

ALK Inhibitor Treatment Patterns and Outcomes in Real-World Patients with ALK-positive Non-Small Cell Lung
Cancer: A Retrospective Cohort Study

Michelle Wang¹, Shadera Slatter¹, Jesse Sussell², Chia-Wei Lin², Sarika Ogale², Debajyoti Datta¹, Atul J. Butte^{1,3},
Lyudmila Bazhenova⁴, Vivek A. Rudrapatna^{1,5}

1 Bakar Computational Health Sciences Institute, University of California San Francisco, San Francisco, California,
USA.

2 Evidence for Access, Genentech Inc., South San Francisco, California, USA.

3 Department of Pediatrics, University of California San Francisco, San Francisco, California, USA.

4 Moores Cancer Center, University of California San Diego, La Jolla, California, USA.

5 Division of Gastroenterology, Department of Medicine, University of California San Francisco, San Francisco,
California, USA.

Running header: Characterization of real-world use and outcomes of ALK TKI therapies.

Corresponding author:

Vivek Rudrapatna

Email: Vivek.Rudrapatna@ucsf.edu

Phone: 415-443-0150

Postal Address:

UCSF Valley Tower, Box 2933 Room 21E

490 Illinois Street, Floor 2

San Francisco, CA 94143

Supplementary Online Content

eTable 1. Definition, source, type, method for extraction or computation of all variables.

eFigure 1. The directed acyclic diagram of ALK TKI and outcomes.

eFigure 2. Adjusted survival probability estimates for alectinib and crizotinib and the forest plots of cox proportional hazard models for mAEFS, rwPFS, and OS in patients without prior systemic treatments.

eFigure 3. Adjusted survival probability estimates for alectinib and crizotinib and the forest plots of cox proportional hazard models for mAEFS, rwPFS, and OS in patients with baseline brain metastasis.

eTable 1

Variable category	Variable name	Definition	Type	Source	Extraction method
Computational	Gender	gender reported by patients themselves or providers	Binary	De-identified structured clinical data warehouse	Computational
	Race	race reported by patients themselves or providers	Nominal	De-identified structured clinical data warehouse	Computational
	Charlson-Comorbidity Index Score	comorbidity index scores calculated by presence of comorbidities using ICD10 codes	Ordinal	De-identified structured clinical data warehouse	Computational
	Distance to treatment center	distance between patient's location to UCSF medical treatment center using zip codes	Continuous	De-identified structured clinical data warehouse	Computational
	Areas of Deprivation Index (ADI)	"represents rankings of neighborhoods by socioeconomic disadvantage in a region It includes factors for the theoretical domains of income, education, employment, and housing quality" - Kind AJH, Buckingham W. Making Neighborhood Disadvantage Metrics Accessible: The Neighborhood Atlas. New England Journal of Medicine, 2018. 378: 2456-2458. DOI: 10.1056/NEJMp1802313. PMID: PMC6051533.		De-identified structured clinical data warehouse	Computational
Demographics	DOB (date of birth)	Date of subject birth	Date	UCSF electronic health record	Manual
	Sex	Subject sex at birth	Binary	UCSF electronic health record	Manual

	Insurance	Medical insurance assigned to subject in UCSF health record	Nominal	UCSF electronic health record	Manual
	Copay	Financial copay documented for initial ALKi	Continuous	UCSF electronic health record	Manual
	Smoking status	Current; former; never; unknown	Nominal	UCSF electronic health record	Manual
	ECOG Status	ECOG performance status within 3 months prior to ALKi initiation	Ordinal	UCSF electronic health record	Manual
	ECOG Date	Date associated with reported ECOG performance status	Date	UCSF electronic health record	Manual
	ALKi Rendering Physician	Oncologist physician providing care at the time of ALKi initiation	Nominal	UCSF electronic health record	Manual
	ALKi Rendering Physician NPI	NPI number associated with ALKi rendering physician	Nominal	UCSF electronic health record	Manual
Disease Characteristics	Date of NSCLC Diagnosis	Date associated with biopsy confirmed diagnosis of NSCLC	Date	UCSF electronic health record	Manual
	Stage of NSCLC	Cancer staging at the time of diagnosis of NSCLC	Ordinal	UCSF electronic health record	Manual
	TNM Staging at time of ALKi	Full clinical staging diagnosed at the time of ALKi initiation	Ordinal	UCSF electronic health record	Manual
	Date of ALK tissue collection	Date in which sample was collected for use in ALK testing	Date	UCSF electronic health record	Manual
	Date of ALK test reported	Date on the pathology/genetic report for ALK finding	Date	UCSF electronic health record	Manual
	Type of ALK test	FISH (fluorescence in situ hybridization); NGS (next generation sequencing)	Binary	UCSF electronic health record	Manual

	Sample for ALK test	Sample collected for ALK testing - tissue biopsy; blood; fluid	Nominal	UCSF electronic health record	Manual
	ALK Fusion Partner	Fusion partner reported on ALK testing	Nominal	UCSF electronic health record	Manual
	ALK Fusion Variant	Fusion variant reported on ALK testing	Nominal	UCSF electronic health record	Manual
	Co-Mutations	Co-mutations noted during FISH/NGS testing	Nominal	UCSF electronic health record	Manual
	Metastasis characterization at baseline	Metastases acquired by subject at the time of ALKi initiation	Nominal	UCSF electronic health record	Manual
	Metastasis characterization acquired during ALKi	New metastases acquired by subject while on ALKi therapy	Nominal	UCSF electronic health record	Manual
	If Brain - # of Mets	If brain mets are reported - the number of brain metastases at the time of diagnosis of brain metastatic disease	Discrete	UCSF electronic health record	Manual
	Histology	squamous cell carcinoma; adenocarcinoma; large cell carcinoma; other	Nominal	UCSF electronic health record	Manual
	De novo status	Yes/no - first occurrence of cancer diagnosis	Binary	UCSF electronic health record	Manual
Prior Treatments	Prior treatment	Yes/no - prior treatment to ALKi documented	Binary	UCSF electronic health record	Manual
	Prior treatment drug	Drug or treatment provided to subject prior to ALKi therapy - chemotherapy; immunotherapy; radiation; surgery	Nominal	UCSF electronic health record	Manual
	Prior treatment onset date	Date of initiation of prior treatment	Date	UCSF electronic health record	Manual

	Prior treatment end date	Date of cessation of prior treatment	Date	UCSF electronic health record	Manual
	Prior LOT	Line of therapy in which prior therapy was documented	Ordinal	UCSF electronic health record	Manual
	Prior dose	Dose of prior therapy prescribed	Discrete	UCSF electronic health record	Manual
	Prior frequency	Frequency of prior therapy prescribed	Ordinal	UCSF electronic health record	Manual
	If radiation - location of treatment	If targeted radiation is a prior therapy - location in which targeted radiation was completed	Nominal	UCSF electronic health record	Manual
	Past clinical trial	Yes/no - participation in previous clinical trial for NSCLC treatment	Binary	UCSF electronic health record	Manual
ALK inhibitor treatment	ALKi used	Initial ALKi prescribed and taken by subject for treatment of NSCLC. Crizotinib; Alectinib; Ceritinib; Brigatinib; Lorlatinib	Nominal	UCSF electronic health record	Manual
	Date of onset of ALKi Treatment	Date of initiation of ALKi therapy	Date	UCSF electronic health record	Manual
	Date of end of ALKi Treatment	Date of cessation of ALKi therapy	Date	UCSF electronic health record	Manual
	ALKi LOT	Line of therapy of initial ALKi in relation to prior therapies used for treatment of NSCLC	Ordinal	UCSF electronic health record	Manual
	ALKi dose	Originally prescribed dose at the initiation of ALKi therapy	Discrete	UCSF electronic health record	Manual
	ALKi frequency	Originally prescribed frequency at the initiation of ALKi therapy	Ordinal	UCSF electronic health record	Manual

Regimen adjustment	Dose adjustment	Yes/no - clinical notation of change in dosage and/or frequency of ALKi therapy	Binary	UCSF electronic health record	Manual
	Date of dose adjustment	Date in which ALKi therapy dosage and/or frequency was changed	Date	UCSF electronic health record	Manual
	Original dose	Current prescribed dose/frequency of ALKi at the time of dose adjustment	Ordinal	UCSF electronic health record	Manual
	New dose	New dose/frequency prescription of ALKi	Ordinal	UCSF electronic health record	Manual
	Reason for dose adjustment	Clinically documented reason for dose adjustment	Nominal	UCSF electronic health record	Manual
Regimen interruption	Regimen Interruption	Yes/no - clinical notation of interruption of ALKi therapy	Binary	UCSF electronic health record	Manual
	Date of Regimen Interruption	Date in which ALKi therapy was paused	Date	UCSF electronic health record	Manual
	Date of Regimen Restart	Date in which ALKi therapy was resumed	Date	UCSF electronic health record	Manual
	Reason for Interruption	Clinically documented reason for regimen interruption	Nominal	UCSF electronic health record	Manual
	If Adverse Event RI	If adverse event - clinical notation of adverse event that caused an interruption in ALKi therapy	Nominal	UCSF electronic health record	Manual
	If Disease Progression RI	If disease progression - type of imaging used to document disease progression that caused an interruption in ALKi therapy	Nominal	UCSF electronic health record	Manual
	If other Interruption	If other - clinical notation of other event that caused an interruption in ALKi therapy	Nominal	UCSF electronic health record	Manual
Ancillary treatment	Ancillary treatment	Yes/no - clinical notation of ancillary treatment	Binary	UCSF electronic	Manual

		prescribed while on initial ALKi therapy		health record	
	Ancillary treatment drug	Name of drug or treatment provided concurrently with ALKi therapy - chemotherapy; immunotherapy; radiation; surgery	Nominal	UCSF electronic health record	Manual
	Ancillary treatment onset date	Date of initiation of ancillary treatment	Date	UCSF electronic health record	Manual
	Ancillary treatment end date	Date of cessation of ancillary treatment	Date	UCSF electronic health record	Manual
	Ancillary dose	Originally prescribed dose at the initiation of ancillary treatment	Discrete	UCSF electronic health record	Manual
	Ancillary frequency	Originally prescribed frequency at the initiation of ancillary treatment	Ordinal	UCSF electronic health record	Manual
	If radiation - location of treatment	If targeted radiation is an ancillary treatment - location in which targeted radiation was completed	Nominal	UCSF electronic health record	Manual
Treatment discontinuation	Treatment discontinuation	Yes/no - clinical notation of ALKi treatment discontinuation	Binary	UCSF electronic health record	Manual
	Date of treatment discontinuation	Date of cessation of ALKi therapy	Date	UCSF electronic health record	Manual
	Reason for discontinuation	Clinically documented reason for treatment discontinuation	Nominal	UCSF electronic health record	Manual
	If Adverse Event TD	If adverse event - clinical notation of adverse event that caused discontinuation of ALKi therapy	Nominal	UCSF electronic health record	Manual
	If Disease Progression TD	If disease progression - type of imaging used to document disease progression that caused discontinuation of ALKi therapy	Nominal	UCSF electronic health record	Manual

	If other discontinuation	If other - clinical notation of other event that caused discontinuation of ALKi therapy	Nominal	UCSF electronic health record	Manual
Next treatment	Next treatment	Yes/no - clinical notation of next treatment following ALKi therapy	Binary	UCSF electronic health record	Manual
	Next treatment drug	Name of drug or treatment provided subsequent to ALKi therapy - chemotherapy; immunotherapy; radiation; surgery	Nominal	UCSF electronic health record	Manual
	Next treatment onset date	Date of initiation of next treatment	Date	UCSF electronic health record	Manual
Serious adverse events	AE - primary diagnosis	Discharge diagnoses for any hospitalization event while on ALKi therapy	Nominal	UCSF electronic health record	Manual
	Encounter	Type of encounter for SAE - hospitalization	Nominal	UCSF electronic health record	Manual
	Date	Date of admission to hospital for SAE	Date	UCSF electronic health record	Manual
Other	Last Date of Observation	If no ALKi treatment discontinuation record - Date of the last clinical record confirming ongoing treatment of ALKi therapy	Date	UCSF electronic health record	Manual
	Encounter type	If last date of observation - type of encounter confirming ongoing treatment of ALKi therapy	Nominal	UCSF electronic health record	Manual
	Seen as consult	Yes/no - receiving primary care of NSCLC outside of UCSF system at the time of ALKi initiation	Binary	UCSF electronic health record	Manual
	If Deceased Date	Date of death as documented in UCSF electronic health record	Date	UCSF electronic health record	Manual
Exclusion	Exclude	Yes/no - exclude based on inclusion/exclusion criteria as detailed in manuscript	Binary	UCSF electronic health record	Manual

	Exclude Reason	Reason for exclusion from study after manual review	Nominal	UCSF electronic health record	Manual
	If ALK Negative - mutation	If no ALK mutation - documentation of other significant mutation/s associated with NSCLC	Nominal	UCSF electronic health record	Manual
	If No NSCLC	If no NSCLC - diagnosis of other cancer as related to ALKi therapy	Nominal	UCSF electronic health record	Manual
	Excluded first ALKi given	If excluded - initial ALKi prescribed to the subject for treatment	Nominal	UCSF electronic health record	Manual

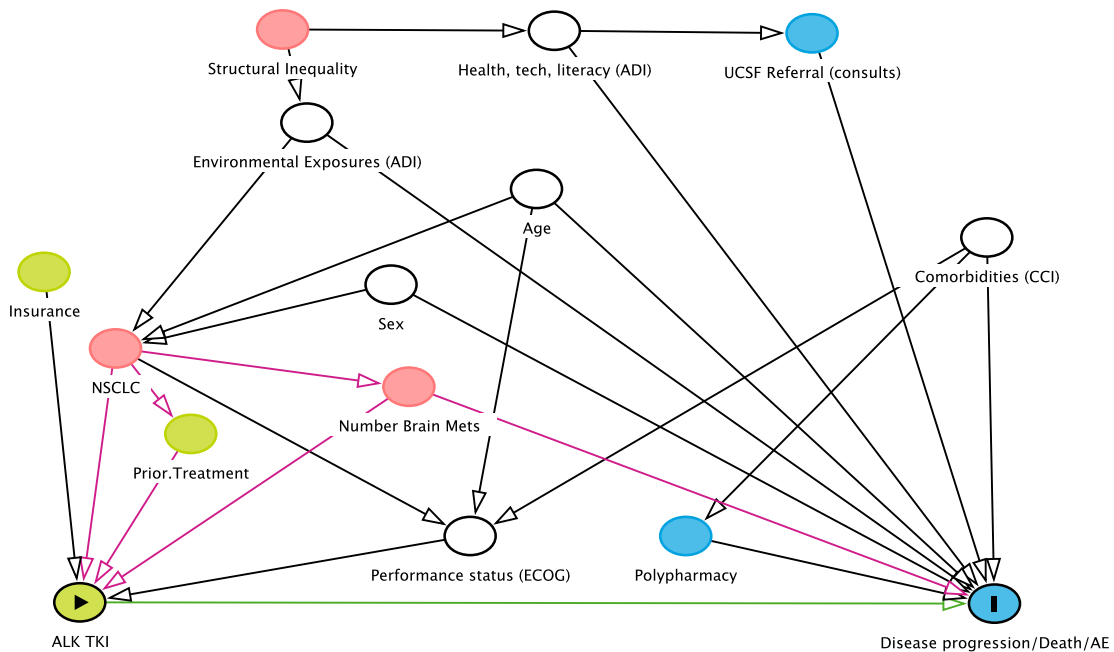


Figure 1 The directed acyclic diagram of ALK TKI and outcomes.

DAG codes:

dag {

"ALK TKI" [exposure,pos="-1.388,1.386"]

"Comorbidities (CCI)" [adjusted,pos="-0.165,-0.250"]

"Disease progression/Death/AE" [outcome,pos="-0.154,1.392"]

"Environmental Exposures (ADI)" [adjusted,pos="-1.082,-0.764"]

"Health, tech, literacy (ADI)" [adjusted,pos="-0.748,-1.176"]

"Number Brain Mets" [pos="-0.944,0.420"]

"Performance status (ECOG)" [adjusted,pos="-0.862,1.089"]

"Structural Inequality" [pos="-1.115,-1.182"]

"UCSF Referral (consults)" [pos="-0.401,-1.164"]

Age [adjusted,pos="-0.772,-0.467"]

Insurance [pos="-1.437,-0.095"]

NSCLC [pos="-1.340,0.248"]

Polypharmacy [pos="-0.571,1.089"]

Prior.Treatment [pos="-1.239,0.631"]

Sex [adjusted,pos="-0.968,-0.038"]

"ALK TKI" -> "Disease progression/Death/AE"

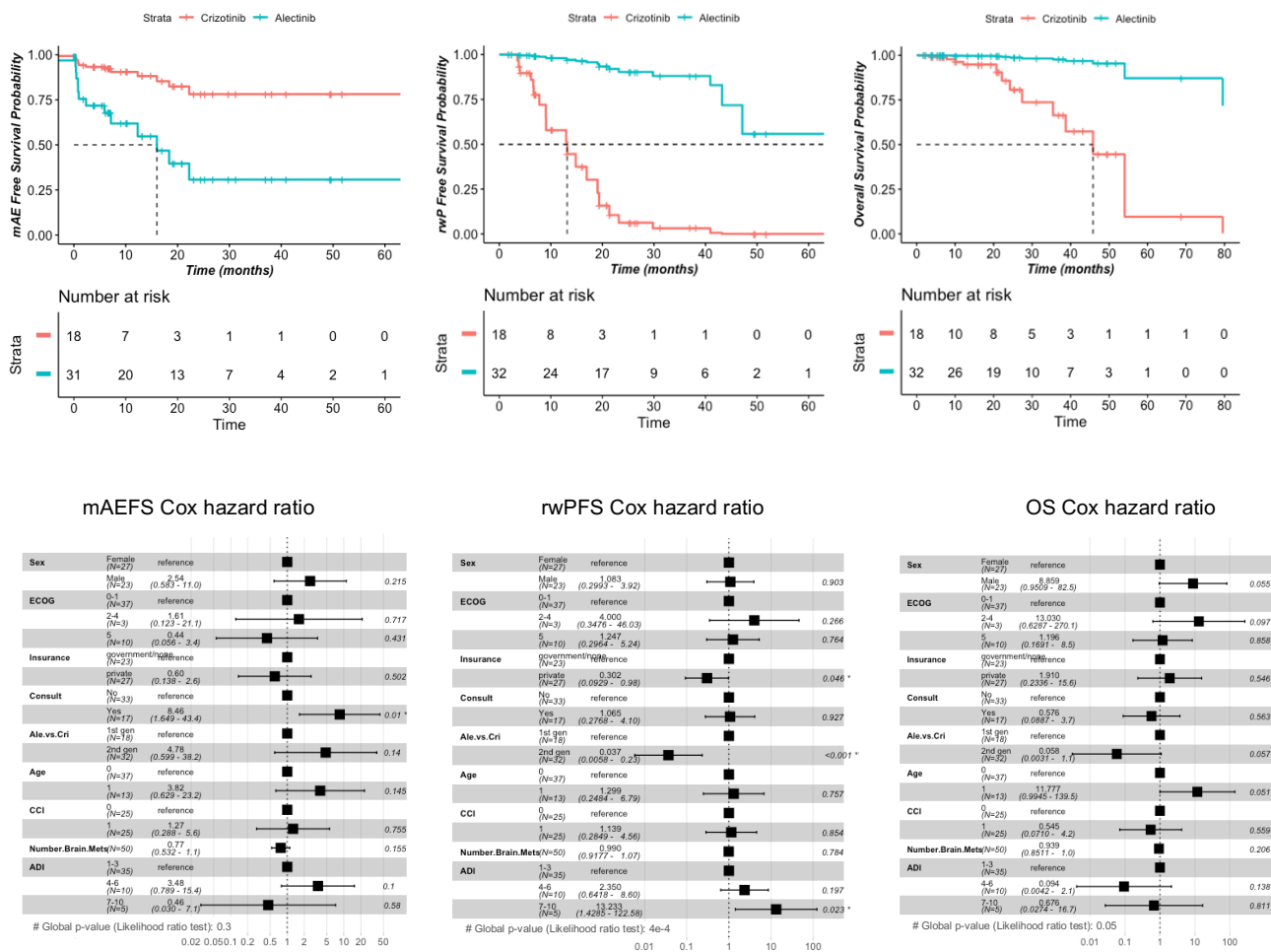
"Comorbidities (CCI)" -> "Disease progression/Death/AE"

"Comorbidities (CCI)" -> "Performance status (ECOG)"

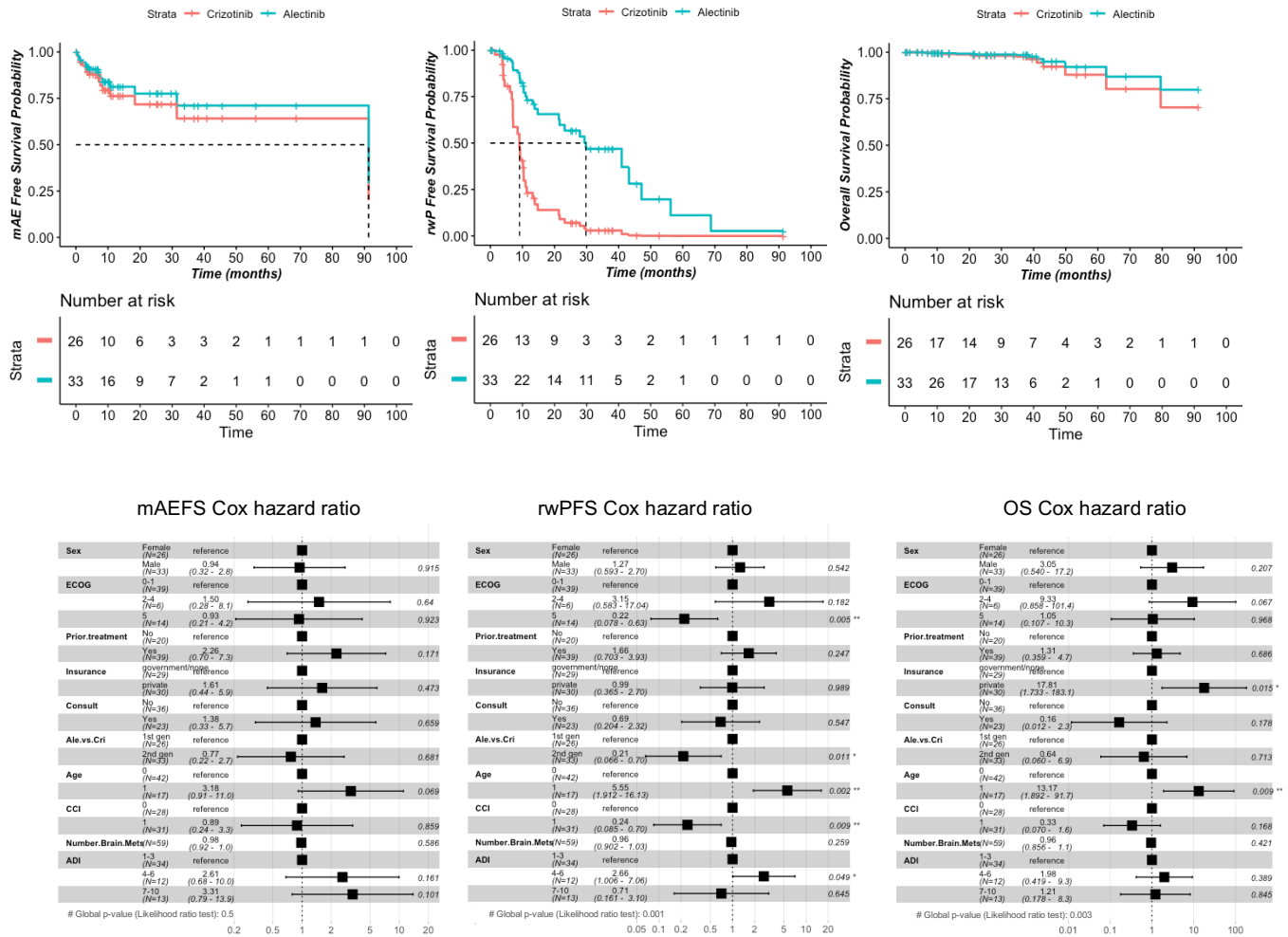
"Comorbidities (CCI)" -> Polypharmacy

"Environmental Exposures (ADI)" -> "Disease progression/Death/AE"

"Environmental Exposures (ADI)" -> NSCLC
"Health, tech, literacy (ADI)" -> "Disease progression/Death/AE"
"Health, tech, literacy (ADI)" -> "UCSF Referral (consults)"
"Number Brain Mets" -> "ALK TKI"
"Number Brain Mets" -> "Disease progression/Death/AE"
"Performance status (ECOG)" -> "ALK TKI"
"Structural Inequality" -> "Environmental Exposures (ADI)"
"Structural Inequality" -> "Health, tech, literacy (ADI)"
"UCSF Referral (consults)" -> "Disease progression/Death/AE"
Age -> "Disease progression/Death/AE"
Age -> "Performance status (ECOG)"
Age -> NSCLC
Insurance -> "ALK TKI"
NSCLC -> "ALK TKI"
NSCLC -> "Number Brain Mets"
NSCLC -> "Performance status (ECOG)"
NSCLC -> Prior.Treatment
Polypharmacy -> "Disease progression/Death/AE"
Prior.Treatment -> "ALK TKI"
Sex -> "Disease progression/Death/AE"
Sex -> NSCLC
}



eFigure 2 Adjusted survival probability estimates for alectinib and crizotinib and the forest plots of cox proportional hazard models for mAEFS, rwPFS, and OS in patients without prior systemic treatments.



eFigure 3 Adjusted survival probability estimates for alectinib and crizotinib and the forest plots of cox proportional hazard models for mAEFS, rwPFS, and OS in patients with baseline brain metastasis.