PRIOR AUTHORIZATION POLICY

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

TAC APPROVAL DATE: 02/28/2018

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
The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 3.2018) 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) (all category 1) and Tagrisso™ (osimertinib tablets) [category 2A] are all recommended for the first-line treatment in patients with sensitizing EGFR-mutation positive NSCLC discovered before first-line chemotherapy. If EGFR mutation is discovered during first-line chemotherapy, complete planned chemotherapy, including maintenance therapy, or interrupt, followed by treatment with Tarceva, Iressa, Gilotrif, or Tagrisso (category 2A). Upon disease progression, T790M testing is recommended in guidelines. Plasma biopsy can be considered if tissue biopsy is not feasible. Patients with asymptomatic progression can consider local therapy; Tagrisso is a category 1 recommended option if T790M mutation-positive. Patients can also continue Tarceva, Gilotrif, or Iressa (category 2A). 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. For symptomatic, systemic isolated lesion, local therapy or continuation of Tarceva, Gilotrif, or Iressa is recommended. For systemic multiple lesions, if T790M mutation-positive, Tagrisso, if not previously given, is the category 1 recommended option. If T790M mutation-negative, initial cytotoxic therapy options listed for adenocarcinoma, or squamous cell carcinoma (e.g., doublet chemotherapy) can be considered in this setting (category 2A). NCCN added a footnote to this recommendation to also consider Gilotrif and Erbitux® (cetuximab for injection) combination regimen in patients with disease progression (T790M-negative multiple systemic lesions) on EGFR-TKI therapy (category 2A).

The NCCN guidelines for central nervous system cancers (version 1.2017) 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
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.

Tarceva is indicated for the treatment of patients with metastatic NSCLC whose tumors have 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. 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 who tumors have other EGFR mutations.

2. Pancreatic Cancer, Locally Advanced, Unresectable, or Metastatic. Approve for 3 years if prescribed in combination with gemcitabine.

Tarceva is indicated in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer. NCCN guidelines for pancreatic adenocarcinoma (version 3.2017) recommend this combination among the other options for systemic therapy in patients with locally advanced unresectable or metastatic disease and good performance status (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. Preferred regimens include clinical trial (strongly recommended), FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin all given as intravenous infusions), or gemcitabine plus Abraxane® (paclitaxel albumin-bound intravenous infusion).

Other Uses with Supportive Evidence

3. Renal Cell Carcinoma (RCC), Advanced – Non-Clear Cell Histology. Approve for 3 years.

The NCCN guidelines for Kidney Cancer (version 3.2018) recommend Tarceva as one of the first-line therapies for relapse or surgically unresectable Stage IV disease with non-clear cell histology (category 2A). 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. Efficacy
of Tarceva is based on the results from a Phase II study in patients with advanced papillary RCC who had not previously received chemotherapy or immunotherapy. The ORR was 11% (n = 5/45; 95% CI: 3, 24), and the disease control rate (defined as stable disease for 6 weeks, or confirmed partial responses or complete responses) was 64%. The median OS was 27 months. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

4. **Bone Cancer – Chordoma.** Approve for 3 years in patients with recurrent disease.

The NCCN bone cancer guidelines (version 1.2018) list single-agent Tarceva as one of the systemic treatment options for patients with recurrent chordoma. 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).

**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). Another retrospective sub-group data analysis from this study showed that early tumor shrinkage (ETS) was more strongly associated with progression-free survival in patients with wild-type KRAS tumors treated with Tarceva (8.3 months for ETS vs. 1.2 months for no ETS; P < 0.01). 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). 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). 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. The 16-week PFS rate was 64% for biliary tract cancer (95% CI: 29.7, 84.5), meeting the 16-week PFS endpoint of ≥ 30%. Median OS was 5.7 months and similar to historical data with single-agent Tarceva therapy. Further well-designed clinical trials are required to establish a place in therapy for Tarceva.

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). 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). Metronomic (frequent low-dose) capecitabine
3. Colorectal Cancer, Metastatic (mCRC). In Phase II studies in patients with untreated mCRC, efficacy has not been demonstrated. In one Phase III trial, patients with mCRC received doublet chemotherapy plus Avastin as initial therapy. 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. 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, 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. The NCCN guidelines for colon cancer (version 2.2016) do not recommend drug combinations such as Tarceva/Avastin for advanced CRC due to their negative effects. 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. 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. 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). 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). Tarceva has failed to demonstrate benefit in patients with recurrent glioblastomas. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

5. Head and Neck Cancer, Squamous Cell, Recurrent and/or Metastatic. According to the NCCN guidelines for head and neck cancer (version 1.2018), available data for the novel agents have not established them as treatment options for metastatic head and neck cancer outside of a clinical trial.
Two Phase II studies assessed the use of Tarceva and Avastin in different settings and showed promising results.34-35 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].34 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).35 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.36 In one Phase II study, 204 patients with locally advanced SCCHN were randomized to receive cisplatin in combination with RT with or without Tarceva.37 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.38 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. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

6. Hepatocellular Carcinoma (HCC), Advanced. Tarceva is only mentioned in the NCCN guidelines for hepatobiliary cancers (version 1.2018) in the context of clinical trials with Avastin as a single agent or in combination with Tarceva or chemotherapy.39 Some Phase II studies have reported activity of Tarceva in patients with HCC while others have not.40-46 In one Phase III trial, patients with advanced HCC were randomized to Nexavar/Tarceva (n = 362) or Nexavar/placebo (n = 358).47 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.48 In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

7. Occult Primary/Cancer of Unknown Primary Site (CUP). Tarceva is not specifically recommended in the NCCN guidelines for occult primary cancer (version 2.2016).49 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).49-51 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). In another Phase II, multicenter study, the combination of paclitaxel and carboplatin with Avastin and Tarceva was active and well-tolerated as first-line therapy in patients with CUP (n = 60).51 After a median follow-up of 19 months, the median PFS time and 2-year OS rates were 8 months (38% PFS at 1 year) and 27%, respectively. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.
8. Renal Cell Carcinoma (RCC), Advanced – Clear Cell Histology. The NCCN kidney cancer guidelines (version 3.2018) recognize Tarceva as one of the first-line therapy options for patients with relapsed or medically unresectable stage IV non-clear cell carcinoma only. Efficacy with Tarceva has not been demonstrated in patients with clear cell histology.

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES


**HISTORY**

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes*</th>
<th>TAC Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected revision</td>
<td>Approval duration extended from 1 year to 3 years</td>
<td>09/03/2014</td>
</tr>
<tr>
<td>Annual revision</td>
<td>No changes to criteria.</td>
<td>01/14/2015</td>
</tr>
<tr>
<td>Annual revision</td>
<td>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.</td>
<td>02/03/2016</td>
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<tr>
<td>Selected revision</td>
<td>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.</td>
<td>11/09/2016</td>
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<tr>
<td>Annual revision</td>
<td>No criteria changes</td>
<td>02/22/2017</td>
</tr>
<tr>
<td>Annual revision</td>
<td>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.</td>
<td>02/28/2018</td>
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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](http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx).