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Management of *ROS1* Rearranged NSCLC

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Clinical Scenario

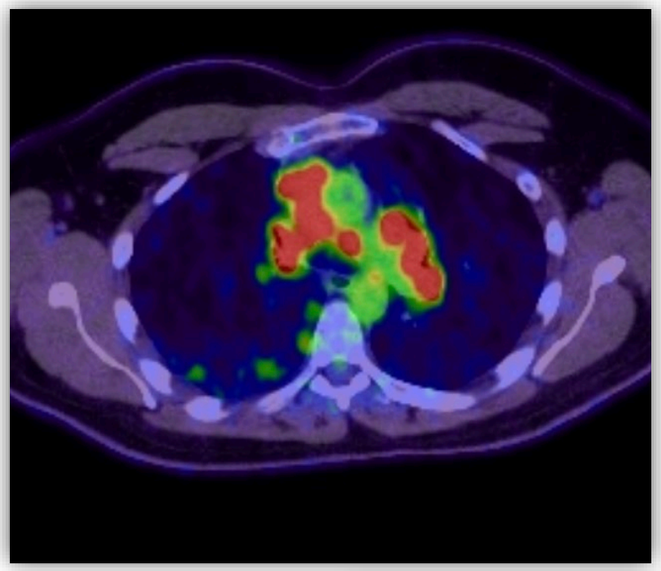
52-year-old male with a no smoking history underwent a CT scan for 6-8 week history of cough

