SUPPLEMENTARY MATERIALS

The cost-effectiveness of brigatinib in adult patients with ALK inhibitor–naive *ALK*-positive non–small cell lung cancer from a US perspective

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SUPPLEMENTARY TABLE 1 Health-related quality of life model

Category	Health State	Value/Option	Source
Utility values[a]	Pre-progression	0.806	HRQoL analysis from ALTA-1L
	Progressed on treatment (general)	0.688	HRQoL analysis from ALTA-1L
	CNS Progressed		
	Brigatinib	0.553	Calculation
	Crizotinib	0.553	Calculation
	Alectinib	0.553	Assumed equal to brigatinib in cost comparison basecase
	Non-CNS Progressed		
	Brigatinib	0.583	Multiplier for impact of brain metastases compared with other metastatic sites based on data from Roughley et al. applied to progressed on treatment utility estimate[b]
	Crizotinib	0.585	
	Alectinib	0.583	
Utility multiplier	Chemo multiplier	90.24%	Blackhall et al. (2014)[c]
	BSC	70.28%	Nafees et al. (2008)[d]
	CNS multiplier	75.36%	Roughley et al. (2014)[b]
Utility decrements	≥1 grade 3/4 AE	–0.024	HRQoL analysis
	Age	–0.0003	Ara and Brazier (2011)[e]

[a]Differences in the utility values within CNS progressed and non CNS progressed are driven by subsequent therapy assumptions as different utilities applied based on receipt of BSC, chemotherapy, or ALKi.

[b]Roughley A, Damonte E, Taylor-Stokes G, Rider A, Munk VC. Impact of brain metastases on quality of life and estimated life expectancy in patients with advanced non-small cell lung cancer. *Value Health*. 2014;17(7):A650. doi: 10.1016/j.jval.2014.08.2364

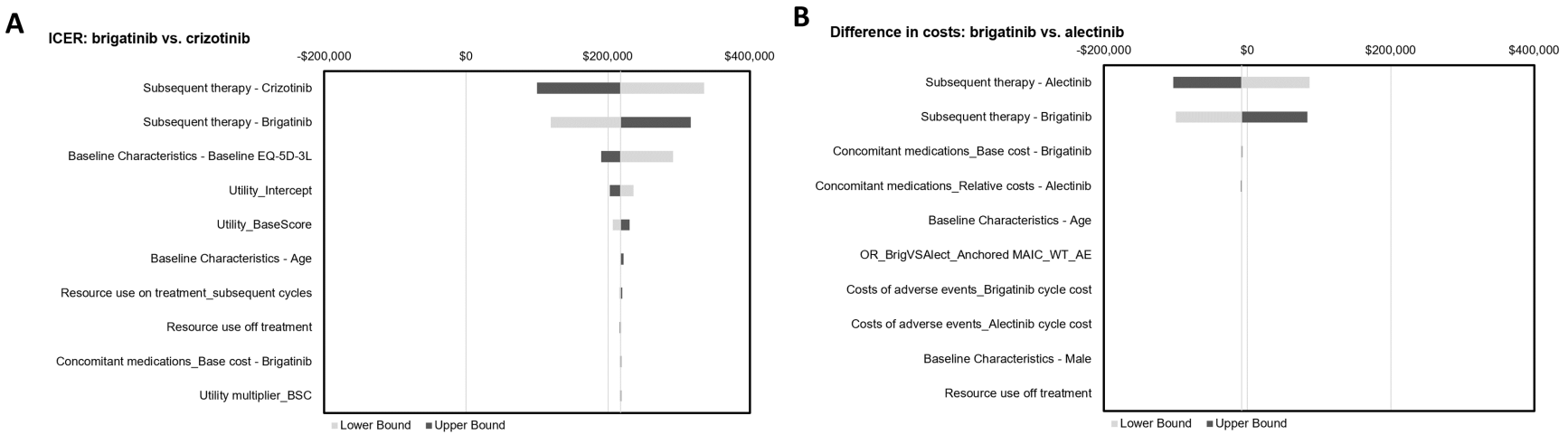
[c]Blackhall F, Kim DW, Besse B, et al. Patient-reported outcomes and quality of life in PROFILE 1007: A randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer. *J Thorac Oncol*. 2014;9(11):1625-33. doi: 10.1097/JTO.0000000000000318

