

Title: Real-world Clinical and Economic Consequences of Next Generation Anaplastic Lymphoma Kinase Positive (ALK+) Tyrosine Kinase Inhibitors (TKIs) in Patients with TKI-naïve ALK+ Metastatic Non-small Cell Lung Cancer in the United States

Authors: Jyoti Malhotra, MD MPH,¹ Elizabeth H. Marchlewicz, PhD MPH,² Yan Zhang, PhD,³ Isabelle Winer, MPH,² Kenneth Pack, BS,² Christopher Danes, PhD,³ Hoa H. Le, PhD,⁴ Luis Hernandez, PhD MPH MSc³

Affiliation:

- 1) City of Hope, Duarte, CA, USA
- 2) Veradigm, Chicago, IL, USA
- 3) Takeda Pharmaceuticals America, Inc., Lexington, MA, USA
- 4) Takeda Development Center America, Inc., Cambridge, MA, USA

Corresponding Author

Luis Hernandez, PhD MPH MSc

luis.hernandez3@takeda.com

Supplementary Table 1. Code Sets

Study Section	Description	Code Type	Code ^a
Patient Selection	lung cancer	ICD-9-CM	162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 165.8, 165.9
		ICD-10-CM	C34*, C399
	Metastasis	ICD-9-CM	196.x, 197.x, 198.x
		ICD-10-CM	C77*, C78*, C79*, C7B*
	ALK TKI	generic names	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
Clinical Characteristics - Metastasis	ROS exclusion criteria	generic names	entrectinib, repotrectinib
	brain	ICD-10-CM	C79.31, C79.32
	bone	ICD-10-CM	C79.5*, C7B.03
	kidney	ICD-10-CM	C79.0*
	liver	ICD-10-CM	C78.7, C7B.02
Treatment Patterns - Therapeutics	angiogenesis inhibitor	generic names	bevacizumab, cabozantinib, everolimus, pazopanib, ramucirumab, vandetanib
		HCPCS	C9142, C9257, J9035, Q5107, Q5118, Q5126, Q5129, J7527, C9025, J9308
	chemotherapy	generic names	bendamustine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, etoposide, gemcitabine, ifosfamide, methotrexate sodium, oxaliplatin, paclitaxel, , pemetrexed, temozolomide, topotecan, vinblastine, vincristine, vinorelbine
		HCPCS	C9042, J9033, J9034, J9036, J9056, J9058, J9059, J9045, J9060, C9087, J8530, J9070, J9071, J9072, J9073, J9074, J9075, J9071, J9171, J9172, J9000, Q2049, Q2050, J9002, J8560, J9181, J9196, J9198, J9199, J9201, J9208, J8610, J8611, J8612, J9250, J9255, J9260, J9260, J9263, J9265, J9267, J9258, J9259, J9264, J9294, J9296, J9297, J9304, J9305, J9314, J9322, J9323, J9324, J9314, J9305, J8700, J9328, J8705, J9351, J9360, J9370, J9371, J9390
	immunotherapy	generic names	atezolizumab, atezolizumab and hyaluronidase-tqjs, cemiplimab, durvalumab, ipilimumab, irinotecan, nivolumab, pembrolizumab, tremelimumab-actl
		HCPCS	C9483, J9022, C9492, J9173, J9228, C9474, J9205, J9206, C9453, J9299, C9027, J9271, C9147, J9347

	targeted therapy	generic names	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib, adagrasib, afatinib, amivantamab, bevacizumab, binimetinib, cabozantinib, capmatinib, cetuximab, dabrafenib, dacomitinib, encorafenib, ensartinib, entrectinib, erlotinib, everolimus, gefitinib, larotrectinib, lazertinib, mobocertinib, necitumumab, nintedanib, osimertinib, pazopanib, pralsetinib, ramucirumab, repotrectinib, selpercatinib, sotorasib, tarlatamab-dlle, trastuzumab, tepotinib, trametinib, vemurafenib, vandetanib, zenocutuzumab-zbco
		HCPCS	C9083, J9061, J9055, J8565, C9475, J9295, J9354, J9355, J9358, Q5112, Q5113, Q5114, Q5116, Q5117, J9355, C9131
Preselected Adverse Events	Affective disorder	ICD-10-CM	F01*, F31*, F32*, F33*, F34*, F39
	Bradycardia/AV Block	ICD-10-CM	I44*, R00.9, R00.1
	Cognitive disorder/mental impairment	ICD-10-CM	R41*
	Cough	ICD-10-CM	R05*
	Diarrhea	ICD-10-CM	R19.7
	Dyspnea/Shortness of breath	ICD-10-CM	R06.0*
	Fatigue	ICD-10-CM	R53*
	Headaches	ICD-10-CM	R51*, G43*, G44*
	Hyperglycemia	ICD-10-CM	R73*
	Hypertension	ICD-10-CM	H35.03*, I10, I11*, I12*, I13*, I15*, I16*, I1A*, I67.4, N26.2
	Hypertriglyceridemia	ICD-10-CM	E78.1
		LOINC	3043-7, 70218-3, 3049-4, 35217-9, 28554-4, 14927-8, 2571-8, 12951-0
	Hypophosphatemia	LOINC	2774-8, 24519-1, 27123-9, 24520-9, 2777-1, 14879-1, 20941-1, 35221-1
	Increased ALT/AST	LOINC	76625-3, 1742-6, 1743-4, 77144-4, 1744-2, 1920-8, 30239-8, 88112-8
	Insomnia	ICD-10-CM	G47.0
	Myalgia	ICD-10-CM	M79.1*
	Nausea/Vomiting	ICD-10-CM	R11*
	Peripheral edema	ICD-10-CM	R60*
	Pneumonitis	ICD-10-CM	J67*, J68.0, J69*, J84*, J95.4
	Psychotic disorder	ICD-10-CM	F20*, F21, F22, F23, F24, F25*, F28, F29

	Rash	ICD-10-CM	R21
	Seizures	ICD-10-CM	G40*
	Speech disorder	ICD-10-CM	R47*
	Suicidal ideation	ICD-10-CM	R45.851 (redacted in dataset)
	Visual disorder	ICD-10-CM	H53*
	Weight gain	ICD-10-CM	R63.5

ALK, anaplastic lymphoma kinase-positive; HCPCS, Healthcare Common Procedure Coding System; ICD-9-CM, International Classification of Diseases, 9th Edition, Clinical Modification; ICD-10-CM, International Classification of Diseases, 10th Edition, Clinical Modification; LOINC, Logical Observation Identifiers, Names, and Codes; ROS1, ROS proto-oncogene 1; TKI, tyrosine kinase inhibitors

^a For these code lists, x is used as a wildcard for ICD-9 codes and * is used as a wildcard for ICD-10 codes

Supplementary Table 2. First line treatment patterns

	Alectinib	Brigatinib	Lorlatinib
	N = 391	N = 32	N = 58
Continuation, n (%)	233 (59.6)	18 (56.3)	38 (65.5)
Discontinuation, n (%)	158 (40.4)	14 (43.8)	20 (34.5)
Restart	15 (9.5)	2 (14.3)	3 (15.0)
Augmentation or switch	94 (59.5)	6 (42.9)	11 (55.0)
No further treatment	49 (31.0)	6 (42.9)	6 (30.0)

N, number

Treatment patterns were determined using the Grady et al algorithm [1]. The only modification to the algorithm was that the gap definition was set at 180 days instead of the 60 days used in the original publication as suggested by Meng et al.'s chart review validation [2].

Continuation was defined as continuing first line therapy until the end of follow-up.

Augmentation was defined as adding an angiogenesis inhibitor > 90 days after the index date or adding a new non-interchangeable agent to the index regimen without evidence of a gap in >28 days in the index treatment regimen. Restart was defined as having a gap in therapy > 180 days, and then initiating treatment with the index agent, an exchange of interchangeable agents, or a reduced regimen. Switching was defined as the introduction of a new non-interchangeable agent after the discontinuation of all prior agents > 28 days after the index date. Discontinuation was defined as evidence of augmentation, restart, switching, or a gap of > 180 days between the end of the first line treatment regimen and the end of follow-up.

1. Grady CB, Hwang W-T, Reuss JE, et al. Determining line of therapy from real-world data in non-small cell lung cancer. *Pharmacoepidemiol Drug Saf.* 2024;33(12):e70049.
2. Meng W, Mosesso KM, Lane KA, et al. An automated line-of-therapy algorithm for adults with metastatic non-small cell lung cancer: validation study using blinded manual chart review. *JMIR Med Inform.* 2021;9(10):e29017.

