HR 1.07; 95% CI: 0.81, 1.43; P = 0.63).
 13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.
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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	Deleted criteria for patients with early breast cancer. Added men to the approval condition, Hormone Receptor Positive Metastatic Breast Cancer. The approval condition, Breast Cancer in Patients Already Started on Tykerb was deleted. In Conditions Not Recommended for Approval, removed Breast Cancer in Patients Initiating Therapy with Tykerb Whose HER2 Tumor Status is Unknown or Negative. HER2-positive disease is required. To the condition Gastric Cancer, added Esophageal or Gastroesophageal Adenocarcinoma.	12/16/2015
Selected revision	In the Policy Statement, added legal language to define woman and man in the Breast Cancer indication. This is noted with “*” next to “woman” and “man” in the criteria. A note was added below the approval criteria to refer to Policy Statement.	10/05/2016
Annual revision	In patients with HR+ metastatic breast cancer receiving Tykerb in combination with an aromatase inhibitor, criteria were added for premenopausal and perimenopausal patients and added requirement that men are receiving a LHRH agonist. Added urothelial carcinoma to the Conditions Not Recommended for Approval.	12/21/2016
Annual revision	In patients with hormone receptor-positive metastatic breast cancer receiving Tykerb in combination with an aromatase inhibitor, LHRH was changed to GnRH. In Conditions Not Recommended for Approval, deleted the condition, Transitional Cell Carcinoma and moved information regarding this use into the condition, Urothelial Carcinoma.	12/13/2017
Annual revision	Added new condition for approval in Chordoma based on guidelines/compendium.	12/20/2018

TAC – Therapeutic Assessment Committee; HR+ -- Hormone receptor positive; HER2 – Human epidermal growth factor receptor 2; LHRH – Luteinizing hormone-releasing hormone; GnRH – Gonadotropin-releasing hormone. * For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.