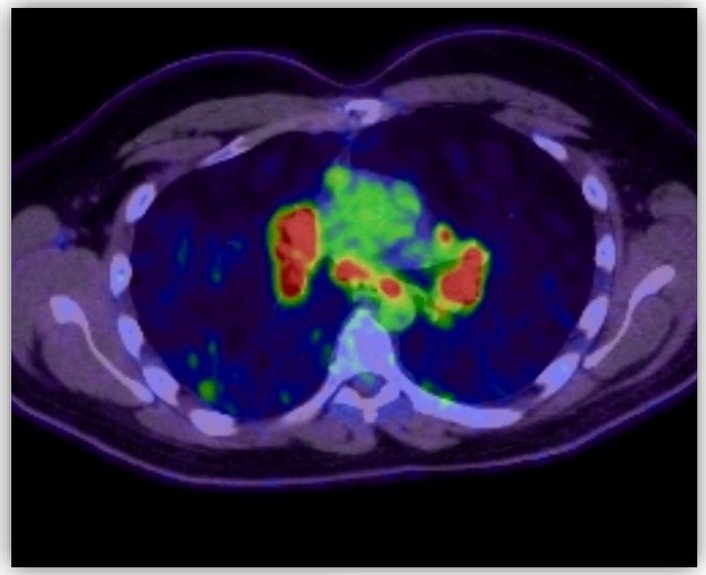
PET CT scan shows extensive disease

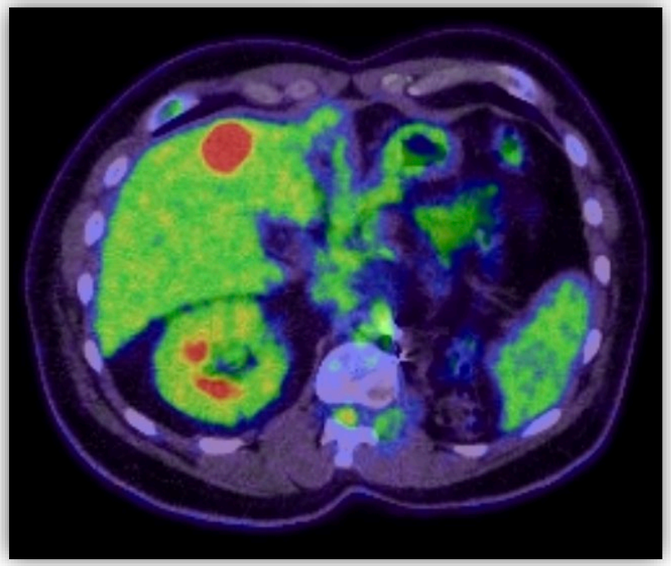
MRI brain is negative

EBUS Bronch Bx is performed, and dx is NSCLC

Controlled hypertension, hyperlipidemia, COPD, PS 0

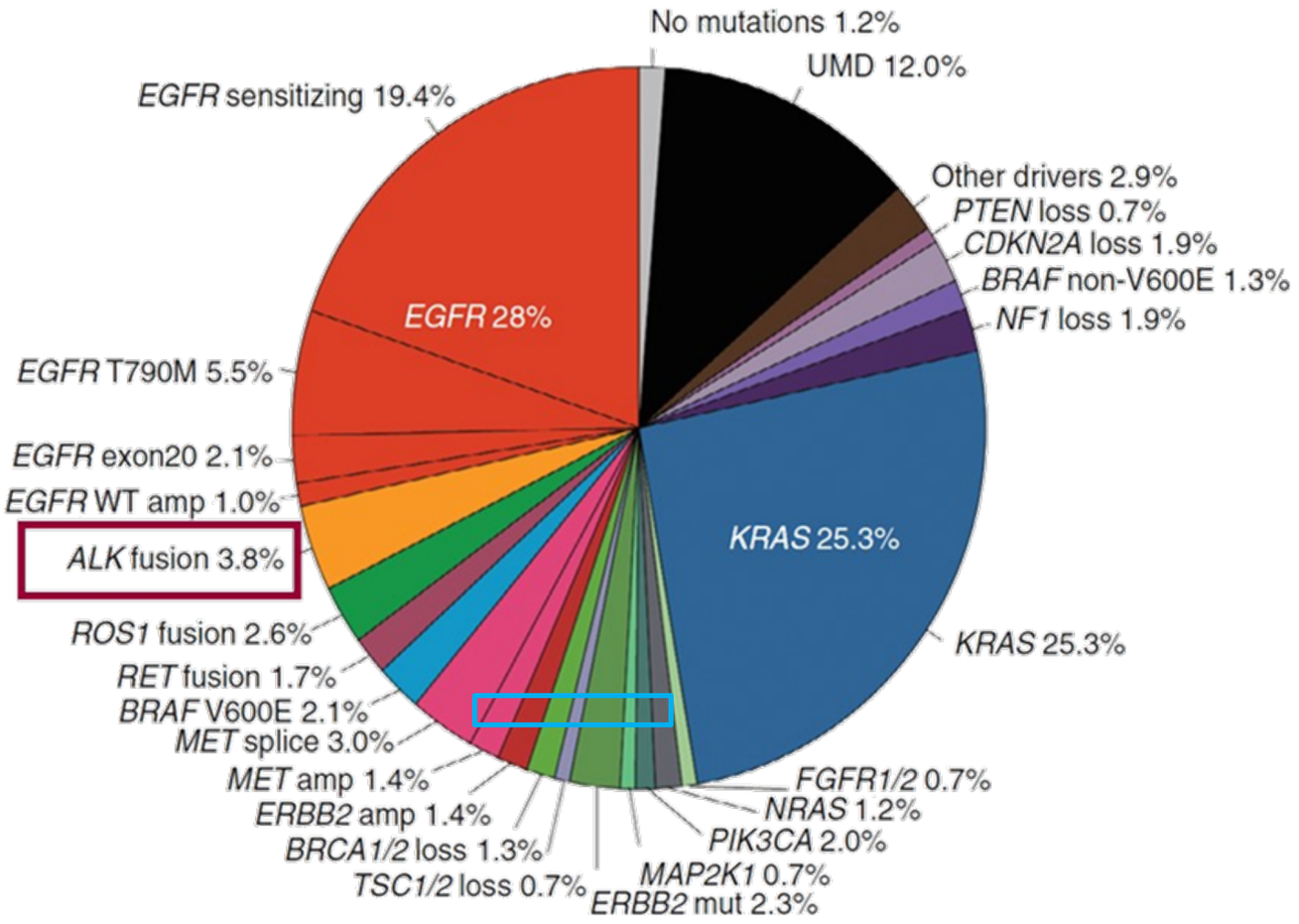






ROS1 Rearranged NSCLC – Testing

- Currently recommended for all non-squamous NSCLC patients with metastatic disease
- FISH Break Apart Probe – may under detect *FIG-ROS1* variant
- IHC for *ROS1* – low specificity (follow up confirmation necessary)
- NGS assays (need to consider using RNA fusion panels)
- Targeted PCR (may miss novel partners)



Clinical Scenario (continued)

- PD-L1 90%
- Molecular testing is performed – ROS1 Fusion Detected
- **How should this patient be treated?**

1L Treatment Decision Framework

Establish histology, PD-L1 expression status, and molecular biomarker status before initiating therapy.

1

ROS1 Fusion Identified *Before* 1L Therapy

Initiate a ROS1 TKI as first-line therapy. Preferred agents with CNS activity should be considered for patients with brain metastases.

2

ROS1 Fusion Identified *After* Initiating 1L Therapy

Interrupt current therapy and transition to a ROS1 TKI (ECOG PS 0–4). It is reasonable to continue current therapy if there is a good response.

If PD-L1 ≥1% is reported before molecular profiling is complete and an urgent start is needed, consider holding immunotherapy for one cycle until actionable alterations are excluded.

Crizotinib	**Entrectinib**
Repotrectinib	**Taletrectinib**

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Key Studies of Approved *ROS1* TKIs in *ROS1+* NSCLC

All four agents were evaluated in single-arm trials enrolling patients with locally advanced or metastatic *ROS1* fusion–positive NSCLC.

Crizotinib 250 mg BID

PROFILE 1001 | Phase 1, single-arm

- N=53 (efficacy-evaluable)
- ECOG PS 0–2; prior treatment allowed

Entrectinib 600 mg QD

ALKA-372-001, STARTRK-1, STARTRK-2 | Phase 1/2, integrated analysis

- N=186; ECOG PS 0–2
- TKI-naïve or TKI-pretreated

Repotrectinib 160 mg QD → BID

TRIDENT-1 | Phase 1/2, single-arm

- N=171; ECOG PS 0–1
- Asymptomatic CNS metastases allowed

Taletrectinib 600 mg QD

TRUST-I and TRUST-II | Phase 2, pooled analysis

- N=273; ECOG PS 0–1
- Stable CNS involvement allowed

Shaw AT, et al. N Engl J Med 2014; Shaw AT, et al. Ann Oncol 2019; Drilon A, et al. JTO Clin Res Rep 2022; Drilon A, et al. N Engl J Med 2024; Pérol M, et al. J Clin Oncol 2025.

Crizotinib in *ROS1*+ NSCLC

Data from the PROFILE 1001 study demonstrate durable responses with crizotinib, though CNS activity remains limited.

Efficacy Endpoints

Endpoint	N=50 (2014 cutoff)	N-53 (2018 cutoff)
Median follow-up months	16.4	62.6
ORR	**72%** (9t% CI: 58-84)	
Median DOR, months	17.6 (14.5–NR)	24.7 (15.2–45.3)
Median PFS, months	19.2 (14.4–NR)	19.3 (15.2–39.1)
Median OS, months	NR	51.4 (29.3–NR)

Selected TRAEs (N=53, ≥15% of patients)

Endpoint	Any Grade, %	Grade 3, %
Vision disorder	87	0
Nausea	51	2
Edema	47	0
Diarrhea	45	0
Hypophosphatemia	17	15
Neutropenia	15	9

No Grade 4 or 5 TRAEs were observed.

Shaw AT, et al. N Engl J Med 2014; Shaw AT, et al. Ann Oncol 2019.

CNS Progression Is Common in Patients Receiving Crizotinib

47%

CNS-only PD

CNS was the **first and only site of progression** in 9/19 patients with ROS1+ NSCLC treated with crizotinib

63%

1L CNS-only PD

Of patients receiving **first-line crizotinib**, 5/8 experienced CNS-only progression

