EE142

Alectinib, Brigatinib, and Lorlatinib as First-Line Therapies for Advanced ALK-Positive Non-Small Cell Lung Cancer: A Cost-Effectiveness Analysis

Rahul Mudumba, MHS[1], Jorge Nieva, MD[2], William V. Padula, PhD[1,3]

[1]Department of Pharmaceutical and Health Economics, Alfred E. Mann School of Pharmacy & Pharmaceutical Sciences, University of Southern California, Los Angeles, CA, USA

[2]Division of Medical Oncology, Department of Medicine, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA

[3]Leonard D. Schaeffer Center for Health Policy and Economics, Los Angeles, CA, USA

OBJECTIVE

To evaluate the cost-effectiveness of alectinib, brigatinib, and lorlatinib as first-line therapies for advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) from a US healthcare sector perspective.

METHODS

Model Type: Four-state partitioned survival model

Interventions: Alectinib, Brigatinib, and Lorlatinib

Target population: First-line advanced ALK+ NSCLC patients

Model Structure: 4 mutually exclusive health states: progression-free (PF), central nervous system (CNS)-related progressed disease (PD), non-CNS progressed disease (non-CNS PD), death

Time Horizon: 5 years

Cycle Length: 1 month

Perspective: US healthcare sector

Clinical Efficacy & Modeling:

Digitized Kaplan-Meier (KM) Curves:
- Extracted estimated patient-level data for progression-free survival (PFS), intracranial PFS (ICPFS), and overall survival (OS) from the ALTA-1L trial using WebPlotDigitizer[1,2]

Reconstructed Survival Data:
- Reconstructed KM data for brigatinib following Guyot et al.'s algorithm and number of patients at risk over time[3]
- Fitted multiple parametric models to KM data for survival extrapolation
- Calculated Akaike Information Criterion (AIC) scores and derived transition parameters for each parametric survival model via maximum likelihood estimation (MLE) in R (v.4.2.2)
- Selected exponential model for PFS, ICPFS, and OS based on AIC scores and clinical plausibility (per NICE recommendation)[4]

Deriving Hazard Ratios (HRs) for Alectinib & Lorlatinib:
- Synthesized HRs from nine published network meta-analyses (NMAs) comparing alectinib and lorlatinib to brigatinib
- Used bootstrapping (10,000 iterations) to derive composite HRs and confidence intervals, avoiding traditional fixed or random-effects meta-analysis[5]

Application of HRs:
- Applied composite HRs to brigatinib's survival curves (PFS, ICPFS, OS) to derive curves for alectinib and lorlatinib arm

Costs (2024 USD):
- Drug acquisition based on median of Department of Veteran Affairs (VA) and wholesale acquisition cost (WAC) prices
- Healthcare utilization
- Adverse event management

Outcomes:
- Quality-adjusted life years (QALYs) derived using health utilities bootstrapped from trials of the 3 therapies[1,6,7]
- Adjusted for adverse events (AEs)
- Discounted at 3% annually

Sensitivity & Scenario Analysis:
- Probabilistic and deterministic sensitivity analysis conducted to test model assumptions and robustness
- Various pricing and efficacy specifications explored

