

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tarceva[®] (erlotinib tablets – Genentech/Astellas/OSI Pharmaceuticals)

TAC APPROVAL DATE: 03/13/2019

OVERVIEW

Tarceva, a kinase inhibitor, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen.¹ Tarceva continues to be indicated for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine. In patients with NSCLC, Tarceva is not recommended for use in combination with platinum-based chemotherapy. The safety and efficacy of Tarceva have not been established in patients with NSCLC whose tumors have other EGFR mutations.

Guidelines

FDA-Approved Indications

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 3.2019 – January 18, 2019) recommend *EGFR* mutation testing in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell) or in NSCLC not otherwise specified (NOS).² Tarceva, Iressa[®] (gefitinib tablets), Gilotrif[™] (afatinib tablets) and Tagrisso[™] (osimertinib tablets) [preferred] are all category 1 recommended for the first-line treatment in patients with sensitizing *EGFR*-mutation positive NSCLC discovered before first-line chemotherapy. Upon disease progression, T790M testing is recommended in guidelines. Tagrisso is a category 1 recommended option if T790M mutation-positive. Patients with symptomatic progression to the brain can consider local therapy, Tagrisso (if T790M mutation-positive) [category 1], or continue on Tarceva, Iressa, or Gilotrif (category 2A). Tagrisso (regardless of T790M status) or pulse Tarceva can be considered for progressive leptomeningeal disease.

The NCCN guidelines for central nervous system cancers (version 1.2019 – March 5, 2019) recommend Tarceva as weekly pulse therapy for leptomeningeal metastases from NSCLC with an *EGFR* exon 19 deletion or exon 21 (L858R) mutation in patients with positive cerebrospinal fluid (CSF) cytology and progression after receiving intra-CSF chemotherapy (category 2B).³ Tarceva, Gilotrif, and Iressa are recommended for brain metastases due to NSCLC; Tagrisso is recommended for T790M mutation-positive NSCLC (all category 2A).

NCCN guidelines for pancreatic adenocarcinoma (version 1.2019 – November 8, 2018) recommend Tarceva and gemcitabine combination for systemic therapy in patients with locally advanced unresectable disease with good performance status (category 2A).⁴ It is also recommended for metastatic disease in this population (category 1). The guidelines state that although this combination significantly improved survival, the actual benefit was small, suggesting that only a subset of patients benefit. Tarceva and gemcitabine is also recommended for second-line therapy for recurrent disease if prior fluoropyrimidine-based therapy is given (category 2A).

Other Uses with Supportive Evidence

The NCCN guidelines for Kidney Cancer (version 3.2019 – February 6, 2019) recommend Tarceva as one of the first-line therapies for relapse or surgically unresectable Stage IV disease with non-clear cell histology (category 2A).⁵ The NCCN panel lists clinical trial and Sutent® (sunitinib capsules) as the preferred options for this indication. Tarceva, either as monotherapy or in combination with Avastin (combination therapy for selected patients with advanced papillary RCC), are category 2A recommended options.

The NCCN bone cancer guidelines (version 1.2019 – August 3, 2018) list single-agent Tarceva as one of the systemic treatment options for patients with recurrent chordoma.⁷ Other systemic therapy options include imatinib with or without cisplatin or sirolimus, Sutent® (sunitinib capsules), Tykerb® (lapatinib tablets) [for patients with EGFR-positive disease], or Nexavar® (sorafenib tablets).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tarceva. All approvals are provided for 3 years in duration as noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

- 1. Non-Small Cell Lung Cancer (NSCLC) – Epidermal Growth Factor Receptor (EGFR) Mutation-Positive.** Approve for 3 years if the patient meets the following criteria (A and B):
 - A)** The patient has *metastatic* NSCLC; AND
 - B)** The patient meets ONE of the following criteria (i or ii):
 - i.** The patient has epidermal growth factor receptor (EGFR) exon 19 deletions as detected by an approved test; OR
 - ii.** The patient has exon 21 (L858R) substitution mutations as detected by an approved test.
- 2. Pancreatic Cancer, Locally Advanced, Unresectable, or Metastatic.** Approve for 3 years if prescribed in combination with gemcitabine.