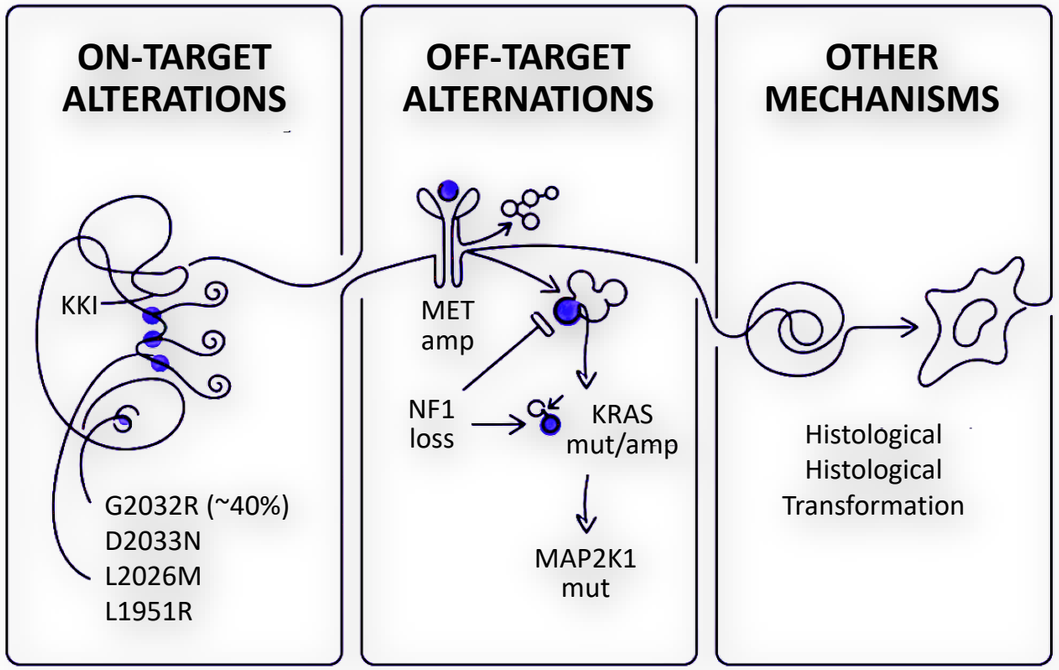
Clinical Implication

Crizotinib has **poor CNS penetration**, making CNS progression a primary mode of treatment failure. This limitation underscores the need for next-generation ROS1 TKIs with robust intracranial activity in patients with or at risk of brain metastases.

CNS progression occurred in a **substantial proportion of patients** — even those without baseline CNS metastases.

Patil T, et al. *J Thorac Oncol* 2018; Angeli E and Bousquet G. *Pharmaceutics* 2021

Resistance Mutations Are Another Common Driver of Disease Progression on Crizotinib



Key Resistance Mechanisms

On-Target: G2032R

The most common resistance mutation, reported **~40%** of patients' post-crizotinib. Other mutations include D2033N, L206M, and L1951R

Off-Target Bypass

MET amplification, NF1 loss, KRAS mutation/amplification, and MAP2K1 mutation activate downstream signaling independent of ROS1.

Other Mechanisms

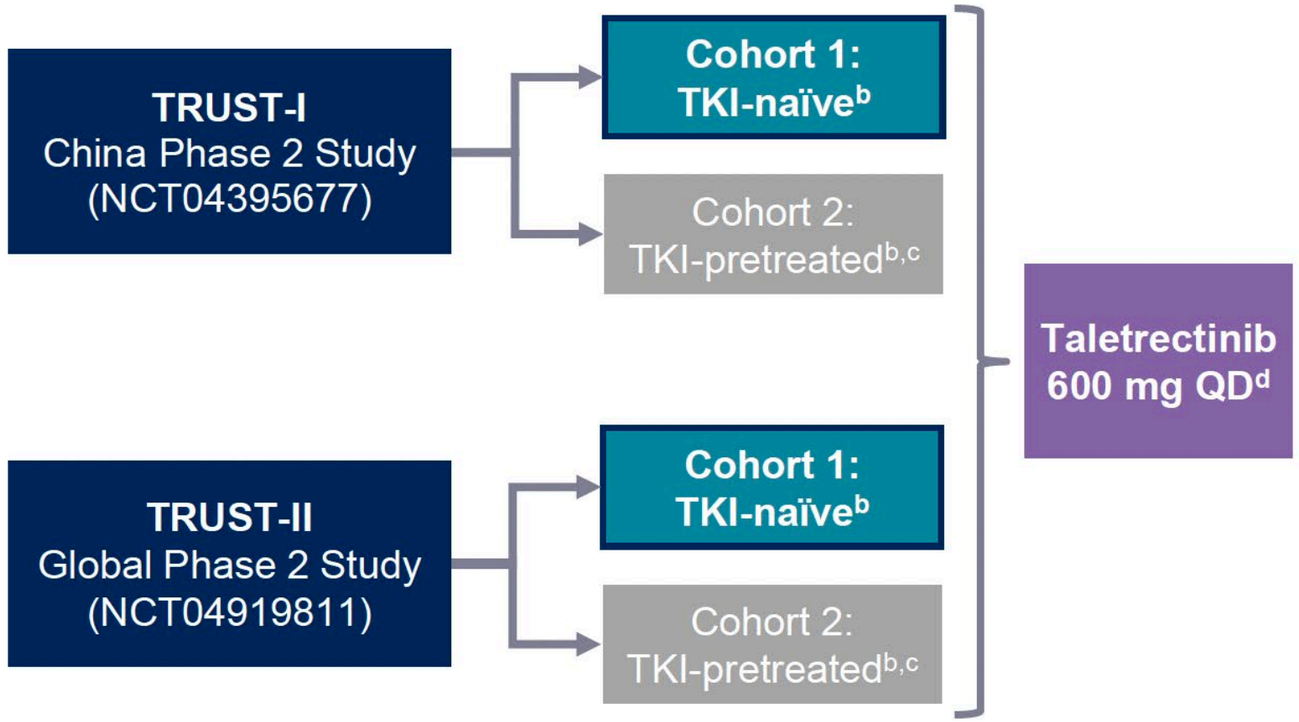
Histological transformation and as-yet uncharacterized mechanisms account for a subset of progression events.

