National PBM Drug Monograph

Erlotinib (Tarceva™)

May 2005

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

- Erlotinib is a small molecule inhibitor of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR).
- EGFR is associated with most epithelial tumors and is associated with cell proliferation and metastasis.
- When compared to best supportive care in second or third-line therapy of advanced non-small cell lung cancer, erlotinib produced statistically significant improvements in overall survival, progression free survival, and response rate. Although the survival benefit is statistically significant, the 2 month benefit is small for a relatively high cost.
- A delay in symptom deterioration showed a trend in favor of erlotinib, however the instrument used to collect this data may not have been appropriately validated for this use.
- EGFR status was only available for about 1/3 of patients, and conclusions about EGFR status of tumors and response and survival cannot be evaluated at this time.
- Pretreatment characteristics associated with a survival benefit include: males, age<65, never smoked, and adenocarcinoma or squamous histologies. In a separate phase II trial, 26% of patients with bronchioloalveolar carcinoma (BAC) had a partial response. Responses were even higher in patients with BAC who had never smoked.
- There is no benefit to continuing therapy once progression of disease has been documented.
- Erlotinib therapy is well tolerated. The majority of adverse events are due to rash and diarrhea and are expected due to the mechanism of action. Most adverse events were grade 1 or 2 and rarely caused dose reductions or discontinuation of the drug.
- As was seen with gefitinib, there is a small risk for the development of interstitial lung disease which can be fatal.
- Due to its hepatic metabolism, there is a theoretical potential for drug interactions with potent inhibitors and inducers of CYP3A4 that may require dose adjustments.
- Erlotinib is an important addition to the second and third-line treatment of advanced non-small cell lung cancer. It improves survival and is well tolerated even in patients with a poorer performance status. Use in first-line therapy of advanced non-small cell lung cancer with combination chemotherapy did not show a survival advantage and it should not be used in that setting.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating erlotinib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Synonym(s): OSI-774

Manufacturer: Genentech/OSI

Pharmacology/Pharmacokinetics[1,2,3,4]

The epidermal growth factor receptor (EGFR) known as HER-1 is part of a group of receptors. EGFR is a transmembrane protein that consists of an extracellular ligand-binding domain, a transmembrane portion, and an intracellular domain with tyrosine kinase activity. Binding of a ligand to the extracellular domain initiates a process of receptor dimerization, tyrosine kinase activity, phosphorylation of the receptor, and activation of signaling proteins involved with cell proliferation. In many epithelial cancers, there is dysregulation of the EGFR, which is key in malignant transformation, cell growth and proliferation, cell survival, and metastasis. EGFR activity can be blocked by monoclonal antibodies or by small molecules that inhibit EGFR tyrosine kinase activity. Erlotinib is an orally available reversible EGFR specific tyrosine kinase inhibitor that binds to ATP binding sites on the intracellular tyrosine kinase domain.

Table #1 Pharmacokinetic Parameters

Parameter	Erlotinib
Metabolism	Primarily CYP3A4, to a lesser extent CYP1A2
Elimination	83% in feces, 8% in urine
Half-life	36hours
Protein Binding	93% bound to albumin and alpha-1 acid glycoprotein
Bioavailability	60%; increased to almost 100% with food

FDA Approved Indication(s) and Off-label Uses

Erlotinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy treatment.

Off label use: head and neck cancer

Current VA National Formulary Alternatives

There are currently no alternative drugs on the VA National Formulary. Common nonformulary drugs in use in this population include docetaxel, pemetrexed, and gefitinib.

Dosage and Administration

The recommended dose of erlotinib is 150mg orally daily at least one hour before or 2 hours after food or a meal. Continue treatment until disease progression or unacceptable toxicity.

Dose Modifications
ALL dose reductions should be in increments of 50mg

Table# 2 Dose Modifications

Parameter	Dose Modification
Acute onset of new or progressive pulmonary symptoms such as dyspnea, cough or fever suggestive of interstitial lung disease (ILD)	Interrupt therapy pending diagnosis of ILD. If ILD is diagnosed, discontinue therapy with erlotinib
Severe diarrhea unresponsive to loperamide or who become dehydrated	Dose reduction or interruption in therapy
Severe skin reactions	Dose reduction or interruption in therapy
Concomitant CYP3A4 inhibitors (atanazavir, clarithromycin, indinavir, intraconazole, nefazodone ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, or voriconazole	Dose reduction IF severe adverse reaction occurs
Pre-treatment with a CYP3A4 inducer (rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, Phenobarbital, and St. John's Ware	Alternative treatments lacking CYP3A4 induction should be considered. If alternative is not available, consider increasing erlotinib dose. If adjusted upward, remember to reduce it upon discontinuation of the CYP3A4 inducer.
Hepatic impairment	Dose reduction or interruption in erlotinib therapy IF severe adverse reactions occur.
Renal impairment	Less than 9% excreted in the urine. No clinical studies in patients with impaired renal function.

Efficacy [5]

Efficacy Measures

Primary Efficacy Outcome: Survival

Secondary Outcomes: Response rate, progression-free survival (PFS), QoL

Table #3 Summary of efficacy findings

Outcome	Erlotinib	Placebo
Overall survival	N=488 6.7 mos HR=0.73 (95%CI 0.6-0.87) P=0.001	N=243 4.7 mos
12 month actuarial survival	31.2%	21.5%
Response CR PR SD PD	 <1% 8 35.1 38.4	 <1 <1 26.5 57.3
PFS	9.86 wks (95%CI 8.43-14.14) HR=0.6 (95%CI 0.51-0.72) P<0.001	7.86 wks (95%CI 7.71-8.14)

- As a second or third line therapy in NSCLC, erlotinib significantly increased survival relative to placebo (best supportive care)
- Favorable results were also seen in response rate and progression free survival versus placebo.
- Response rates were higher among women, patients with adenocarcinoma histology, patients who never smoked, and patients with EGFR positive tumors. These differences in response did not always translate into survival benefit. For example, women have a better response but men have a survival benefit.
- A survival analysis of patient subsets determined that the following pretreatment characteristics are associated with a survival benefit: positive or unknown EGFR status, never smoked, male, age <65, adenocarcinoma and squamous histologies, <10% weight loss in the previous 6 months

- EGFR status was measured in only 31% of erlotinib patients and 35% of placebo patients. This small number of patients produced hazard ratios with wide confidence intervals. In patients in the erlotinib arm, the patients who were EGFR positive and negative were prognostically different. It is difficult at this time to fully evaluate the significance of EGFR status in terms of response and survival.
- QoL was measured using two EORTC questionnaires and focused on three symptoms: cough, dyspnea, and pain. The FDA did not agree with the sponsor that the instruments were validated for singling out these three symptoms. Although there was a trend for erlotinib to delay deterioration in these scores, the FDA will not allow those claims in the labeling.
- In a univariate analysis of Progression Free Survival (PFS), Performance Status of 2-3 and Progressive Disease as the best response to prior therapy were associated with a worse PFS. In a univariate exploratory analysis of Overall Survival, the median hazard ratio for patients with Performance Status 2-3 (N=245) was 0.77, with 95%CI of 0.6-1.0 (in PS 0-1 [N=475], HR=0.73, 95%CI 0.6-0.9).

For further details on the efficacy results of the clinical trials, refer to

Appendix: Clinical Trials (page 8).

Adverse Events (Safety Data)

Table #4 Adverse Events in ≥10% of patients

	Erlotinib N=485			Placebo N=242		
Event	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Rash	75%	8%	<1%	17%	0%	0%
Diarrhea	54	6	<1	18	<1	0
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

Deaths and Other Serious Adverse Events (optional)
Death occurred in 32% of erlotinib patients and 29% of placebo patients during treatment or within 30 days of the last dose. The rate of death from protocol complications is 0.8% in the erlotinib arm and 0.4% in the placebo arm.

Common Adverse Events
Rash and diarrhea

Other Adverse Events
Liver Function Tests: elevated AST/ALT, and bilirubin have been observed, were mainly transient and associated with liver metastasis. If severe consider dose reduction or interruption.

GI bleeding: infrequent cases reported, some associated with warfarin therapy and some with concomitant NSAID therapy.

No notable differences in safety between males and females and between younger patients and those older than 65 years old.

Tolerability
Single oral doses of 1000mg in healthy volunteers and 1600mg in cancer patients have been tolerated. Twice daily dosing of 200mg in healthy volunteers was poorly tolerated after a few days (unacceptable incidence of severe diarrhea, rash, and liver transaminase elevation).

For further details on the safety results of the clinical trials, refer to

Appendix: Clinical Trials (page 8).

Precautions/Contraindications

Precautions
Hepatotoxicity: Asymptomatic increases in transaminases have been observed and should be monitored periodically during treatment. Dose reduction or interruption in therapy should be considered if changes in liver function are severe.

Patients with Hepatic Impairment: Erlotinib exposure may be increased in patient with hepatic impairment since erlotinib appears to be cleared primarily by the liver.

Elevated INR: INR elevations and infrequent reports of bleeding including GI bleeding have been reported. Some cases involve patients taking concomitant warfarin. Patients taking warfarin should have their INR monitored regularly while taking erlotinib.

