Afatinib (GILOTRIF)

National Drug Monograph

October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Afatinib is a second-generation tyrosine kinase inhibitor. It binds to EGFR, HER2, and HER4 inhibiting TKI autophosphorylation and ErbB signaling. Inhibits *in vitro* proliferation of cells expressing wild type EGFR, or those expressing selected exon 19 deletions or exon 21 (L858R) substitution mutations including some with a secondary T790M mutation.
Indication(s) Under Review in this document (may include off label)	First-line 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. Limitations of use: Safety and efficacy of afatinib have not been established in patients whose tumors have other EGFR mutations.
Dosage Form(s) Under Review	Tablets: 40 mg, 30 mg, and 20 mg
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy	*Pregnancy Category D* *See Special Populations for additional information*

Executive Summary	
Efficacy	• 1st line therapy of adenocarcinoma non-small cell lung cancer in patients whose tumor harbors a common activating mutation (LUX-Lung 3 and LUX-Lung 6) afatinib demonstrated a significant increase in PFS versus standard chemotherapy. In a combined analysis of OS, patients with a common EGFR mutation had an OS benefit driven by tumors with an exon 19 deletion. • 3rd or 4th line therapy of adenocarcinoma non-small cell lung cancer (LUX-Lung 1) afatinib plus Best Supportive Care improved PFS but not OS versus BSC alone. Afatinib also improved patient reported symptoms of dyspnea and shortness of breath. • 2nd line therapy of squamous carcinoma non-small cell lung cancer (LUX-Lung 8) afatinib modestly improved PFS and OS versus erlotinib. • 2nd line therapy of squamous head and neck cancer (LUX-Head & Neck 1) afatinib modestly improved PFS but not OS compared to IV methotrexate.
Safety	• Most common adverse reactions: diarrhea, rash, stomatitis, paronychia, dry skin, decreased appetite, pruritus • Serious adverse reactions: diarrhea, vomiting, dyspnea, fatigue, hypokalemia • Fatal adverse reaction due to interstitial lung disease, sepsis, pneumonia • Warning/Precautions: diarrhea, interstitial lung disease, exfoliative and bullous skin reactions, hepatic toxicity, keratitis, embryofetal toxicity,

Other Considerations	**Outcome in clinically significant area**	NSCLC adenocarcinoma 1st line (vs chemo): PFS: 11.1 vs 6.9mos and 11 vs 5.6mos OS (combined): 25.8 vs 24.5 mos Clinically meaningful improvement in dyspnea/shortness of breath NSCLC adenocarcinoma 3rd or 4th line (vs placebo): OS: 10.8 vs 12 mos PFS: 3.3 vs 1.1 mos NSCLC squamous 2nd line (vs erlotinib): PFS: 2.6 vs 1.9 mos OS: 7.9 vs 6.8 mos Head and neck cancer 2nd line (vs methotrexate): PFS: 2.6 vs 1.7 mos OS: 6.8 vs6.0 mos
	Effect Size	NSCLC 1st line: PFS: HR 0.58(0.43-0.78) p=0.001 and 0.28(0.20-0.39) p<0.001 OS (Combined): HR 0.91 (95%CI 0.75-1.11) p=0.37 OS common mutations: HR 0.81 (95%CI 0.66-0.99) p=0.037 NSCLC 3rd or 4th: PFS: HR 0.38(0.31-0.48) p<0.0001 OS: HR 1.08(0.86-1.35) p=0.74 NSCLC squamous 2nd line: PFS: HR 0.81(0.69-0.96) p=0.0103 OS: HR 0.81(0.69-0.95) p=0.0077 Head and Neck 2nd line: PFS: HR 0.80(0.65-0.98) p=0.030 OS HR 0.96(0.77-1.19) p=0.70
	Potential Harms	NSCLC: ≥gr3 Diarrhea (15%), Stomatitis (9%), Rash (16%), Paronychia (11%), cystitis (1%), decreased appetite (4%) HNC: ≥gr3 Rash (10%), Diarrhea (9%), Stomatitis (6%), Fatigue (6%), Nausea (2%), Decreased appetite (3%), Dehydration (2%), Anemia (1%), Pruritus (1%)
	Net Clinical Benefit	NSCLC 1st line: Substantial NSCLC 3rd or 4th line: Minimal NSCLC squamous 2nd line: Moderate Head and Neck 2nd line: Minimal
Projected Place in Therapy	• 1st line therapy of patients with advanced adenocarcinoma non-small cell lung cancer whose tumors harbor a common EGFR mutation (exon 19 deletion or exon 21 L858R substitution) as measured by and FDA approved test.	

