IASLC
2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Best of WCLC 2023: ALK, ROS1 and BRAF Positive Lung Cancers

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ALK

2007	2012	2017	2020	2020-
Discovery of EML4-ALK translocation	Crizotinib (PROFILE-1014)	Alectinib (ALEX)	Brigatinib (ALTA-1L)	Ongoing Lorlatinib (CROWN)

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A Randomized, Phase Ⅲ Study of Iruplinalkib (WX-0593) vs Crizotinib in ALK TKI-Naïve, Locally Advanced or Metastatic *ALK*-Positive Non-Small Cell Lung Cancer (INSPIRE)

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INSPIRE: Phase Ⅲ, Open-Label, Randomized, Multicenter Study

Key Eligibility Criteria

- Stage ⅢB/IV NSCLC
- ALK positive centrally confirmed by FISH (Abbott Molecular), or by local NMPA-approved tests
- ECOG PS 0-1
- ALK TKI-naïve
- Previously treated with ≤1 chemotherapy regimen

Randomized 1:1 (N=292)

Iruplinalkib 180 mg qd with 7-day lead-in at 60 mg qd

Crizotinib 250 mg bid

Stratification factors:

- Previous chemotherapy regimens (0/1)
- Baseline CNS metastases (present/no)
- Previous radiotherapy to CNS metastases (yes/no)

Treatment until PD, intolerable toxicity, and other reasons for discontinuation

Primary endpoint

- IRC-assessed PFS per RECIST v1.1

Key secondary endpoints

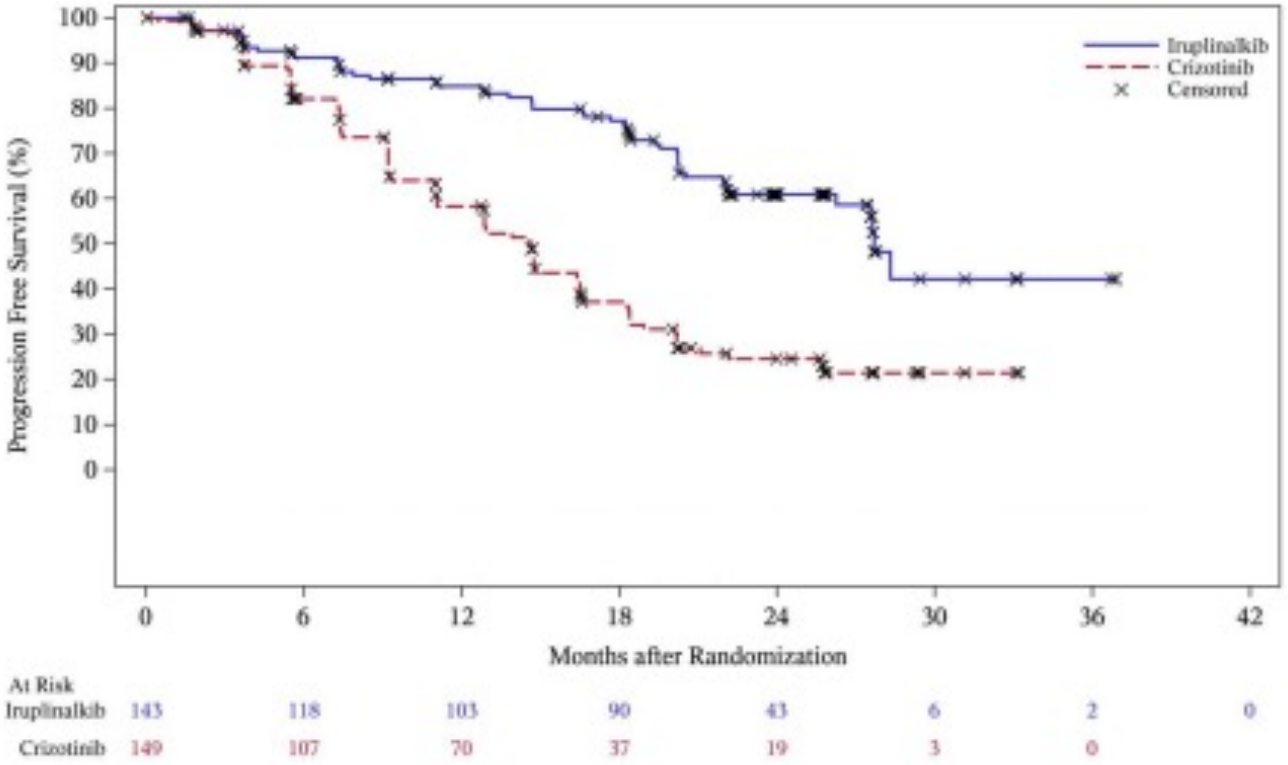
- Investigator-assessed PFS
- ORR and DoR (IRC and investigator)
- Intracranial ORR (IRC and investigator)
- OS
- Safety

Trial fully accrued in 2 December 2020
Data cutoff date: 13 November 2022
This study is registered with Center for Drug Evaluation of NMPA (CTR20191231) and Clinicaltrials.gov (NCT04632758).

Abbreviations: NSCLC, non-small cell lung cancer; NMPA, National Medical Products Administration; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committees; CNS, central nervous system; PFS, progression-free survival; ORR, objective response rate; DoR, duration of response; OS, overall survival; PD, progressive disease

	Iruplinalkib (N=143)	Crizotinib (N=149)
Age, years, median (range)	55.0 (25-76)	55.0 (31-75)
Sex, n (%)		
Male	72 (50.3)	62 (41.6)
Female	71 (49.7)	87 (58.4)
Race, n (%)		
Asian	143 (100.0)	149 (100.0)
ECOG PS, n (%)		
0	30 (21.0)	38 (25.5)
1	112 (78.3)	109 (73.2)
2	1 (0.7)	2 (1.3)
Disease stage at study entry, n (%)		
IIIB/IIIC	15 (10.5)	8 (5.4)
IV	128 (89.5)	141 (94.6)
CNS metastases present at baseline by investigator, n (%)	37 (25.9)	44 (29.5)
Previous radiotherapy to CNS metastases, n (%)	2 (1.4)	4 (2.7)
Previous chemotherapy, n (%)	24 (16.8)	25 (16.8)

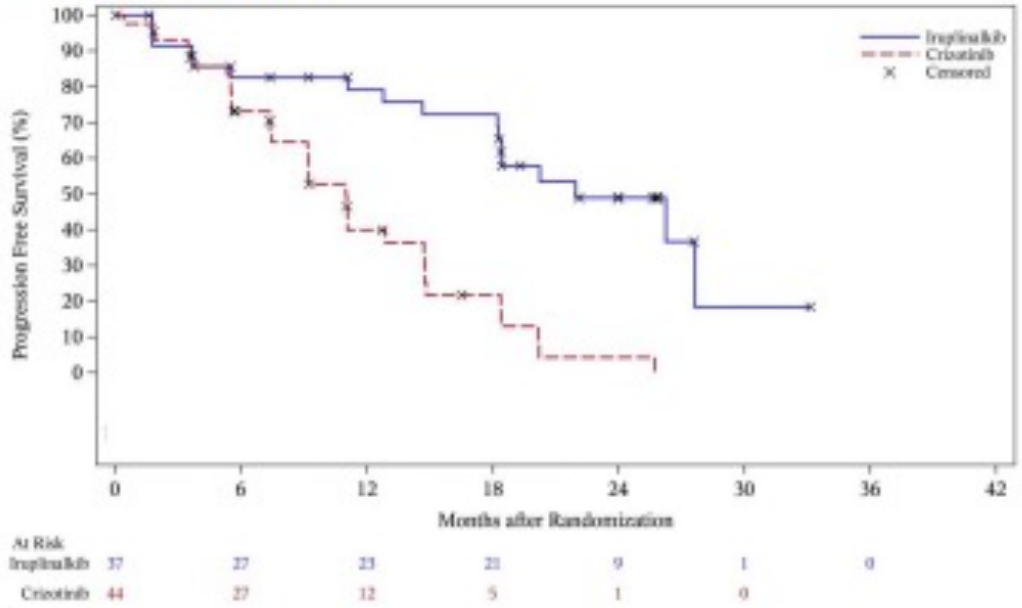
Primary Endpoint: IRC-Assessed PFS (ITT)



	Iruplinalkib (N=143)	Crizotinib (N=149)
Median PFS (95% CI), mo	27.70 (26.25-NE)	14.62 (11.07-16.49)
Hazard ratio (98.02% CI)	0.344 (0.226-0.523)	
P value (log-rank test)	<0.0001	

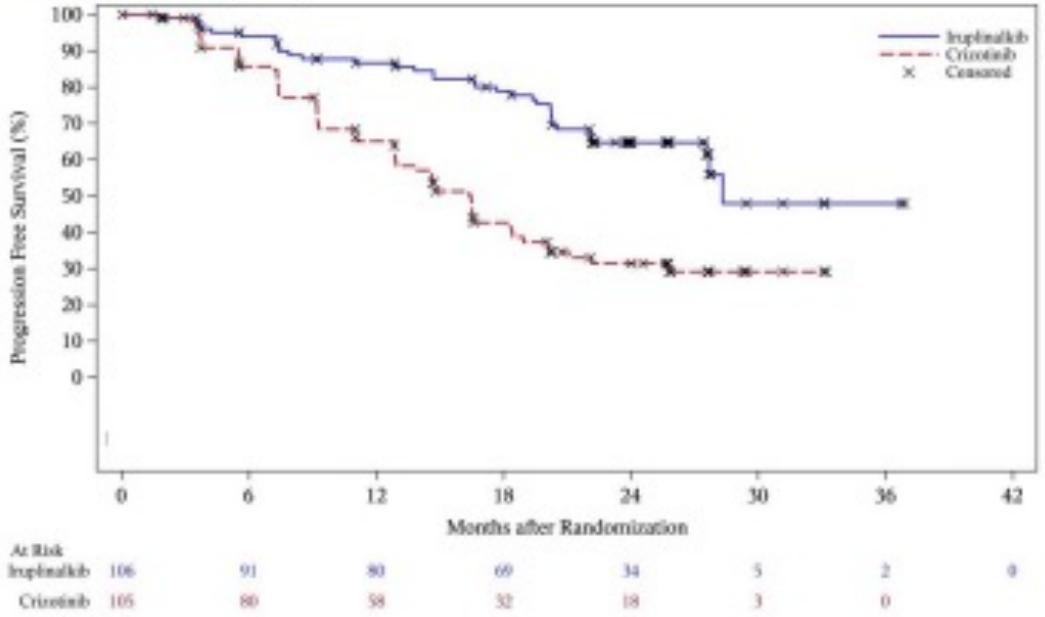
	Median follow-up (range), mo
Iruplinalkib	23.98 (0-36.9)
Crizotinib	24.54 (0-33.2)

IRC-assessed PFS in patients with baseline CNS metastases (ITT)



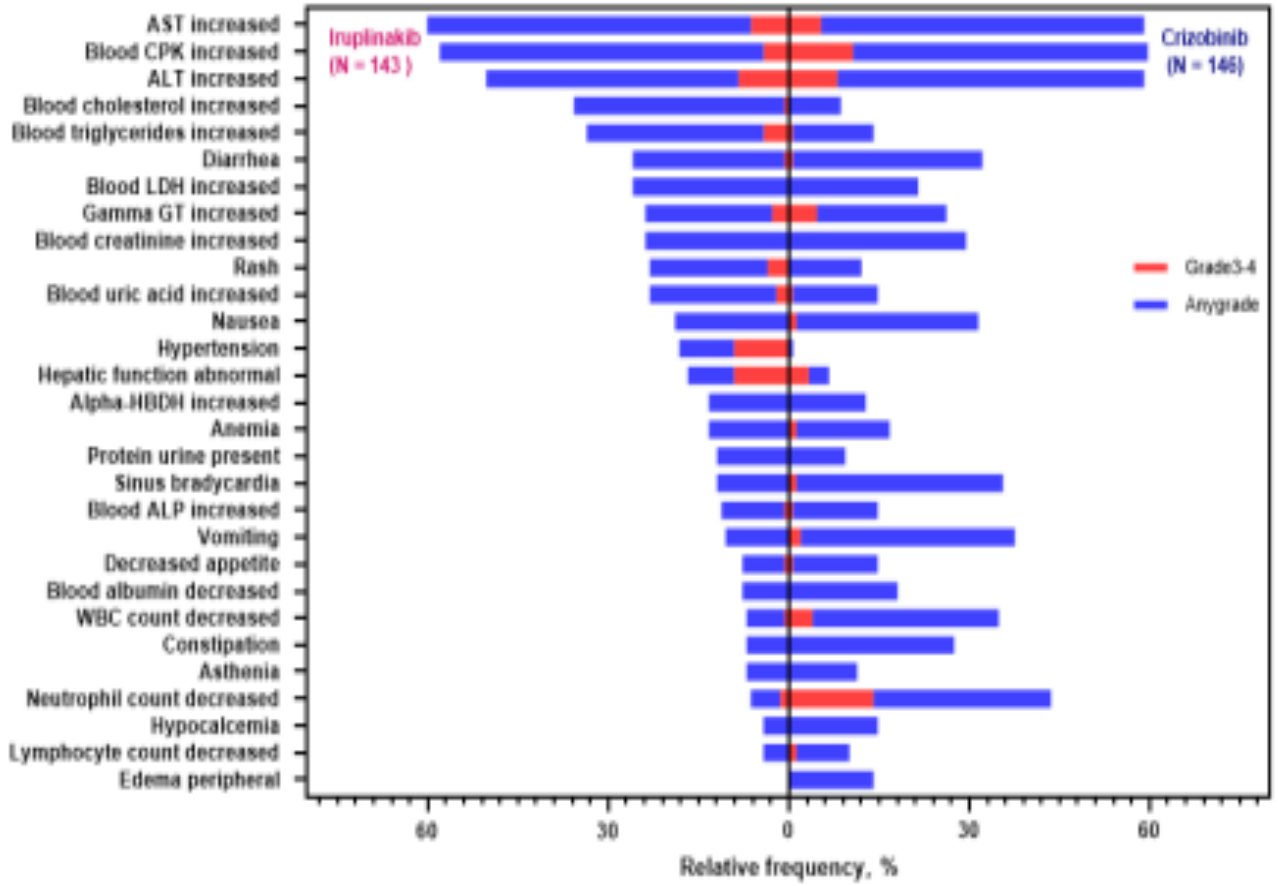
	Iruplinalkib (N=37)	Crizotinib (N=44)
Median PFS (95% CI), mo	21.95 (18.23-NE)	11.01 (7.46-14.72)
Hazard ratio (95% CI)	0.242 (0.119-0.493)	
P value (log-rank test)	<0.0001	

IRC-assessed PFS in patients without baseline CNS metastases (ITT)



	Iruplinalkib (N=106)	Crizotinib (N=105)
Median PFS (95% CI), mo	28.32 (27.56-NE)	16.46 (12.88-18.43)
Hazard ratio (95% CI)	0.360 (0.236-0.548)	
P value (log-rank test)	<0.0001	

TRAEs in ≥10% of patients in either treatment group (safety population)



	Iruplinalkib (N=143)	Crizotinib (N=149)
Median treatment duration, mo	23.92	12.94
Any TRAEs, n (%)	141 (98.6)	148 (99.3)
Grade 3-4 TRAEs, n (%)	74 (51.7)	74 (49.7)
Serious TRAEs, n (%)	20 (14.0)	16 (10.7)
Fatal TRAEs, n (%)	0	2 (1.3)
TRAEs leading to treatment discontinuation, n (%)	8 (5.6)	7 (4.7)
TRAEs leading to dose reduction, n (%)	40 (28.0)	49 (32.9)

	Comparator Arm	PFS	OS
Crizotinib MO	Chemotherapy	10.9 months	NR
Alectinib	Crizotinib	35 months	NR
Brigatinib	Crizotinib	30.8 months	NR
Lorlatinib	Crizotinib	NR	NR
Ceritinib	Chemotherapy	16.6 months	NR
Iruplinalkib	Crizotinib	27.7 months	NR

	Intracranial Response
Crizotinib	20%
Alectinib	81%
Brigatinib	78%
Lorlatinib	82%
Iruplinalkib	90%

Lorlatinib in Previously Treated ALK + Advanced NSCLC (Lu et al. Poster, WCLC 2023):

-67 patients with prior crizotinib
- CNS ORR 63%

Peters et al. NEJM 2017
Camidge et al. NEJM 2018
Shaw et al. NEJM 2020

Comparative efficacy and safety of lorlatinib vs alectinib and brigatinib using matching adjusted indirect comparisons (MAIC)

-Formal Indirect treatment comparison study
-Compared Lorlatinib (CROWN) vs Alectinib (ALEX) and Lorlatinib vs Brigatinib (ALTA-1L)

Lorlatinib overall had improved PFS compared to Alectinib and Brigatinib

Risk of grade 3 or more AEs higher with lorlatinib compared to alectinib, but not to brigatinib

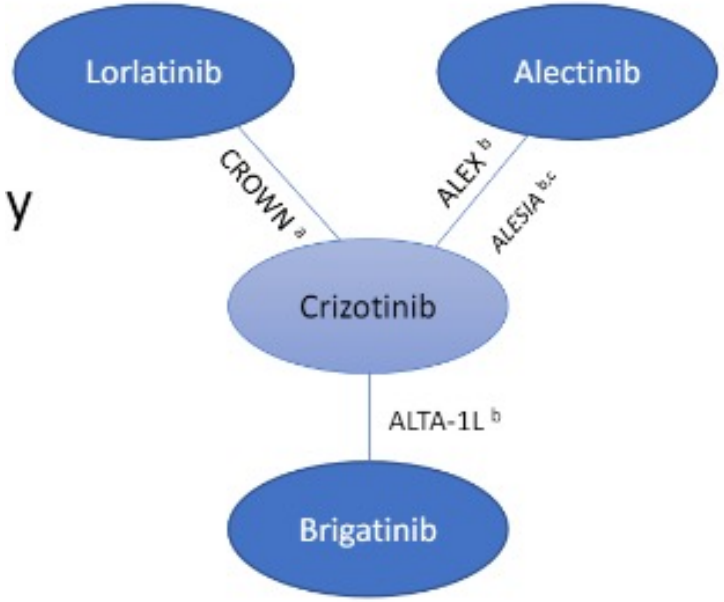
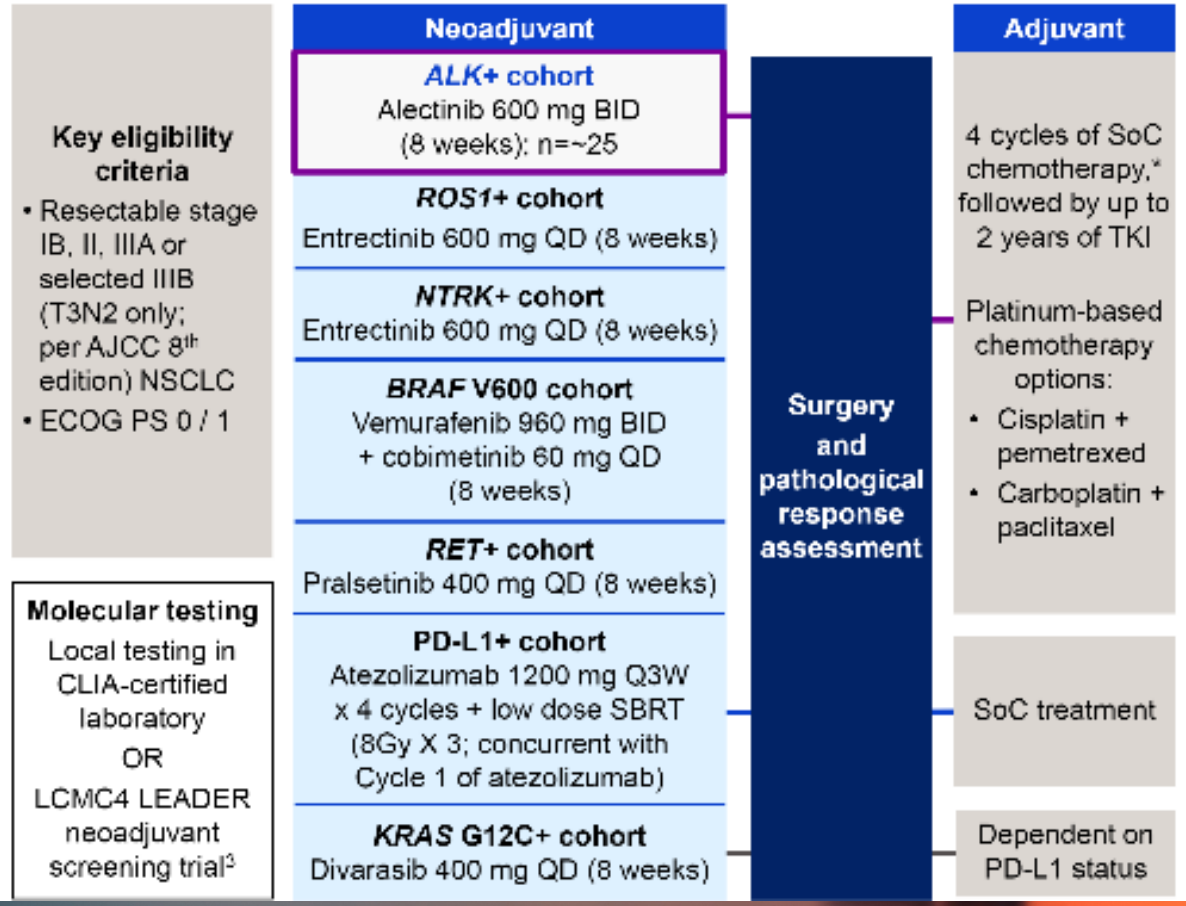


Figure 1. Network of RCTs identified in targeted literature review

Garcia, CA, EP12.02 Presented WCLC 2023

NAUTIKA 1: Neoadjuvant Alectinib

Figure 1. NAUTIKA1 trial design



- Neoadjuvant alectinib 600 mg BID for 8 weeks followed by surgery
- Primary endpoint –MPR (**<10% residual viable tumor cells)**
- **12 patients have enrolled**
  - **PCR 3/9 pts (33%)**
  - **MPR 6/9 (66%)**

- 8 patients with R0 resection and received adjuvant treatment

Lee, J et al. Poster 1795 WCLC 2023
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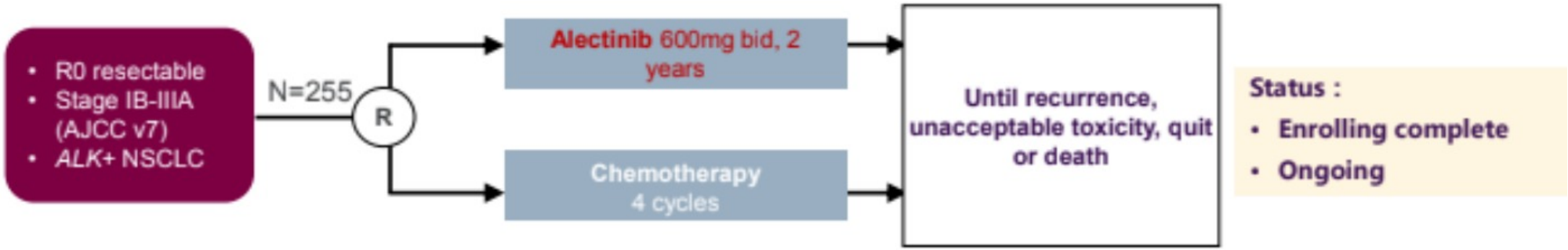
Adjuvant Alectinib

ALINA: Phase III, Randomized, Multicenter Study of adjuvant **Alectinib**



Stratification factors:
Stage (IB vs II vs IIIA)
Race (Non-Asian vs Asian)

Primary endpoint:
DFS

ALINA Study of Alectinib Meets Primary DFS End Point in ALK+ NSCLC

Sep 1, 2023

ROS1

2007
Discovery of ROS1 rearrangement

2016
Crizotinib (PROFILE-1001)

2017
Ceritinib (ASCEND-5)

2019
Entrectinib (STARTRK-2)

2019
Lorlatinib (

2020
Repotrectinib (TRIDENT-1)

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Repotrectinib in patients with *ROS1* fusion-positive non-small cell lung cancer: update from the pivotal phase 1/2 TRIDENT-1 trial

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TRIDENT-1: overview of phase 1/2 trial design

Phase 1/2 patient eligibility

- Locally advanced or metastatic solid tumors harboring *ROS1* or *NTRK1-3* gene fusions[a]
- Asymptomatic CNS metastases allowed

Phase 1[b] dose escalation cohorts

RP2D
160 mg QD x 14 days, then 160 mg BID[c]

Phase 2 dose expansion cohorts[d]

ROS1+ advanced NSCLC

EXP-1	EXP-2	EXP-3	EXP-4
ROS1 TKI-naïve	1 prior ROS1 TKI AND 1 prior platinum-based chemo	2 prior ROS1 TKIs AND no prior chemo	1 prior ROS1 TKI AND no prior chemo
(n = 110)[e]	(n = 60)[e]	(n = 40)[e]	(n = 60)[e]

Phase 2 (*ROS1*+ advanced NSCLC cohorts)

Primary endpoint

cORR by BICR using RECIST v1.1

Key secondary endpoints

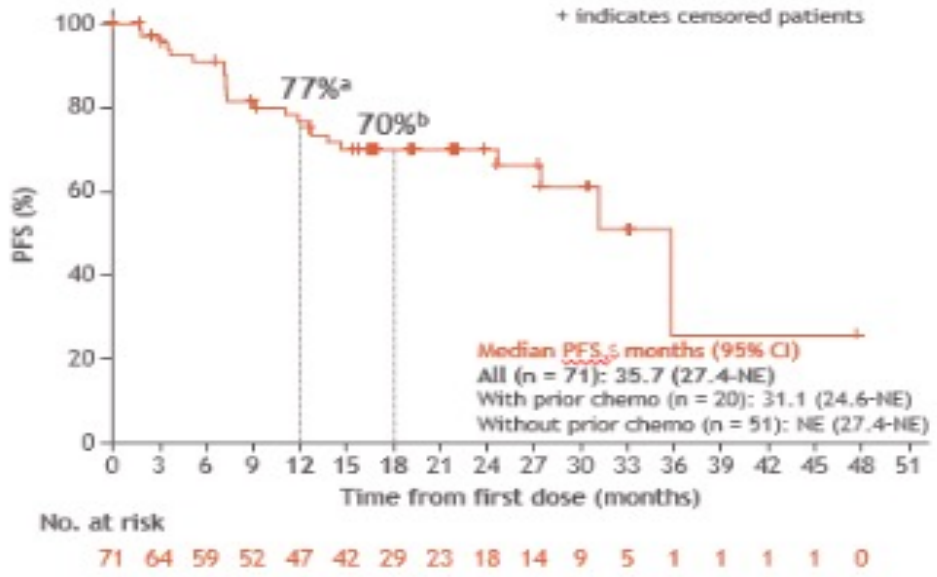
- DOR,[f] CBR,[f] TTR[f]
- cORR[e] in TKI-pretreated patients harboring *ROS1* G2032R
- PFS,[f] OS
- icORR by mRECIST v1.1 in patients with measurable brain metastases
- Safety, patient-reported outcomes

- Primary efficacy population includes patients pooled from phase 1[g] and 2 who began repotrectinib treatment approximately 14 months prior to data cutoff date of December 19, 2022

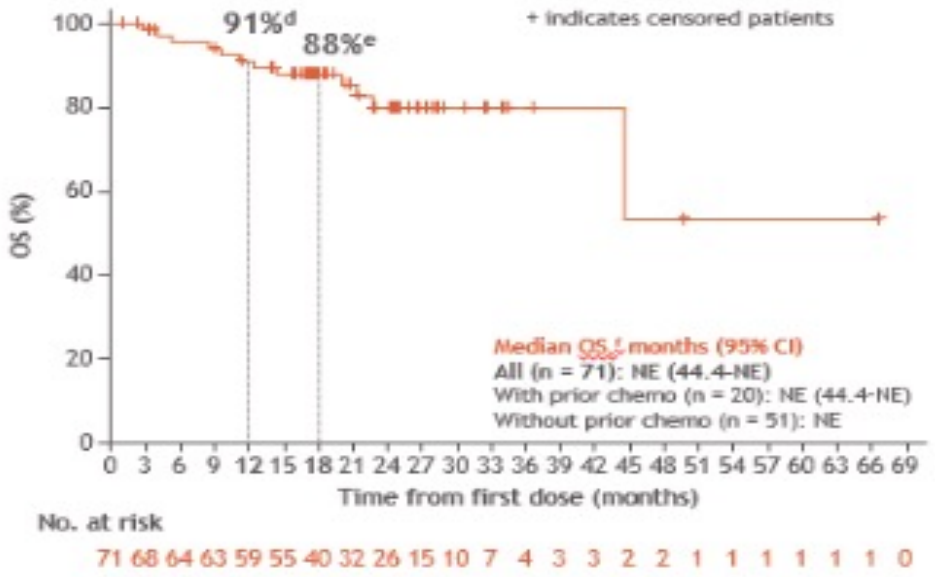
	ROS1 TKI-naïve (n = 71[a])	1 prior ROS1 TKI AND no prior chemo (n = 56[b])
Median age, years (range)	57 (28–80)	57 (33–78)
Region, n (%)		
US	11 (16)	17 (30)
Asia	41 (58)	23 (41)
Other[c]	19 (27)	16 (29)
Female, n (%)	43 (61)	38 (68)
ECOG PS, n (%)		
0	24 (34)	18 (32)
1	47 (66)	38 (68)
Never smoked, n (%)	45 (63)	36 (64)
Brain metastasis per BICR, n (%)	17 (24)	26 (46)
Resistance mutation,[d,e] n (%)		
Solvent front (G2032R)	Not applicable	6 (11)
0	51 (72)	0
1	16 (22)	56 (100)
Prior TKI treatment,[i] n (%)		
Crizotinib	Not applicable	46 (82)
Entrectinib		9 (16)

PFS and OS in TKI-naïve patients with *ROS1*+ advanced NSCLC

PFS



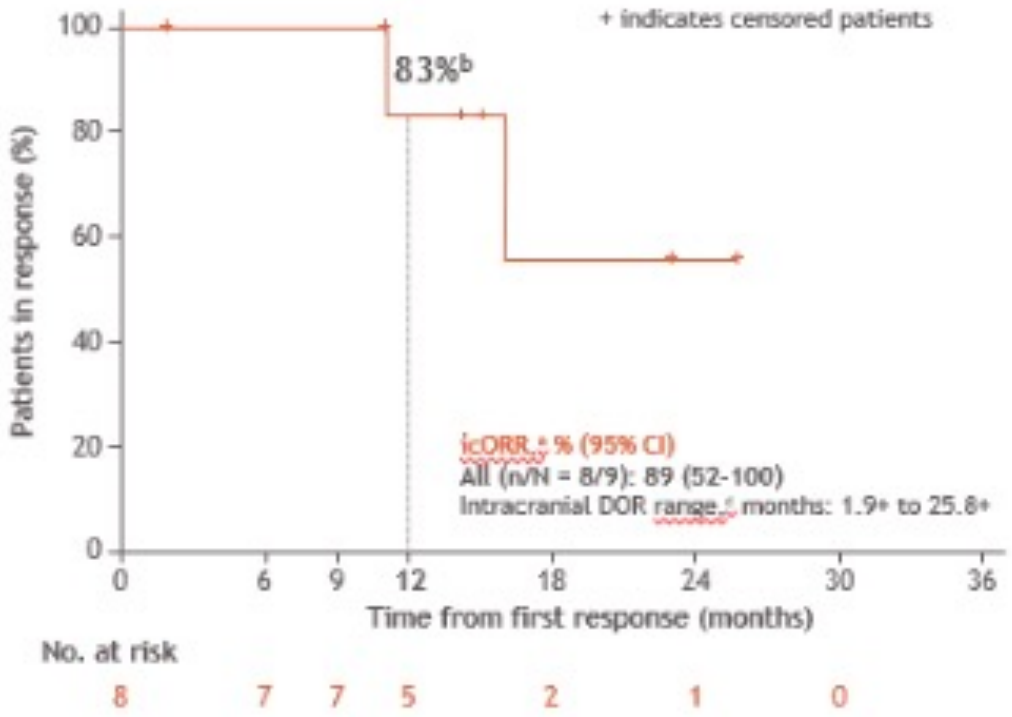
OS



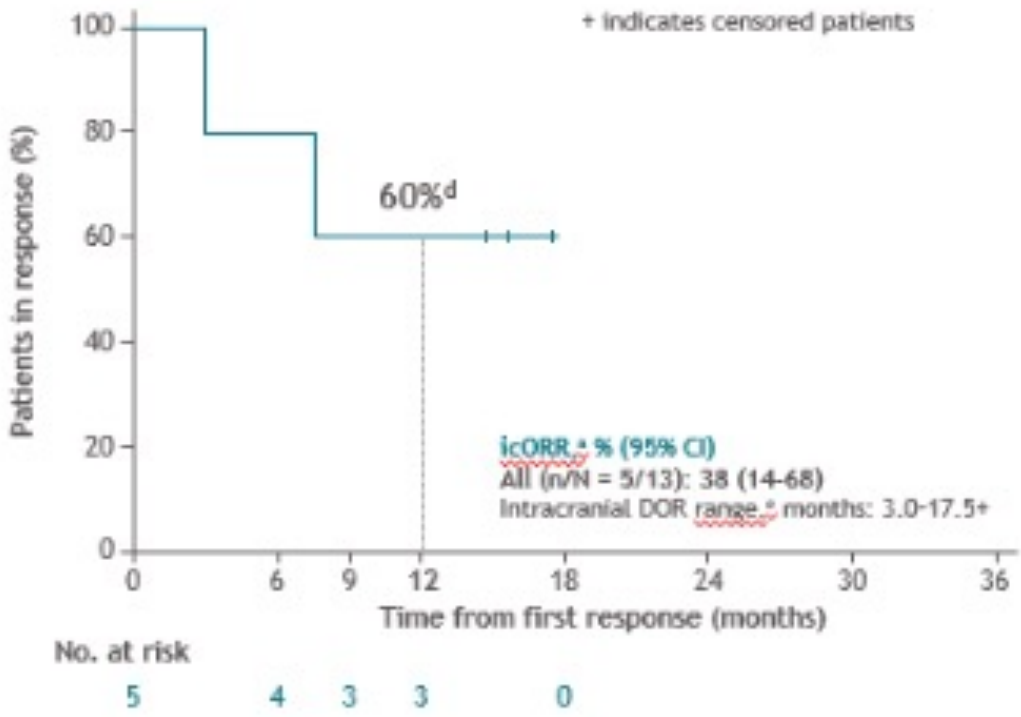
	TKI Naive	Prior TKI, no prior chemo
ORR	79%	38%
mPFS	35.7 months	9 months

Intracranial DOR[a] in TKI-naïve and TKI-pretreated patients with measurable baseline brain metastasis

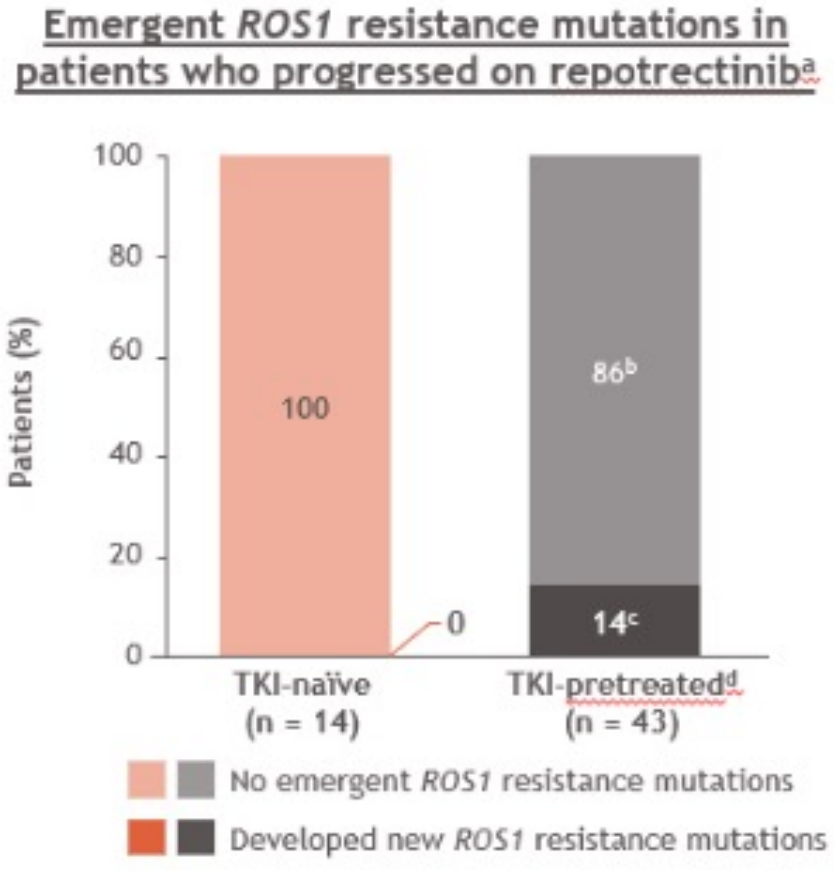
ROS1 TKI-naïve

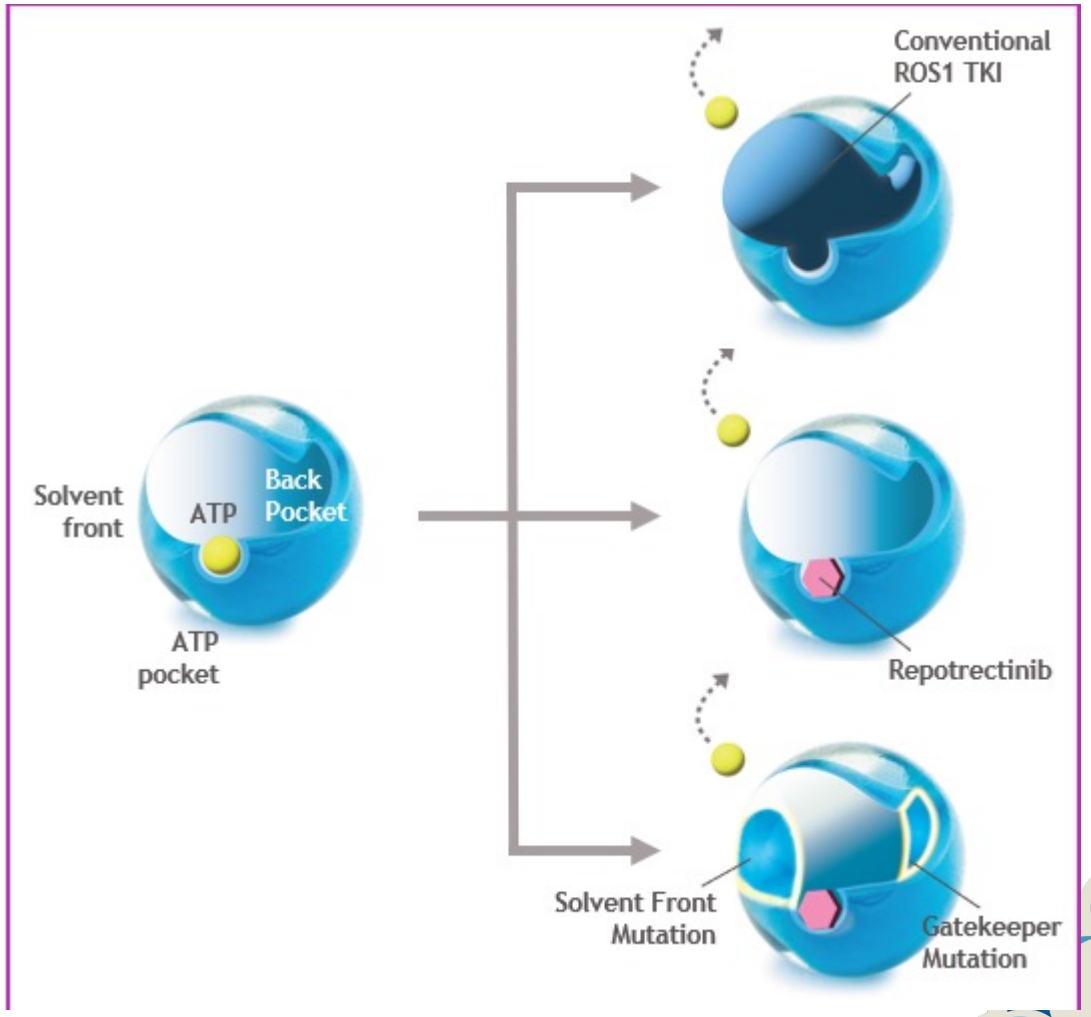


1 prior ROS1 TKI and no prior chemo



Acquired ROS1 resistance





	Comparator Arm	PFS	OS
Ceritinib	Chemotherapy	19.3 months	NR
Crizotinib	NA	19.2 months	NR
Entrectinib	NA	19 months	NR
Lorlatinib	NA	21 months	NR
Repotrectinib	NA	35.7 months	NR

	Intracranial Response
Crizotinib	20%
Entrectinib	55%