Other Uses with Supportive Evidence

- 3. Renal Cell Carcinoma (RCC), Advanced – Non-Clear Cell Histology.** Approve for 3 years.
 - 4. Bone Cancer – Chordoma.** Approve for 3 years in patients with recurrent disease.
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CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tarceva 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. Biliary Cancer.** There were no differences in PFS and OS between gemcitabine/oxaliplatin and gemcitabine/oxaliplatin with the addition of Tarceva in patients with metastatic biliary-tract cancer (cholangiocarcinoma, gallbladder cancer, or ampulla of Vater cancer) in one Phase III, open-label, randomized study (n = 268); however, in a subgroup of patients with cholangiocarcinoma, the addition of Tarceva to chemotherapy resulted in a significantly prolonged PFS (5.9 months vs. 3.0 months; P = 0.049).^{7,8} In patients with advanced (unresectable or metastatic) cholangiocarcinoma or gallbladder cancer, combination therapy with Avastin and Tarceva showed clinical activity in one Phase II study (n = 56).⁹ Among six patients with confirmed PRs, the median duration of response was 8.4 months (95% CI: 6.0, 11.7). Eighty-seven percent of patients progressed with a median time to disease progression of 4.4 months (95% CI: 3.0, 7.8). Median OS was 9.9 months (95% CI: 7.2, 13.6). As single-agent therapy in one Phase II study, Tarceva showed benefit in patients with unresectable or metastatic biliary cancer previously treated with not more than one prior systemic or locoregional therapy (n = 42).¹⁰ In all, 17% (n = 1/7) of patients (95% CI: 7% to 31%) were progression free at 6 months. One Phase II trial evaluated the efficacy of Tarceva and docetaxel in patients with refractory (up to two prior systemic therapies) hepatocellular (n = 14) and biliary (n = 11) cancers.¹¹ The 16-week PFS rate was 64% for biliary tract cancer (95% CI: 29.7, 84.5), meeting the 16-week PFS endpoint of $\geq 30\%$. Median OS was 5.7 months and similar to historical data with single-agent Tarceva therapy.
 - 2. Breast Cancer.** One Phase II, non-randomized, open-label, bi-institutional trial did not support beneficial effect of Tarceva plus Avastin in patients with metastatic breast cancer with stage IV disease that was stable or had progressed after treatment with one or two chemotherapy regimens; if the patient's tumor was human epidermal growth factor receptor-2 (HER-2) positive, prior therapy with Herceptin[®] (trastuzumab for injection) was required (n = 38).¹² As single-agent therapy, Tarceva had minimal activity in unselected, previously treated women with locally advanced or metastatic breast cancer in one multicenter, Phase II study (n = 69).¹³ Metronomic (frequent low-dose) capecitabine tablets and cyclophosphamide plus Avastin and Tarceva was effective in patients with untreated advanced metastatic HER-2 negative, estrogen receptor-negative, and progesterone receptor-poor advanced breast cancer (n = 26).¹⁴ Among 24 patients assessable for response, 4% of patients has a CR [n = 1], 58% of patients had PR (n = 14), 21% of patients had stable disease (SD) > 9 weeks duration (n = 5) and 4% of patients (n = 1) had early progression of disease. The overall clinical benefit (CR + PR + SD > 24 weeks) was 75% (95% CI: 53, 90). Median time to progression was 43 weeks (95% CI: 21, 69). OS was 108 months (95% CI: 70, 110).
 - 3. Colorectal Cancer, Metastatic (mCRC).** In Phase II studies in patients with untreated mCRC, efficacy has not been demonstrated.¹⁵⁻¹⁸ In one Phase III trial, patients with mCRC received doublet chemotherapy plus Avastin as initial therapy.¹⁹ Patients without tumor progression were randomized to maintenance therapy with Avastin plus Tarceva (n = 80) or Avastin alone (n = 79). Median PFS was 5.7 months with the combination and 4.2 months with Avastin alone (HR 0.79; 95% CI: 0.55, 1.12; P = 0.19). The rate of any Grade 3/4 toxicity was 53% with Avastin/Tarceva vs. 13% with Avastin alone. Another Phase III trial, OPTIMOX3, assessed the efficacy of maintenance Avastin plus Tarceva therapy (n = 224) after induction chemotherapy compared with Avastin alone (n = 228) in patients with unresectable metastatic colorectal cancer.²⁰ The median PFS from maintenance was 5.4 months in the Avastin plus Tarceva group compared with 4.9 months in the Avastin group (HR 0.81; 95% CI: 0.66,
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1.01; P = 0.059). The median OS from maintenance was 24.9 months compared with 22.1 months for Avastin plus Tarceva and Avastin alone, respectively. The Phase III Nordic ACT2 trial demonstrated that the addition of Tarceva to Avastin as maintenance therapy in patients with KRAS wild-type mCRC did not significantly improve PFS or OS.²¹ The NCCN guidelines for colon cancer (version 4.2018) do not recommend drug combinations such as Tarceva/Avastin for advanced CRC due to their negative effects.²² The panel also recommends *against* use of Tarceva as a single agent or in combination in patients with disease progression after receiving standard therapies.