MODEL OVERVIEW

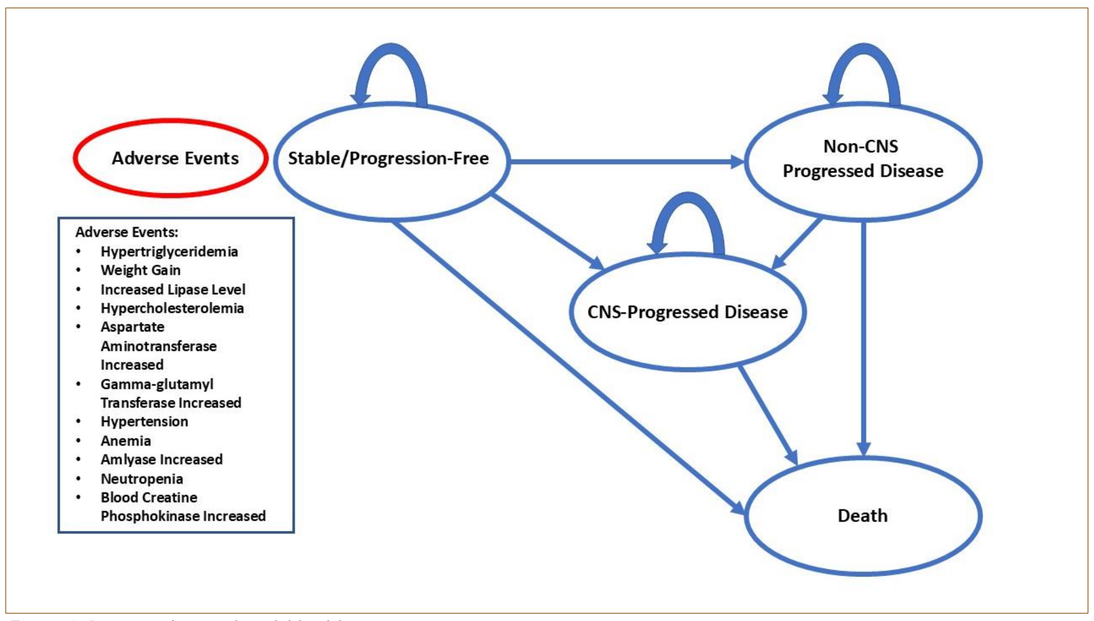

Figure 1. Partitioned survival model health states.

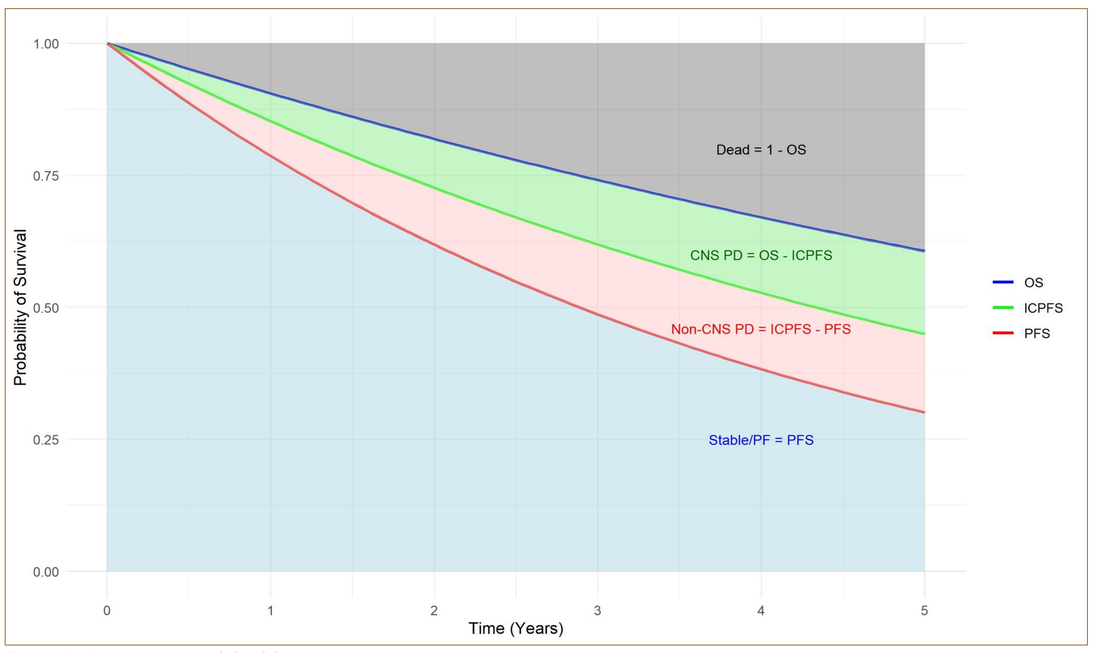

Figure 2. Proportion in each health state over time.

RESULTS

Base Case	Discounted Costs	Life Years	Discounted QALYs	ICER vs Alectinib	ICER vs Brigatinib	NMB @ $100,000 WTP	NMB @ $150,000 WTP	NMB @ $200,000 WTP	NMB @ $250,000 WTP
Alectinib	$1,105,814	4.04	2.85	-	**$245,536 /QALY**	-$820,690	-$678,127	-$535,565	-$393,003
Brigatinib	$1,059,283	3.78	2.66	$245,536 /QALY	-	-$793,109	-$660,022	-$526,936	-$393,848
Lorlatinib	$1,163,519	3.92	2.88	$2,135,236 /QALY	**$481,385 /QALY**	-$875,692	-$731,779	-$587,865	-$443,952
Scenario Analyses									
Decreased Long-term efficacy (5-year horizon)	Discounted Costs	Life Years	Discounted QALYs	ICER vs Brigatinib	ICER vs Alectinib	NMB @ $100,000 WTP	NMB @ $150,000 WTP	NMB @ $200,000 WTP	NMB @ $250,000 WTP
Alectinib	$1,076,992	3.93	2.78	$147,606 /QALY	-	-$798,821	-$659,735	-$520,650	-$381,564
Brigatinib	$1,059,283	3.77	2.66	-	$147,606 /QALY	-$793,109	-$660,022	-$526,936	-$393,849
Lorlatinib	$1,139,797	3.86	2.80	$588,886 /QALY	$3,751,088 /QALY	-$859,951	-$720,028	-$580,105	-$440,182
Dosage Heterogeneity (5-year horizon)	Discounted Costs	Life Years	Discounted QALYs	ICER vs Brigatinib	ICER vs Alectinib	NMB @ $100,000 WTP	NMB @ $150,000 WTP	NMB @ $200,000 WTP	NMB @ $250,000 WTP
Alectinib	$1,154,723	4.04	2.85	$167,499 /QALY	-	-$869,599	-$727,037	-$584,474	-$441,912
Brigatinib	$1,122,981	3.78	2.66	-	$167,499 /QALY	-$856,807	-$723,720	-$590,634	-$457,547
Lorlatinib	$1,194,131	3.92	2.88	$328,586 /QALY	$1,458,171 /QALY	-$906,304	-$762,390	-$618,477	-$474,563

Table 2. Model results.

**QALY* quality-adjusted life year; *ICER* incremental cost-effectiveness ratio; *NMB* net monetary benefit; *WTP* willingness-to-pay