Boulanger MC, et al. Oncologist 2024

TRUST-I & TRUST-II Clinical Trials

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC with ROS1 fusion
- Age ≥18 years[a]
- ECOG PS 0–1
- Brain metastases were allowed if stable



Endpoints

Primary:

- IRC-assessed cORR per RECIST v1.1

Key Secondary:

- DOR
- PFS
- OS
- IC-ORR
- Safety

- The efficacy population reported here included **TKI-naïve patients** from TRUST-I and TRUST-II with ≥1 measurable baseline lesion per RECIST v1.1 by IRC who started treatment on taletrectinib 600 mg QD
- Safety was evaluated in **TKI-naïve and TKI-pretreated patients** with ROS1+ NSCLC from Phase 1 and Phase 2 trials who received ≥1 dose of taletrectinib 600 mg QD

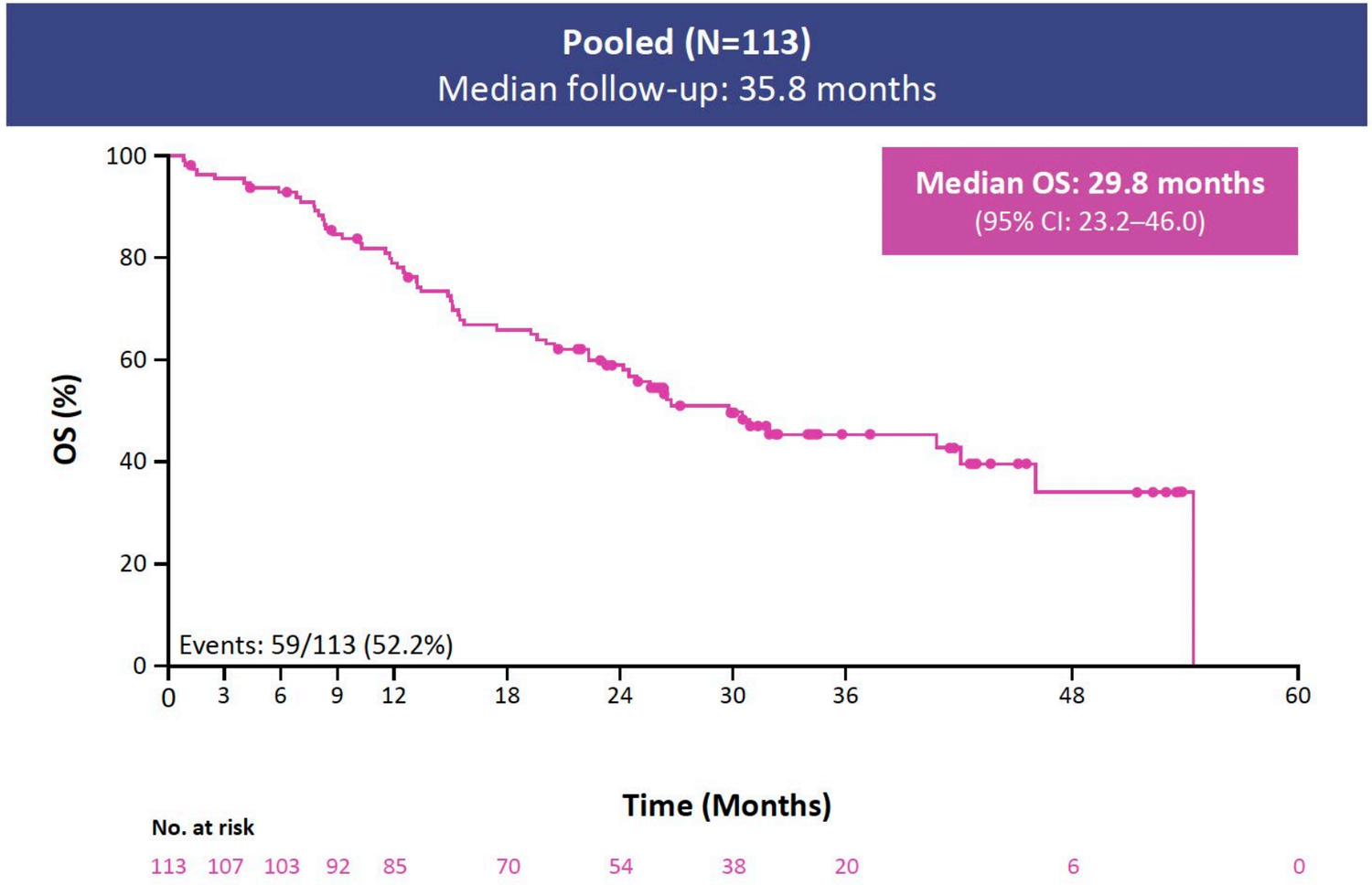
Next-Generation TKIs Show Activity in TKI-Pretreated *ROS1*+ NSCLC