Background

Purpose for review

The purposes of this monograph are to (1) evaluate evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating afatinib 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.

Issues to be determined:

- Evidence of need?
- Does afatinib offer any advantage to erlotinib or gefitinib?
- What safety issues need to be considered?
- Are there specific drug issues with afatinib that are best managed by the non-formulary process, prior authorization, or criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations
Erlotinib	Prior authorization-Facility
Non-formulary Alternative (if applicable)	**Other Considerations**
Gefitinib	Recently reintroduced in the US market.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to October 2015) using the search term afatinib. The search was limited to the PubMed Clinical Queries Filter for Therapy (specific/narrow and sensitive/broad) and studies performed in humans and published in the English language. Reference lists of review articles and the FDA Medical Review were searched for relevant studies and unpublished data. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Non-Small Cell Lung Cancer

Study	Setting	Pts	ECOG PS	Treatment	Response rate (%)	PFS Months	OS Months
LUX-Lung 1[1] **Phase III** **Boehringer Ingelheim** **NA, Europe, Asia**	Adenocarcinoma 3rd or 4th line (failure of erlotinib, gefitinib or both and 1-2 lines of chemotherapy)	N=585 East Asian 58% Female 60% Never smoker 63% Mutation+ 68%	0 25% 1 68%	Afatinib orally daily + BSC Vs Placebo orally daily +BSC 1º OS 2nd PFS, ORR, HRQoL	PR+SD: 58% vs 18%	3.3 mos vs 1.1 mos HR 0.38 (95%CI 0.31-0.48)	10.8 mos vs 12 mos HR 1.08 (95%CI 0.86-1.35)
LUX-Lung 1[2] **Symptom and QoL benefit**					Afatinib arm: <u>Greater improvement in NSCLC symptoms</u>: Cough, dyspnea, pain, shortness of breath, pain in chest, pain in arm or shoulder, pain in other parts <u>Worsening of scores</u>: appetite loss, diarrhea, sore mouth, dysphagia <u>Global score improvements</u>: fatigue, global health status/QoL <u>Delayed time to deterioration of scores</u>: cough (HR 0.60), pain (HR 0.73), pain in chest (HR 0.61), pain in shoulder/arm (HR 0.71) constipation (HR 0.46), hemoptysis (HR 0.89), fatigue (HR 0.97), insomnia (HR 0.70) <u>Shorter time to</u>		

						deterioration: appetite loss, dysphagia, sore mouth, diarrhea		
LUX-Lung 3[3] **Phase III** **Boehringer Ingelheim** **Asia, Europe, NA, SA, Australia**	Adenocarcinoma and proven EGFR mutation 1st line	N=345 Males 36.1% Age med 61.5 White 26.5% East Asian 71.7% Never smoker 67.4% Former smoker 30.4% Stage IIIb 8.7% Stage IV 91..3% EGFR mutation Exon 19 del 49.1% L858R 39.6% Other 11.3%	0 1	40% 60%	Afatinib orally daily Vs Cisplatin 75 mg/m^2 IV and pemetrexed 500 mg/m^2 IV once every 21 days up to a maximum of 6 cycles 1º PFS 2nd ORR, OS, PROs	ORR 56% vs 23% Duration of response: 11.1 mos vs 5.5 mos	PFS: 11.1 mos vs 6.9 mos (HR 0.58 95%CI 0.43-0.78) PFS common mutations 13.6 mos vs 6.9 mos (HR 0.47 95%CI 0.34-0.65)	OS: no difference at time of data cutoff; median not yet reached in either group
Symptom control and QoL in LUX-Lung 3[4]						Afatinib clinically meaningful improvements: Dyspnea (64% vs 50%) Shortness of breath (57% vs 36%) Pain (P=.051) Cough (P=.244) **Afatinib** Delay in time to deterioration: Cough (HR 0.60 95%CI 0.41-0.87) Dyspnea (HR 0.68 95%CI 0.51-0.93) Pain (HR 0.83 95%CI 0.62-0=1.10) Worsening of symptoms: Diarrhea (83% vs 24%) Sore mouth (81% vs 61%) Dysphagia (57% vs 38%) Shorter time to deterioration of symptoms: Diarrhea, sore mouth **Chemotherapy**: Worsening of symptoms: Fatigue (39% vs 25%) Nausea (61% vs 42%) Shorter time to deterioration of symptoms: Fatigue, nausea, vomiting No difference for improvement proportions or time to deterioration of global health status/QoL		
LUX-Lung 6[5] **Phase III** **Boehringer**	Adenocarcinoma with EGFR mutation	N=364; N=242 afatinib Male: 36% SE Asian: 5.8%	0 1	19.8% 80.2%	Afatinib orally daily (could increase to 50 mg) Vs	ORR: 66.9% vs 23% (OR 7.28 95%CI 4.36-12.18) Duration of response:	PFS: 11 mos vs 5.6 mos (HR 0.28 95%CI	OS immature at primary analysis:

Ingelheim **China, Thailand, South Korea**	1st line	S. Korean: 4.5% Chinese: 89.7% Never smoked: 74.8% Stage IIIb: 6.6% Stage IV: 93.4% EGFR mutation Exon 19 deletion: 51.2% L858R: 38% Uncommon: 10.7%		Gemcitabine 1000mg/m^2 IV D1 & 8 plus cisplatin 75 mg/m^2 IV D1 every 21 days until progression 1° PFS 2nd ORR, disease control, duration of response, PROs	9.7 mos vs 4.3 mos Disease control: OR 3.84 (95%CI 2.04-7.24) PROs Improved with afatinib: cough, dyspnea, pain Time to deterioration longer in afatinib for cough, dyspnea, pain Overall health status and QoL improvement: 62.7% vs 32.7%	0.2-0.39)	22.1 mos vs 22.2 mos
OS analysis from LUX-Lung 3 and LUX-Lung 6[6] **Boehringer Ingelheim**	See LUX-Lung 3 and LUX-Lung 6	See LUX-Lung 3 and LUX-Lung 6	See LUX-Lung 3 and LUX-Lung 6	See LUX-Lung 3 and LUX-Lung 6	See LUX-Lung 3 and LUX-Lung 6	See LUX-Lung 3 and LUX-Lung 6	*Overall Survival* LUX-Lung 3 HR 0.88 (95%CI 0.66-1.17) LUX-Lung 6 HR 0.93 (95%CI 0.72-1.22) Combined HR 0.91 (95%CI 0.75-1.11) *Common EGFR mutations* LUX-Lung 3 HR 0.78 (95%CI 0.58-1.06) LUX-Lung 6 HR 0.83 (95%CI 0.62-1.09) Combined HR 0.81 (95%CI 0.66-0.99) *OS Exon 19 deletion* LUX-Lung 3 HR 0.54 (95%CI 0.36-0.79) LUX-Lung 6 HR 0.64 (95%CI 0.44-0.94) Combined HR 0.59 (95%CI 0.45-0.77) *OS L858r substitution* LUX-Lung 3 HR 1.30 (95%CI 0.80-2.11) LUX-Lung 6 HR 1.22 (95%CI

							0.81-1.83) Combined HR 1.25 (95%CI 0.92-1.71)
Uncommon mutations in LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6[7] **Boehringer Ingelheim**	Post-hoc combined analysis of uncommon EGFR mutations	G1: point mutations and duplications in exons 18-21 G2: de novo Thr790Met mutation alone or in combination G3: exon 20 insertions	See LL3 and LL6	See LL3 and LL6	G1: 71.1% G2: 14.3% G3:8.7%	PFS G1: 10.7 mos G2: 2.9mos G3: 2.7 mos	OS G1: 19.4 mos G2 :8.1 mos G3: 4.1 mos
LUX-Lung 8[8] **Phase III** **Boehringer Ingelheim** **23 countries**	Squamous 2nd Line (progressed after at least 4 cycles of platinum-based therapy)	N=795 N=398 Afatinib Male: 84% Age: 65 Non-eastern Asian: 78% Eastern Asian: 22* Never smoker: 7% Squamous: 96% Previous Carboplatin: 63% Cisplatin: 41% Stage IIIB: 12% Stage IV: 88%	0 32% 1 68% 2 <1%	Afatinib orally daily Vs Erlotinib 150mg orally daily 1º: PFS 2nd:OS, ORR, Disease control, PROs	ORR:6% vs 3% p=0.0551 SD: 31% vs 26% PD: 33% vs 43% Disease control: 51% vs 39% Improved HRQoL: 36% vs 28% Improved scores cough: 43% vs 35% No difference: dyspnea, pain Afatinib delayed time to deterioration of dyspnea: 2.6 mos vs 1.9 mos	PFS (initial) 2.4 mos vs 1.9 mos HR 0.82 (95%CI 0.68-1.00 p=0.0427) PFS (final) 2.6 mos vs 1.9 mos HR 0.81 (95%CI 0.69-0.96)	OS 7.9 mos vs 6.8 mos HR 0.81 (95%CI 0.69-0.95) 6m survival: 63.6 vs 54.6% 12m survival: 36.4 vs 28.2% 18m survival: 22 vs 14.4%

NSCLC=non-small cell lung cancer; BSC=best supportive care; OS=Overall Survival; PFS=progression free survival; ORR=objective response rate; HRQoL=health-related quality of life; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; PR=partial response; CR=complete response; HR=hazard ratio; SD=stable disease; PROs=patient-reported outcomes;

- The role of afatinib in lung cancer was evaluated in 5 phase III trials
- In 1st line therapy in patients with adenocarcinoma and EGFR mutations, LUX-Lung 3 compared afatinib to cisplatin plus pemetrexed and LUX-Lung 6 compared afatinib to cisplatin plus gemcitabine. A pooled analysis of overall survival from these 2 trials found a survival advantage with afatinib therapy in patients with common mutations (exon 19 deletion or exon 21 L858R substitution mutation) with a HR of 0.81. A subgroup analysis found the OS advantage was driven by patients with the exon 19 deletion. A meta-analysis of progression-free survival in first-line EGFR-TKI therapy (erlotinib, gefitinib, or afatinib) found patients with an exon 19 deletion had a longer PFS versus those with an exon 21 L858R substitution.[9]
- LUX-Lung 1 evaluated afatinib vs best supportive care in 3rd or 4th line therapy of adenocarcinoma following therapy with erlotinib or gefitinib, reversible EGFR tyrosine kinase inhibitors, plus 1-2 lines of chemotherapy. There was no statistical difference in the primary endpoint of OS but afatinib did produce a longer progression-free survival in this heavily pretreated population. In a phase II trial LUX-Lung 4[10], patients with NSCLC who progressed during prior therapy with erlotinib, gefitinib, or both received afatinib. 8.2% achieved a partial response, 57.4% stable disease, and the median duration of response was 24.4 weeks. The PFS (secondary endpoint) was 4.4 months.
- LUX-Lung 5 evaluated continuing afatinib therapy beyond progression plus paclitaxel versus single agent investigator's choice chemotherapy in patients with adenocarcinoma who failed ≥1 line of chemotherapy and erlotinib or gefitinib. Afatinib plus paclitaxel improved PFS (HR 0.60) and response rate (32.1% vs 13.2%). There was no difference in OS.[11]
- LUX-Lung 8 evaluated afatinib vs erlotinib in 2nd line therapy of squamous cell NSCLC. Afatinib modestly increased PFS and OS compared to erlotinib but with increased incidence of diarrhea and stomatitis.
- Evidence Grade: Moderate

Head and Neck Carcinoma

Study	Setting	Pts	ECOG PS	Treatment	Response rate (%)	PFS Months	OS Months
LUX-Head & Neck 1[12]	Recurrent or	N=483 N=322 to afatinib	0: 28% 1: 72%	Afatinib 40mg orally daily; increase to 50	ORR: 10% vs 6% P=0.10	2.6 mos vs 1.7 mos	6.8 mos vs 6 mos

Boehringer Ingelheim	metastatic Squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx not amenable to salvage sx or XRT	N=161 to methotrexate Male: 85% Age <65: 74% Smoking hx ≥10 yrs: 79% Alcohol units per week ≤7 78% Locoregional: 33% Metastatic: 15% Both: 51%	mg p 4 weeks of minimal adverse reactions Vs Methotrexate 40 mg/m^2 IV bolus once weekly; increase to 50 mg/m^2 p 2 weeks of no evidence of adverse events 1º PFS 2nd OS, ORR	Disease control: 49% vs 39% p=0.035 Patient reported outcomes: Afatinib associated: Delayed time to deterioration of global health status, pain, swallowing Improvement in QoL scores: NSS different	HR 0.80 (95%CI 0.65-0.98)	HR 0.96 (95% CI 0.77-1.19)

- In 2nd line therapy of recurrent or metastatic head and neck cancers, afatinib modestly improved PFS but not OS. Afatinib positively affected some patient reported outcomes compared to methotrexate.
- Evidence Grade: Moderate