Lorlatinib	60%
Repotrectinib	89%

Almquist et al. JCO Oncol Pract 2020
Lin et al. ASCO Annual Meeting 2023

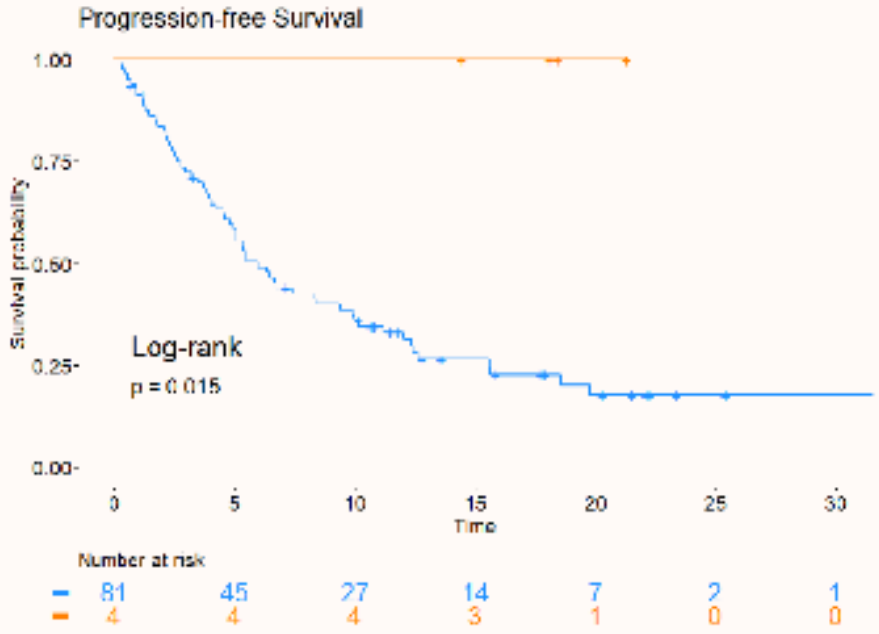
BRAF

BRAF status and response to IO or Chemo-IO

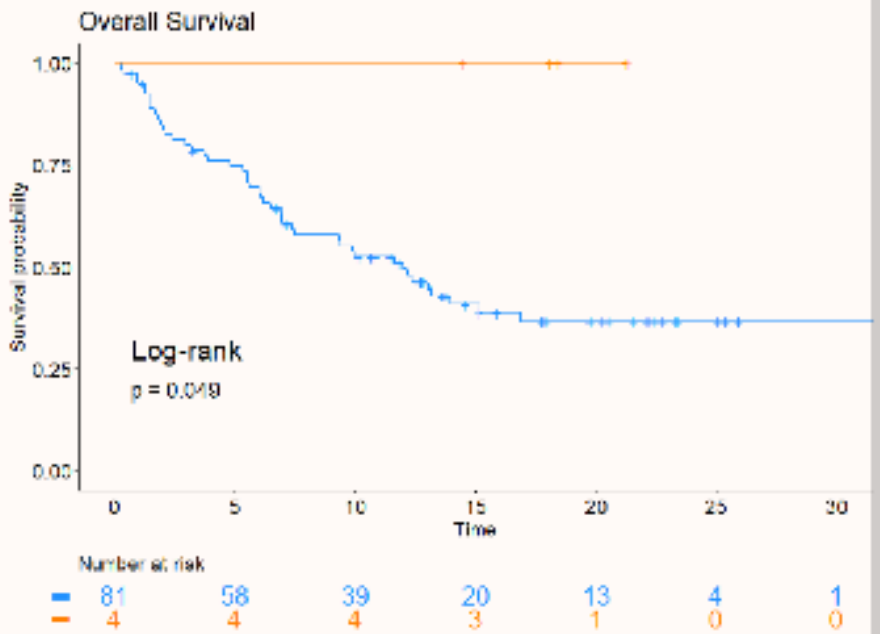
3. Association of *BRAF and ERBB3* status with patient survival

4.71 % of patients with Pathogenic/likely-pathogenic ***BRAF*** variants

PFS



OS



De Lope et al. Poster 2108 WCLC 2023
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Thank you