METASTATIC ROS 1 POSITIVE NON SMALL CELL LUNG CANCER.

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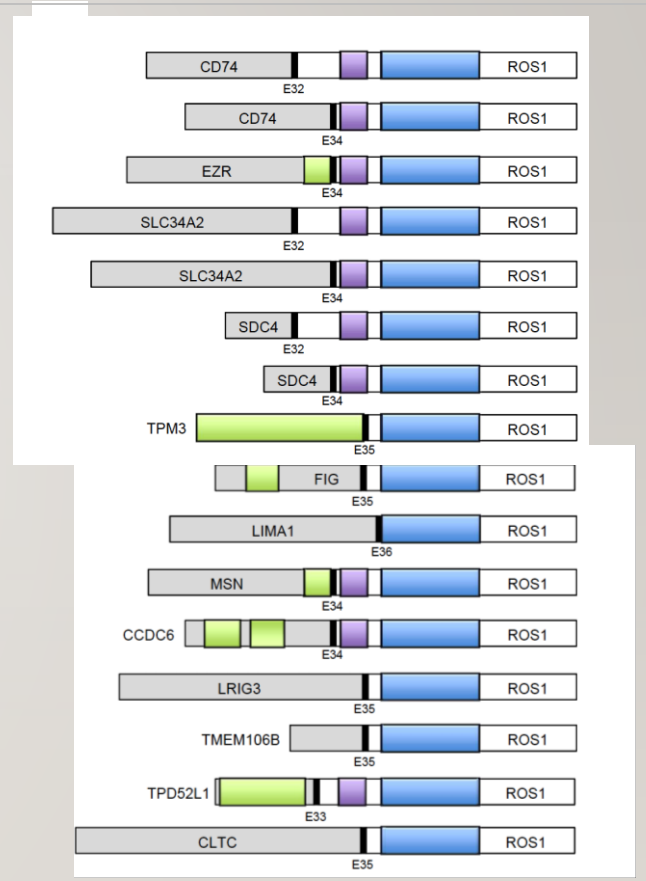
ROS 1 GENOMIC ALTERATION.

- ROS1 is an oncogene on Chromosome 6(6q22).
- ROS 1 rearrangements are seen in 22 different malignancies.
- In Non Small Cell Lung cancer(NSCLC) ROS1 rearrangements are seen in 1-2% of all cases.
- Typically seen in younger patients, never or light smokers and adenocarcinoma subtype.
- Rarely seen in large cell and squamous carcinomas too.

ROS1 REARRANGEMENTS IN NSCLC

Background

- *ROS1* rearrangements lead to fusion of a portion of ROS1, including its tyrosine kinase domain, to a variety of different partner proteins.
- ROS1 fusion kinases are constitutively activated and function as potent oncogenic drivers.
- ROS1 is phylogenetically related to ALK, resulting in sensitivity to some ALK tyrosine kinase inhibitors (TKIs).



Lin JJ, Shaw AT. *J Thorac Oncol.* 2017;12:1611–1625.

NSCLC, non-small cell lung cancer.

1. Bergethon K. *J Clin Oncol.* 2012;30:863–870. 2. Dugay F, et al. *Oncotarget.* 2017;8:53336-53351.

3. Davies KD, Doebele RC. *Clin Cancer Res.* 2013;19:4040–4045. 4. Lin JJ, Shaw AT. *J Thorac Oncol.* 2017;12:1611–1625.

TREATMENT OF ROS1 POSITIVE LUNG CANCER

- Crizotinib
- Entrectinib
- Lorlatinib

CRIZOTINIB IN ROS POSITIVE LUNG CANCER

- The kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites.
- Crizotinib binds with high affinity to both ALK and ROS1.
- Crizotinib inhibits ROS cell signalling and cell vitality ***in-vitro.***
- Hence, Crizotinib was the logical first choice for ROS +ve lung cancer.

PROFILE 1001: ROS1 EXPANSION COHORT (N=53)*

Study Design

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–Aug 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

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

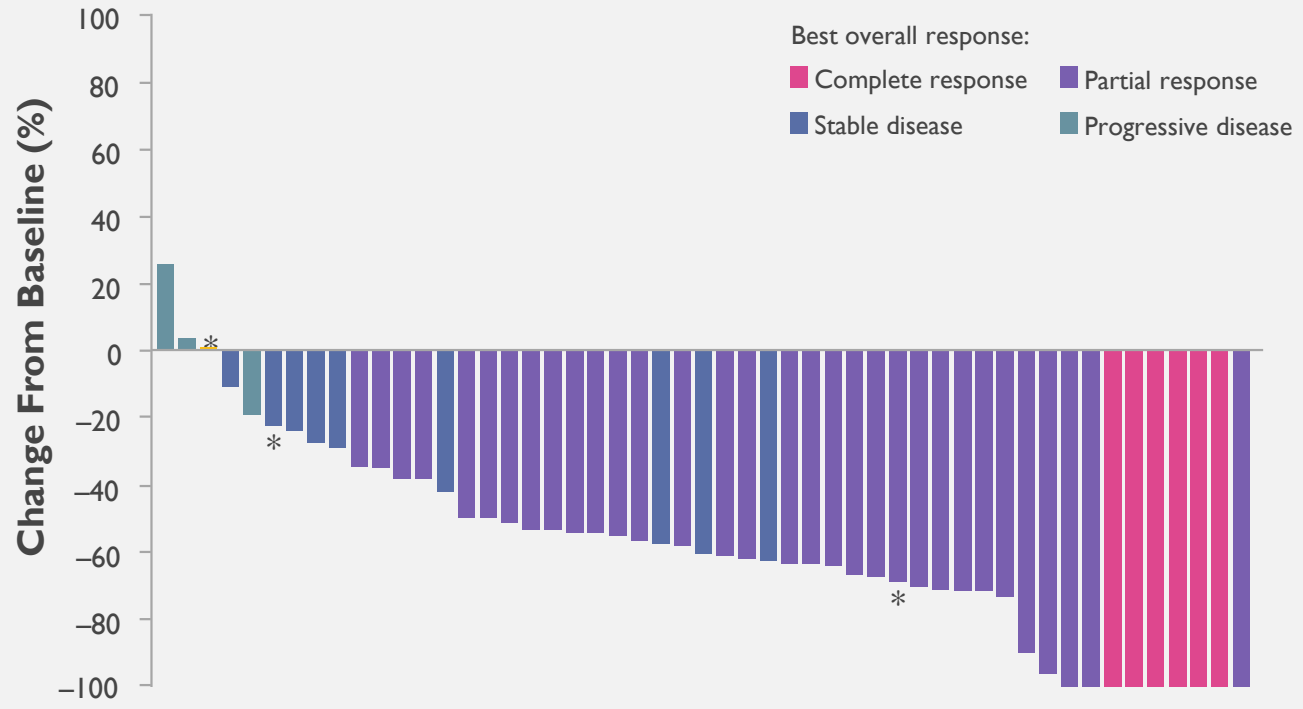
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Patients

Characteristic		*ROS1*-rearranged NSCLC (N=53)
Age, years	Median (range)	55.0 (25–81)
Sex, n (%)	Male	23 (43.4)
	Female	30 (56.6)
Race, n (%)	White	30 (56.6)
	Asian	21 (39.6)
	Black	2 (3.8)
Smoking status, n (%)	Never smoked	40 (75.5)
	Former smoker	13 (24.5)
Histological classification, n (%)	Adenocarcinoma	51 (96.2)
	Other[a]	2 (3.8)
ECOG PS, n (%)[b]	0	23 (43.4)
	1	29 (54.7)
Number of prior advanced / metastatic regimens, n (%)[c]	0	7 (13.2)
	1	22 (41.5)
	>1	24 (45.3)

ANTITUMOR ACTIVITY

Best % Change from Baseline in Target Lesion Size (N=51)[a]



*Indicates tumor assessment by RECIST v1.1.
a. Excludes 2 patients: one with early death and one with indeterminate response.

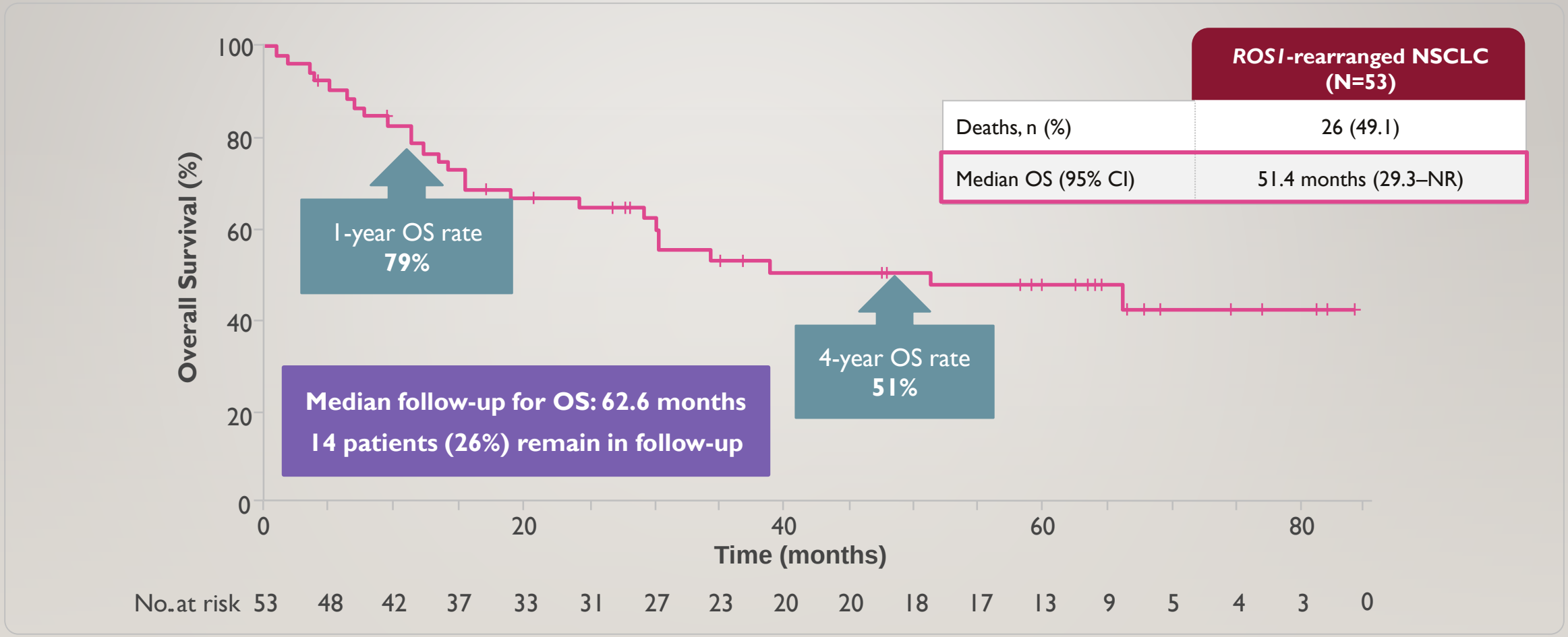
	ROS1-rearranged NSCLC (N=53)
BOR, n (%)	
CR	6 (11.3)
PR	32 (60.4)
SD	10 (18.9)
PD	3 (5.7)
NE†	2 (3.8)
ORR, %	71.7
95% CI	57.7–83.2
Median TTR, wks	7.9
Range	4.3–103.6
Median DOR,‡ mos	24.7
95% CI	15.2–45.3

† Responses could not be evaluated in 2 patients because of early death or indeterminate response; ‡ Estimated using the Kaplan-Meier method.

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

PROFILE 1001: OVERALL SURVIVAL



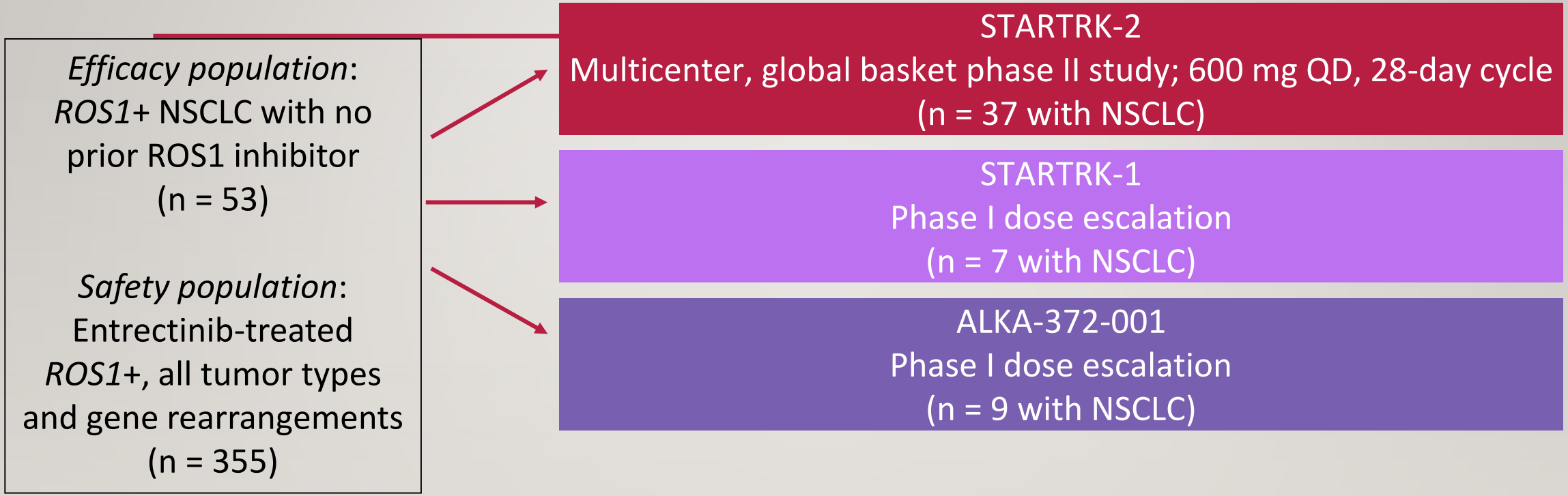
ROS1 POSITIVE LUNG CANCER

- Crizotinib was approved for frontline use in this population.
- However, 36% patients have Central Nervous System(CNS) involvement at baseline or they develop CNS metastases later in the course of disease.
- Crizotinib has low activity in CNS.
- CNS is the first-and at times only-site of progression in ROS +ve lung cancer patients treated with Crizotinib.
- Hence a search for treatment with better CNS activity was ongoing.

ENTRECTINIB IN *ROS1*+ NSCLC

- Entrectinib: oral, potent, selective multikinase TKI(ROS1/NTRK/ALK) with CNS activity
  - More potent ROS1 inhibitor than crizotinib in preclinical studies
  - Can cross blood–brain barrier and remain within CNS
    - Demonstrated activity in primary brain tumors, secondary CNS metastases

ENTRECTINIB IN *ROS1*+ NSCLC: INTEGRATED ANALYSIS



- Primary endpoints: ORR, DoR
- Secondary endpoints: PFS, OS, intracranial ORR and DoR, safety/tolerability

ENTRECTINIB IN *ROS1*+ NSCLC: ORR (BICR ASSESSMENT)

Response	Total (N = 53)	CNS Disease at Baseline (n = 23)	No CNS Disease at Baseline (n = 30)
ORR, n (%)	**41 (77.4)** (95% CI: 63.8-87.7)	**17 (73.9)** (95% CI: 51.6-89.8)	**24 (80.0)** (95% CI: 61.4-92.3)
CR, n (%)	3 (5.7)	0	3 (10.0)
PR, n (%)	38 (71.7)	17 (73.9)	21 (70.0)
SD, n (%)	1 (1.9)	0	1 (3.3)
PD, n (%)	4 (7.5)	4 (17.4)	0
Non-CR/non-PD, n (%)	3 (5.7)	0	3 (10.0)
Missing or unevaluable, n (%)	4 (7.5)	2 (8.7)	2 (6.7)
Clinical benefit rate (CR/PR/SD for ≥ 6 mos), n (%)	41 (77.4) (95% CI: 63.8-87.7)		
Median DoR, mos	24.6 (95% CI: 11.4-34.8)	12.6 (95% CI: 6.5-NE)	24.6 (95% CI: 11.4-34.8)