Potential Off-Label Use

Author	Tumor setting	Phase	Patients	Treatment	Results
Seiwert, et al.[13] 2014	**Head and neck**, recurrent or metastatic squamous cell after platinum-based therapy	II	121	Afatinib vs weekly cetuximab	Tumor shrinkage 9.9% vs 6.8%
Lin, et al.[14] 2012	**Breast HER2+,** pre-treated with trastuzumab	II	41	Afatinib	ORR 10% (PR only)
Hickish, et al.[15] 2014	**Metastatic colorectal cancer**, 2nd or 3rd line KRAS wild-type and KRAS mutation	II	91	Afatinib vs weekly cetuximab	KRAS wild type ORR 3% vs 20% KRAS mutated (afatinib only) Disease control rate 12% SD

Clinical trials in progress:

- HER2+ gastric cancer
- Refractory urothelial cancers
- Neoadjuvant therapy in squamous cell head and neck carcinoma
- Combination therapy in NSCLC, gastroesophageal cancers, other solid tumors
- EGFR mutation+ lung cancer in >70 year olds
- Recurrent glioma

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• None
Warnings/Precautions	• Diarrhea may cause dehydration and renal failure. Hold doses if not controlled by antidiarrheal therapy. • Bullous and Exfoliative Skin Disorders: severe bullous, blistering, and exfoliating lesions in 0.15%. Discontinue therapy if life-threatening reactions. Withhold therapy for severe/prolonged reactions. • Interstitial Lung Disease (ILD): withhold for acute onset or worsening of pulmonary symptoms. Occurs in 1.5%. • Hepatic toxicity: Fatal hepatic impairment in 0.18%. Monitor liver function tests periodically. Withhold or discontinue therapy for severe or worsening liver function tests. • Keratitis: Withhold for keratitis evaluation; withhold or discontinue for

	confirmed ulcerative keratitis. Occurs in 0.8%. • Embryofetal toxicity: Can cause fetal harm. Advise females of child-bearing potential of potential hazard to fetus; use highly effective contraception.

Safety Considerations

- Diarrhea is consistently a problem across all clinical trials with afatinib. In the one trial that directly compared afatinib to erlotinib (LUX-Lung 8), afatinib produced more serious diarrhea (4% vs 2% in erlotinib) and related adverse reactions (dehydration in 2% and acute renal failure in 1%). 27% of afatinib patients required dose reductions due to adverse reactions compared to 14% in the erlotinib arm.
- Acneiform rash is common with all EGFR-TKIs. Tetracycline has been reported effective in treating the rash. A report from a single institution found that preventive treatment with tetracycline 250mg every 12 hours for 4 weeks reduced the incidence and severity of afatinib-induced acneiform rash.[16]
- Risk of Interstitial Lung Disease (ILD): A meta-analysis of the risk of ILD with all EGFR-TKIs assessed 24 phase III clinical trials. The overall incidence in 5265 patients was 1.6%. The overall incidence of high-grade (≥grade 3 associated with increase morbidity) was 0.9%. No difference in rate of ILD was observed in non-Asian countries between gefitinib and afatinib. Combined results demonstrated an increased risk for all grade ILD with gefitinib but not erlotinib or afatinib. Gefitinib and erlotinib increased the risk of high-grade ILD but not afatinib.[17]

Adverse Reactions

Common adverse reactions	≥20% diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite, pruritus
Death/Serious adverse reactions	Serious • Diarrhea (6.6%), vomiting (4.8%), dyspnea, fatigue, hypokalemia (1.7% each) Fatal • Pulmonary toxicity/interstitial lung disease-like reactions (1.3%), sepsis (0.43%), pneumonia (0.43%)
Discontinuations due to adverse reactions	Adenocarcinoma-first line • 8% (vs 12% cisplatin plus pemetrexed LUX-Lung3) • 8.7% (vs 39.8% cisplatin plus gemcitabine LUX-Lung6) Squamous-second line • 17.3% (vs 13.2% erlotinib LUX-Lung8)

Drug Interactions

Drug-Drug Interactions

- Afatinib is a substrate and inhibitor of P-glycoprotein (P-gp). Patients who require a concomitant P-gp inhibitor should reduce daily dose of afatinib by 10mg. Resume previous dose after discontinuation of P-gp inhibitor as tolerated. Patients who require a P-gp inducer should increase the daily dose of afatinib by 10mg as tolerated and resume the previous dose 2-3 days after discontinuing P-gp inducer.
- In a phase I trial in healthy male volunteers, afatinib administered 1 hour after a potent P-gp inhibitor (ritonavir) resulted in a 38.5% increased Cmax and 47.6% increased AUC. Minimal increases were seen when ritonavir was given simultaneously or 6 hours after afatinib. In combination with rifampicin, a potent P-gp inducer, afatinib AUC decreased 33.8% and Cmax decreased 21.6%. There was no change in terminal half-life in either comparison. The authors concluded that maximal inhibition or induction of P-gp had no clinically relevant effect on exposure to afatinib.[18]
- Afatinib is a substrate and inhibitor of the transporter Breast Cancer Resistance Protein (see package insert)
- *In vitro* data indicate that drug-drug interactions with afatinib due to inhibition or induction of CYP450 enzymes are unlikely. Afatinib is neither an inhibitor nor inducer of CYP450 enzymes.