4. **Glioblastoma Multiforme (GBM).** In one Phase II study, concurrent radiation therapy (RT) and temozolomide in combination with Tarceva in patients newly diagnosed with glioblastoma (n = 27) was not efficacious.²³ In two Phase II studies, Tarceva plus temozolomide given during and after RT produced favorable median survival, and PFS, as well as 12- or 14-month survival rates in patients with newly diagnosed GBM or gliosarcoma.^{24,25} In patients with newly diagnosed (untreated; could have had resection) GBM or gliosarcoma who received Tarceva plus temozolomide during and after radiation, median survival was longer with Tarceva plus temozolomide vs. historical controls (19.3 months vs. 14.1 months, respectively; HR for survival 0.64; 95% CI: 0.45, 0.91; P = 0.01) in one open-label, single-center, Phase II trial (n = 65).²⁴ The historical controls were comparable patients from two prospective, Phase II trials (n = 128); the first trial included the use of Thalomid® (thalidomide capsules) in combination with temozolomide during and after radiotherapy; the second that included the use of *cis*-retinoic acid with temozolomide during and after radiotherapy. In one open-label, Phase I/II trial, treatment with Tarceva plus temozolomide during and after RT resulted in favorable survival rate (61% of patients were alive at 1 year) and median PFS (7.2 months) in patients with newly diagnosed GBM (following resection); however, there was no significant difference in OS with the addition of Tarceva compared with the temozolomide/RT arm of a historical control trial (15.3 months vs. 15 months, respectively).²⁵ Tarceva has failed to demonstrate benefit in patients with recurrent glioblastomas.²⁶⁻²⁹
5. **Head and Neck Cancer, Squamous Cell, Recurrent and/or Metastatic.**

Two Phase II studies assessed the use of Tarceva and Avastin in different settings and showed promising results.³⁰⁻³¹ One multicenter, Phase II trial assessed the addition of Avastin and Tarceva to chemoradiation as first-line treatment for previously untreated patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [n = 60].³⁰ After a median follow-up of 32 months the estimated 3-year PFS and OS rates were 71% and 82%, respectively. After induction therapy, 65% of patients had major responses; after completion of therapy 95% of patients had either partial or complete radiographic responses. One multi-institutional Phase I/II study enrolled patients with recurrent or metastatic SCCHN (previously treated with ≤ 1 prior regimen for recurrent disease) to receive Tarceva and Avastin (n = 56).³¹ The median OS and PFS durations were 7.1 months (95% CI: 5.7, 9.0) and 4.1 months (95% CI: 2.8, 4.4), respectively. Treatment with Tarceva monotherapy produced few PRs in unselected (EGFR status not known at baseline) patients with locally recurrent and/or metastatic SCCHN in one open-label, Phase II clinical trial (n = 115); 38.3% of patients achieved SD for a median of 16.1 weeks.³² In one Phase II study, 204 patients with locally advanced SCCHN were randomized to receive cisplatin in combination with RT with or without Tarceva.³³ Complete response rates evaluated by central review were reported in 40% of patients (n = 42/105) on cisplatin/RT vs. 52% of patients (n = 51/99) on cisplatin/RT/Tarceva (P = 0.08). At a median follow-up of 26 months and 54 progression events, there was no difference in PFS between the two treatment arms (HR 0.0; P = 0.71). In a Phase II study, patients with recurrent SCCHN were treated with Tarceva for 12 months (n = 31). The OS was 61% at 1 year and 56% at 2 years.³⁴ Disease-free survival was 54% at 1 year and 45% at 2 years. The mean time to recurrence (n = 16) was 8.7 months. Only 8 patients completed the full 12-month course of Tarceva; the median duration of Tarceva therapy was 5 months.