[d]Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 2008;6:84. doi: 10.1186/1477-7525-6-84

[e]Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health.* 2011;14(4):539-45. doi: 10.1016/j.jval.2010.10.029

AE, adverse event; ALK, anaplastic lymphoma kinase tyrosine kinase inhibitors; BSC, best supportive care; CNS, central nervous system.

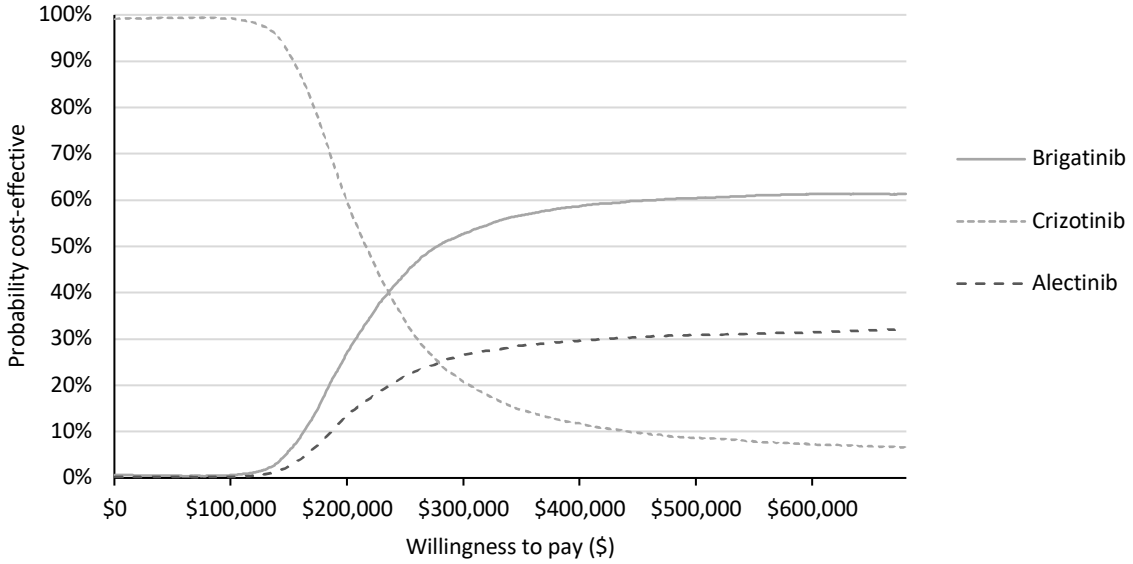
SUPPLEMENTARY FIGURE 1 Univariate sensitivity analysis tornado diagrams



A. Brigatinib vs. crizotinib; B. Brigatinib vs. alectinib.

BIRC, blinded independent review committee; Brig, brigatinib; CNS, central nervous system; HR, hazard ratio; ICER, Incremental cost-effectiveness ratio; MAIC, match-adjusted indirect comparison; OS, overall survival; PD, progressive disease; PFS, progression-free survival; WT, weight.

