Selection of first line therapy for ROS1 Rearranged NSCLC

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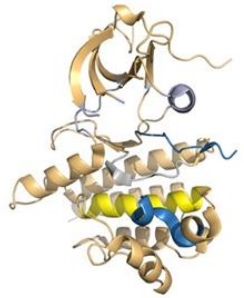
Discussion

- Historical Perspective
- Pathobiology
- Clinical Features of ROS 1 + population
- Testing for ROS1
- Drugs active against ROS1
- Trial Data
- Approved Drugs in First Line

Incidence

- Lung Cancer: 1,000,000 deaths
- NSCLC: 80% of all lung cancers
- ROS1 Fusions: 1-2% of NSCLC



Active CD74-ROS1

↓

Non-Small Cell Lung Cancer

Adapted from Pharmacol Res 2017; 121: 202-212

Reported Prevalence of *ROS1*-Rearranged NSCLCs[3,a]

	No. of Patients Screened	No. of ROS1+ Tests (%)
North America	1,240	20 (**1.6**)
Europe	1,828	37 (**2.0**)
Asia	5,375	121 (**2.3**)

- R : Receptor Tyrosine Kinase
- O : Oncogenic Factor
- S : Sarcoma

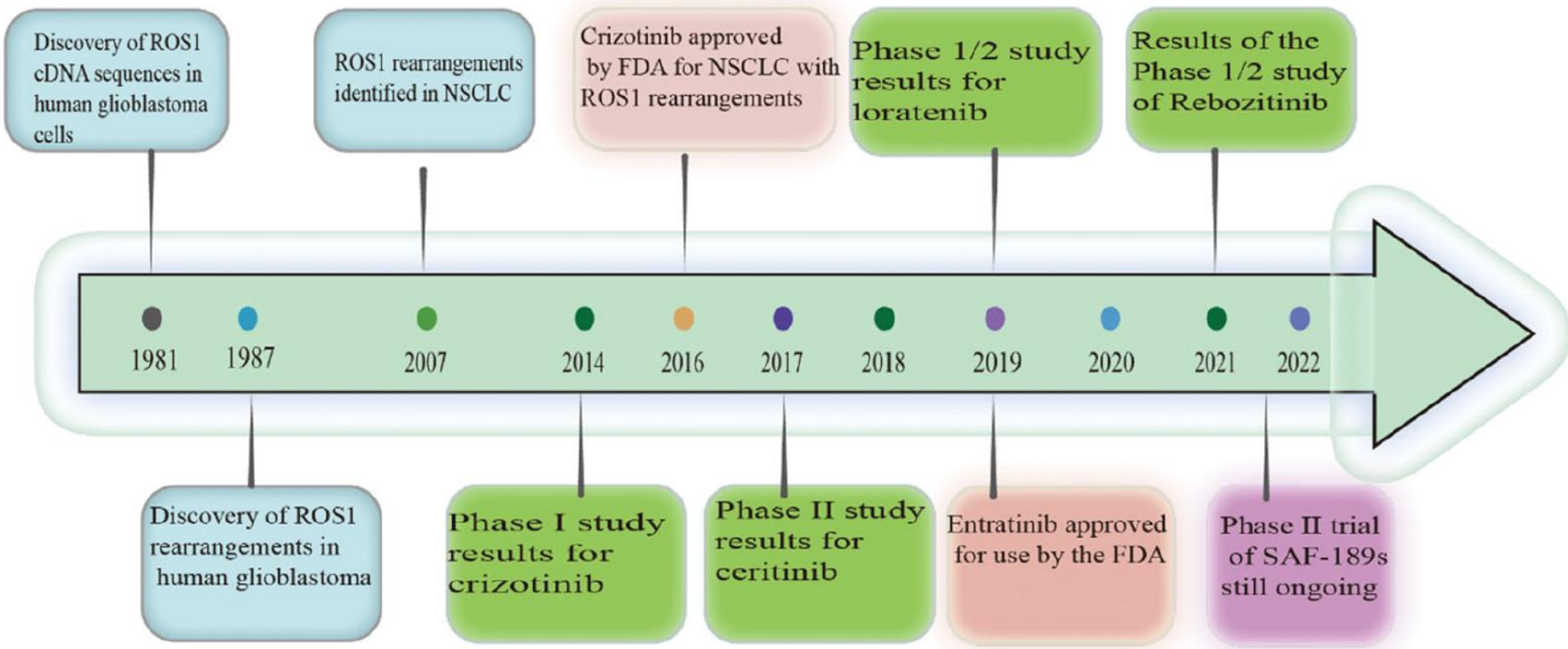
Initially discovered in Glioblastoma Cell lines and later in GBM tumor tissue. (Fig-Ros fusion)

Historical Perspective

ROS1

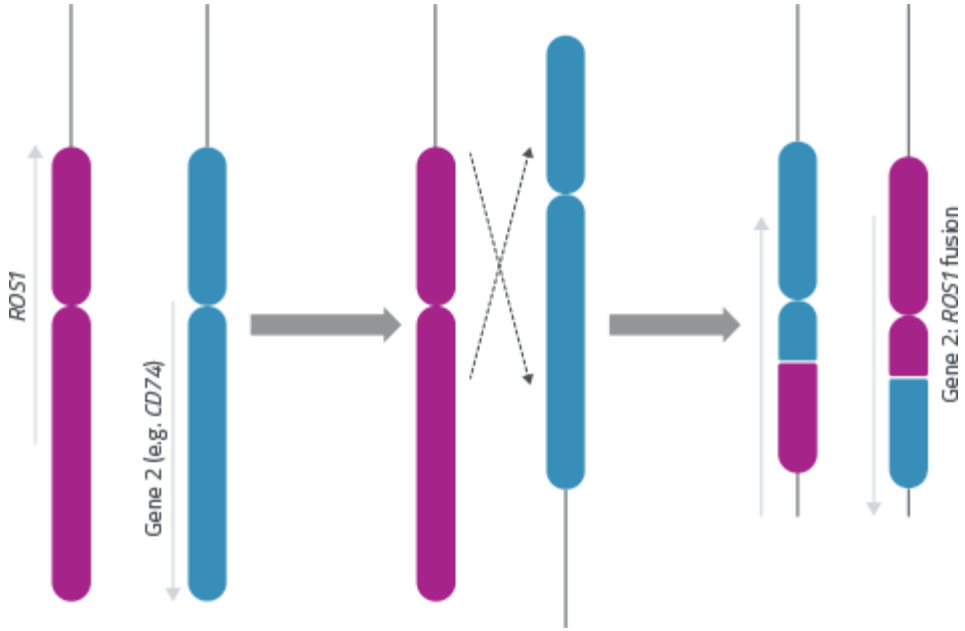
- 1981: First isolation of cDNA of ROS by Birchmeier et al
- 2007: ROS1 fusion identified in NSCLC cell lines
- Other cancers with ROS1 fusions:
- Cholangio Ca, Ovarian cancer, Angio sarcoma, IMFT, Acanthous melanoma

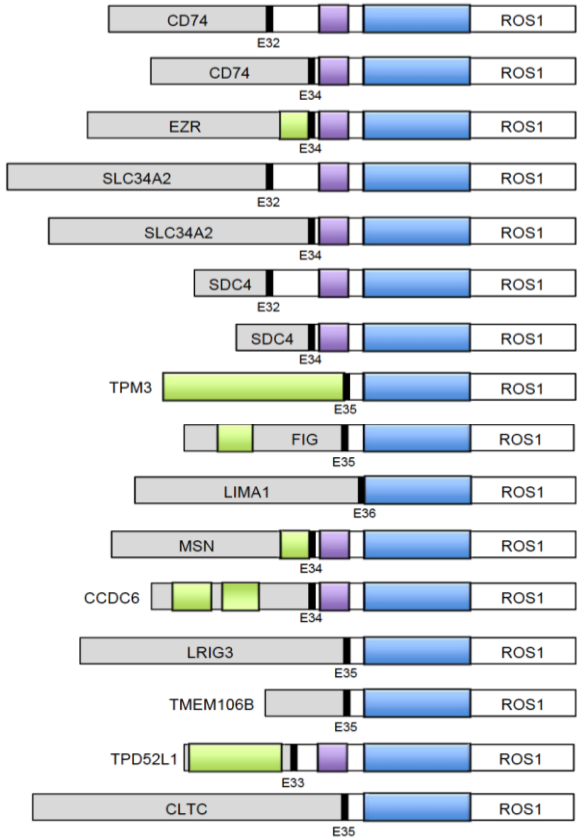
Timeline of the ROS1 targeted therapies



Pathobiology

- ROS 1 located on Chromosome 6q22
- Fusion Partners with ROS: CD74 is most common

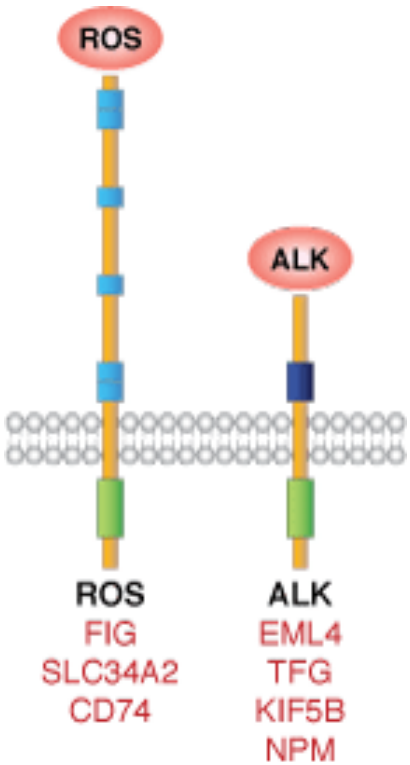


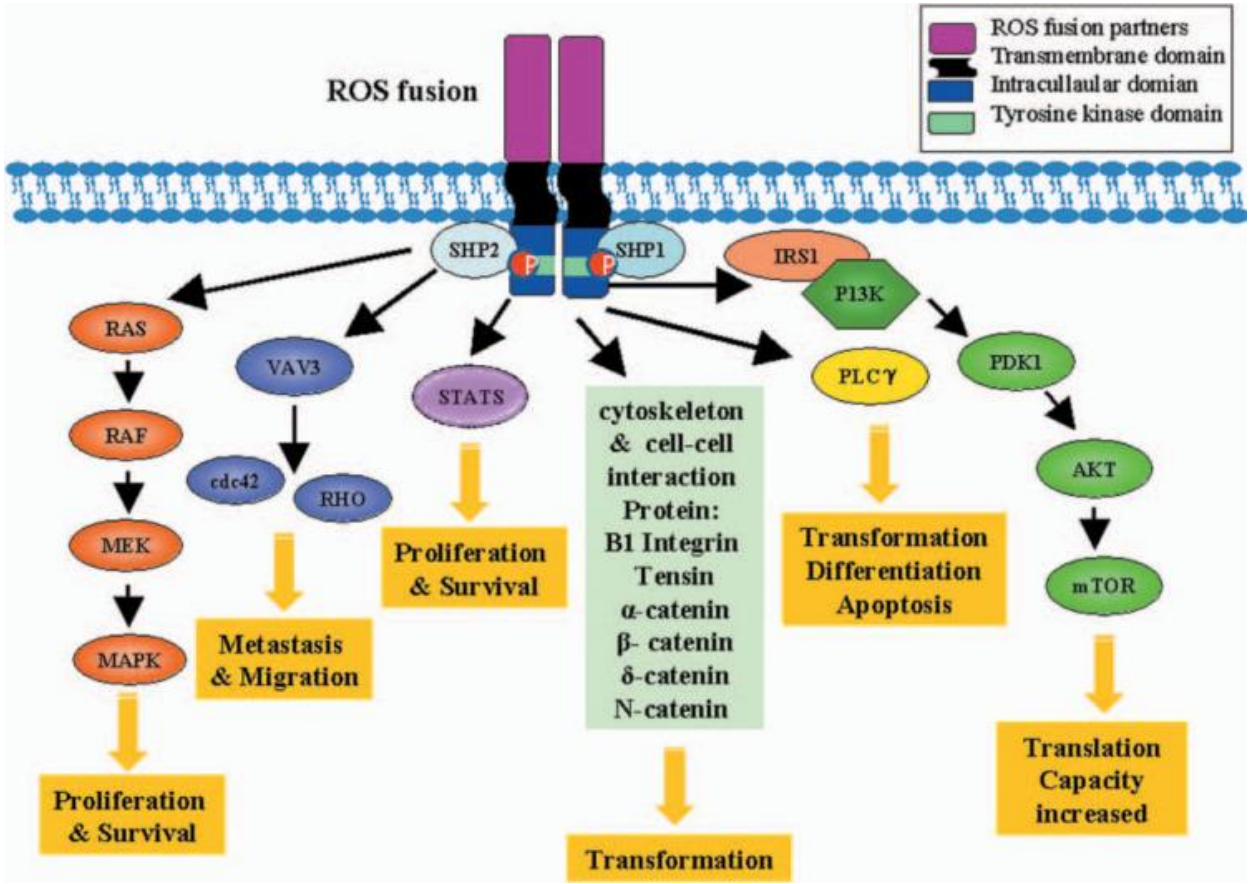


- **1.** Lin JJ, Shaw AT. *J Thorac Oncol.* 2017;12:1611–25. **2.** Chin LP, et al. *J Thorac Oncol*. 2012;7:1625–1630. **3.** Tsao MS, et al. *IASLC Atlas of ALK and ROS1 Testing in Lung Cancer*. 2016. Reprinted courtesy of the International Association for the Study of Lung Cancer.

An Orphan Receptor, capable of driving tumorigenesis

- The ligand is not known, Physiological function is not known
- Main role during embryogenesis, limited physiological role in adults
- Re- expressed during oncogenesis and acts as a driver by activating predominantly RAS/RAF/MEK/ERK pathway , and also JAK-STAT and PI3K-AKT-mTOR pathways


ROS
ALK
ROS
FIG
SLC34A2
CD74
ALK
EML4
TFG
KIF5B
NPM

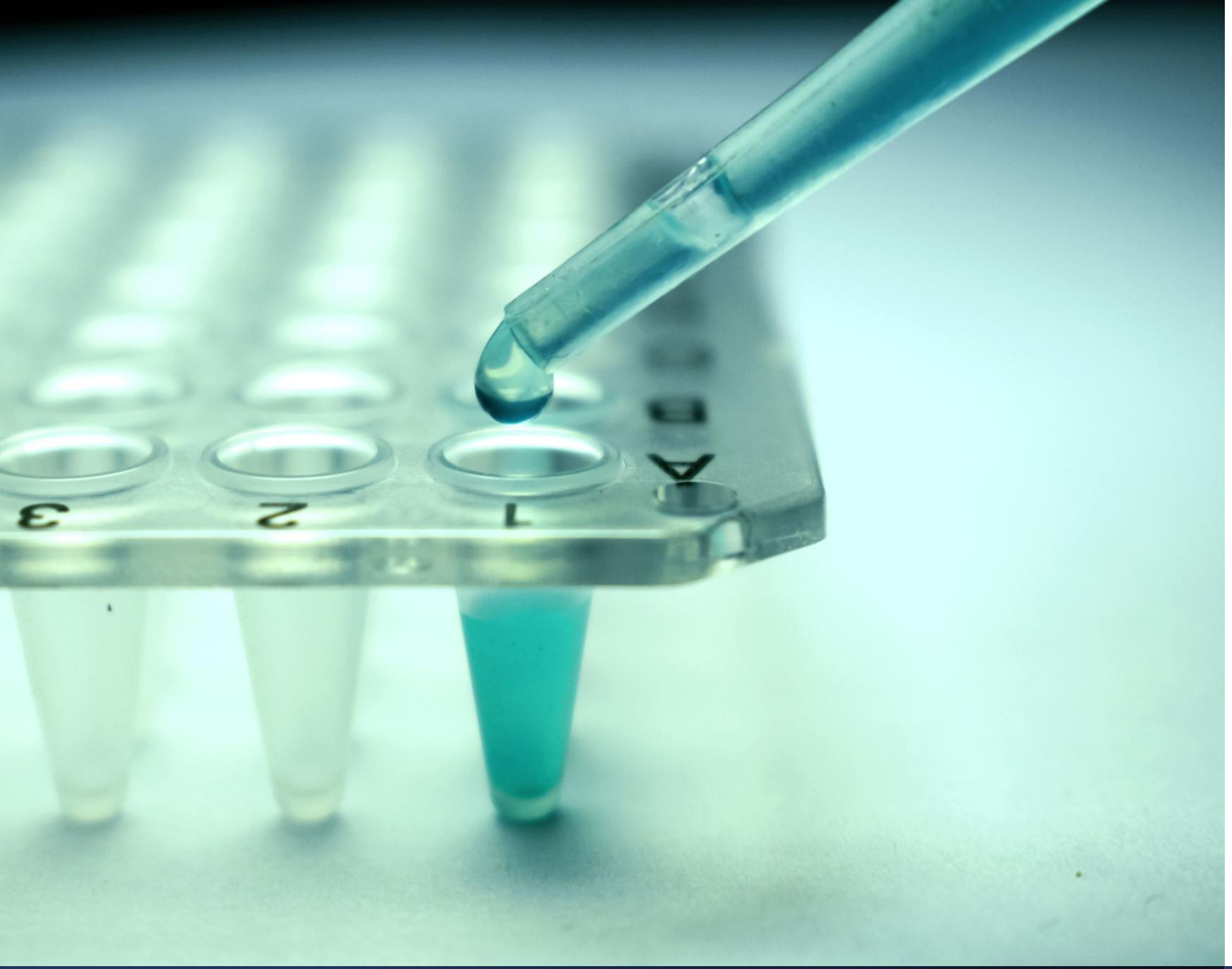

ROS fusion partners
Transmembrane domain
Intracullaular domian
Tyrosine kinase domain
ROS fusion
SHP2
SHP1
RAS
RAF
MEK
MAPK
VAV3
cdc42
RHO
STATS
IRS1
P13K
PLCγ
PDK1
AKT
mTOR
cytoskeleton & cell-cell interaction Protein:
B1 Integrin
Tensin
α-catenin
β- catenin
δ-catenin
N-catenin
Proliferation & Survival
Metastasis & Migration
Proliferation & Survival
Transformation
Transformation Differentiation Apoptosis
Translation Capacity increased

Type of Mutation and Co-Mutation matters

- CD74 ROS fusions: Seems to have more brain mets at baseline and different PFS with Crizotinib than other fusions
- TP53 mutation is most common co-mutation with ROS Fusions
- Patients with TP53 co-mutation has shorter survival with Crizotinib (Effect of Loraltinib – an area of research!)

Clinical Features of ROS1 + NSCLC

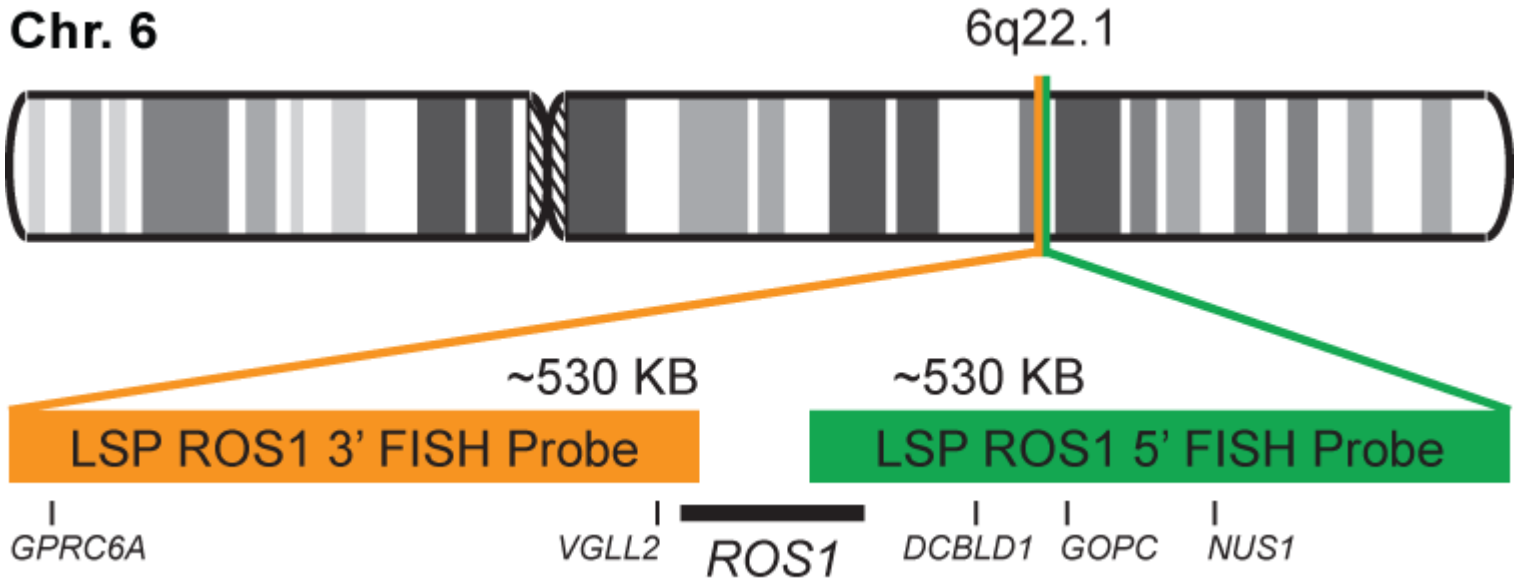
- Non- smokers
- Female Sex
- Adeno Carcinoma

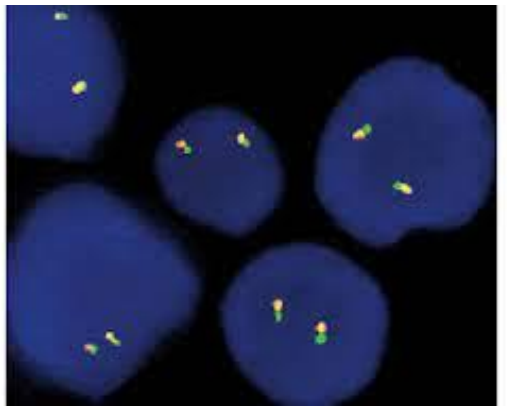


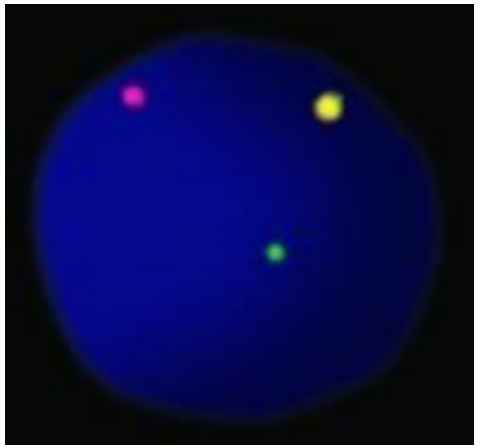
Testing for ROS1 Fusions in NSCLC

- Testing for ROS1 is mandatory as per all societal guidelines

Break Apart FISH







IHC IS A SCREENING TEST ONLY!

DO NOT START TREATMENT BASED ON POSITIVE IHC REPORT

All IHC POSITIVE REPORTS to be confirmed by FISH

NO TRIALS HAVE USED IHC FOR SELECTION OF ROS+ PATINETS

Clinical Trial Data for ROS1 positive NSCLC

ALK inhibitors as ROS inhibitors

- There is more than 60% homology between TK domain of ALK and ROS
- Pre-clinical studies : ALK inhibitors efficacy in ROS + tumors

Kohno T, Nakaoku T, Tsuta K, et al. Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer. Transl Lung Cancer Res. 2015;4(2):156–164.

Drugs active against ROS1 positive NSCLC

- Four drugs have significant activity against ROS1+ NSCLC:
- Crizotinib, Ceritinib, Entrectinib and Lorlatinib.
- Each drug yields an overall response rates exceeding 60%.
- Ceritinib, Lorlatinib, and Entrectinib possessing intracranial activity.
- Drug in trial: Repotrectinib

- **NCCN Guidelines recommend certain TKIs that target ROS1 for the treatment of *ROS1* rearrangement-positive metastatic NSCLC[1,a,b]**

FDA-Approved TKIs in ROS1+ Metastatic NSCLC		Year of Initial Approval
Crizotinib[2]	Crizotinib is FDA approved for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive or ROS1-positive as detected by an FDA-approved test.	2012
Entrectinib[3]	Entrectinib is FDA approved for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive.	2019

- [a]The NCCN Guidelines for Non-Small Cell Lung Cancer provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays.
- [b]Refer to the NCCN Guidelines for specific treatment recommendations for each setting. Not all agents in a drug class are recommended for each setting.

- ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Crizotinib

- Crizotinib is an oral TKI that targets ALK/ROS1/MET.
- FDA Approval of Crizotinib is based on profile 1001 extension cohort results
- This is a Phase 1 , single arm, Multi centered, study involving 53 ROS1 patients

Crizotinib in advanced *ROS1*-rearranged non-small cell lung cancer (NSCLC): overall survival (OS) and updated safety from PROFILE 1001

Alice T. Shaw, Gregory J. Riely, Yung-Jue Bang, Dong-Wan Kim, D. Ross Camidge, Geoffrey I. Shapiro, Tiziana Usari, Sherry C. Wang, Keith D. Wilner, Jeffrey W. Clark, Sai-Hong Ignatius Ou

Annals of Oncology 30: 1121–1126, 2019

PROFILE 1001: ROS1 expansion cohort (N=53)*

Key entry criteria

- Locally advanced or metastatic, histologically confirmed NSCLC
- Positive for *ROS1* rearrangements by local molecular profiling[a]
- ECOG PS 0 or 1[b]
- Treated brain metastases allowed if stable for ≥2 weeks

Enrollment period
Oct 2010–Sept 2013

Crizotinib
250 mg BID PO,
continuous 28-day[c] cycles

Treatment beyond PD was allowed.

Endpoints

- Objective response rate derived by investigator (ORR; RECIST v1.0[d])
- Duration of response (DOR)
- Time to tumor response (TTR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety (CTCAE v3.0)

This is an updated investigator-assessed analysis of the PROFILE 1001 study [e].

Data cutoff date:
June 30, 2018

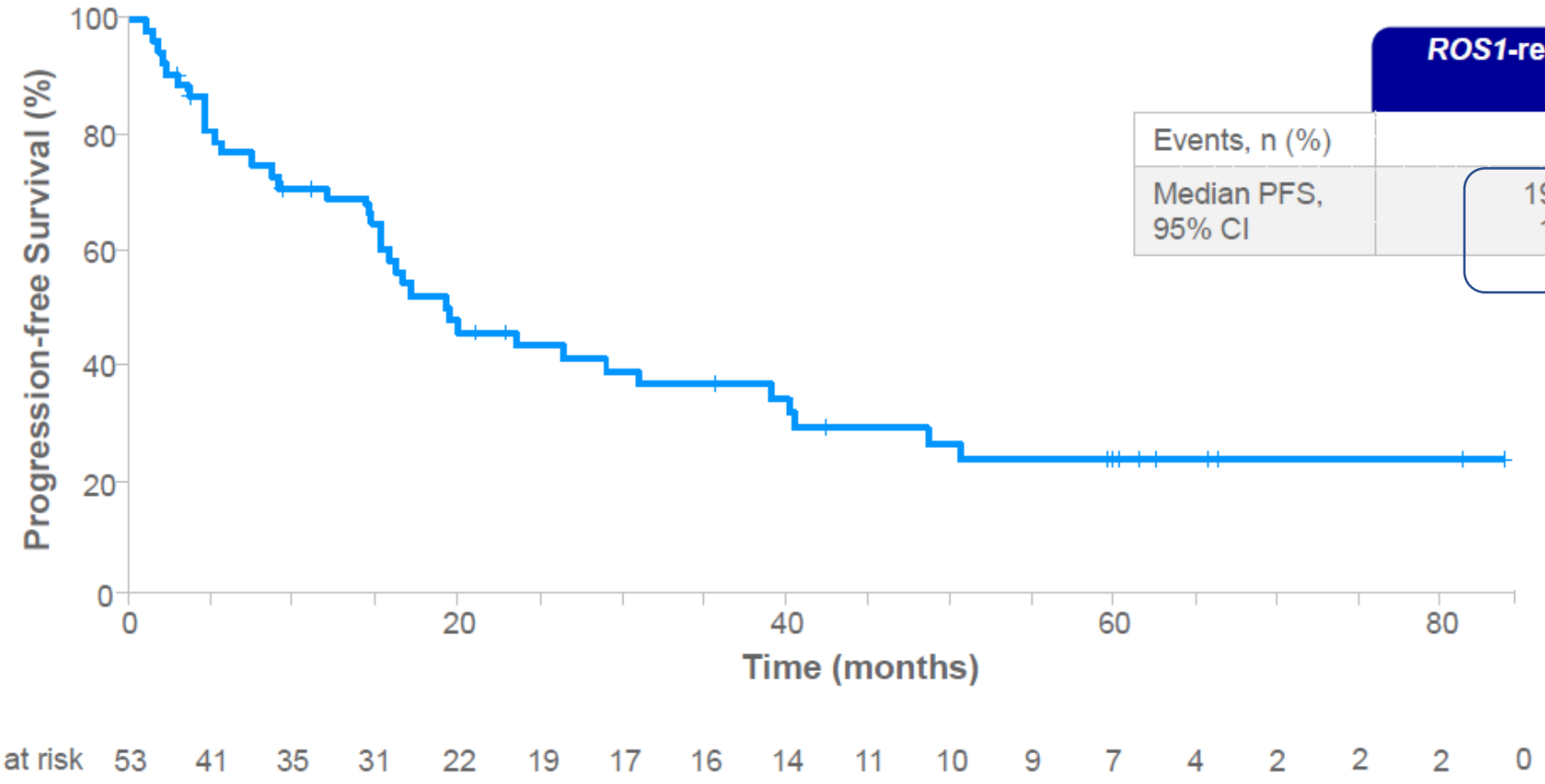
*Additional 3 patients from a separate cohort were retrospectively determined to be ROS1-positive and included in the updated analyses.
[a]ROS1 testing by central laboratory in 2 of the patients from a separate cohort.
[b]ECOG PS 2 could enroll upon investigator and sponsor agreement.
[c]21-day cycles for the 3 patients from a separate cohort.
[d]RECIST v1.1 for the 3 patients from a separate cohort.
e. Results from the updated analysis are not included in the Xalkorilabel. IRR assessment was not conducted for the updated analysis.

BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors.

Please see summary of prescribing information on last slide

Shaw et al. Annals of Oncology 30: 1121–1126, 2019

PROFILE 1001: Progression-Free Survival

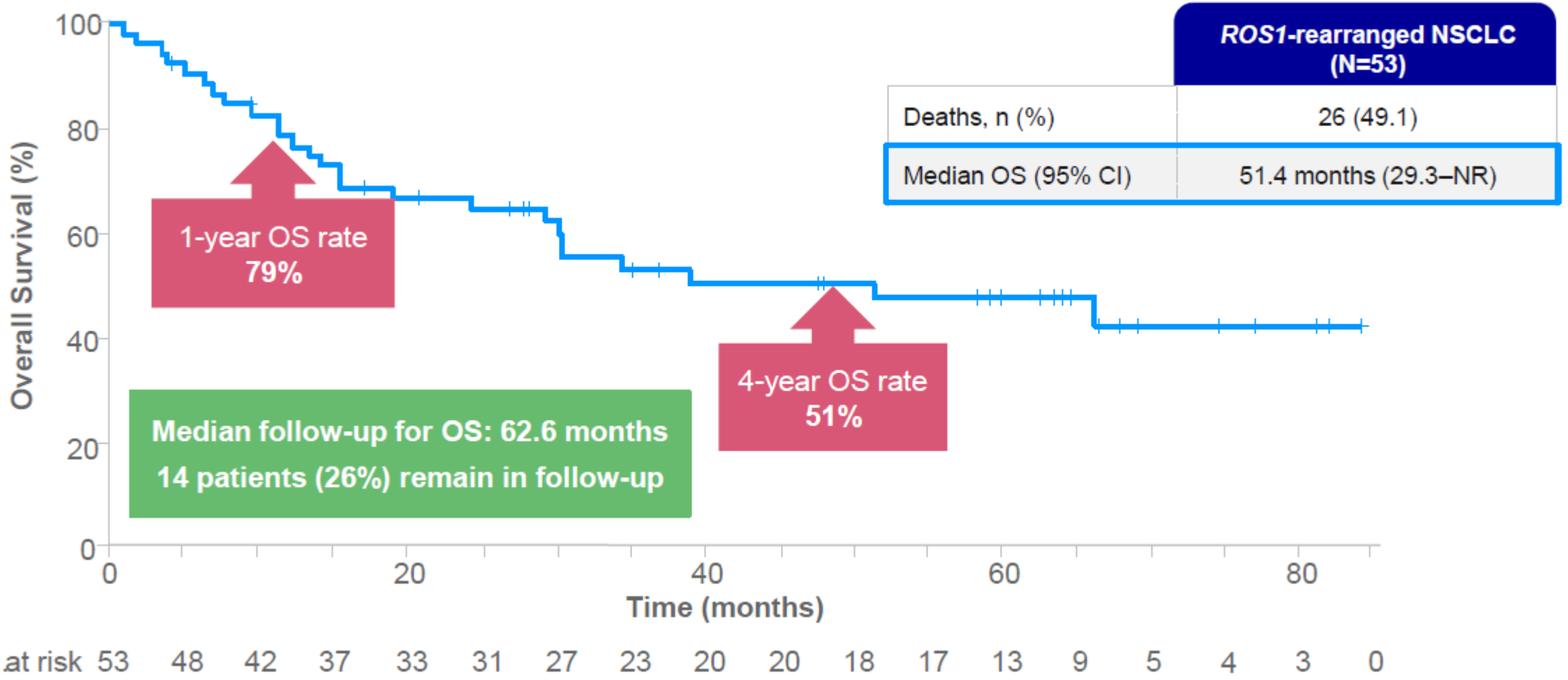


	ROS1-rearranged NSCLC (N=53)
Events, n (%)	36 (67.9)
Median PFS, 95% CI	19.3 months 15.2–39.1

Adapted from Shaw et al. Annals of Oncology 30: 1121–1126, 2019

CI, confidence interval; NR, not reached; NSCLC, non-small cell lung cancer; PFS, progression-free survival.
Shaw AT et al. Annals of Oncology 30: 1121–1126, 2019

PROFILE 1001: Overall Survival



NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival.
Shaw AT et al. Annals of Oncology 30: 1121–1126, 2019

Adapted from Shaw et al. Annals of Oncology 30: 1121–1126, 2019

Safety Summary

Safety Summary, n (%)	ROS1-rearranged NSCLC (N=53)
TRAEs	53 (100)
Grade 3 TRAEs[a]	19 (35.8)
Serious TRAEs[b]	2 (3.8)
TRAEs leading to permanent treatment discontinuation	0
Deaths Disease under study TRAEs Unknown	26 (49.1) 22 (41.5) 0 4 (7.5)

Adapted from Shaw et al. Annals of Oncology 30: 1121–1126, 2019

Median duration of treatment:
22.4 months (95% CI: 15.0–35.9)

CI, confidence interval; NSCLC, non-small cell lung cancer; TRAE, treatment-related adverse event.

[a]There were no Grade 4 or 5 TRAEs. [b]Bradycardia (Grade 2) and renal cyst (Grade 3) in one patient and gastrointestinal amyloidosis (Grade 3) in the other patient.

Treatment-related Adverse events in ≥10% of Patients

TRAEs, n (%)	ROS1-rearranged NSCLC (N=53)	
	Any Grade	Grade 3[a]
Vision disorder[b]	46 (86.8)	0
Nausea	27 (50.9)	1 (1.9)
Edema[b]	25 (47.2)	0
Diarrhea	24 (45.3)	0
Vomiting	20 (37.7)	2 (3.8)
Elevated transaminases[b]	19 (35.8)	2 (3.8)
Constipation	18 (34.0)	0
Bradycardia[b]	11 (20.8)	0
Fatigue	11 (20.8)	0
Dizziness[b]	10 (18.9)	0
Dysgeusia	10 (18.9)	0
Hypophosphatemia	9 (17.0)	8 (15.1)
Decreased appetite	8 (15.1)	1 (1.9)
Neutropenia[b]	8 (15.1)	5 (9.4)
Rash	7 (13.2)	0

[a]There were no Grade 4 or 5 TRAEs. [b]Clustered term comprising AEs that represent similar clinical symptoms/syndromes.

NSCLC, non-small cell lung cancer; TRAE, treatment-related adverse event.

Please see summary of prescribing information on last slide

Shaw et al. Annals of Oncology 30: 1121–1126, 2019

Crizotinib

---------- **WARNINGS AND PRECAUTIONS**----------

- Hepatotoxicity: Fatal hepatotoxicity has occurred. Monitor with periodic liver testing. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (2.5, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Permanently discontinue in patients with ILD/pneumonitis. (2.5, 5.2)
- QT Interval Prolongation: Monitor electrocardiograms and electrolytes in patients who have a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (2.5, 5.3)
- Bradycardia: XALKORI can cause bradycardia. Monitor heart rate and blood pressure regularly. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (2.5, 5.4)
- Severe Visual Loss: XALKORI can cause visual changes including severe visual loss. Discontinue XALKORI in patients with severe visual loss. Monitor and evaluate for ocular toxicity throughout treatment. (2.5, 5.5)
- Gastrointestinal Toxicity in Patients with ALCL: XALKORI can cause severe nausea, vomiting, diarrhea, and stomatitis. Provide standard antiemetic and antidiarrheal agents. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (2.4, 2.5, 5.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.7, 8.1, 8.3)

PROFILE 1001: Summary

- In this updated investigator-assessed analysis of PROFILE 1001 (N=53) (data cutoff: June 30, 2018):
  - Median PFS: 19.3 months (95% CI: 15.2–39.1)
  - ORR: 72% (95% CI: 57.7–83.2)
  - Median DOR: 24.7 months (95% CI: 15.2–45.3)
  - Median TTR: 7.9 weeks (range: 4.3-103.6)

- The most common Grade 3 TRAEs included hypophosphatemia (n=8), neutropenia (n=5), vomiting and elevated transaminases (n=2, each)
  - No new safety signals were observed with long-term Crizotinib treatment

- This analysis provides an update and supports the continued use of Crizotinib in the treatment of patients with *ROS1*-rearranged advanced NSCLC

NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

Shaw AT et al. Annals of Oncology 30: 1121–1126, 2019

Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non–Small-Cell Lung Cancer

Yi-Long Wu, James Chih-Hsin Yang, Dong-Wan Kim, Shun Lu, Jianying Zhou, Takashi Seto, Jin-Ji Yang, Noboru Yamamoto, Myung-Ju Ahn, Toshiaki Takahashi, Takeharu Yamanaka, Allison Kemner, Debasish Roychowdhury, Jolanda Paolini, Tiziana Usari, Keith D. Wilner, Koichi Goto

OxOnc: Study Design

Open-label, multinational, single-arm, multicenter phase II clinical trial (NCT01945021)

Key entry criteria:

- ≥18 years old
- *ROS1*-positive by central RT-PCR testing[a]
- Negative for translocation or inversion events involving the *ALK* gene[b]
- Locally-advanced or metastatic NSCLC
- ≤3 lines of prior systemic chemotherapy (excluding any prior therapy against ALK or ROS1)
- ECOG PS 0 or 1
- Measurable disease
- Brain metastases allowed if patients asymptomatic, or if treated, neurologically stable for ≥2 weeks

Crizotinib 250 mg BID PO, continuous dosing in 28 day cycles (n=110 planned, 127 enrolled)

Endpoints:

- Primary
  - ORR (RECIST 1.1, by IRR)
- Secondary
  - DoR
  - TTR
  - DCR
  - PFS
  - OS
  - Safety
  - Patient-reported outcomes (EORTC QLQ-C30 and QLQ-LC13)

[a]*ROS1* status determined using a validated AmoyDx RT-PCR assay performed by three regional laboratories.
[b]*ALK* status determined using one of three locally approved assays (Abbott Vysis *ALK* FISH test, Ventana ALK IHC test, or AmoyDx *ALK* RT-PCR test).

Adapted from Wu YL, *et al*. *J Clin Oncol* 2018; 36(10): 1405-1411

Wu YL, *et al*. J Clin Oncol. 2018 May 10;36(14):1405-1411

OxOnc: Summary of Efficacy Endpoints (1)

End point	Total (N=127)
Best overall response,[a] n (%)	
Complete response	17 (13.4)
Partial response	74 (58.3)
Stable disease	21 (16.5)
Progressive disease	9 (7.1)
Early death[b]	2 (1.6)
Indeterminate	4 (3.1)
Objective response rate,[a] n (%)	91 (71.7)
95% CI[c]	63.0–79.3
Time to first tumor response,[a] months	
Median	1.9
Range	1.6–15.8

Adapted from Wu YL, *et al*. *J Clin Oncol* 2018; 36(10): 1405-1411

[a]By independent radiology review; [b]Death within 42 days of first dose; Grade 5 respiratory failure, not related to treatment (n=1) and Grade 5 pneumonia, not related to treatment (n=1); [c]Calculated using the exact method based on *F*-distribution.

Wu YL, *et al*. J Clin Oncol. 2018 May 10;36(14):1405-1411

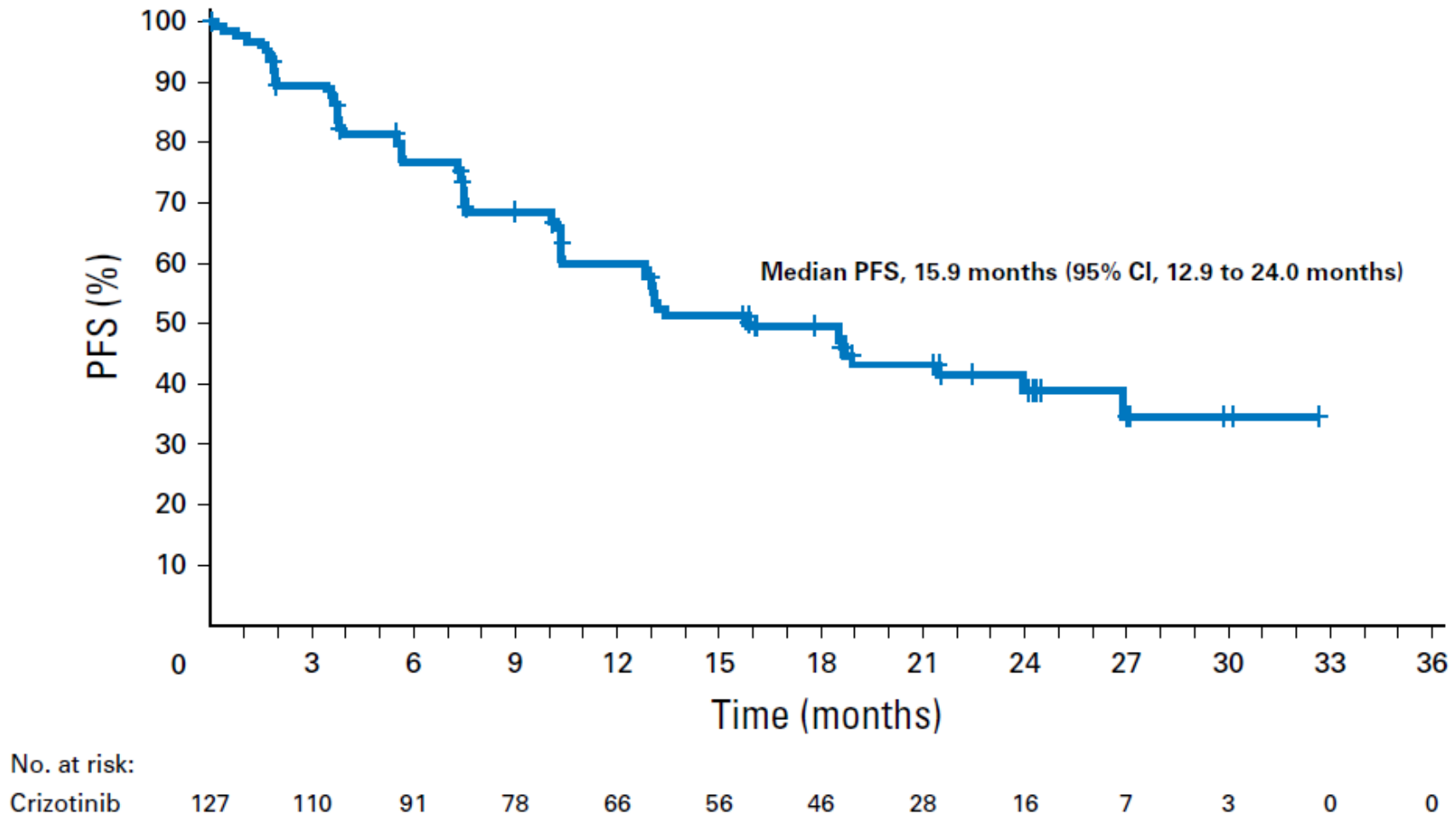
OxOnc: ORR[a] by Baseline Characteristic (1)

Characteristic	Total crizotinib (N=127)	
	No. of patients	ORR, % (95% CI)
Country		
China	53 of 74	71.6 (59.9–81.5)
Japan	17 of 26	65.4 (44.3–82.8)
Other	21 of 27	77.8 (57.7–91.4)
Sex		
Male	34 of 54	63.0 (48.7–75.7)
Female	57 of 73	78.1 (66.9–86.9)
Age group		
<65 years	78 of 106	73.6 (64.1–81.7)
≥65 years	13 of 21	61.9 (38.4–81.9)
Smoking history		
No	68 of 91	74.7 (64.5–83.3)
Yes	23 of 36	63.9 (46.2–79.2)

[a]Assessed by independent radiological review.

Wu YL, *et al*. J Clin Oncol. 2018 May 10;36(14):1405-1411

OxOnc: Progression-free Survival[a]



Adapted from Wu YL, *et al*. *J Clin Oncol* 2018; 36(10): 1405-1411

[a]Assessed by independent radiological review.

Wu YL, *et al*. J Clin Oncol. 2018 May 10;36(14):1405-1411

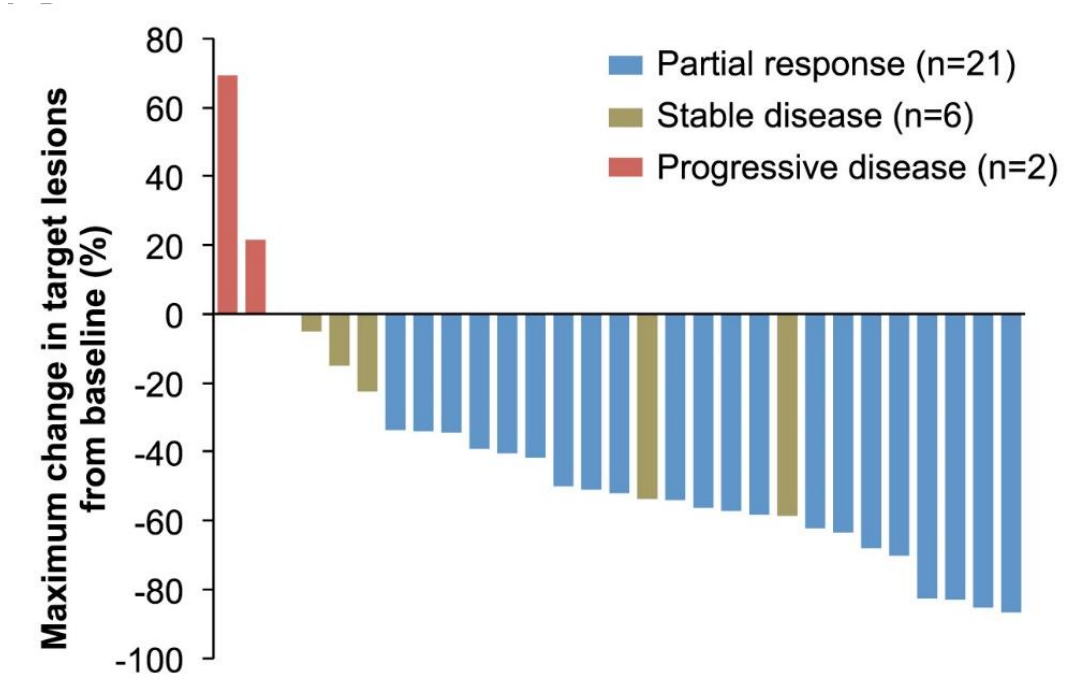
Safety and Efficacy of Crizotinib in Patients With Advanced or Metastatic *ROS1*-Rearranged Lung Cancer (**EUCROSS**): A European Phase II Clinical Trial

Sebastian Michels, Bartomeu Massutí Hans-Ulrich Schildhaus , Jeremy Franklin, Martin Sebastian , Enriqueta Felip , Christian Grohé, Delvys Rodriguez-Abreu Diana S Y Abdulla , Helge Bischoff , Christian Brandts , Enric Carcereny , Jesús Corral, Anne-Marie C Dingemans Eva Pereira , Jana Fassunke , Rieke N Fischer , Masyar Gardizi, Lukas Heukamp Amelia Insa Anna Kron , Roopika Menon, Thorsten Persigehl , Martin Reck , Richard Riedel, Sacha I Rothschild , Andreas H Scheel , Matthias Scheffler, Petra Schmalz , Egbert F Smit , Meike Limburg, Mariano Provencio , Niki Karachaliou , Sabine Merkelbach-Bruse , Martin Hellmich , Lucia Nogova, Reinhard Büttner , Rafael Rosell , Jürgen Wolf

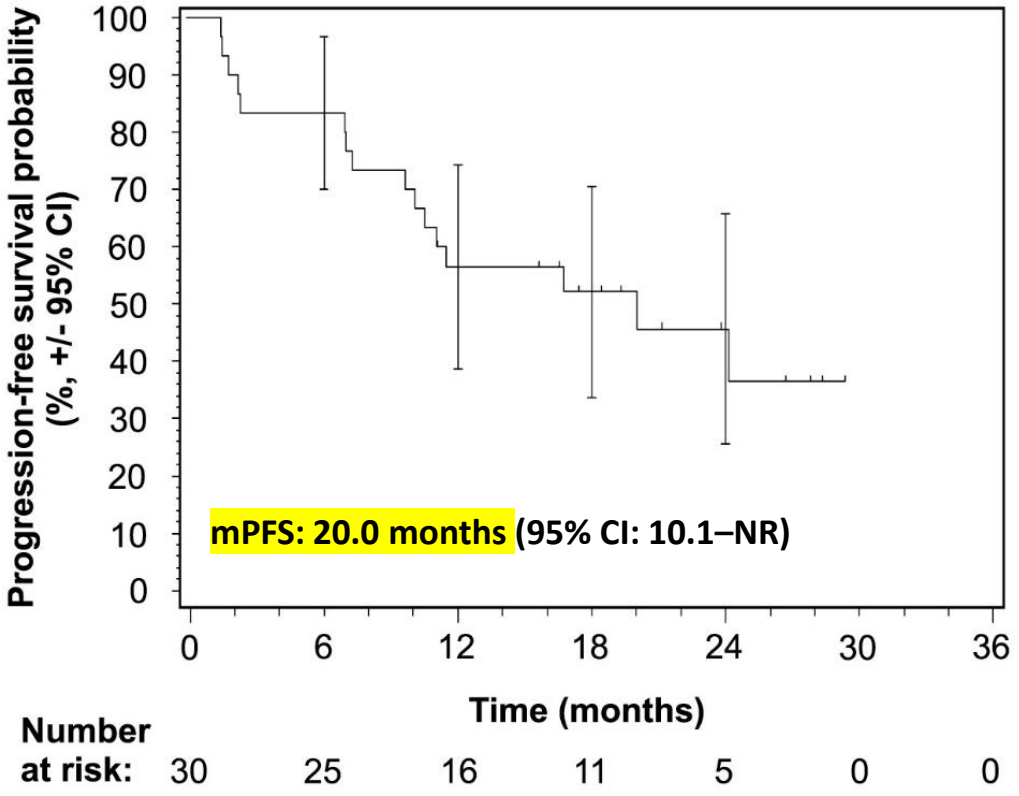
Michels et al. J Thorac Oncol 2019 Jul;14(7):1266-1276

EUCROSS: Efficacy of Crizotinib in Metastatic ROS1-Rearranged Lung Cancer

Response-evaluable population (n = 30)



Maximum change in target lesions from baseline (%) as assessed by investigator (RECIST v 1.1)



Progression-free survival as assessed by investigator

Michels et al. J Thorac Oncol 2019 Jul;14(7):1266-1276

EUCROSS: Updated OS
Presented in ASCO 2022

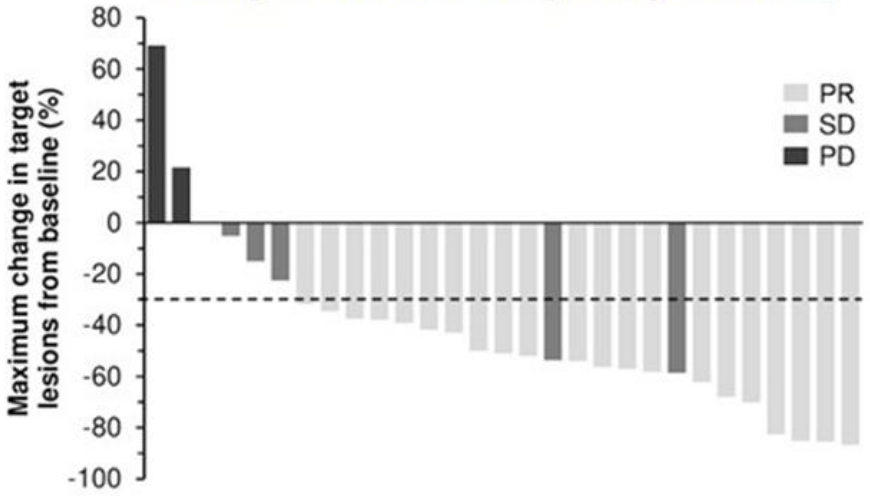
Time-to-Event Endpoints as Assessed by the Investigators for the Response-Evaluable Population

	Efficacy set (N=30)	*TP53* wt (N=13)	*TP53* mut (N=5)	No CNS mets (N=23)	CNS mets (N=6)
Progression-free survival (PFS)					
Median PFS (months, 95% CI)	19.4 (10.1-31.3)	24.1 (10.1-NR)	7.0 (1.7-20.0)	20.0 (10.1-36.9)	9.4 (1.7-NR)
PFS at 12 months (%; 95% CI)	56.5 (38.7-74.3)	60.6 (33.5-87.7)	40.0 (0.0-82.9)	60.9 (40.9-80.8)	33.3 (0.0-71.7)
PFS at 24 months (%; 95% CI)	43.1 (24.1-62.2)	40.0 (0.0-82.9)	0.0 (0.0-0.0)	48.8 (26.7-70.9)	16.7 (0.0-46.5)
Significance, p		0.0219		0.2092	
Overall survival (OS)					
Median OS (months; 95% CI)	NR (17.1-NR)	NR (16.4-NR)	17.1 (1.7-NR)	NR (17.1-NR)	21.1 (1.7-NR)
OS at 24 months (%; 95% CI)	65.6 (45.5-79.8)				
OS at 48 months (%; 95% CI)	55.0 (35.4-70.9)				
Log-rank, p		0.015		0.1373	

Response Analysis in the Response-Evaluable Population

	Local radiologic assessment		Independent radiologic assessment	
	% (N)	95% CI	% (N)	95% CI
ORR	70.0 (21)	0.506-0.853	70.0 (21)	0.506-0.853
Complete response	0.0 (0)		3.3 (1)	
Partial response	70.0 (21)		66.7 (20)	
DCR	90.0 (27)	0.735-0.979	83.3 (25)	0.653-0.945
Stable disease	20.0 (6)		13.3 (4)	
Non-CR/non-PD	0.0 (0)		6.7 (2)	
Progressive disease	6.7 (2)		6.7 (2)	
NE	3.3 (1)		3.3 (1)	

Investigator-Assessed Response (RECIST 1.1)



Michels et al. ASCO 2022, Poster Abs9078

Entrectinib

- 36% of patients of ROS+ NSCLC has base line brain mets
- Up to 50% of patients develop brain mets after crizotinib
- Drug with Intracranial efficacy is very important in these subset

- Entrectinib : Multikinase inhibitor : ALK, ROS, and NTRK , penetrates BBB

THE LANCET
Oncology

ARTICLES | VOLUME 21, ISSUE 2, P261-270, FEBRUARY 01, 2020

Purchase

Entrectinib in *ROS1* fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials

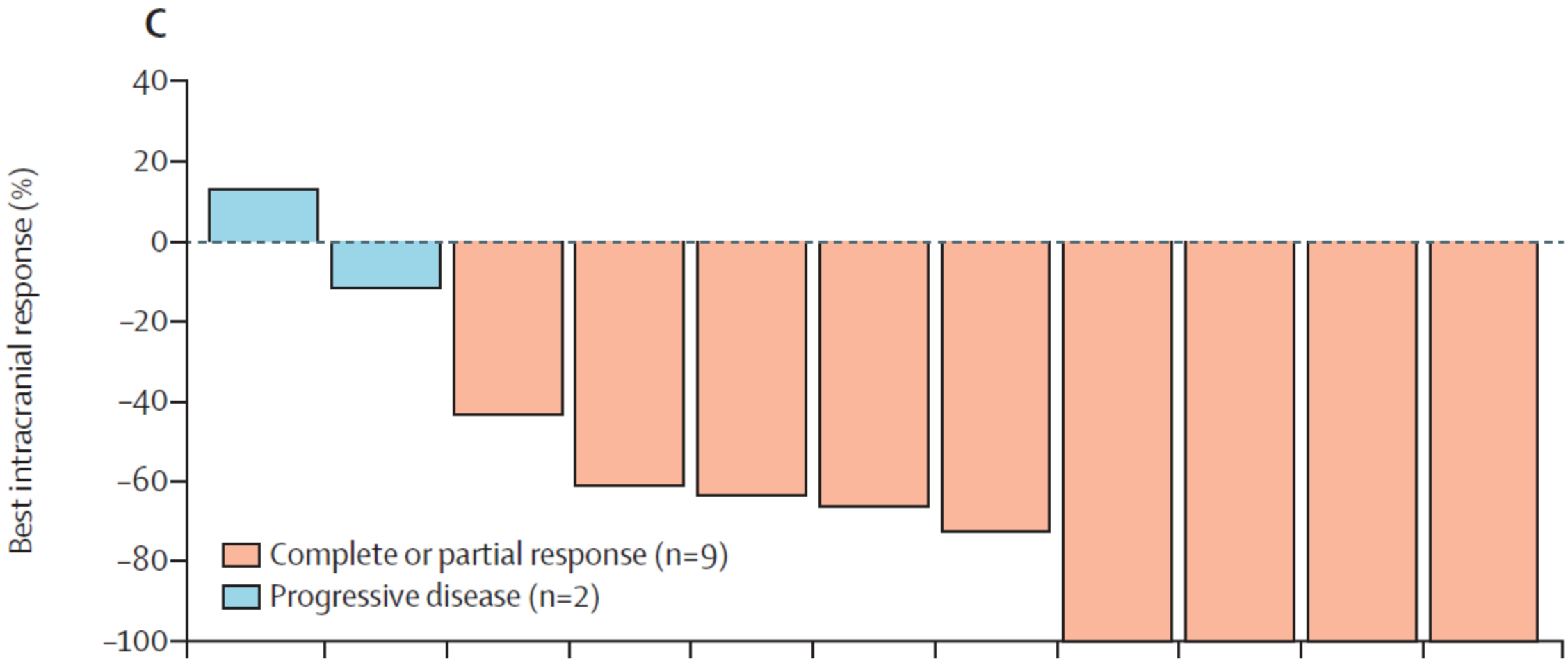
Alexander Drilon, MD * • Prof Salvatore Siena, MD * • Rafal Dziadziuszko, MD • Fabrice Barlesi, MD • Matthew G Krebs, MD • Prof Alice T Shaw, MD • et al. Show all authors • Show footnotes

Published: December 11, 2019 • DOI: https://doi.org/10.1016/S1470-2045(19)30690-4 • Check for updates