Supplementary Table 3. Classification of inverse probability of treatment weighting model covariates by variable type, with rationale for inclusion.

Variable	Measurement	DAG classification	Rationale: effect on treatment selection	Rationale: effect on outcomes
Age	<65 vs. ≥65 years	True confounder	Older patients may have greater comorbidity burden, leading clinicians to favor agents with more established tolerability profiles or to avoid intensive regimens.	Age independently predicts performance status, treatment tolerability, PFS, OS, and HCRU.
Sex	Male / female	True confounder	ALK+ NSCLC has a slight female predominance; sex may influence physician prescribing patterns and patient preference for specific agents.	Sex affects pharmacokinetics, toxicity profiles, and treatment response; female sex has been associated with improved survival outcomes in NSCLC.
Race	White / Black / Asian / Other or unknown	True confounder	ALK rearrangements are more prevalent in Asian populations; race may influence access to next-generation TKIs and specialist care in the US.	Race is associated with differences in drug metabolism (e.g., CYP3A4 activity), treatment response, access to care, and economic outcomes including costs and HCRU.
Baseline brain metastasis	Present / absent at index date	True confounder	Presence of CNS metastases strongly drives selection of next-generation TKIs (alectinib, brigatinib, lorlatinib) given their superior blood–brain barrier penetration vs. crizotinib.	Brain metastases independently worsen PFS and OS, increase HCRU (e.g., CNS-directed radiation), and substantially raise total direct medical costs.
Time from metastasis to index date	Days (continuous)	True confounder	Longer intervals may reflect diagnostic delays, indolent disease, or prior systemic therapy, all of which can influence which TKI is ultimately initiated.	This variable is a proxy for disease trajectory and time-to-treatment; longer delays are associated with worse prognostic profiles and higher downstream HCRU.
Index year	Calendar year of TKI initiation	True confounder	Guideline evolution (e.g., preferred-agent updates) and sequential FDA approvals of next-generation TKIs mean that calendar time strongly predicts which agent was available and selected.	Secular trends in clinical practice, supportive care intensity, and healthcare costs mean that outcomes and resource use vary systematically by year of treatment initiation.

ALK, anaplastic lymphoma kinase; DAG, directed acyclic graph; CNS, central nervous system; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitors; TTNT, time to next treatment; TTD, time to discontinuation.

Note on excluded variable types: No instrumental variables (affecting treatment only, with no direct path to outcomes) or collider variables (caused by both treatment and outcome) were identified among the covariates included in the IPTW model. All six variables were measured prior to or at the index date (TKI initiation), confirming they are not downstream consequences of treatment assignment.

Supplementary Table 4. Distribution of Inverse Probability of Treatment Weights Before and After Winsorization

	All patients		Alectinib		Brigatinib		Lorlatinib	
	Before	After	Before	After	Before	After	Before	After
Minimum	0.14	0.21	0.84	0.84	0.21	0.21	0.14	0.21
1st Percentile	0.21	0.21	0.85	0.85	0.21	0.21	0.14	0.21
99th Percentile	2.55	2.55	1.57	1.57	2.55	2.55	8.03	2.55
Maximum	8.03	2.55	2.48	2.48	2.55	2.55	8.03	2.55
Mean	1.01	0.99	1.00	1.00	0.99	0.99	1.08	0.92
Standard deviation	0.51	0.32	0.16	0.16	0.55	0.55	1.35	0.71
Sum	484.9	475.3	390.2	390.2	31.8	31.8	62.8	53.2

Supplementary Table 5. Schoenfeld residual test results for the proportional hazards assumption

	Unweighted Model		IPTW-Weighted Model	
	χ^2	p-value	χ^2	p-value
rwTTNT	4.52	0.10	6.12	0.047
rwTTD	4.20	0.12	3.48	0.18
rwPFS	0.95	0.62	1.56	0.46
rwOS	2.83	0.24	7.02	0.030

IPTW, inverse probability of treatment weighting; rwOS, real-world overall survival; rwPFS, real-world progression free survival; rwTTD, real-world time to treatment discontinuation; rwTTNT, real-world time to next treatment

Note on p-value: an alpha level of 0.05 was used to assess statistical significance as the three groups were assessed together rather than conducting a pairwise comparison.

Supplementary Table 6. Full breakdown of second line of therapy^a

	Alectinib	Brigatinib	Lorlatinib
	N = 391	N = 32	N = 58
no additional lines	282 (72.1)	24 (75.0)	44 (75.9)
index TKI	15 (3.8)	2 (6.3)	3 (5.2)
index TKI+chemotherapy	5 (1.3)	-	2 (3.4)
index TKI+chemotherapy+immunotherapy	-	-	1 (1.7)
index TKI+chemotherapy+targeted therapy	1 (0.3)	-	-
index TKI+other TKI	1 (0.3)	1 (3.1)	-
index+targeted therapy	6 (1.5)	-	1 (1.7)
alectinib		-	1 (1.7)
alectinib+lorlatinib		-	1 (1.7)
brigatinib	14 (3.6)		1 (1.7)
brigatinib+chemotherapy	1 (0.3)		-
chemotherapy	8 (2.0)	1 (3.1)	-
chemotherapy+immunotherapy	7 (1.8)	-	1 (1.7)
chemotherapy+targeted therapy	-	-	1 (1.7)
immunotherapy	1 (0.3)	-	1 (1.7)
immunotherapy+chemotherapy+targeted therapy	1 (0.3)	-	-
lorlatinib	36 (9.2)	3 (9.4)	
lorlatinib+chemotherapy	6 (1.5)	-	
lorlatinib+chemotherapy+targeted therapy	2 (0.5)	1 (3.1)	
lorlatinib+immunotherapy	1 (0.3)	-	
lorlatinib+targeted therapy	2 (0.5)	-	
targeted therapy	2 (0.5)	-	1 (1.7)

N, number; TKI, tyrosine kinase inhibitor

^aAll results presented as n (%)

Supplementary Table 7. Baseline characteristics of the weighted population^a

	Alectinib	Brigatinib	Lorlatinib	P-value		
	N = 390.2	N = 31.8	N = 53.2	A vs B	B vs L	A vs L
Age, years Index, mean (SD)	58.8 (12.5)	58.9 (13.7)	60.5 (11.9)	0.981	0.575	0.367
Sex, n (%)				0.923	0.970	0.948
Female	216 (55.2)	17 (54.4)	29 (54.8)			
Male	175 (44.8)	15 (45.6)	24 (45.2)			
Race, n (%)				0.602	0.376	0.852
White	201 (51.6)	16 (50.4)	30 (56.3)			
Black	24 (6.1)	2 (7.4)	3 (4.8)			
Asian	42 (10.7)	3 (9.6)	6 (12.0)			
Other	63 (16.1)	3 (8.2)	9 (16.9)			
Unknown/Not Reported	61 (15.5)	8 (24.4)	5 (10.0)			
Geographic Region, n (%)				0.716	0.636	0.041
North East	83 (21.3)	4 (13.4)	8 (15.7)			
Midwest	83 (21.3)	7 (22.0)	6 (12.0)			
South	112 (28.8)	9 (29.2)	21 (40.1)			
West	112 (28.6)	11 (35.4)	16 (30.9)			
Other/Unknown	0 (0.0)	0 (0.0)	1 (1.3)			
Payer, n (%)				0.320	0.540	0.756
Commercial	222 (56.8)	18 (55.3)	33 (61.8)			
Medicare Advantage	98 (25.2)	12 (36.8)	13 (25.2)			
Medicare Fee-for-service	12 (3.0)	0 (0.0)	2 (3.3)			
Medicaid	59 (15.0)	3 (8.0)	5 (9.6)			
Year of Index, n (%)				0.955	0.901	0.894
2020	66 (16.8)	5 (15.7)	6 (11.8)			
2021	101 (25.9)	9 (29.7)	14 (27.0)			
2022	117 (30.1)	10 (31.8)	16 (29.7)			
2023	80 (20.4)	6 (19.1)	13 (23.8)			
2024	26 (6.8)	1 (3.7)	4 (7.8)			
Days from first metastasis diagnosis to index date, median (IQR)	42 (24, 151)	59 (31, 384)	104 (36, 378)	0.202	0.545	0.0138
Duration of follow-up in days, median (IQR)	488 (232, 817)	471 (161, 887)	420 (240, 735)	0.951	0.862	0.654
Anti-cancer treatment between metastasis and index date, n (%)	107 (27.4)	6 (19.3)	12 (22.7)	0.318	0.707	0.468
NCI comorbidity index, mean (SD)	0.63 (0.65)	0.71 (0.53)	0.59 (0.68)	0.523	0.404	0.660
Baseline metastases						
Brain	155 (39.7)	13 (39.8)	22 (41.2)	0.995	0.896	0.835
Bone	184 (47.2)	15 (46.2)	21 (38.7)	0.921	0.492	0.243
Liver	80 (20.5)	4 (13.7)	3 (5.5)	0.353	0.196	0.009
Kidney	7 (1.8)	0 (0.0)	0 (0.0)	0.448	0.997	0.327

A, alectinib; B, brigatinib; L, lorlatinib; N, number; IQR, interquartile range; SD, standard deviation

Supplementary Table 8. Results from restricted mean survival time analyses of rwTTNT, rwTTD, rwPFS, and rwOS for weighted and unweighted populations

	Tau	Alectinib vs. Brigatinib		Lorlatinib vs. Brigatinib		Alectinib vs. Lorlatinib	
		Difference (95% CI)	p-value	Difference (95% CI)	p-value	Difference (95% CI)	p-value
Weighted							
rwTTNT	830	-81.6 (-160.4, 16.1)	0.096	-125.0 (-253.3, 23.1)	0.108	43.4 (-72.1, 155.9)	0.516
rwTTD	828	-29.3 (-158.1, 98.5)	0.618	-16.6 (-184.1, 150.7)	0.870	-12.7 (-139.9, 112.6)	0.826
rwPFS	636	-13.8 (-119.1, 114.6)	0.846	-60.1 (-189.3, 90.1)	0.450	46.3 (-48.7, 128.9)	0.320
rwOS	813	-48.3 (-72.1, -14.3)	0.012	-32.1 (-82.9, 13.0)	0.148	-16.2 (-55.6, 37.1)	0.482
Unweighted							
rwTTNT	830	-58.5 (-143.9, 30.9)	0.188	-83.6 (-194.2, 35.7)	0.190	25.1 (-70.2, 109.9)	0.606
rwTTD	828	5.1 (-117.3, 130.6)	0.930	-0.4 (-141.6, 154.4)	0.996	5.5 (-99.6, 108.9)	0.908
rwPFS	636	11.4 (-86.3, 104.4)	0.840	21.7 (-101.3, 153.6)	0.736	-10.2 (-95.1, 69.5)	0.850
rwOS	813	-43.4 (-72.2, -1.6)	0.048	-55.1 (-121.0, 10.4)	0.090	11.7 (-44.0, 75.5)	0.746

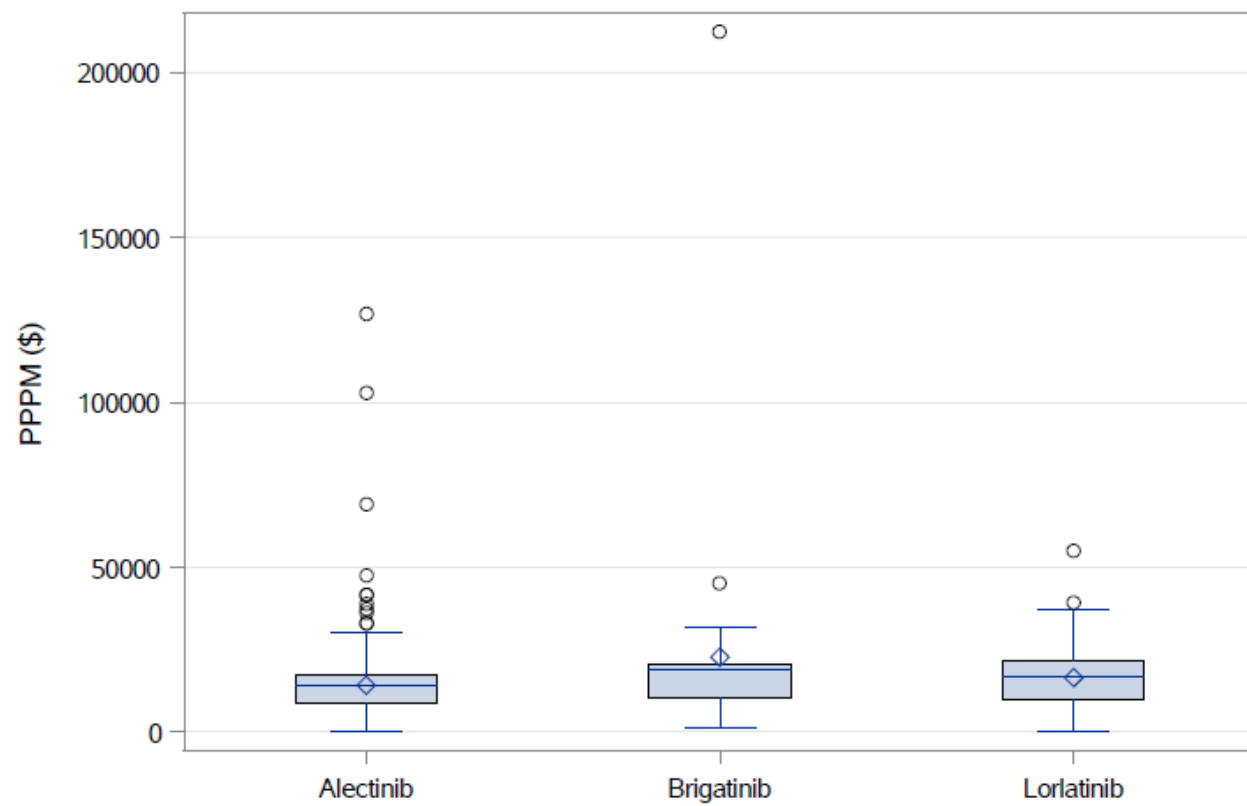
CI, confidence interval; rwOS, real-world overall survival; rwPFS, real-world progression free survival; rwTTD, real-world time to treatment discontinuation; rwTTNT, real-world time to next treatment

Supplementary Table 9. All-cause healthcare utilization and costs of the unweighted population

	Alectinib	Brigatinib	Lorlatinib	P-value ^a		
	N = 391	N = 32	N = 58	A vs B	B vs L	A vs L
HCRU, mean (SD)						
Total hospitalized days	3.2 (7.9)	1.7 (4.0)	2.8 (6.3)	0.292	0.346	0.765
Number of ED visits	0.8 (1.8)	0.8 (1.6)	0.9 (1.9)	0.983	0.730	0.579
Number of OP office visits	26.4 (26.0)	24.9 (29.3)	20.4 (19.8)	0.746	0.389	0.090
Number of laboratory visits	14.2 (12.5)	12.4 (12.8)	10.2 (13.7)	0.442	0.444	0.024
Number of radiology visits	8.7 (8.4)	7.1 (7.9)	7.6 (9.8)	0.288	0.803	0.351
Number of other OP services	22.5 (58.3)	17.8 (27.6)	26.8 (66.7)	0.654	0.473	0.612
Number of pharmacy claims	48.6 (55.1)	66.9 (90.4)	54.1 (61.4)	0.089	0.426	0.487
Total Healthcare Costs, PPPM, mean (SD)	\$20,598 (\$12,128)	\$27,838 (\$38,390)	\$24,522 (\$12,990)	0.012	0.550	0.023
Inpatient costs, PPPM	\$1,453 (\$4,673)	\$621 (\$2,123)	\$1,228 (\$3,031)	0.319	0.318	0.722
ED visit costs, PPPM	\$268 (\$787)	\$175 (\$481)	\$474 (\$1,340)	0.515	0.227	0.095
OP office visit costs, PPPM	\$449 (\$563)	\$378 (\$426)	\$376 (\$347)	0.487	0.981	0.339
Laboratory visit costs, PPPM	\$231 (\$442)	\$328 (\$676)	\$308 (\$850)	0.257	0.912	0.285
Radiology visit costs, PPPM	\$933 (\$1,348)	\$1,711 (\$4,236)	\$1,018 (\$2,094)	0.015	0.302	0.680
Other OP service costs, PPPM	\$1,255 (\$2,156)	\$600 (\$855)	\$1,991 (\$4,895)	0.089	0.115	0.050
Pharmacy costs, PPPM	\$16,008 (\$9,908)	\$24,025 (\$35,394)	\$19,125 (\$10,421)	0.001	0.328	0.027