Pulmonary Toxicity: infrequent reports of Interstitial Lung Disease (ILD) including fatalities. In clinical trials, the incidence was 0.8% in both the placebo and erlotinib groups. The incidence in erlotinib-treated patients from all studies is 0.6%. Patients suspected of having ILD have diagnosis reported as pneumonitis, interstitial pneumonia, interstitial lung disease, oblitertive bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome, and lung infiltration. Symptoms can start any time during therapy (range 5 days-9 months) and include new or progressive dyspnea, cough, and fever. Erlotinib therapy should be interrupted when a diagnosis of ILD is pending.

Pregnancy Category: Category D

Geriatric Use: Survival benefit was maintained across all age groups. No meaningful differences in pharmacokinetics or safety were observed in older patients.

Contraindications
None

Look-alike / Sound-alike (LA / SA) Error Risk Potential

This section must contain the following paragraph:

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based

on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name erlotinib: gefitinib, imatinib

Severity Category: mild to moderate

LA/SA for trade name Tarceva™: Pexeva

Severity Category: mild

Drug Interactions

Drug-Drug Interactions
Ketoconazole-Concomitant treatment with ketoconazole, a potent CYP3A4 inhibitor increases erlotinib AUC by 2/3. Caution when administering erlotinib with strong CYP3A4 inhibitors (see Dose Modifications).

Rifampicin-Concomitant treatment with rifampicin, a potent inducer of CYP3A4 decreases erlotinib AUC by 2/3. If administering erlotinib with a potent inducer of CYP3A4, consider increasing erlotinib dose (see Dose Modifications).

Acquisition Costs

Table #5 Erlotinib comparative costs

Drug	Dose	Cost/Day/patient ($)	Cost/Month/patient ($)
Erlotinib	150mg	50.55 per day (1061.55/ for 21 days)	1516.50
Pemetrexed $1441.60/vial	500mg/m^2	$2883.20/every 21 days	
Docetaxel 100mg=$754.23 20mg= $185.81	75mg/m^2	$1311.66/every 21 days	

Pharmacoeconomic Analysis

There are no published pharmacoeconomic evaluations of erlotinib.

Conclusions

Clinical Efficacy: When compared to best supportive care, erlotinib produces significantly longer overall survival, response rate, and progression free survival when used as second or third line therapy for patients with advanced non-small cell lung cancer. Prognostic characteristics associated with a survival benefit include male, age <65, never smoked, and adenocarcinoma or squamous histology. EGFR status was only measured in a small number of patients, and the significance of EGFR tumor status and survival is unclear at this time. Quality of life parameters were measured and there was a trend for delay in deterioration of measured symptoms, however the instruments utilized do not appropriate validation for singling out specific symptoms and therefore claims on symptom improvement are not allowed by the FDA in labeling. In earlier phase II trials in bronchioloalveolar carcinoma (BAC), a subtype of adenocarcinioma, erlotinib produced partial responses in 26% of patients who had either 0 or 1 previous chemotherapy courses. Of note, patients with BAC who never smoked had an objective response rate of 50% versus 15% in former or current smokers.[6,7]

Two phase III trials that evaluated erlotinib plus chemotherapy to chemotherapy alone in first-line treatment of advanced non-small cell lung cancer ("TRIBUTE" and "TALENT) failed to show a survival advantage with the addition of erlotinib.

Clinical Safety: Erlotinib is well tolerated with rash and diarrhea being the most common adverse events. The majority of adverse events were mild to moderate and rarely resulted in dose reductions or discontinuation. There is a potential for drug interactions with potent inhibitors and inducers of CYP3A4. Use in the geriatric population does not require dose adjustments.

Cost: The cost of erlotinib is less than injectable chemotherapy agents that could be used for second-line therapy. The cost of erlotinib is more than the cost of gefitinib.

Recommendations

Second-line therapy for advanced non-small cell lung cancer generally produces poor results. Until recently, the only drug approved for second-line use was docetaxel. Now, pemetrexed and erlotinib also have approval in this population. In addition, erlotinib can be used as third-line therapy similar to gefitinib. Recently, survival trials with gefitinib failed to show a survival benefit over best supportive care unlike erlotinib which did show a survival advantage. Erlotinib, unlike docetaxel and pemetrexed, is given orally and is well tolerated and may be useful for patients with a poorer performance status or transportation issues.

Erlotinib therapy is appropriate for second or third-line therapy of patients with advanced non-small cell lung cancer. Documentation of objective response or stable disease and symptom improvement (cough, dyspnea) during therapy will assist in identifying patients likely to benefit from continued treatment. There is no benefit to continuing treatment once progression is documented. Consideration should be given to performance status and transportation needs when choosing second-line therapy.