Risk Evaluation

As of October 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Afatinib 20mg, 30mg, 40mg tab	Afinitor Axitinib Ceritinib Crizotinib Erlotinib Gefitinib	None	None	Imatinib
Gilotrif	None	None	None	Gengraf

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- Afatinib and erlotinib are a Category 1 recommendation by NCCN for 1st line treatment of advanced NSCLC with EGFR sensitizing mutation
- ASCO Guidelines for Systemic Therapy for Stage IV NSCLC recommends for 1st line therapy in patients with a sensitizing EGFR mutation either afatinib, erlotinib or gefitinib (Evidence Quality High; Strength of Recommendation Strong for each)
- The National Institute for Health and Care Excellence (NICE) in the UK recommends afatinib as an option for patients with locally advanced or metastatic non-small cell lung cancer if the tumor tests positive for the EGFR mutation and the patient has not previously received an EGFR tyrosine kinase inhibitor.

Outcome in clinically significant area	NSCLC adenocarcinoma 1st line: PFS: 11.1 vs 6.9mos and 11 vs 5.6mos OS (combined): 25.8 vs 24.5 mos Clinically meaningful improvement in dyspnea/shortness of breath NSCLC adenocarcinoma 3rd or 4th line: OS: 10.8 vs 12 mos PFS: 3.3 vs 1.1 mos NSCLC squamous 2nd line: PFS: 2.6 vs 1.9 mos OS: 7.9 vs 6.8 mos Head and neck cancer 2nd line: PFS: 2.6 vs 1.7 mos OS: 6.8 vs6.0 mos
Effect Size	NSCLC 1st line: PFS: HR 0.58(0.43-0.78) p=0.001 and 0.28(0.20-0.39) p<0.001 OS (Combined): HR 0.91 (95%CI 0.75-1.11) p=0.37 OS common mutations: HR 0.81 (95%CI 0.66-0.99) p=0.037 NSCLC 3rd or 4th: PFS: HR 0.38(0.31-0.48) p<0.0001 OS: HR 1.08(0.86-1.35) p=0.74 NSCLC squamous 2nd line: PFS: HR 0.81(0.69-0.96) p=0.0103 OS: HR 0.81(0.69-0.95) p=0.0077 Head and Neck 2nd line:

	PFS: HR 0.80(0.65-0.98) p=0.030 OS HR 0.96(0.77-1.19) p=0.70
Potential Harms	NSCLC: ≥gr3 Diarrhea (15%), Stomatitis (9%), Rash (16%), Paronychia (11%), cystitis (1%), decreased appetite (4%) HNC: ≥gr3 Rash (10%), Diarrhea (9%), Stomatitis (6%), Fatigue (6%), Nausea (2%), Decreased appetite (3%), Dehydration (2%), Anemia (1%), Pruritus (1%)
Net Clinical Benefit	NSCLC 1st line: Substantial NSCLC 3rd or 4th line: Minimal NSCLC squamous 2nd line: Moderate Head and Neck 2nd line: Minimal

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

- Recommended dose is 40 mg orally once daily until disease progression or no longer tolerated. Take at least 1 hour before or 2 hours after a meal.
- Do not take missed dose within 12 hours of next dose.
- Dose Modification
  - Withhold for any drug-related adverse reactions:
    - NCI CTCAE Grade 3 or higher
    - Diarrhea Grade 2 or higher persisting for 2 or more consecutive days while taking anti0diarrheal medication
    - Cutaneous reactions of Grade 2 that are prolonged (>7 days) or intolerable
    - Renal dysfunction Grade 2 or higher
  - Resume treatment when adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Resume at reduced dose of 10 mg per day less than the dose at which adverse reaction occurred.
- Permanently discontinue for:
  - Life-threatening bullous, blistering, exfoliative skin lesions
  - Confirmed interstitial lung disease
  - Severe drug-induced hepatic impairment
  - Persistent ulcerative keratitis
  - Symptomatic left ventricular dysfunction
  - Severe or intolerable adverse reaction occurring at a dose of 20mg per day
- Reduce dose by 10mg per day for concomitant therapy with a P-gp inhibitor
- Increase dose by 10 mg per day for concomitant therapy with a P-gp inducer