SUPPLEMENTARY FIGURE 2 Cost-effectiveness acceptability curve



SUPPLEMENTARY TABLE 2 Scenario analyses – cost-effectiveness vs. crizotinib and cost-comparison vs. alectinib (basecase)

Scenario	Brigatinib vs. crizotinib, ICER	Brigatinib vs. alectinib, cost difference[a]
Clinical effectiveness scenarios		
Population		
ITT	$217,607	-$8,546
Parametric model fits for OS		
Weibull	$192,111	-$7,817
Gompertz	$169,483	-$7,137
Log-logistic	$207,637	-$7,416
Log-normal	$210,504	-$7,303
Gamma	$197,143	-$8,001
Gen. Gamma	$171,073	-$7,330
Exponential	$217,607	-$8,546
Parametric model fits for PFS BIRC		
Weibull	$240,464	-$8,200
Gompertz	$254,150	-$7,533
Log-logistic	$258,734	-$7,763
Log-normal	$259,625	-$7,664
Gamma	$233,017	-$8,309
Gen. Gamma	$255,068	-$7,700
Exponential	$217,607	-$8,546
Parametric model fits for CNS-PFS		
Weibull	$217,608	–

Scenario	Brigatinib vs. crizotinib, ICER	Brigatinib vs. alectinib, cost difference[a]
Gompertz	$225,994	–
Log-logistic	$219,296	–
Log-normal	$220,007	–
Gamma	$217,186	–
Gen. Gamma	$225,623	–
Exponential	$217,607	–
Treatment switching adjustments		
No switching adjustment	$217,607	–
Adjusted for official switchers using RPSFTM, no censoring	$241,890	–
Adjusted for official switchers using RPSFTM, re-censoring	$215,143	–
Adjusted for all switchers using RPSFTM, no re-censoring	$246,051	–
Adjusted for all switchers using RPSFTM, re-censoring	$221,334	–
Utility source		
Utility sourced from Chouaid et al.	$249,671	–
Utility sourced from ALTA-1L	$217,607	–
Cost scenarios		
Time on treatment		
Weibull	$96,704	-$9,858
Gompertz	$111,088	-$9,666
Log-logistic	$243,587	-$9,006
Log-normal	$195,553	-$9,320

Scenario	Brigatinib vs. crizotinib, ICER	Brigatinib vs. alectinib, cost difference[a]
Gamma	$97,468	-$9,855
Gen. Gamma	$40,654	-$10,203
Exponential	$98,436	-$9,851
Treat until progression	$217,607	-$8,546
Treat one cycle post-progression	$215,409	-$8,477
Treat two cycles post-progression	$213,210	-$8,407
Treat three cycles post-progression	$211,011	-$8,338
Relative dose intensity		
Apply relative dose intensity	$217,607	-$8,546
Exclude relative dose intensity calculations	$248,263	$21,743
Source of subsequent therapy		
Source from ALTA-1L and relevant clinical trials	$165,990	$72,740
Ceritinib dose (subsequent therapy)		
750 mg	$215,138	-
Discount rate scenarios		
No discount rate applied to costs and health outcomes	$214,518	-$12,461
Discount rate of 3% for both cost and health outcomes	$217,607	-$8,546

Scenario	Brigatinib vs. crizotinib, ICER	Brigatinib vs. alectinib, cost difference[a]
Time horizon scenarios		
5-years	$221,489	-$12,227
10-years	$242,895	-$10,546
30-years	$217,607	-$8,546

[a]Cost-saving unless otherwise stated.
BIRC, blinded independent review committee; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS; overall survival; PFS, progression-free survival; RPSFTM, rank preserving structural failure time models.