Lung cancer has the second highest incidence in the VA population. There are currently no third-line therapies with a survival benefit and no oral second-line therapies for patients who have a poorer performance status (ECOG 2-3) other than erlotinib. Criteria for Use will be developed.

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[1] Grunwald V, Hidalgo M. Development of the epidermal growth factor receptor inhibitor Tarceva™ (OSI-774). Adv Exp Med Biol 2003; 532:235-46.

[2] Bonomi P. Erlotinib: a new therapeutic approach for non-small cell lung cancer. Expert Opin Invest Drugs 2003;12:1395-1401.

[3] Product Package Insert Tarceva™. Genetech Oncology, San Franciso, California. 2004.

[4] Hidalgo M, Bloedow D. Pharmacokinetics and pharmacodynamics: maximizing the clinical potential of erlotinib (Tarceva). Sem Oncology 2003; 30, Suppl 7:25-33.

[5] Food and Drug Administration Medical Review at: http://www.fda.gov/cder/foi/nda/2004/21-743_Tarceva_medr.PDF accessed April 18, 2005.

[6] DeGrendele H. Epidermal growth factor receptor inhibitors, gefitinib and erlotinib (Tarceva™, OSI-774), in the treatment of bronchioloalveolar carcinoma. Clinical Lung Cancer 2003; 5:83-5.

[7] Sandler A. Clinical experience with the HER1/EGFR tyrosine kinase inhibitor erlotinib. Oncology 2003 (suppl);17(11):17-22.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to April 2005) using the search terms erlotinib and Tarceva. The search was limited to studies performed in humans and published in English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Appendix Table Erlotinib Clinical Trials

Citation
Design
Analysis type

Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
BR.21 Phase III DB, PC, MC Outcomes: Overall survival Response rate PFS QoL Safety QoL assessed using the EORTC QLQ-C30 plus the lung cancer module LC13.	Inclusion criteria 1. NSCLC locally advanced or metastatic 2. Failure of at least one chemotherapy regimen Exclusion criteria (optional)		See table below	See table below QoL concentrated on 3 clinically significant symptoms: cough, dyspnea, and pain Erlotinib delayed deterioration of cough, deterioration of dyspnea, and deterioration of pain. Use of palliative treatments was similar in each arm.	Most patients experienced rash and diarrhea, generally grades 1 and 2. GI symptoms included anorexia, nausea, and vomiting, mostly grades 1 and 2 4 patients on erlotinib developed interstitial lung disease (0.8%) 81% of erlotinib patients tolerated therapy without dose reduction ECG: the most frequent events were atrial fib (5 patients) and sinus tachycardia (3 patients); no QT prolongation 32% of erlotinib patients died during treatment or within 30 days of the last dose versus 29% in the placebo

	Erlotinib N=488	Placebo N=243
Gender Male	 65%	 66%
Age ≥65	 39%	 37%
Race White	 78%	 77%
PS 0 1 2 3	 13% 52 26 9	 14% 54 23 9
Histology AdenoCA Squamous	 50% 30	 49 32
No. of prior chemo regimens 1 2 3	 50% 49 1	 50% 49 1
Prior Platinum No Yes	 7% 93	 8% 92
Prior Taxane No Yes	 64% 36	 63% 37
Best response to prior therapy CR or PR SD PD	 38% 34 28	 38% 34 28

Outcome	Erlotinib	Placebo
Overall survival	6.7 mos HR=0.73 (95%CI 0.6-0.87) P=0.001	4.7 mos
12 month actuarial survival	31.2%	21.5%
Survival Skin rash No rash	 9.49 mos 2.22 mos	 Similar survival pattern
Response CR PR SD PD	 <1% 8 35.1 38.4	 <1 <1 26.5 57.3
Duration of response CR+PR SD	 34.3 wks 24.4 wks	 15.9 wks 18.7 wks
PFS	9.86 wks (95%CI 8.43-14.14) HR=0.6 (95%CI 0.51-0.72) P<0.001	7.86 wks (95%CI 7.71-8.14)

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
					group.
A248-1007 Phase II MC, open-label Erlotinib following failure of platinum based combination chemotherapy in advanced NSCLC		Erlotinib 150mg/day until progression or unmanageable toxicity	N=57 2 prior chemotherapies (1-8) 60% female 91% white Age 62 years PS 1 in 77% Ex-smokers 74%	CR 2 PR 5 Response Rate 12.3% SD 38.6% PD 49.1% Overall survival 8.4 months	

DB=double blind, PC=placebo controlled, MC=multicenter, NSCLC=non-small cell lung cancer, PFS=progression free survival, QoL=quality of life, P=performance status, CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease