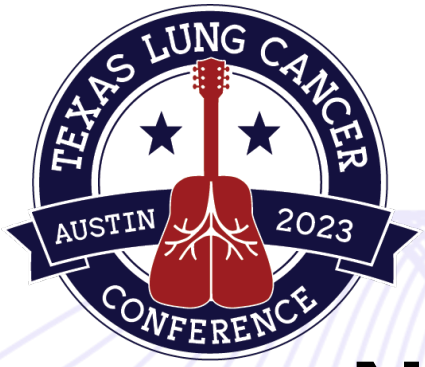

NSCLC WITH ALK AND ROS1 ALTERATIONS

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April 1, 2023

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IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
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Creating Aha! Moments In Healthcare

Objectives

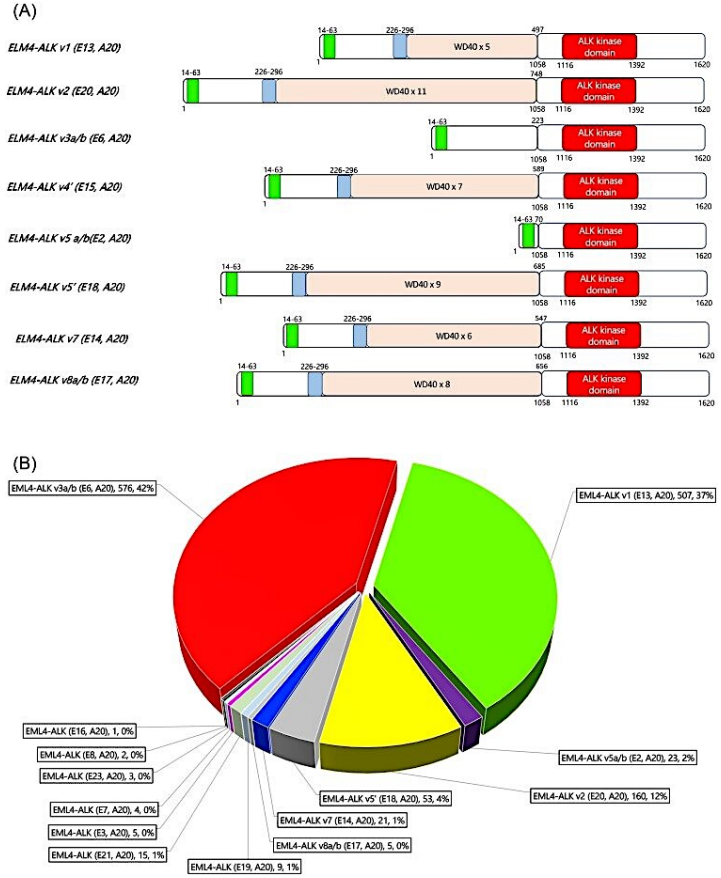
- ALK mutational overview
- Select ALK Pivotal Trials: Data / updates
- Selecting 1L tx in ALK
- ALK in Early stage NSCLC
- ROS1 Directed Therapy
- ROS1 Resistance

NSCLC

- Increasingly recognized as various molecular diseases
- Percentage of patients with targetable oncogene drivers now approaches 50%
- Therapeutic approaches completely depend on the discovery of relevant alterations
  - NGS for ALL patients with NSCLC, in community and academic settings is necessary and reasonable
  - Molecular alterations are both diagnostic and prognostic

ALK Alterations

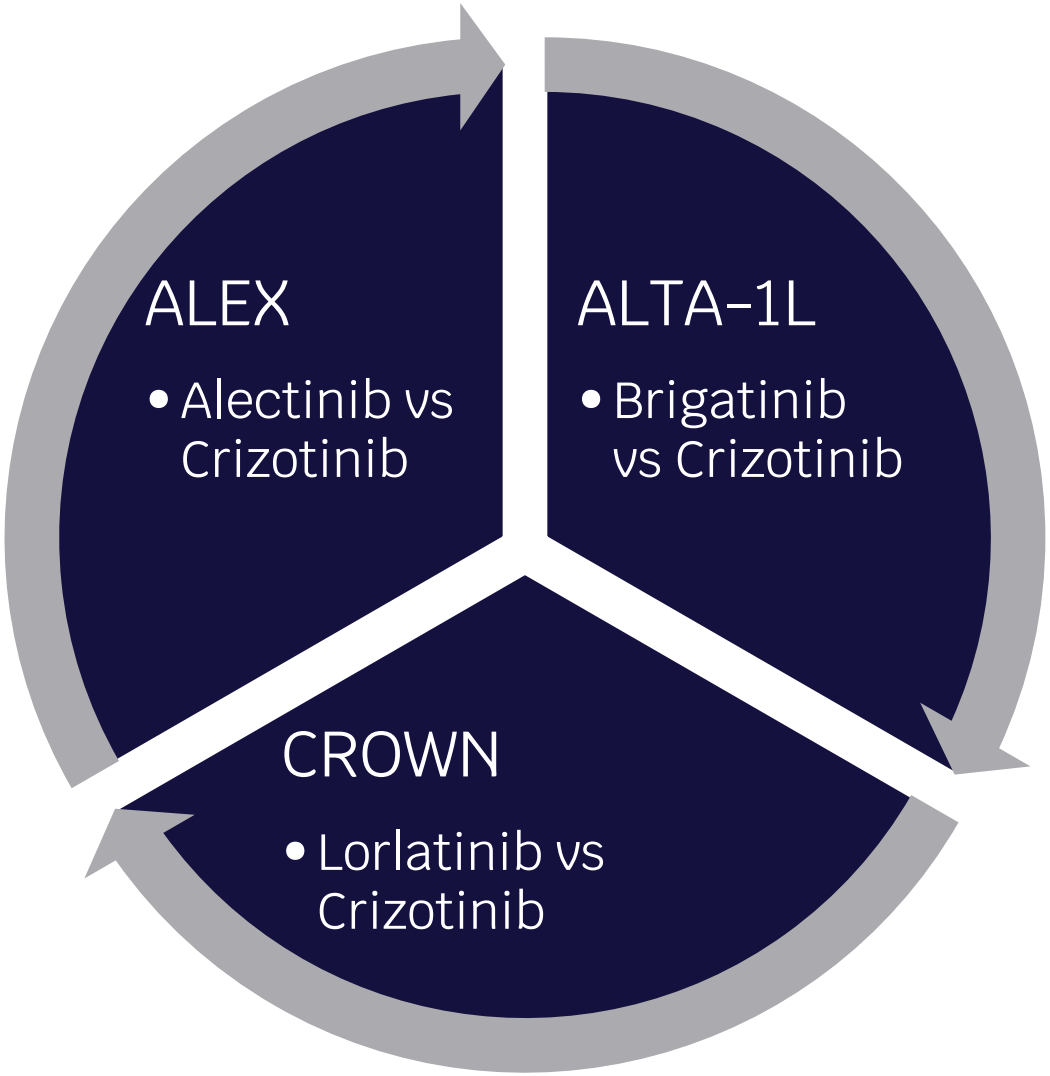
Anaplastic Lymphoma Kinase Alterations/Fusions



- ALK aberrantly expressed in multiple tumor types
- Rearrangements involving ALK gene loci on chromosome 2
- Most commonly EML4-ALK fusions occur
- Variants 1 and 3 are the most common co-occurring fusion partners (~80%)
- Differential treatment response and resistance patterns related to various arrangements

https://www.alkpositive.org/blog/2021/9/12/identifying-and-understanding-eml4-alk-variants-and-tp53-mutations-to-optimize-treatment-of-alk-fusion-positive-alk-nsclc

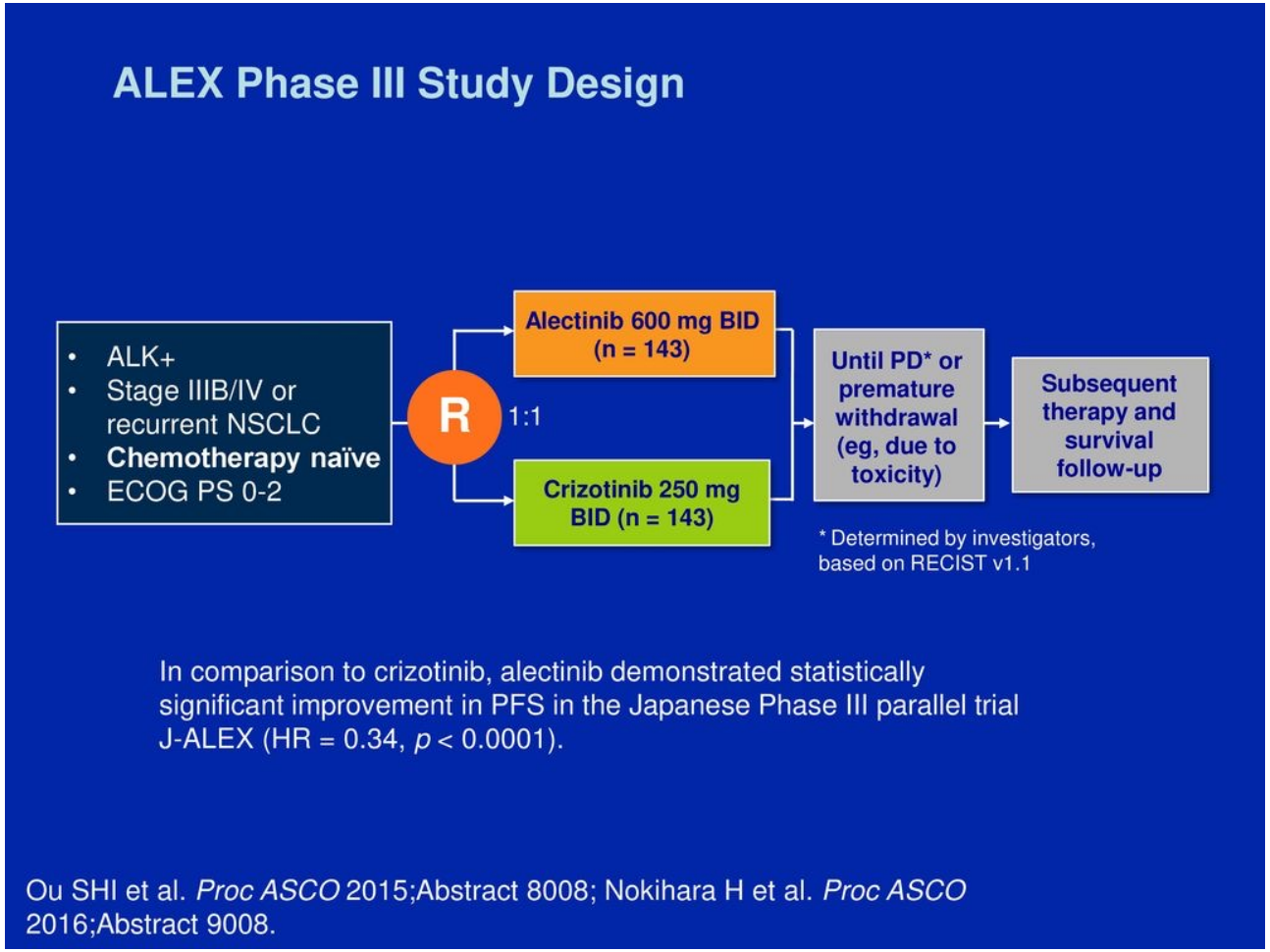
Pivotal ALK Trials



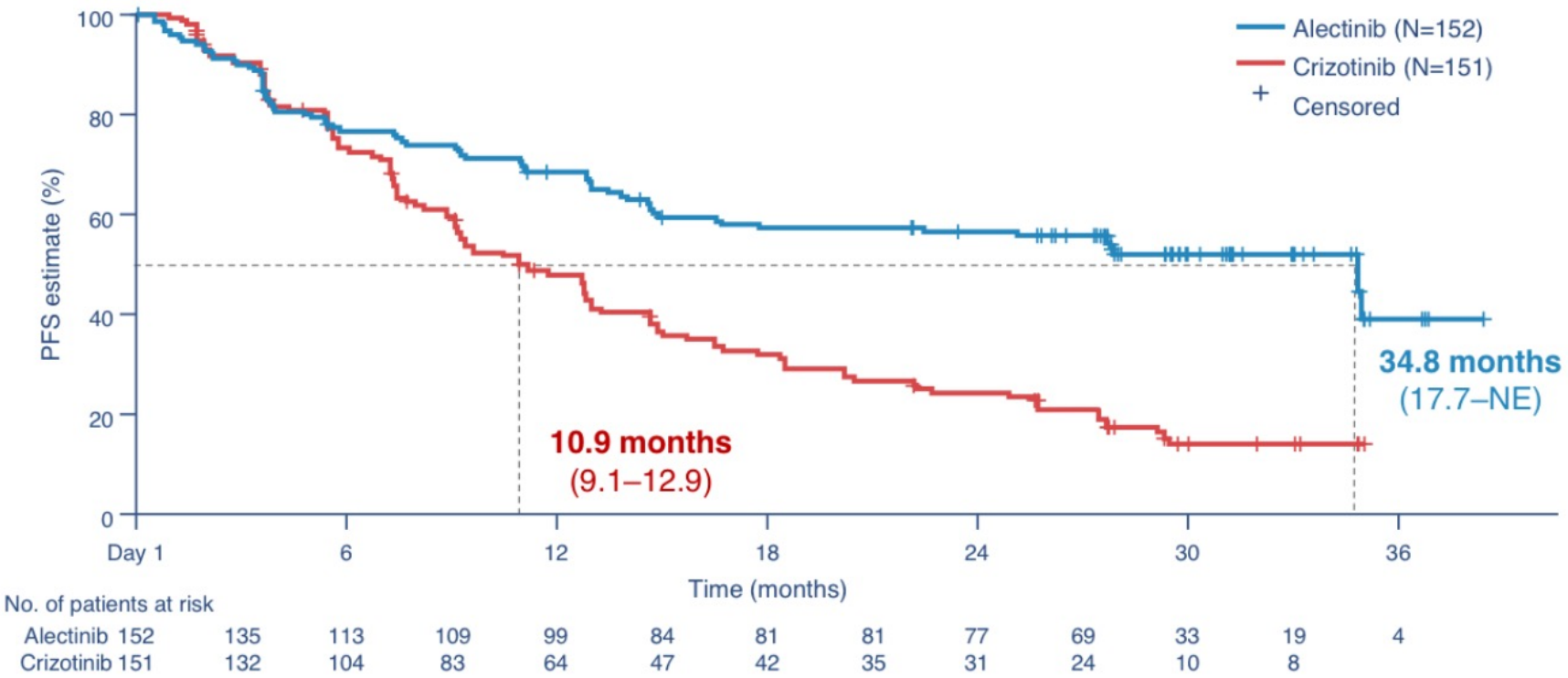
• Profile 1014	Crizotinib
• ASCEND-4	Ceritinib
• eXalt3	Ensartinib

Alectinib

- **2nd generation ALK Inhibitor**
- **Compared to Crizotinib in ALEX trial**
- **Statistically significant improvement in PFS**
- **CNS penetrant and active**
  - 12-mo incidence of CNS progression 9.4% vs 41.4% with crizotinib



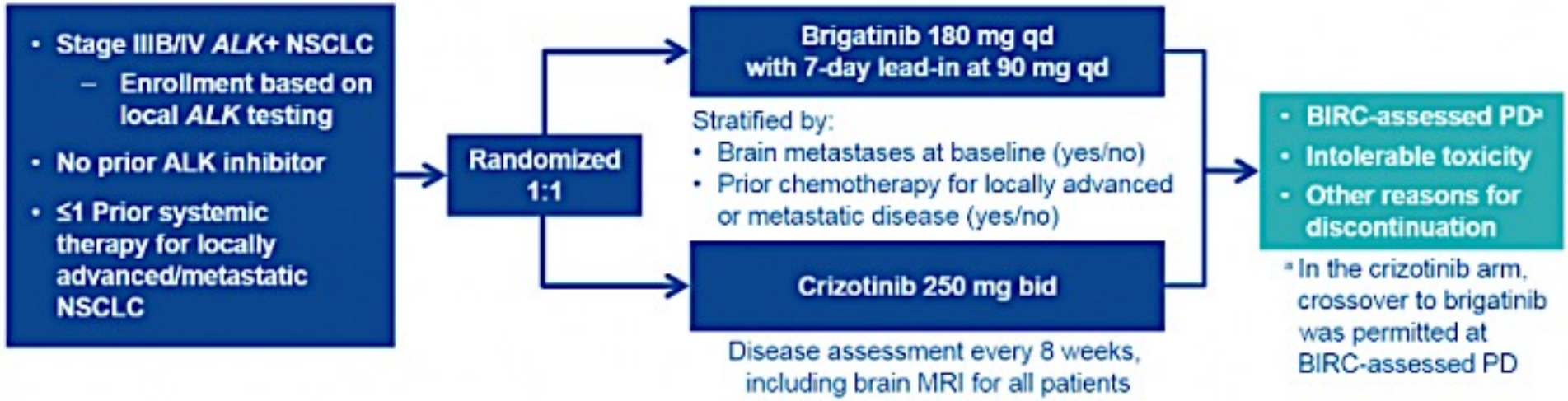
ALEX Trial PFS Analysis



Updated efficacy and safety data from the global phase III ALEX study of alectinib(AL) versus crizotinib(CZ) in untreated advanced ALK+ NSCLC Camige et. Al ASCO 2018

Brigatinib

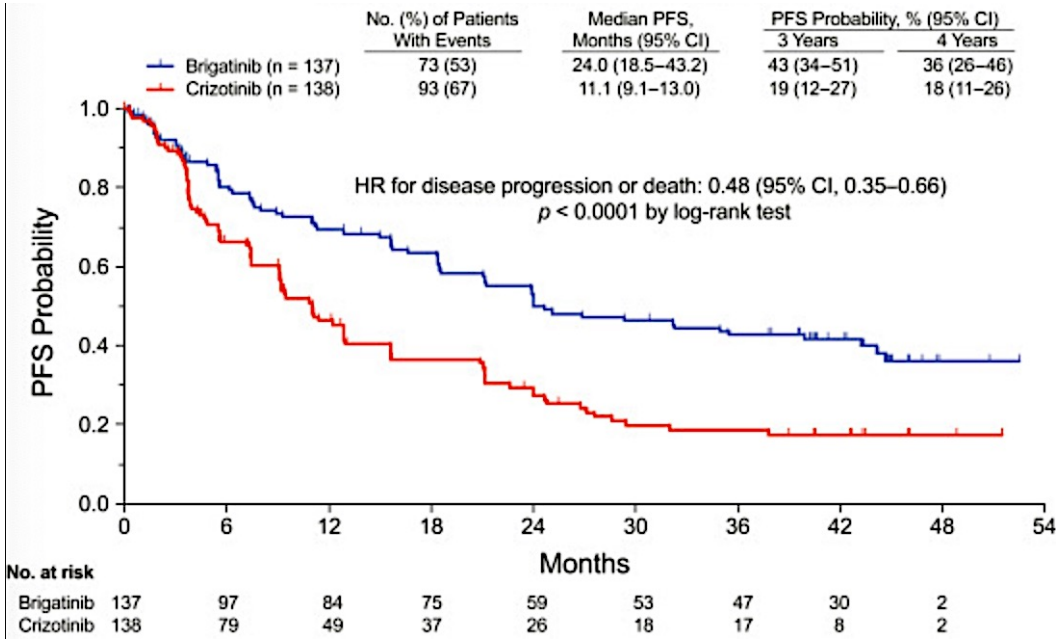
ALTA-1L Trial Design



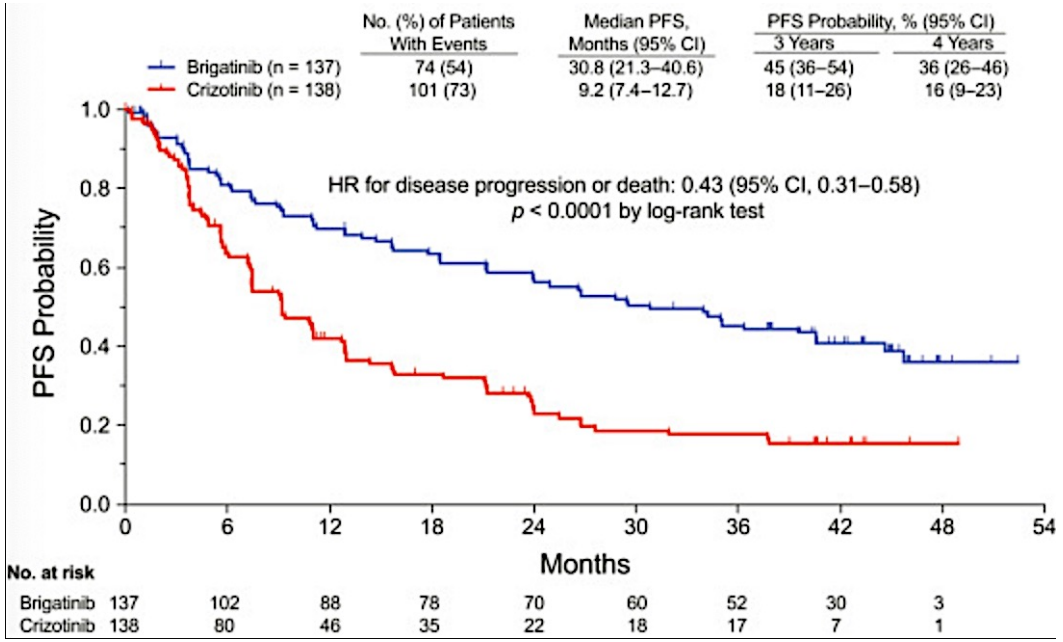
https://clin.larvol.com/trial/NCT02737501

ALTA-1L Final PFS Analysis

BIRC-Assess Systemic PFS: ITT Population

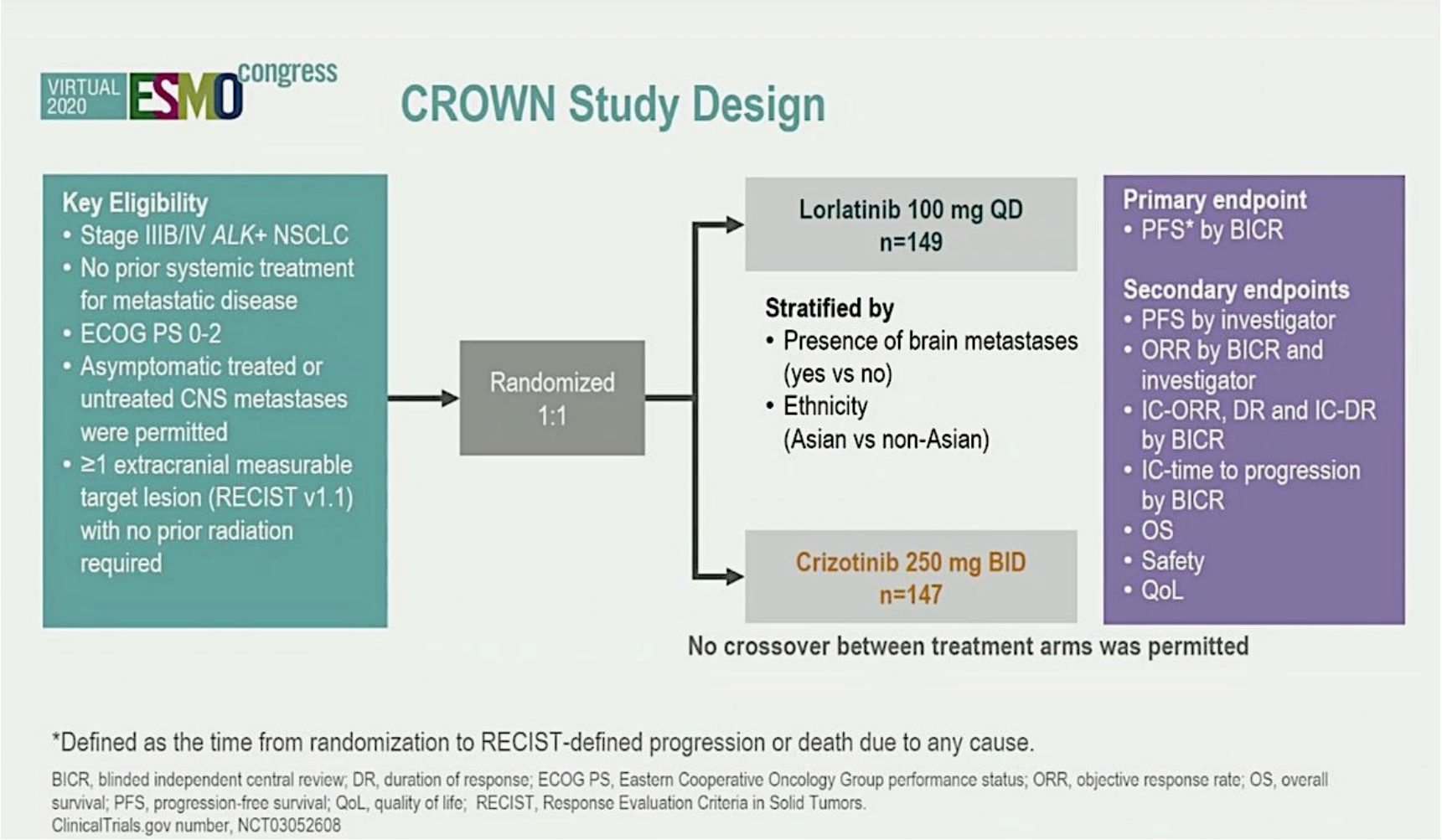


Investigator-Assessed Systemic PFS: ITT Population



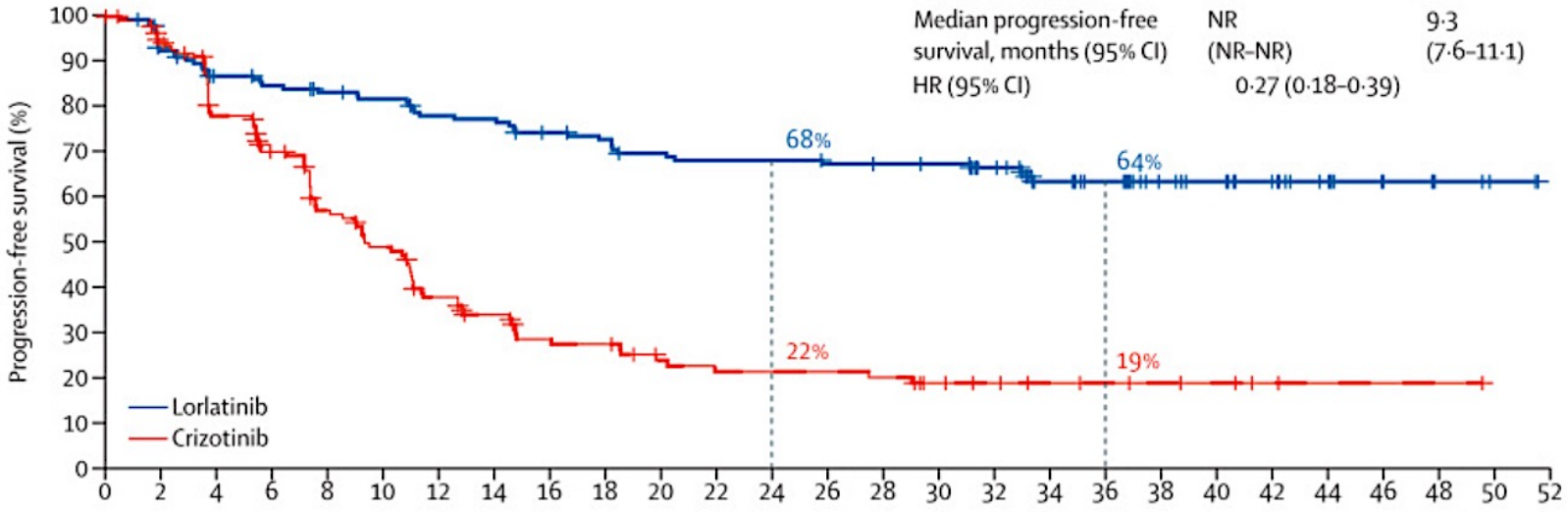
Journal of Thoracic Oncology Volume 16, Issue 12, December 2021, Pages 2091-2108

Lorlatinib


VIRTUAL 2020 ESMO congress
CROWN Study Design
Key Eligibility
• Stage IIIB/IV ALK+ NSCLC
• No prior systemic treatment for metastatic disease
• ECOG PS 0-2
• Asymptomatic treated or untreated CNS metastases were permitted
• ≥1 extracranial measurable target lesion (RECIST v1.1) with no prior radiation required
Randomized 1:1
Lorlatinib 100 mg QD n=149
Stratified by
• Presence of brain metastases (yes vs no)
• Ethnicity (Asian vs non-Asian)
Crizotinib 250 mg BID n=147
Primary endpoint
• PFS* by BICR
Secondary endpoints
• PFS by investigator
• ORR by BICR and investigator
• IC-ORR, DR and IC-DR by BICR
• IC-time to progression by BICR
• OS
• Safety
• QoL
No crossover between treatment arms was permitted
*Defined as the time from randomization to RECIST-defined progression or death due to any cause.
BICR, blinded independent central review; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.
ClinicalTrials.gov number, NCT03052608

CROWN Trial PFS: ITT Population

	Lorlatinib (n=149)	Crizotinib (n=147)
Events	49	92
Number censored	100	55
Median progression-free survival, months (95% CI)	NR (NR–NR)	9·3 (7·6–11·1)
HR (95% CI)	0·27 (0·18–0·39)	



Number at risk (number censored)

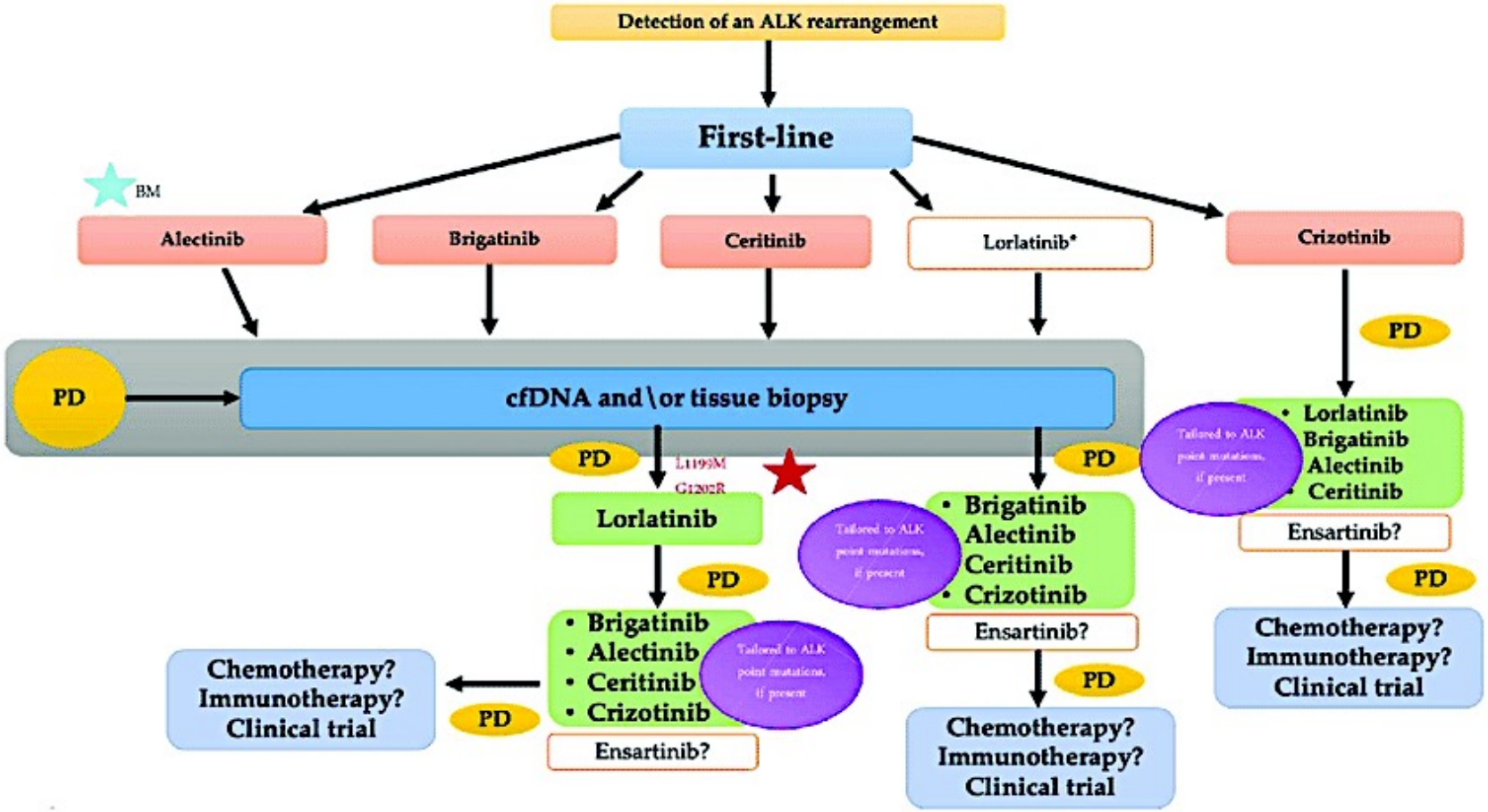
Lorlatinib	149	133	122	118	114	111	105	104	98	95	90	88	88	86	85	83	72	55	50	34	31	23	15	7	4	2	0
	(0)	(5)	(8)	(9)	(11)	(12)	(13)	(13)	(15)	(16)	(17)	(17)	(17)	(18)	(19)	(21)	(31)	(45)	(50)	(66)	(69)	(77)	(85)	(93)	(96)	(98)	(100)
Crizotinib	147	126	100	85	64	54	40	33	26	25	19	17	17	17	16	11	9	7	6	5	4	2	1	1	1	0	0
	(0)	(13)	(18)	(23)	(29)	(30)	(32)	(35)	(37)	(37)	(40)	(40)	(40)	(40)	(40)	(44)	(46)	(48)	(49)	(50)	(51)	(53)	(54)	(54)	(54)	(55)	..

The Lancet: Updated analysis of data from the phase 3, randomized, open-label CROWN study Published: December 16, 2022

	ALEX	ALTA-1	CROWN
Comparative Agents	Alectinib vs Crizotinib	Brigatinib vs Crizotinib	Lorlatinib vs Crizotinib
Primary EP	PFS-BIRC	PFS-BIRC	PFS-BIRC
ORR	82.9% vs 75.5%	71% vs 60%	76% vs 58%
Median OS	NR vs 57.4 mos	NR both groups	NR both groups
Median PFS	34.8 mos vs 10.9 mos	24 mos vs 11 mos	NR vs 9.3 mos
Hazard Ratio	0.43	0.49	0.28
Toxicities of Interest	Anemia Myalgia	Hypertension Elevated CK	Mood and Cognitive effects Peripheral neuropathy Weight gain

Peters et al., NEJM, 2017; Shaw et al., NEJM, 2020; Camage et al., NEJM, 2018; Solomon et al., JCO 2018.

Selection/Sequencing Considerations



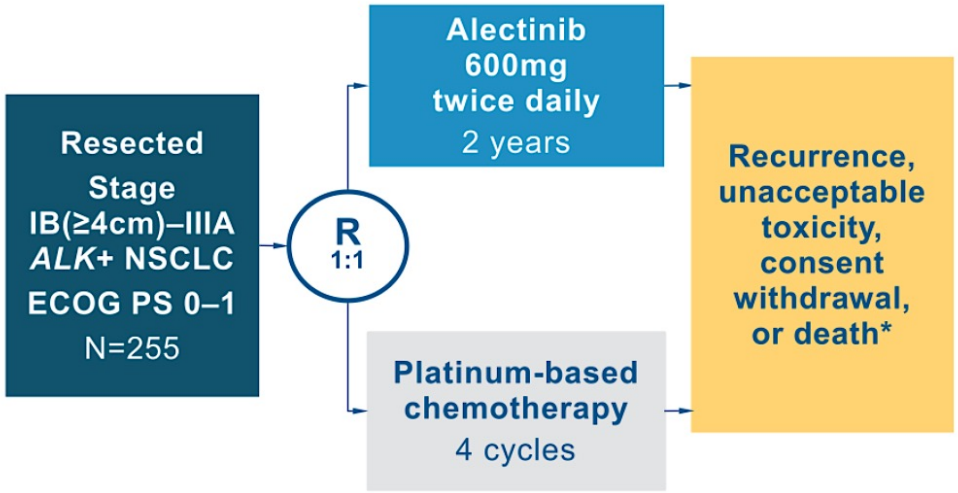
Gristina, Valerio & La Mantia, Maria & Iacono, Federica & Galvano, Antonio & Russo, Antonio & Bazan, Viviana. (2020). The Emerging Therapeutic Landscape of ALK Inhibitors in Non-Small Cell Lung Cancer. Pharmaceuticals. 13. 474. 10.3390/ph13120474.

ALK-Inhibition in Early Stage ALK Rearranged NSCLC

ALINA

- Randomized open label Phase III
- Evaluating efficacy and safety of adjuvant alectinib vs chemotherapy

Figure 1. ALINA study design



- **Primary endpoint: disease-free survival (DFS)**

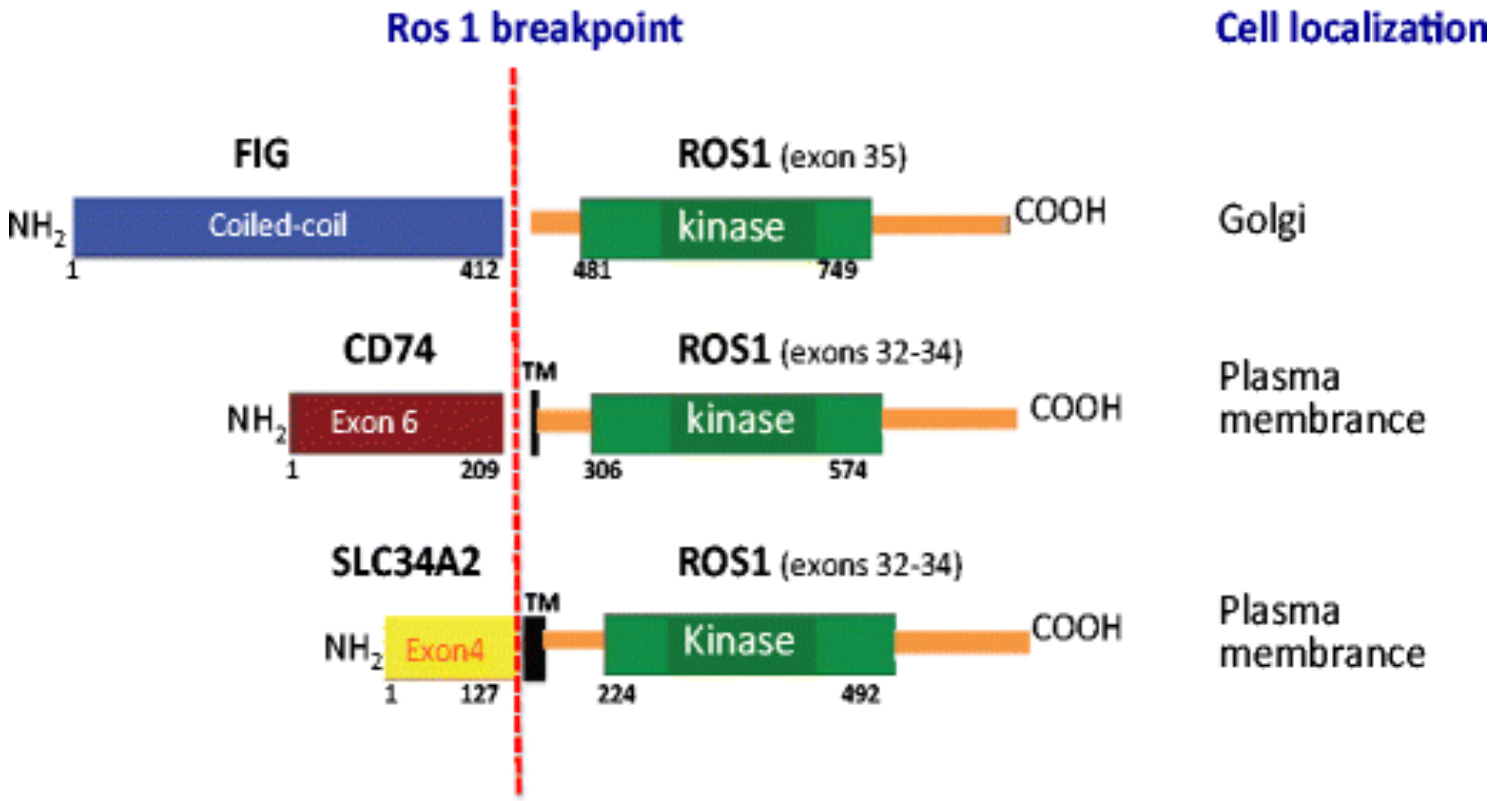
*Further treatment at investigator's decision and survival follow-up
ECOG PS, Eastern Cooperative Oncology Group performance status

ALINA: A PHASE III STUDY OF ALECTINIB VERSUS CHEMOTHERAPY AS ADJUVANT THERAPY IN PATIENTS WITH STAGE IB–IIIA ANAPLASTIC LYMPHOMA KINASE-POSITIVE (ALK+) NON-SMALL-CELL LUNG CANCER (NSCLC) ASCO-2019

ROS1 In NSCLC

Crizotinib
Entrectinib
Resistance
Next Generation ROS1 Inhibitors

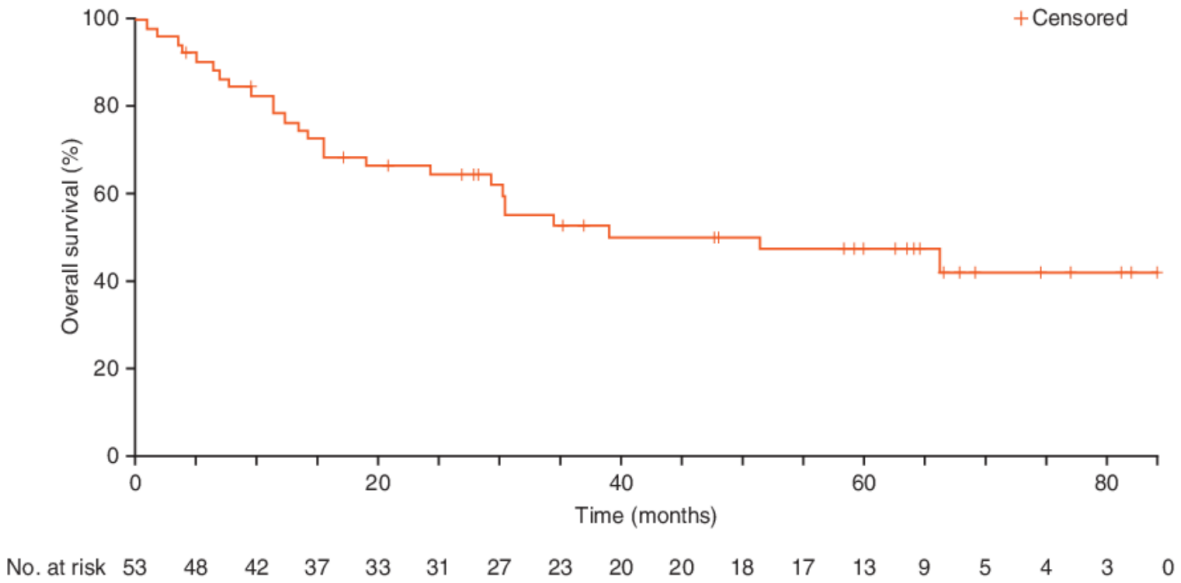
Most frequent ROS1 fusion proteins described in lung adenocarcinoma



Crizotinib in ROS1 NSCLC

PROFILE 1001

- Initially developed in MET and ALK fusion + NSCLC
- Phase I Profile 1001 expanded to include ROS1 + NSCLC
- N = 50 with ORR 72 % (95% CI 58-84)
- 86% of patients having had prior treatment
- Median PFS 19.2 months (95% CI 14.4 to NR)
- Median OS 51.4 months (62.6 mos follow-up)
- FDA approved in 2016 for ROS1 + NSCLC