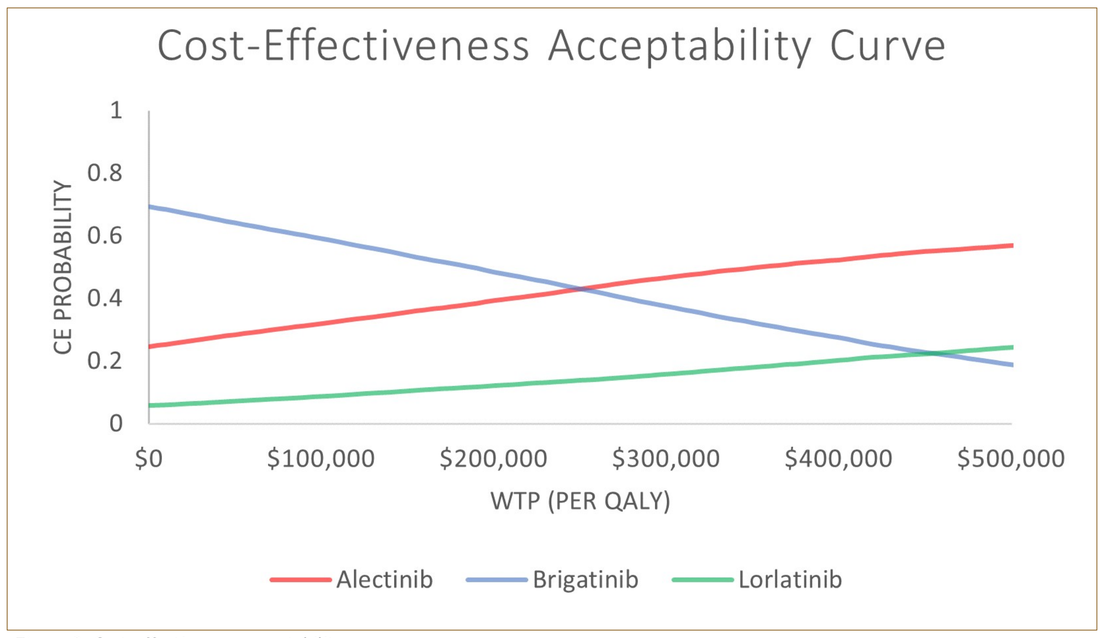

Figure 3. Cost-effectiveness acceptability curve.

MODEL INPUTS

Variable	Base-Case Value
Clinical Inputs	
PFS Hazard Rate	0.024
ICPFS Hazard Rate	0.016
OS Hazard Rate	0.010
Alectinib vs. Brigatinib PFS HR	0.831
Alectinib vs. Brigatinib OS HR	0.750
Lorlatinib vs. Brigatinib PFS HR	0.593
Lorlatinib vs. Brigatinib OS HR	0.860
Cost Inputs	
Alectinib Drug cost per month/cycle	$15,651
Brigatinib Drug cost per month/cycle	$16,344
Lorlatinib Drug cost per month/cycle	$17,676
Total Monthly Healthcare Service Costs in PF state	$10,049
Total Monthly Non-CNS PD Costs for Alectinib Arm	$15,504
Total Monthly Non-CNS PD Costs for Brigatinib Arm	$16,162
Total Monthly Non-CNS PD Costs for Lorlatinib Arm	$15,669
Total Monthly CNS PD Costs for Alectinib Arm	$25,766
Total Monthly CNS PD Costs for Brigatinib Arm	$26,730
Total Monthly CNS PD Costs for Lorlatinib Arm	$26,007
Adverse Event Costs (Event)	
Aspartate aminotransferase increased	$9,132
Hypertension	$32,935
Anaemia	$25,269
Neutropenia	$21,429
Health Utility Inputs	
Progression-Free	0.802
Progressed Disease (Non-CNS)	0.732
CNS-Progressed Disease	0.552
Disutilites Induced by Adverse Events	
Any Grade 3+ Adverse Event	-0.037

Table 1. Key model parameters.

RESULTS

Base case:
- Incremental cost-effectiveness ratios (ICERs) for alectinib and lorlatinib compared to brigatinib were $245,536/QALY and $481,386/QALY, respectively

Sensitivity Analysis:
- At a willingness-to-pay threshold of $150,000 per QALY, brigatinib had a 54% chance of being the cost-effective option, with alectinib at 36% and lorlatinib at 10%

Scenario Analysis:
- Decreased efficacy scenario yielded an ICER of $147,606/QALY for alectinib vs. brigatinib
- Dosage heterogeneity revealed an ICER of $167,499/QALY for alectinib vs. brigatinib

CONCLUSION

While alectinib and lorlatinib demonstrate enhanced efficacy, brigatinib emerges as the cost-effective first-line therapy for ALK+ NSCLC in the US at willingness-to-pay thresholds below $250,000/QALY.

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CONTACT

Rahul Mudumba: mudumba@usc.edu

PhD Student,

Department of Pharmaceutical and Health Economics, Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences, University of Southern California

Los Angeles, CA, USA