SUPPLEMENTARY TABLE 3 Scenario analyses – cost-effectiveness vs. alectinib

Scenario	Brigatinib vs. alectinib, ICER
Cost-effectiveness brigatinib vs. alectinib	
Unadjusted Bucher (ITT, OS and PFS BIRC), no adjustment for switching	$159,858
Unadjusted Bucher (ITT, OS and PFS BIRC), treatment switching all switchers, no re-censoring	$198,793
Unadjusted Bucher (ITT, OS and PFS BIRC), treatment switching all switchers, re-censoring	$293,116
Unadjusted Bucher (ITT, OS and PFS BIRC), treatment switching official switchers only, no re-censoring	$194,683
Unadjusted Bucher (ITT, OS and PFS BIRC), treatment switching official switchers only, re-censoring	$261,223
Anchored MAIC (ITT, OS and PFS BIRC), no adjustment for switching	$142,336
Anchored MAIC (ITT, OS and PFS BIRC), treatment switching all switchers, no re-censoring	$92,898
Anchored MAIC (ITT, OS and PFS BIRC), treatment switching all switchers, re-censoring	$122,218
Anchored MAIC (ITT, OS and PFS BIRC), treatment switching official switchers only, no re-censoring	$86,902
Anchored MAIC (ITT, OS and PFS BIRC), treatment switching official switchers only, re-censoring	$124,733
Unanchored MAIC (ITT, OS and PFS BIRC)	$149,298

Scenario	Brigatinib vs. alectinib, ICER
Unadjusted Bucher (ITT, OS and PFS INV), no adjustment for switching	$163,948
Unadjusted Bucher (ITT, OS and PFS INV), treatment switching all switchers, no re-censoring	$207,133
Unadjusted Bucher (ITT, OS and PFS INV), treatment switching all switchers, re-censoring	$304,461
Unadjusted Bucher (ITT, OS and PFS INV), treatment switching official switchers only, no re-censoring	$202,660
Unadjusted Bucher (ITT, OS and PFS INV), treatment switching official switchers only, re-censoring	$272,659
Anchored MAIC (ITT, OS and PFS INV), no adjustment for switching	$150,918
Anchored MAIC (ITT, OS and PFS INV), treatment switching all switchers, no re-censoring	$38,174
Anchored MAIC (ITT, OS and PFS INV), treatment switching all switchers, re-censoring	$109,127
Anchored MAIC (ITT, OS and PFS INV), treatment switching official switchers only, no re-censoring	$21,524
Anchored MAIC (ITT, OS and PFS INV), treatment switching official switchers only, re-censoring	$114,429
Unanchored MAIC (ITT, OS and PFS INV)	$91,002

BIRC, blinded independent review committee; ICER, incremental cost-effectiveness ratio; INV, investigator; ITT, intention-to-treat; MAIC, matched adjusted indirect comparisons; OS, overall survival; PFS, progression-free survival.

SUPPLEMENTARY TABLE 4 Health state costs (basecase)

	Pre-Progression	Progressed disease	End of life
Discounted			
Brigatinib	$614,014	$328,859	$1,415
Crizotinib	$347,810	$392,699	$1,488
Alectinib	$610,143	$340,785	$1,415

SUPPLEMENTARY TABLE 5 Drug Costs (ALKis)

	Brigatinib[a]	Brigatinib	Alectinib	Crizotinib
Dose	90 mg OD	180 mg OD	600 mg BD	250 mg BD
Mode	Oral	Oral	Oral	Oral
Pack size (#tablets)	7	30	240	60
mg/capsule	90	180	150	250
Live price/pack(cycle)	$3,819.00	$16,364.00	$15,395.60	$17,701.53
Source	Micromedex REDBOOK. WAC for 7 day therapy initiation course. Accessed 11/13/2020, dose as per ALTA 1L	Micromedex REDBOOK. WAC. Accessed 11/13/2020, dose as per ALTA 1L	Micromedex REDBOOK. WAC. Accessed 11/13/2020; dose as per ALEX	Micromedex REDBOOK. WAC. Accessed 11/13/2020; dose as per ALTA 1L

[a]Brigatinib 7 day lead in.

ALK, anaplastic lymphoma kinase tyrosine kinase inhibitors; OD, once-daily; BD, twice-daily.