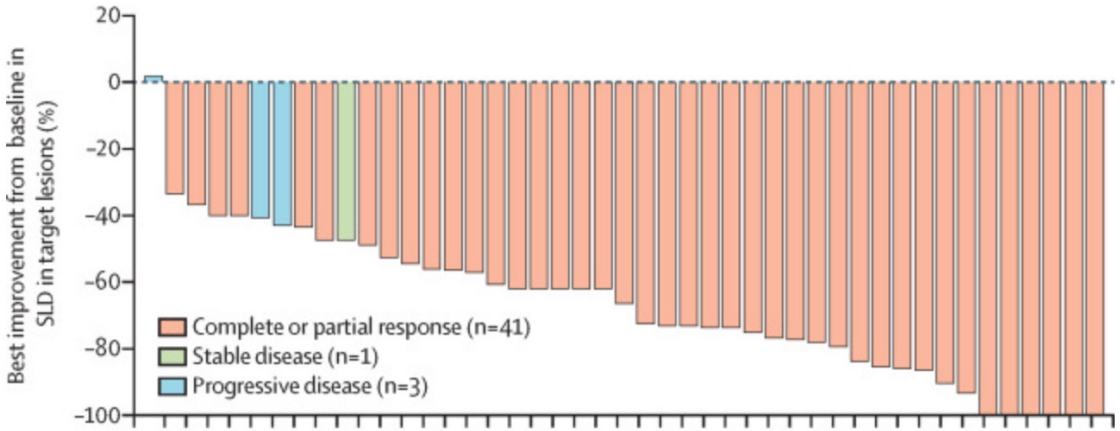


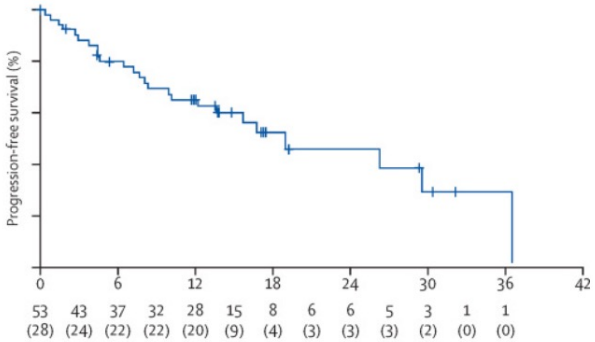
Shaw Crizotinib, Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001}, Alice T. Shaw and Gregory Riely and Y-J. Bang and D. W. Kim and D. Ross Camidge and Benjamin J. Solomon and Marileila Varella-Garcia and A. John Iafrate and Geoffrey I. Shapiro and Tiziana Usari and S. C. Wang and Keith D. Wilner and J. W. Clark and Sai-Hong Ignatius Annals of Oncology, 2019, volume={30}, pages 1121-1126

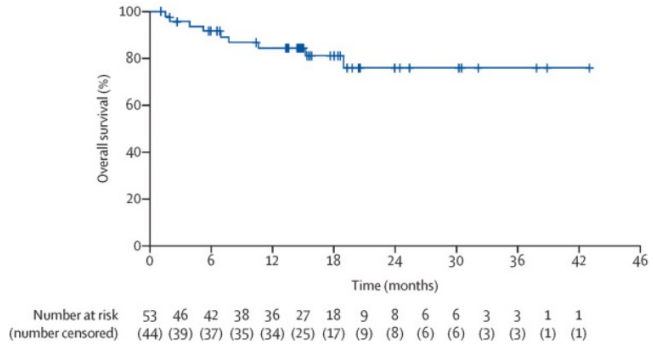
Entrectinib in ROS-1+ NSCLC

Integrated Data from ALKA, STARTRK-1/2

Endpoint	N = 53 patients
ORR	77%
mPFS	19 mo
mDOR	24.6 mo
Intracranial ORR	55%
mPFS in pts with brain mets	13 mos







Doebele R, et al. WCLC 2018 Abstract OA02.01.

Addressing Resistance in ROS1 + NSCLC

Determine Pattern of Progression

- **Oligoprogression-**
  - local therapy (RT, Ablation, resection)
- **CNS-Only**
  - Next Gen ROS1 inh.-
  - lorlatinib, repotrectinib, taletrectinib or entrectinib if prior crizotinib
- **Systemic Progression-**
  - On target- Next Gen ROS1 inhibitors
    - Ex G2032R tx'ed with Repo, Tale or NVL-520
  - Off target- Next Gen Ros1 Inhibitors, Chemo, Clinical trials or TKI combinations

ROS1 Inhibitors- Pharmacodynamic and Efficacy Profile

	Crizotinib	Ceritinib	Lorlatinib	Brigatinib	Cabozantinib	Foretinib	Entrectinib	AZD3463	Repotrectinib	Ensartinib
Cthrough (ng/mL)	237 to 800	1400		552	1080	46 to 900				
Cthrough (nM)	530 to 913					70	1330		425	
CSF/plasma conc.	0.001 to 0.003						0.4		0.04	
WT CD74-ROS	2 to 44	11 to 230	0.05 to 1	2.7 to 30	0.5 to 9	1.8 to 14	5.3 to 10	10	0.2	39
WT SLC34A2-ROS1	21	506	1.15			19				
WT FIG-ROS	41 to 60	304 to 488	0.2			6				
E1935G	350					6.6				
L1947R	1420					17.9				
L1951R	8.8 to 97	76.4 to 611		611	0.18 to 20.7					
G1971E	605					8.7				
E1974K	23	42.3		10.3	6.8	6.2		30.9		
V1979A	b	b								
V1979M	b									
1981 Tins[c]	d	d	d							
L1982F	4.7 to 6.9	23 to 27			0.08 to 2.94	15.3				
S1986 Y/F[a]	116 to 125	73 to 99	1 to 1.6							
E1990G	4.0	22.1			0.34					
F1994L	3.3	19.4			0.01					
M2001T[c]	d	d	d							
K2003I	1.4 to 1.5	4.5 to 11.7			0.28 to 0.32					
F2004C	40.5	68.7		20.2	56.8	23.5		19.9		
E2020K	41.1	97.8		24.9	10.5	9.7		53.2		
F2024 C/V[c]	d	d	d							
L2026Ma	22.4 to 259	4.6 to 90	1.1 to 2	3.5 to 200	0.92 to 11	3.2 to 8.6	3500	1800		
L2028-[c]										
G2032Ra	254 to 2700	276 to 2200	160 to 508	170 to 1172	1.4 to 26	39.7 to 90	1813 to 2200		8.4	372
D2033Na	140 to 200	306 to 535	0.38 to 3.3	69.1 to 128	0.2 to 0.65	2.2	169		1.3	402
T2036-[c]										
C2060G	690					13.6				
F2075 V/C	17 to 23	68.7 to 92		9.1 to 14.1	4.9 to 31.4	9.7 to 16		6.2, 41.6		
V2089M	15.6	42.8		6.7	7.5	2.9		16.1		
V2098I	10.9 to 901	44.4		9.0	1.7	2.5 to 9.9		12.5		
G2101Aa	27.1	0.06	d			0.004				
D2113 N/G	25.4 to 29.6	118 to 163		24	15.3 to 41.2	8.5 to 25.4		40 to 42.5		
M2134I	14.2	55.7		11.1	4.3	5.4		15.2		
L2155S	405	185				534				
L2223S	1.13	11.2			0.07					
L2223X		b								

https://www.clinical-lung-cancer.com/article/S1525-7304%2819%2930149-4/pdf

Summary

- **Many options available for targeting ALK in 1st line ALK+ NSCLC**
  - Initial NGS critical to confirm presence of oncogene
  - Consider disease burden, co-morbidities, patient preference when selecting agent
  - Repeat sequencing at progression essential for selecting next therapy
    - On vs off target mechanism of resistance to influence tx
    - Clinical trial availability for certain resistance mechanisms
- **ROS1 fusion positive NSCLC**
  - Responds well to initial TKI therapy
  - Resistance inevitable with on and off target resistance patterns, as well as infrequent histologic transformation
  - Repeat biopsy and sequencing is best practice for patients who progress
  - Remember clinical trials for these patients

Thank you!