Special Populations (Adults)

	Comments
Elderly	• No differences in safety between patients 65 years and older (32%) and younger patients.
Pregnancy	• Pregnancy Category D. Can cause fetal harm based on mechanism of action. Embryotoxic in animals. In animals with maternal toxicity, led to abortions at late gestational stages. If used during pregnancy or if patient becomes pregnant while on therapy, apprise of potential hazard to fetus.
Lactation	• No known if afatinib is present in human breast milk. Found in milk of lactating rats. Due to potential for harm to infants, a decision to discontinue nursing or discontinue the drug should be considered.
Females and Males of Reproductive Potential	• Females: Contraceptive planning and prevention counseling. Advise to use highly effective contraception during afatinib therapy and for at least 2 weeks after stopping therapy.
Renal Impairment	• Not studied in patients with severely impaired renal function. Adjustments not necessary in patients with mild (CLcr 60-89 mL/min) renal impairment. Closely monitor patients with moderate

	(CLcr 30-59 mL/min) to severe (CLcr <30 mL/min) renal impairment and adjust dose if not tolerated. • A case report of a 60yo woman with lung cancer who developed hepatorenal syndrome and required chronic hemodialysis tolerated afatinib 30 mg daily for 2 months but did not tolerate a dose increase to 40mg daily.[19]
Hepatic Impairment	• Not studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to starting dose not necessary for mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust dose if not tolerated. • Pharmacokinetic parameters of afatinib were assessed in patients with mild or moderate hepatic impairment and healthy controls. Mild to moderate hepatic impairment had no clinically relevant effect on single dose pharmacokinetics of 50mg of afatinib compared to healthy controls.[20]
Pharmacogenetics/genomics	• Use in patients with EGFR exon 19 deletion or exon 21 (l858R) substitution mutations as detected by FDA-approved test. • Safety and efficacy not established in patients whose tumors have other EGFR mutations.

Projected Place in Therapy (this section may be edited prior to final approval of document and web posting)

- Lung cancer remains a leading cause of death from cancer. Patients with advanced lung cancer experience a number of disease-related symptoms which can result in psychological stress and negative impact quality of life.
- In recent years, treatment decisions for patients with advanced non-small cell lung cancer are now based on a precision medicine model, selecting specific therapy based on tumor histology or molecular characteristics making NSCLC a heterogeneous group of diseases.
- In VA, lung cancer is among the top 3 cancers diagnosed each year.
- The relative incidence of adenocarcinoma has been rising with subsequent decreases in the incidence of other types of NSCLC like squamous cell and small cell lung cancer.
- Fifteen to thirty percent of non-Asian patients with a lung adenocarcinoma have an activating mutation of the Epidermal Growth Factor Receptor gene; 30-60% of Asian patients with lung adenocarcinoma have EGFR mutation.
- EGFR mutations are now readily identified in tumor samples using FDA approved tests, which has implications for tailoring treatment especially in the first-line setting.
- Gefitinib (recently re-introduced into the US market) and erlotinib are first generation reversible EGFR tyrosine kinase inhibitors (TKIs). Afatinib is a second generation irreversible inhibitor of EGFR, HER2, and HER4. In vitro inhibition of cells with an acquiredT790M mutation at concentrations transiently achieved in patients has been demonstrated. However clinically, significant activity against cells with an acquired resistance due to a point mutation on exon 20 (T790M) has not been demonstrated in clinical trials.
- Afatinib has demonstrated high quality evidence in 2 randomized, phase III trials (LUX-Lung 3 and LUX-Lung 6) of efficacy in the 1st line treatment of patients with advanced adenocarcinoma non-small lung cancer whose tumors harbor one of the two common activating EGFR gene mutations (exon 19 deletion or exon 21 L858R substitution). Compared to standard chemotherapy regimens in this setting, afatinib significantly prolonged progression-free survival. In a combined analysis, overall survival was also prolonged for patients with one of the two common EGFR mutations; this was driven primarily by tumors with the exon 19 deletion.
- Guidance documents from ASCO, NCCN and NICE recommend afatinib as a first-line option for patients with advanced adenocarcinoma of the lung whose tumor contains a common EGFR activating mutation.
- Afatinib should be available for use in 1st line therapy for patients with advanced adenocarcinoma of the lung whose tumor harbors a common activating EGFR gene mutation (i.e. exon 19 deletion or exon 21 L858R substitution mutation).
- Currently, erlotinib was recently added to the VA National Formulary restricted to Prior Authorization at the facility level (PA in development). There are some minor safety differences among the EGFR TKIs which can be

considered when making treatment decisions. Differences in potential drug interactions and adverse event profiles can affect the choice of an EGFR TKI.

