PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erlotinib Prior Authorization Policy
- Erlotinib (Tarceva® tablets – Genentech/Astellas/OSI Pharmaceuticals; generics)

REVIEW DATE: 03/17/2021

OVERVIEW
Erlotinib, a kinase inhibitor, is indicated for the following uses:[1]
- **Non-Small Cell Lung Cancer**, treatment of tumors with 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. The safety and efficacy of erlotinib have not been established in patients with NSCLC whose tumors have other EGFR mutations.
- **Pancreatic Cancer**, first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine.

Guidelines
- **Non-Small Cell Lung Cancer:** The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 4.2021 – March 3, 2021) recommend *EGFR* mutation testing in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell) or in NSCLC not otherwise specified (NOS).[2] Erlotinib, Iressa® (gefitinib tablets), Gilotrif™ (afatinib tablets) Vizimpro® (dacomitinib 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. Erlotinib + Cyramza (ramucirumab injection) and erlotinib + bevacizumab are both category 2A recommended options.
- **Pancreatic Cancer:** NCCN guidelines for pancreatic adenocarcinoma (version 2.2021 – February 25, 2021) recommend erlotinib and gemcitabine combination for systemic therapy in patients with locally advanced unresectable disease with good performance status (category 2A).[4] Gemcitabine + erlotinib is also recommended for metastatic disease in this population (category 1).
- **Bone Cancer:** The NCCN bone cancer guidelines (version 1.2021 – November 20, 2020) list single-agent erlotinib as one of the systemic treatment options for patients with recurrent chordoma.[6] 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).
- **Renal Cell Carcinoma:** The NCCN guidelines for Kidney Cancer (version 2.2021 – February 3, 2021) recommend erlotinib as one of the first-line therapies for relapse or surgically unresectable Stage IV disease with non-clear cell histology (category 2A).[5] Erlotinib, either as monotherapy or in combination with bevacizumab (combination therapy for selected patients with advanced papillary RCC), are category 2A recommended options.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of erlotinib. All approvals are provided for 3 years in duration as noted below.

Automation: None.
RECOMMENDED AUTHORIZATION CRITERIA
Coverage of erlotinib is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 3 years if the patient meets the following criteria (A and B):
   A) Patient has metastatic epidermal growth factor receptor (EGFR) mutation-positive disease; AND
   B) Patient meets ONE of the following criteria (i or ii):
      i. Patient has epidermal growth factor receptor (EGFR) exon 19 deletions as detected by an approved test; OR
      ii. Patient has exon 21 (L858R) substitution mutations as detected by an approved test.

2. **Pancreatic Cancer.** Approve for 3 years if the medication is used in combination with gemcitabine.

Other Uses with Supportive Evidence

3. **Bone Cancer.** Approve for 3 years in patients who meet the following criteria (A and B):
   A) Patient has chordoma; AND
   B) Patient has tried at least one previous therapy.

4. **Renal Cell Carcinoma (RCC).** Approve for 3 years if the patient has relapsed or Stage IV non-clear cell histology RCC.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of erlotinib is not recommended in the following situations:

1. **Biliary Cancer.** There were no differences in PFS and OS between gemcitabine/oxaliplatin and gemcitabine/oxaliplatin with the addition of erlotinib 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 erlotinib 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 bevacizumab and erlotinib 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, erlotinib 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 erlotinib 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 ≥ 30%. Median OS was 5.7 months and similar to historical data with single-agent erlotinib therapy.

2. **Breast Cancer.** One Phase II, non-randomized, open-label, bi-institutional trial did not support beneficial effect of erlotinib plus bevacizumab 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 trastuzumab was required (n = 38).[12] As single-agent therapy, erlotinib 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 Bevacizumab and erlotinib 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 bevacizumab as initial therapy.[19] Patients without tumor progression were randomized to maintenance therapy with bevacizumab plus erlotinib (n = 80) or bevacizumab alone (n = 79). Median PFS was 5.7 months with the combination and 4.2 months with bevacizumab alone (HR 0.79; 95% CI: 0.55, 1.12; P = 0.19). The rate of any Grade 3/4 toxicity was 53% with bevacizumab/erlotinib vs. 13% with bevacizumab alone. Another Phase III trial, OPTIMOX3, assessed the efficacy of maintenance bevacizumab plus erlotinib therapy (n = 224) after induction chemotherapy compared with bevacizumab alone (n = 228) in patients with unresectable metastatic colorectal cancer.[20] The median PFS from maintenance was 5.4 months in the bevacizumab plus erlotinib group compared with 4.9 months in the bevacizumab 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 bevacizumab plus erlotinib and bevacizumab alone, respectively. The Phase III Nordic ACT2 trial demonstrated that the addition of erlotinib to bevacizumab as maintenance therapy in patients with KRAS wild-type mCRC did not significantly improve PFS or OS.[21]

4. **Glioblastoma Multiforme (GBM).** In one Phase II study, concurrent radiation therapy (RT) and temozolomide in combination with erlotinib in patients newly diagnosed with glioblastoma (n = 27) was not efficacious.[22] In two Phase II studies, erlotinib 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.[23,24] In patients with newly diagnosed (untreated; could have had resection) GBM or gliosarcoma who received erlotinib plus temozolomide during and after radiation, median survival was longer with erlotinib 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).[23] 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 erlotinib 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 erlotinib compared with the temozolomide/RT arm of a historical control trial (15.3 months vs. 15 months, respectively).[24] Erlotinib has failed to demonstrate benefit in recurrent glioblastomas.[25-28]

5. **Head and Neck Cancer, Squamous Cell, Recurrent and/or Metastatic.** Two Phase II studies assessed the use of erlotinib and bevacizumab in different settings and showed promising results.[29,30] One multicenter, Phase II trial assessed the addition of bevacizumab and erlotinib to chemoradiation as first-line treatment for previously untreated patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [n = 60].[29] 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 erlotinib and

bevacizumab (n = 56).[30] 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 erlotinib 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.[31] In one Phase II study, 204 patients with locally advanced SCCHN were randomized to receive cisplatin in combination with RT with or without erlotinib.[32] 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/erlotinib (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 erlotinib for 12 months (n = 31). The OS was 61% at 1 year and 56% at 2 years.[33] 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 erlotinib; the median duration of erlotinib therapy was 5 months.

6. **Hepatocellular Carcinoma (HCC), Advanced.** Some Phase II studies have reported activity of erlotinib in patients with HCC while others have not.[34-36] In one Phase III trial, patients with advanced HCC were randomized to Nexavar/erlotinib (n = 362) or Nexavar/placebo (n = 358).[37] Median OS, the primary endpoint, was similar in both groups: 9.5 vs. 8.5 months for Nexavar/erlotinib 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 erlotinib demonstrated better short-term and long-term efficacy compared with other drugs.[38]

7. **Occult Primary/Cancer of Unknown Primary Site (CUP).** The combination of bevacizumab and erlotinib (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).[39]

8. **Renal Cell Carcinoma (RCC), Advanced – Clear Cell Histology.** Efficacy with erlotinib 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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