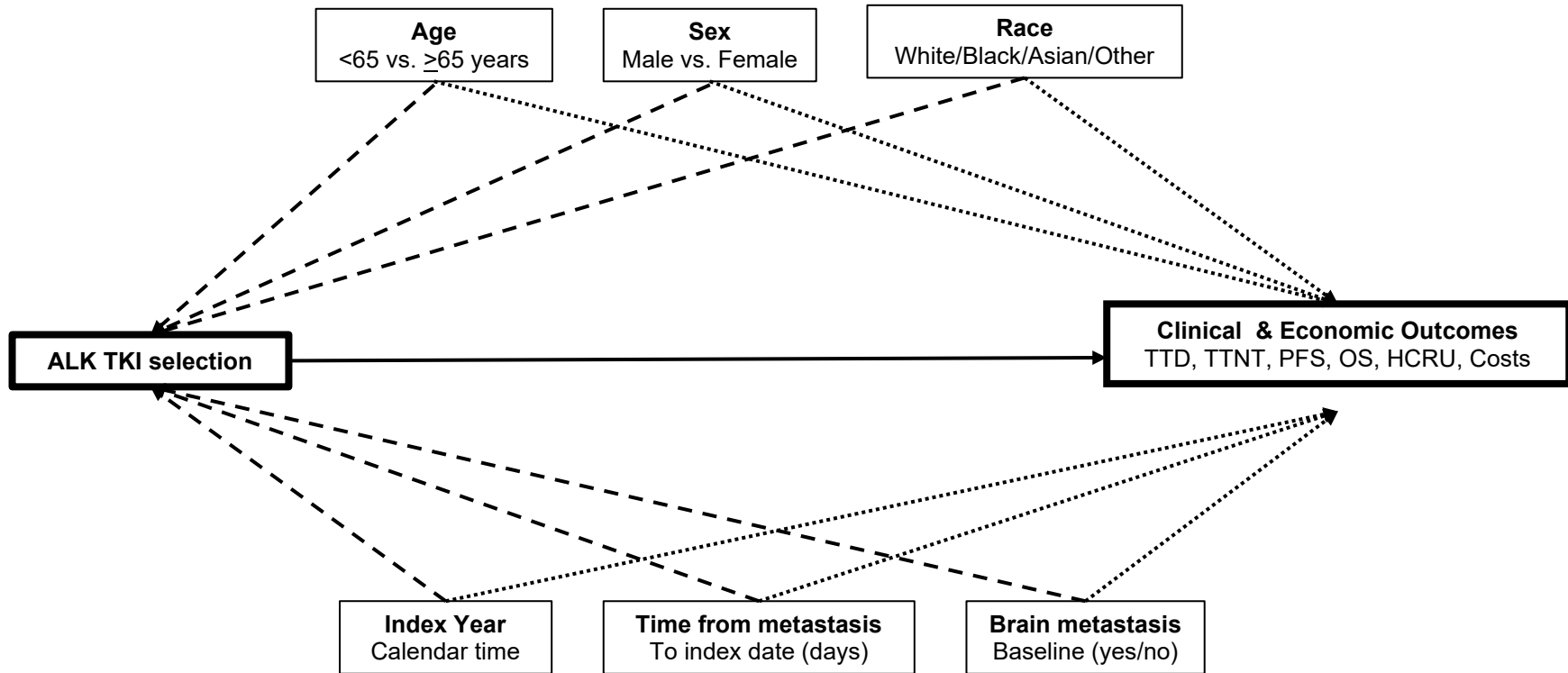
A, alectinib; B, brigatinib; ED, emergency department; HCRU, healthcare resource utilization; IQR, interquartile range; L, lorlatinib; OP, outpatient; PPPM, per-patient per-month; SD, standard deviation

Supplementary Figure 1. Box Plot of Monthly Pharmacy Costs Following Imputation



PPPM, per-patient per-month

Supplementary Figure 2. Directed acyclic graph illustrating the assumed causal relationships among covariates, treatment assignment, and outcomes in the inverse probability of treatment weighting model.



ALK+, anaplastic lymphoma kinase positive; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitors; TTNT, time to next treatment; TTD, time to discontinuation.

Supplementary Figure 3. Kaplan-Meier plots of treatment effectiveness outcomes for the unweighted population: A) real-world time to next treatment, B) real-world time to discontinuation, C) real-world progression free survival, and D) real-world overall survival