Patients in Integrated analysis

	All patients in integrated analysis (n=53)
Age, years	53 (46–61)
Sex	
Female	34 (64%)
Male	19 (36%)
Ethnicity	
White	31 (59%)
Asian	19 (36%)
Black or African–American	3 (6%)
Eastern Cooperative Oncology Group performance status	
0	20 (38%)
1	27 (51%)
2	6 (11%)
Smoking status	
Never smoker	31 (59%)
Previous or current smoker	22 (42%)
Histology*	
Adenocarcinoma	52 (98%)
Other†	1 (2%)
CNS disease present at baseline‡	23 (43%)
Measurable	5 (9%)
Not measurable	18 (34%)
Previous CNS disease treatment§	8 (35%)
Stereotactic radiotherapy	3 (13%)
Whole brain with or without stereotactic radiotherapy	5 (22%)
No previous CNS disease treatment§	15 (65%)
Number of previous systemic therapies	
0	17 (32%)
1	23 (43%)
2 or more	13 (25%)
Gene fusion	
CD74–ROS1	21 (40%)
SLC34A2–ROS1	7 (13%)
SDC4–ROS1	6 (11%)
EZR–ROS1	5 (9%)
TPM3–ROS1	2 (4%)
Unknown¶	12 (23%)

	Integrated efficacy-evaluable population (n=53)	Patients with baseline CNS disease (n=23)*	Patients with no baseline CNS disease (n=30)*
Objective responses, n; % (95% CI)	41; 77% (64–88)	17; 74% (52–90)	24; 80% (61–92)
Best overall response			
Complete response, n (%)	3 (6%)†	0	3 (10%)
Partial response, n (%)	38 (72%)†	17 (74%)	21 (70%)
Stable disease, n (%)	1 (2%)	0	1 (3%)
Progressive disease, n (%)	4 (8%)	4 (17%)	0
Non-complete response or non-progressive disease, n (%)	3 (6%)	0	3 (10%)
Missing or unevaluable, n (%)‡	4 (8%)	2 (9%)	2 (7%)
Duration of response			
Median, months (95% CI)	24·6 (11·4–34·8)	12·6 (6·5–NE)	24·6 (11·4–34·8)
Progression-free survival			
Median, months (95% CI)	19·0 (12·2–36·6)	13·6 (4·5–NE)	26·3 (15·7–36·6)
Intracranial activity	..	20·0‡	..
Overall response, n; % (95% CI)	..	11; 55% (32–77)	..
Best intracranial response			
Complete response, n (%)	..	4 (20%)	..
Partial response, n (%)	..	7 (35%)	..
Stable disease, n (%)	..	0	..
Progressive disease, n (%)	..	3 (15%)	..
Non-complete response or non-progressive disease, n (%)	..	4 (20%)	..
Missing or unevaluable, n (%)§	..	2 (10%)	..


C
Best intracranial response (%)
40
20
0
–20
–40
–60
–80
–100
Complete or partial response (n=9)
Progressive disease (n=2)

Side effects 10% and above : Entrectinib

	Grade 1–2	Grade 3	Grade 4
Dysgeusia	56 (42%)	1 (<1%)	0
Dizziness	43 (32%)	1 (<1%)	0
Constipation	44 (33%)	0	0
Diarrhoea	35 (26%)	3 (2%)	0
Weight increase	26 (19%)	10 (7%)	0
Fatigue	32 (24%)	0	0
Paraesthesia	23 (17%)	0	0
Nausea	23 (17%)	0	0
Peripheral oedema	22 (16%)	0	0
Myalgia	19 (14%)	2 (2%)	0
Vomiting	19 (14%)	0	0
Blood creatinine increase	17 (13%)	1 (<1%)	0
Aspartate aminotransferase increase	14 (10%)	2 (2%)	0
Alanine aminotransferase increase	13 (10%)	3 (2%)	0

Entrectinib

---------- WARNINGS AND PRECAUTIONS----------

- Congestive Heart Failure: Assess left ventricular ejection fraction prior to initiation of ROZLYTREK in patients with symptoms or known risk factors for CHF. Monitor patients for clinical signs and symptoms of congestive heart failure (CHF). For patients with myocarditis, with or without a decreased ejection fraction, MRI or cardiac biopsy may be required to make the diagnosis. For new onset or worsening CHF, withhold ROZLYTREK, reassess LVEF and institute appropriate medical management. Reduce dose or permanently discontinue ROZLYTREK based on severity of CHF or worsening LVEF. (2.4, 5.1)
- Central Nervous System (CNS) Effects: CNS adverse reactions including cognitive impairment, mood disorders, dizziness, and sleep disturbances can occur with ROZLYTREK. Withhold and then resume at same or reduced dose upon improvement or permanently discontinue ROZLYTREK based on severity. (2.4, 5.2)
- Skeletal Fractures: ROZLYTREK increases the risk of fractures. Promptly evaluate patients with signs or symptoms of fractures. (5.3)
- Hepatotoxicity: Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue ROZLYTREK based on severity. If withheld, resume ROZLYTREK at same or reduced dose based on severity. (2.4, 5.4)
- Hyperuricemia: Assess serum uric acid levels prior to initiation and periodically during treatment with ROZLYTREK. Monitor patients for signs and symptoms of hyperuricemia. Initiate treatment with urate-lowering medications as clinically indicated and withhold ROZLYTREK for signs and symptoms of hyperuricemia. Resume at same or reduced dose upon improvement based on severity. (2.4, 5.5)
- QT Interval Prolongation: Monitor patients who have or who are at risk for QTc interval prolongation. Assess QT interval and electrolytes at baseline and periodically during treatment. Withhold and then resume at same or reduced dose, or permanently discontinue ROZLYTREK based on severity. (2.4, 5.6)
- Vision Disorders: Withhold for new visual changes or changes that interfere with activities of daily living until improvement or stabilization. Conduct an ophthalmological evaluation as appropriate. Resume at same or reduced dose upon improvement or stabilization. (2.4, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

Ceritinib in ROS1 NSCLC

Journal of Clinical Oncology > List of Issues > Volume 35, Issue 23 >

ORIGINAL REPORTS | Thoracic Oncology

Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non–Small-Cell Lung Cancer Harboring *ROS1* Rearrangement

Sun Min Lim, Hye Ryun Kim, Jong-Seok Lee, Ki Hyeong Lee, Yun-Gyoo Lee, Young Joo Min, ...

Show More

Table 2. Independent Review Committee–Assessed Activity

Best Response	All Patients, No. (%)	Crizotinib-Naïve Patients, No. (%)
No. of patients	32	30
CR	1 (3)	1 (3)
PR	19 (59)	19 (63)
SD	6 (19)	6 (20)
PD	2 (6)	2 (7)
Not evaluable*	4 (12)	2 (7)
ORR, % (95% CI)	62 (45 to 77)	67 (48 to 81)
DCR (CR + PR + SD), % (95% CI)	81 (65 to 91)	87 (70 to 95)

Abbreviations: CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

*As a result of early death (n = 3) or withdrawal (n = 1) before first response evaluation.

Table 3. Adverse Events That Occurred at Grades 1 to 2 in 10% or More Patients or at Grades 3 to 5

Adverse Event	Grade, No. (%)			
	1 to 2	3	4	5
Diarrhea	25 (78)	0	0	0
Nausea	19 (59)	1 (3)	0	0
Anorexia	18 (56)	1 (3)	0	0
Vomiting	17 (53)	0	0	0
Cough	15 (47)	0	0	0
Abdominal pain	13 (41)	0	0	0
Musculoskeletal pain	13 (41)	0	0	0
Fatigue	7 (22)	5 (16)	0	0
Dyspnea	7 (22)	0	0	1 (3)
Fever	6 (19)	0	0	0
Pruritus	5 (16)	0	0	0

Lorlatinib in ROS1-positive NSCLC

Being studied in First line ROS+ patients

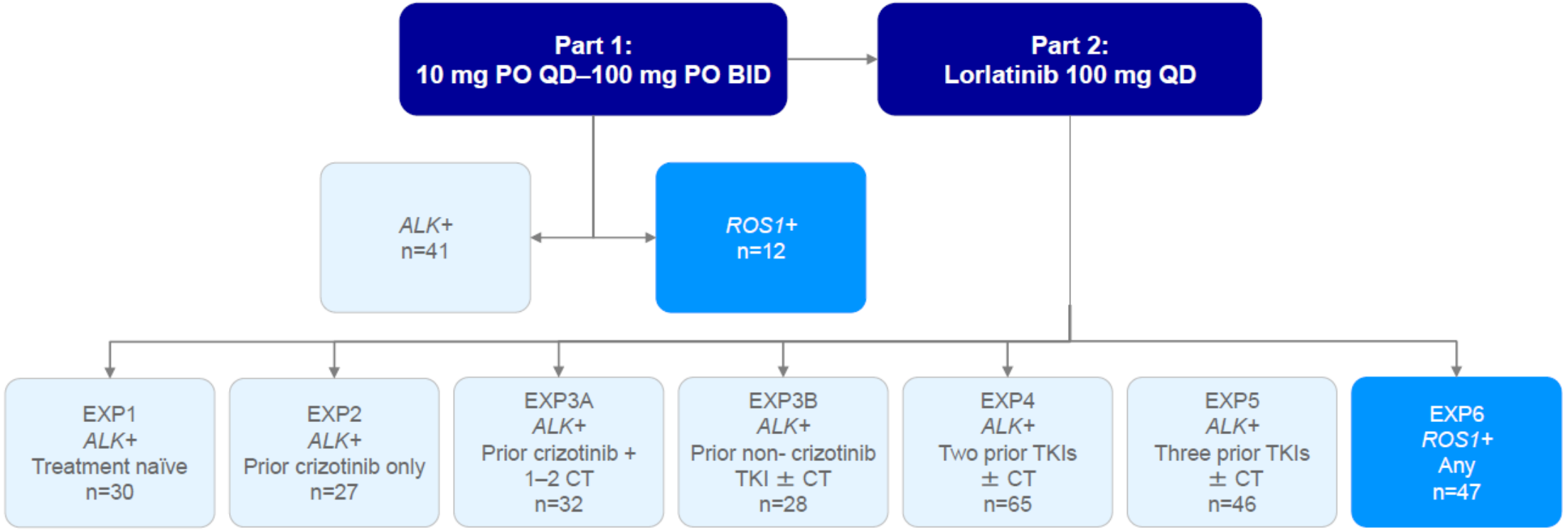
- In previously treated crizotinib, the most common cause of Crizotinib resistance is the solvent front mutation ROS1 G2032R, which has been shown to sterically impede drug binding

- Lorlatinib is an oral ALK/ROS1 TKI that was studied in a Phase I/II study of treatment naïve and previously treated NSCLC, including a cohort of *ROS1*-positive patients

CNS, central nervous system; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.
Shaw A, et al. *Lancet Oncol.*2019 Dec;20(12):1691–1701.

Lorlatinib Study B7461001: Overall Study Design

Multicenter, Open-Label, Single-Arm Phase 1–2 Trial (NCT01970865)



BID, twice daily; CT, chemotherapy; EXP, expansion cohort; PO, orally; QD, once daily.
LORVIQUA®(lorlatinib) is not approved for this use by EMA.
Shaw A, et al. *Lancet Oncol.*2019 Dec;20(12):1691–1701.
Solomon BJ, et al. *Lancet Oncol.*2018 Dec;19(12):1654-1667

Tumor Response of ROS1 Patients

- Among all 69 patients with *ROS1*-positive NSCLC, responses were observed in 28 patients (41%; 95% CI: 29–53).
- The table below describes the tumor response in patients who were TKI-naïve or had received prior crizotinib only.

		TKI-naïve	Prior crizotinib only
Overall	n	21	40
Best overall response, n (%)	Complete response	2 (10)	2 (5)
	Partial response	11 (52)	12 (30)
	Stable disease	6 (29)	16 (40)
	Objective progression	2 (10)	4 (10)
	Indeterminate	0	6 (15)
Confirmed ORR, n (%)		13 (62)	14 (35)
95% CI*		38–82	21–52
Time to first tumor response, months	Median (IQR)	1.4 (1.4–1.4)	2.1 (1.4–2.8)
Duration of response, months	Median (95% CI†)	25.3 (7.5–31.9)	13.8 (9.7–NR)

- **TKI-naïve patients:** Objective response was observed in 5 (45%; 95% CI: 17–77) of 11 patients with baseline CNS metastases and 8 (80%, 44–98) of 10 patients without baseline CNS metastases.
- **Prior crizotinib only patients:** Objective response was observed in 6 (25%; 95% CI: 10–47) of 24 patients with baseline CNS metastases and 8 (50%, 25–75) of 16 patients without baseline CNS metastases.

* Using exact method based on binomial distribution; † Using Brookmeyer and Crowley method.
CI, confidence interval; IQR, interquartile range; NR, not reached; NSCLC, non-small cell carcinoma; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
Shaw A, et al. Lancet Oncol. 2019 Dec;20(12):1691–1701.

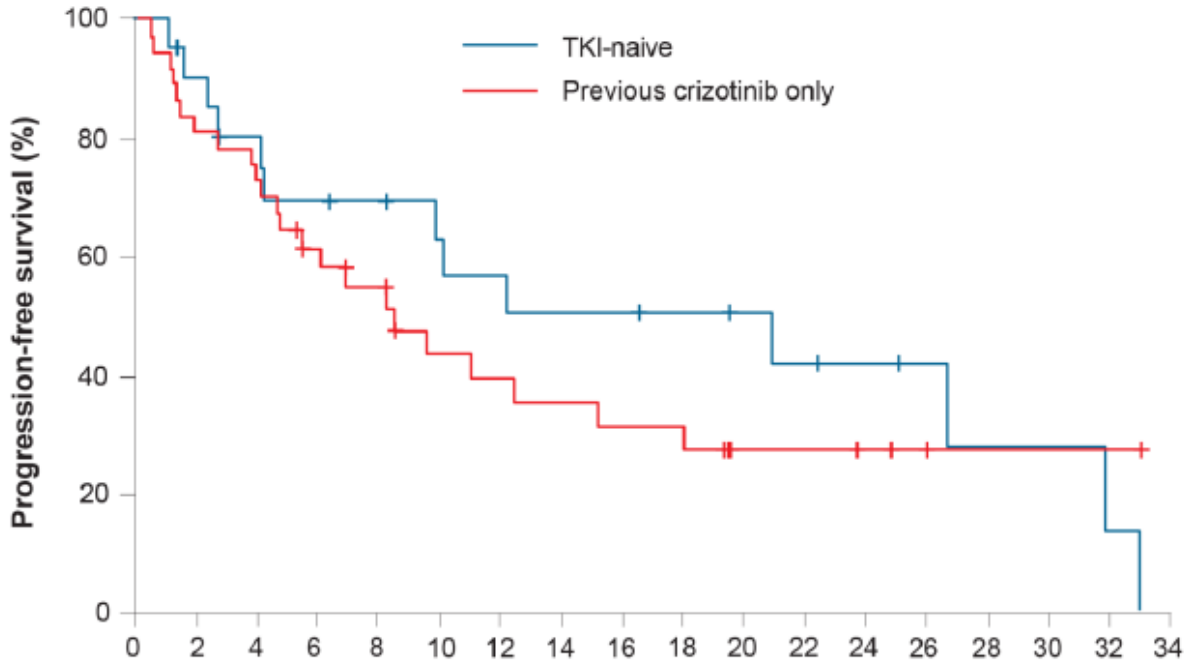
Intracranial Response

		TKI-naïve	Prior crizotinib only
INTRACRANIAL			
No. of patients with baseline CNS metastases*		11	24
Best overall intracranial response, n (%)	Complete response	5 (45)	9 (38)
	Partial response	2 (18)	3 (13)
	Stable disease	2 (18)	6 (25)
	Objective progression	2 (18)	2 (8)
	Indeterminate†	0	4 (17)
Confirmed intracranial ORR, n (%)		7 (64)	12 (50)
95% CI‡		31–89	29–71
Duration of intracranial response, months Median (95% CI§)		NR (5.7–NR)	NR (11.0–NR)

- Six TKI-naïve patients had measurable baseline CNS metastases and 4 (67%; 95% CI: 22–96) of these patients achieved intracranial responses
- Of the 10 prior crizotinib, only patients with measurable baseline CNS metastases, 5 (50%; 95% CI: 19–81) achieved an intracranial response

•*CNS metastases were measurable and non-measurable. †Patients defined as indeterminate if (1) only baseline assessments available; (2) tumor assessments incomplete; or (3) first response assessment of stable disease at an interval less than 6 weeks from treatment start and no subsequent disease evaluation. ‡Using exact method based on binomial distribution; §Using Brookmeyer and Crowley method.
•CI, confidence interval; CNS, central nervous system; NR, not reached; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
Shaw A, et al. Lancet Oncol. 2019 Dec;20(12):1691–1701.

Progression-Free Survival



Number at risk (number censored)

TKI-naive	21 (0)	18 (1)	15 (2)	13 (2)	12 (3)	10 (4)	9 (4)	8 (4)	8 (4)	7 (5)	6 (6)	5 (6)	4 (7)	3 (8)	2 (8)	2 (8)	1 (8)	0 (8)
Previous crizotinib only	40 (0)	30 (3)	26 (4)	20 (6)	16 (8)	11 (10)	10 (10)	9 (10)	8 (10)	8 (10)	4 (13)	4 (13)	3 (14)	1 (16)	1 (16)	1 (16)	1 (16)	0 (17)

	TKI-naïve (n=21)	Prior crizotinib only (n=40)
Events, n (%)	13 (62)	23 (58)
Median PFS, months (95% CI)	21.0 (4.2–31.9)	8.5 (4.7–15.2)

Vertical lines on the curves indicate censoring of data.
CI, confidence interval; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Shaw A, et al. Lancet Oncol. 2019 Dec;20(12):1691–1701.

Drugs approved for ROS1 + NSCLC

- FDA : Crizotinib, Entrectinib
- EMA: Crizotinib, Entrectinib
- NCCN: Crizotinib, Ceritinib, Entrectinib

Table 2. Main clinical trials about ROS1 TKIS in patients with ROS1 fusion-positive NSCIC.

ROS1 TKI	Clinical trial (phase)	No of patients	Median PFS (months)	Median OS (months)	ORR%	ROS1 testing technique
Crizotinib	PROFILE 1001 (I)	53	19.3	51.4	72	51 FISH 2 RT-PCR
	OxOnc101(II)	127	15.9	32.5	71.7	RT-PCR
	EUCROS (II)	30	20.0	NR	70	NR
	AcSe(II)	36	5.5	17.2	69	FISH
	METROS(II)	26	22.8	NR	65	FISH
Entrectinib	Drilon et al.(II)	53	19	NR	77	FISH
Ceritinib	Lim et al. (II)	30	9.3	24	67	FISh
Lorlatinib	Shaw et al. (1/II)	21	21.0	NR	62	NR
Brigatinib	Hochmair et al.	14	NR	20.0	85.7	NR
Repotrectinib	Cho et al.(I/II)	11	24.6	NR	91	NR

TKI: tirosine kinase inhibitor; ORR: objective response rate; mPFS: median progression free survival; mOS: median overall survival; NR: not reached

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

RGETED THERAPY OR IMMUNOTHERAPY FOR ADVANCE

quamous)[8]

X

Positive

***ALK* Rearrangement Positive**
- First-line therapy
  - Alectinib[15,16]
  - Brigatinib[17]
  - Ceritinib[18]
  - Crizotinib[15,19]
  - Lorlatinib[20]
- Subsequent therapy
  - Alectinib[21,22]
  - Brigatinib[23]
  - Ceritinib[24]
  - Lorlatinib[25]

***ROS1* Rearrangement Positive**
- First-line therapy
  - Ceritinib[24]
  - Crizotinib[27]
  - Entrectinib[28]
- Subsequent therapy
  - Lorlatinib[29]
  - Entrectinib[28]

***BRAF* V600E Mutation Positive**
- First-line therapy
  - Dabrafenib/trametinib[30,31]
  - Dabrafenib[30]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[31,32]

***NTRK1/2/3* Gene Fusion Positive**
- First-line/Subsequent therapy
  - Larotrectinib[33]
  - Entrectinib[34]

Chemotherapy in ROS1 positive Cancers

- ROS1-positive patients with advanced disease responded more effectively to pemetrexed-based CT regimens than patients with other driver mutations in NSCLC, with significantly better overall survival (OS).
- Their objective remission rate (ORR) was estimated at 60%, their disease control rate (DCR) at 89.5% and their PFS at 7 months.
- One proposed reason for this sensitivity to PEM is lower level of expression of Thymidylate Synthase in ROS+ NSCLC

Sincere Thanks from Assam Cancer Care Foundation

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