SUPPLEMENTARY TABLE 6 Unit costs for resource use

Items	Unit cost (£)	Source
Oncology outpatient (f)	$25.63	CMS Physician Lookup CPT 99211 - office/outpatient visit
Oncology outpatient (s)	$92.47	CPT 99213
GP visit	$92.47	Assumed equal to oncology outpatient
Cancer nurse	$92.47	Assumed equal to oncology outpatient
Biochemistry	$10.56	CMS Physician Lookup CPT 80053 - comprehensive metabolic panel
Full blood test	$7.77	CMS Physician Lookup CPT 85025 - complete blood count
CT scan	$180.97	CMS Physician Lookup CPT 70460 - computed tomography, head/brain
X-ray	$34.2	CMS; CPT 71046
MRI	$226.64	CMS Physician Lookup CPT 70551 - MRI
ECG	$80.6	CMS; CPT 93224
Steroids (dexamethasone)	$55.51	
Stereotactic radiotherapy	$1,076.66	CMS; CPT 77372; note that these procedural costs (SRS, WBRT, resection) may not fully capture costs as there may be management-associated costs after treatment
Whole brain radiotherapy	$428.84	CMS; CPT 77432
Surgical resection	$1,510.17	CMS; CPT 32480 (partial removal of lung)

CT, computed tomography; GP, general practitioner; ECG, electrocardiogram; MRI, magnetic resonance imaging.

SUPPLEMENTARY TABLE 7 Adverse event costs

Adverse event	Unit cost
Blood creatinine phosphokinase increased	$200.48
Amylase increased	$200.48
Nausea	$7,042
Hypertension	$7,013
Increased AST	$200.48
Increased ALT	$200.48
Increased lipase level†	$200.48
Neutropenia	$1,3378
Anaemia	$8,013
Diarrhoea	$7,042
Vomiting	$7,042
Gamma-glutamyl transferase increased	$200.48
Myalgia	$0
Fatigue	$0
Pneumonia	$10,756
Acute kidney injury	$5,604

Adverse event	Unit cost
Weight decreased	$0
Dizziness	$0
Dysgeusia	$0
Asthenia	$8,811
Neoplasm Progression	$12,805
Dyspnoea	$0
Pulmonary embolism	$9,517
Blood Alkaline Phosphatase Increased	$200.48
Hypercholesterolemia	$200.48
Hypertriglyceridemia	$200.48
Edema	$10,655
Weight increased	$0
Peripheral Neuropathy	$9,222
Cognitive defects	$7,203
Mood effects	$0
Hyperlipidemia	$200.48

ALT, alanine aminotransferase; AST, aspartate transaminase.

SUPPLEMENTARY TABLE 8 Subsequent therapy[a]

Subsequent therapy distributions, %	Brigatinib	Crizotinib	Alectinib
Brigatinib	0.00	30.00	30.00
Crizotinib	0.00	0.00	0.00
Alectinib	30.00	20.00	0.00
Ceritinib	5.00	10.00	5.00
Lorlatinib	50.00	20.00	50.00
Immunotherapy	5.00	5.00	5.00
VEGF-R	0.00	0.00	0.00
Chemotherapy	10.00	15.00	10.00
Best supportive care	100.00	100.00	100.00

[a]It is assumed that all patients will receive best supportive care following active subsequent therapies.
VEGF-R, vascular endothelial growth factor receptor.

SUPPLEMENTARY TABLE 9 Disaggregated costs

Intervention	Treatment	Concomitant medications	Resource use on treatment	Resource use off treatment	Subsequent therapy	Terminal care	Adverse events	Total
Brigatinib	$606,333	$3,909	$12,919	$23,797	$319,187	$1,460	$179	$968,833
Crizotinib	$341,964	$2,066	$6,299	$27,675	$376,703	$1,529	$51	$758,314
Alectinib	$602,504	$3,909	$12,919	$23,797	$331,664	$1,460	$78	$977,379
Ceritinib	$254,041	$2,949	$9,679	$17,451	$276,126	$1,577	$202	$562,931
Lorlatinib	$1,027,436	$6,765	$22,555	$8,309	$175,290	$1,464	$367	$1,242,185