- The potential number of patients who require an EGFR TKI is relatively small due to the limitation to tumors with an EGFR gene mutation. There may be an opportunity to choose a workhorse agent in this class based on price.

References

[1] Miller VA, Hirsch V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012; 13:528-38.
[2] Hirsch V, Cadranel J, Cong XJ, et al. Symptom and quality of life benefit of afatinib in advanced non-small cell lung cancer patients previously treated with erlotinib or gefitinib; results of a randomized phase IIb/III trial (LUX-Lung 1). J Thoracic Oncology 2013;8:229-237).
[3] Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-3334.
[4] Yang JC-H, Hirsch V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3342-3350.
[5] Wu Y=L, Zhou C, Hu C-P, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harboring EGFR mutations (LUX-Lung 6): an open-label, randomized phase 3 trial. Lancet Oncol 2014:15:213-22.
[6] Yang JC-H, Wu T-L, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomized, phase 3 trials. Lancet Oncol 2015;16:141-51.
[7] Yang JC-H, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harboring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 2, and LUX-Lung 6. Lancet Oncol 2015;830-38.
[8] Soria J-C, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomized controlled phase 3 trial. Lancet Oncol 2015;16:897-907.
[9] Zhang Y, Sheng J, Kang S, et al. Patients with exon 19 deletion were associated with longer progression-free survival compared to those with L858R mutation after first-line EGFR-TKIs for advanced non-small cell lung cancer: a meta-analysis. PLOS One 2014;9:e107161.
[10] Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol 2010;31:3335-3341.
[11] Schuler MH, Yang C-H, Park K, et al. Continuation of afatinib beyond progression: results of a randomized, open-label, phase III trial of afatinib plus paclitaxel (P) versus investigator's choice chemotherapy (CT) in patients (pts) with metastatic non-small cell lung cancer (NSCLC) progressed on erlotinib/gefitinib (E/G) and afatinib-LUX-Lung 5. J Clin Oncol 2014;32:5s(abstract 8019).
[12] Machiels J-PH, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the heat and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomized phase 3 trial. Lancet Oncol 2015;16:583-94.
[13] Seiwert TY, Fayette J, Cupisoll D, et al. A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. Ann Oncol 2014;25:1813-1820.
[14] Lin NU, Winer EP, Wheatley D, et al. A phase II study of afatinib (BIBW 2992), an irreversible ErbB family blocker, in patients with HER2-positive metastatic breast cancer progressing after trastuzumab. Breast Cancer Res Treat 2012;133:1057-1065.
[15] HickishT, Cassidy J, Propper D, et al. A randomized, open-label phase II trial of afatinib versus cetuximab in patients with metastatic colorectal cancer. Europ J Cancer 2014;50:3136-3144.
[16] Arrieta O, Vega-Gonazalez MT, Lopez-Macias D, et al. Randomized, open-label trial evaluation the preventive effect of tetracycline on afatinib induced-skin toxicities in non-small cell lung cancer patients. Lung Cancer 2015;88:282-288.

[17] Qi W-X, Sun Y-J, Shen Z, Yao Y. risk of interstitial lung disease associated with EGFR-TKIs in advanced non-small-cell lung cancer: a meta-analysis of 24 phase III clinical trials. J Chemotherapy 2015:27:40-51.
[18] Wind S, Giessmann T, Jungnik A, et al. Pharmacokinetic drug interactions of afatinib with rifampicin and ritonavir. Clin Drug Investig 2014;34:173-182.
[19] Bersanelli M, Tiseo M, Aritoli F, et al. Gefitinib and afatinib treatment in an advanced non-small cell lung cancer (NSCLC) patient undergoing hemodialysis. Anticancer Research 2014; 34:3185-3188.
[20] Schnell D, Buschke S, Fuchs H, et al. Pharmacokinetics of afatinib in subjects with mild or moderate hepatic impairment. Cancer Chemother Pharmacol 2014;74:267-275.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

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Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.

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