- 12-mo probability of EFS
- Median follow-up from first response: 16.6 mos

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

ENTRECTINIB IN *ROS1*+ NSCLC: SURVIVAL OUTCOMES

- Median follow-up: 15.5 mos

	Total (N = 53)	CNS Disease at Baseline (n = 23)	No CNS Disease at Baseline (n = 30)
Median PFS by BICR, mos	**19.0** (95% CI: 12.2-36.6)	**13.6** (95% CI: 4.5-NE)	**26.3** (95% CI: 15.7-36.6)
Patients with PFS event, n (%)	25 (47.2)	11 (47.8)	14 (46.7)
▪ PD, n	20	8	12
▪ Death, n	5	3	2

- 12-mo probability of PFS: 65%
- 12-mo probability of OS: 85%

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

Slide credit: clinicaloptions.com

ENTRECTINIB IN *ROS1*+ NSCLC: SAFETY SUMMARY

- N = 355 patients in 3 clinical trials
- Most AEs grade 1/2, reversible
- Treatment-related AEs
  - Leading to treatment discontinuation: 3.9%
  - Leading to dose reduction: 27.3%
  - Leading to dose interruption: 25.4%
  - Serious AEs: 8.5%
  - No deaths due to treatment-related AEs

Treatment-Related AE in ≥ 10% of Patients, n (%)	Safety-Evaluable Population (N = 355)	
	All Grades	Grade 3/4
Dysgeusia	147 (41.4)	1 (0.3)
Fatigue	99 (27.9)	10 (2.8)
Dizziness	90 (25.4)	2 (0.6)
Constipation	84 (23.7)	1 (0.3)
Nausea	74 (20.8)	0
Diarrhea	81 (22.8)	5 (1.4)
Weight increased	69 (19.4)	18 (5.1)
Paresthesia	67 (18.9)	0
Blood creatinine increased	54 (15.2)	2 (0.6)
Myalgia	54 (15.2)	2 (0.6)
Peripheral edema	50 (14.1)	1 (0.3)
Vomiting	48 (13.5)	0
Anemia	43 (12.1)	16 (4.5)
Arthralgia	44 (12.4)	2 (0.6)
AST increased	39 (11.0)	4 (1.1)

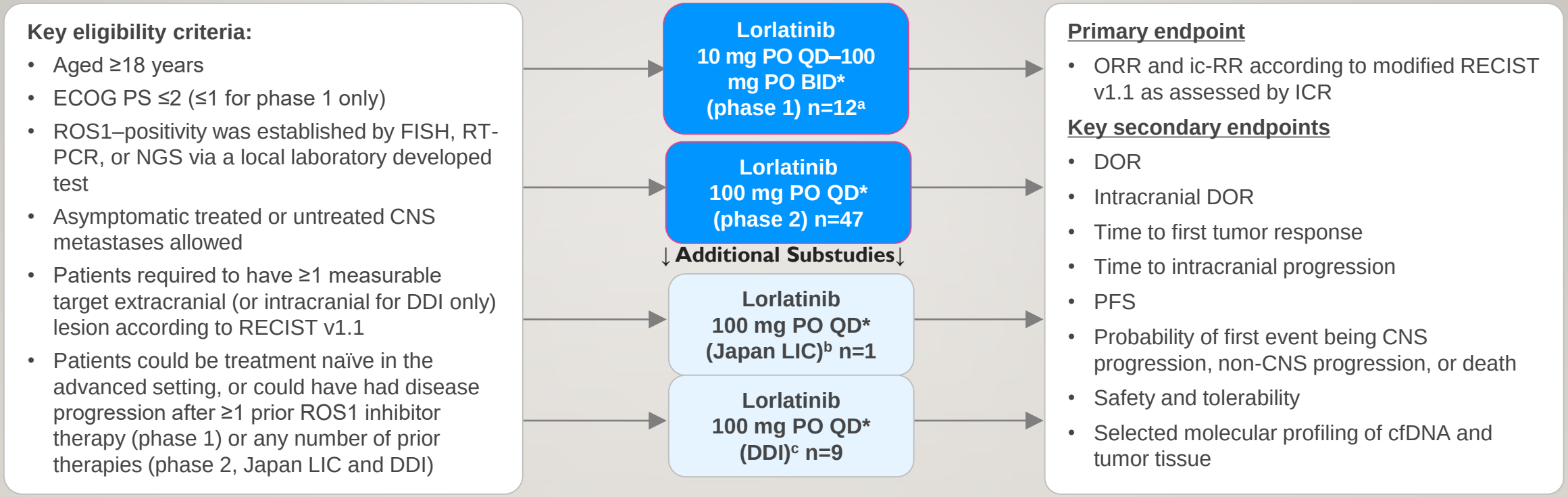
Doebele RC, et al. WCLC 2018. Abstract OA02.01.