6. **Hepatocellular Carcinoma (HCC), Advanced.** Some Phase II studies have reported activity of Tarceva in patients with HCC while others have not.³⁵⁻³⁷ In one Phase III trial, patients with advanced HCC were randomized to Nexavar/Tarceva (n = 362) or Nexavar/placebo (n = 358).³⁸ Median OS, the primary endpoint, was similar in both groups: 9.5 vs. 8.5 months for Nexavar/Tarceva and Nexavar/placebo, respectively (HR 0.929; P = 0.408). A network meta-analysis of 11 randomized controlled trials with 6,594 patients with advanced hepatocellular carcinoma concluded that Nexavar in combination with Tarceva demonstrated better short-term and long-term efficacy compared with other drugs.³⁹
7. **Occult Primary/Cancer of Unknown Primary Site (CUP).** The combination of Avastin and Tarceva (alone or combined with paclitaxel and carboplatin) had activity as first- or second-line therapy in patients with occult primary tumors (adenocarcinoma, poorly differentiated carcinoma, poorly differentiated adenocarcinoma, poorly differentiated squamous carcinoma).⁴⁰ In one Phase II trial, the combination of Avastin and Tarceva induced PRs in 10% of patients and stable disease in 61% of patients (n = 51).⁵⁰ The median survival was 7.4 months (1-year survival, 33%), which, in retrospective comparison was superior to that observed by the same group with gemcitabine alone and gemcitabine and irinotecan (3 and 4.5 months, respectively).
8. **Renal Cell Carcinoma (RCC), Advanced – Clear Cell Histology.** Efficacy with Tarceva has not been demonstrated in patients with clear cell histology.⁵
9. 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
Selected revision	Approval duration extended from 1 year to 3 years	09/03/2014

Annual revision	No changes to criteria.	01/14/2015
Annual revision	Minor wording changes with NSCLC indication. Simplified RCC non-clear cell histology approval criteria. Removed cervical cancer, meningioma, mesothelioma, and prostate cancer from Conditions Not Recommended for Approval due to lack of any new data in past few years. Combined Glioblastoma, Newly diagnosed and Maintenance therapy with recurrent therapy since both are not approved uses. Matched Renal Cell Carcinoma indication wording for both clear cell and non-clear cell histology.	02/03/2016
Selected revision	In NSCLC indication, deleted approval for locally advanced NSCLC (without EGFR mutation-positive tumors) as subsequent therapy or switch-maintenance therapy based on revised FDA approved indication for Tarceva. Also deleted the word “FDA” in reference to approved tests for detecting EGFR mutations to line up with other oncology policies. Added “Epidermal Growth Factor Receptor (EGFR) Mutation-Positive” to indication descriptor.	11/09/2016
Annual revision	No criteria changes	02/22/2017
Annual revision	Added approval condition for Chordoma based on guideline recommendations. Deleted approval condition “Patient has been started on Tarceva” to align with other oncology policies. Deleted the following conditions from “Conditions not recommended for approval” section due to lack of relevant new data supporting use or guideline support: bladder cancer, endometrial cancer, esophageal and esophagogastric cancer, gastric cancer, and ovarian cancer.	02/28/2018
Annual revision	No criteria changes	03/13/2019

TAC – Therapeutic Assessment Committee; NSCLC – Non-small cell lung cancer; EGFR – Epidermal growth factor receptor;
 . * For a further summary of criteria changes, refer to respective TAC minutes available at:
<http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.