Slide credit: clinicaloptions.com

CRIZOTINIB FAILED ROS 1+VE LUNG CANCER

- The most common cause of crizotinib resistance is the solvent front mutation ROS1 G2032R, which has been shown to sterically impede drug binding.
- While acquired resistance is a major cause of crizotinib failures, relapses are also common in the CNS, likely due to the poor blood-brain barrier penetration of crizotinib
- 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
- As of now, Lorlatinib is not approved for use in ROS1+ve Lung cancer.

ROS1 PATIENT POPULATION, N=69



Data cutoff date:
February 2, 2018

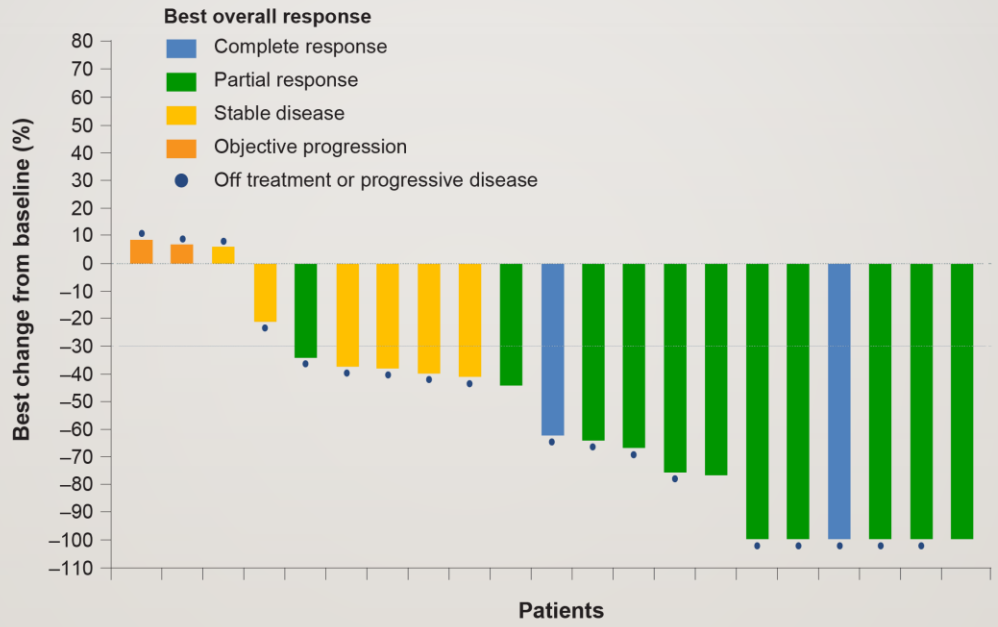
TUMOR RESPONSE OF ROS1 PATIENTS

- 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.

BEST PERCENT CHANGE IN TUMOR SIZE FROM BASELINE IN PATIENTS WHO WERE PREVIOUSLY ROS1 TKI-NAÏVE



- Of the 21 ROS1 TKI-naïve patients, 13 (62%; 95% CI, 38–82) had an objective response, with 2 (10%) patients achieving a CR and 11 (52%) achieving a PR.

EXTRACRANIAL RESPONSE

		TKI-naïve	Prior crizotinib only
EXTRACRANIAL			
No. of patients		21	40
Best overall response, n (%)	**Complete response**	2 (10)	2 (5)
	Partial response	11 (52)	12 (30)
	Stable disease	6 (29)	17 (43)
	Objective progression	2 (10)	3 (8)
	Indeterminate*	0	6 (15)
Confirmed ORR, n (%)		13 (62)	14 (35)
95% CI†		38–82	21–52

- Extracranial responses were consistent with overall responses observed in both ROS1 TKI-naïve patients and in patients who had received prior crizotinib only

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

ROS1 +VE LUNG CANCER

- Crizotinib remains the standard of care.
- However, intracranial and extracranial failures are inevitable.
- Strategies to tackle Crizotinib failures are being developed.
- Entrectinib for better efficacy and Lorlatinib for better intracranial response look promising.