Repotrectinib and taletrectinib demonstrate meaningful efficacy after prior *ROS1* TKI therapy — including activity against the G2032R resistance mutation and intracranial disease.

Endpoint	Entrectinib (N18)	Repotrectinib (N=56)	Taletrectinib (N=113)
Study	STARTRK-2	TRIDENT-1	TRUST-I & II
Prior crizotinib, %	100	82	91
ORR, % (95% CI)	11 (1–35)	**38** (25–52)	**56** (46–65)
ORR in G2032R, %	NA	59 (n=10/17)	61.5 (n=8/13)
Median DOR, months	NA (range 7.4–29.3)	14.8 (7.6–NE)	**16.6 (10.6–27.3)**
Median PFS, months	4.7 (2.9–43.5)	9.0 (6.8–19.6)	**9.7 (7.4–12.0)**
Median OS, months	43.5 (10.6–NE)	25.1 (17.8–NE)	NR
IC-ORR, % (95% CI)	19 (4–46); n=16	38 (14–68); n=13	**66 (47–81); n=32**

Drilon A, et al. JTO Clin Res Rep 2022; Drilon A, et al. N Engl J Med 2024; Pérol M, et al. J Clin Oncol 2025.

OS in TKI-Pretreated Patients From the Pooled Efficacy Analysis



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ROS1 TKIs Have Distinct Safety Profiles

Parameter	Crizotinib (N=53)	Entrectinib (N18)	Repotrectinib (N=56)	Taletrectinib (N=113)
Top TRAE (any grade)	• Vision disorders (87%) • Nausea (51%) • Edema (47%) • Diarrhea (45%) • Vomiting (38%)	• Dysgeusia (43%) • Weight gain (38%) • Dizziness (35%) • Constipation (32%) • Diarrhea (30%)	• Dizziness (58%) • Dysgeusia (50%) • Paresthesia (30%) • Constipation (26%) • Anemia (26%)	• AST increased (70%) • ALT increased (67%) • Diarrhea (61%) • Nausea (44%) • Vomiting (41%)
Grade ≥3 TRAEs, %	36	43	29	33
Dose reduction, %	NA	35	35	28
Dose interruption, %	NA	36	35	27
Discontinuation, %	0	7	3	3

Shaw AT, et al. Ann Oncol 2019; Fan Y, et al. Clin Lung Cancer 2023; Drilon A, et al. N Engl J Med 2024; Pérol M, et al. J Clin Oncol 2025.

Efficacy in TKI Naïve Setting

Next-Generation TKIs in TKI-Naïve Advanced ROS1+ NSCLC: Entrectinib vs Repotrectinib

Comparison of integrated entrectinib data from ALKA-372-001, STARTRK-1, and STARTRK-2 (N=168) with repotrectinib data from TRIDENT-1 (N=71).

Entrectinib
ALKA-372-001, STARTRK-1, STARTRK-2; N=168
Overall Efficacy

68%

ORR
Median DOR: 20.5 months
Median PFS: 15.7 months
Median OS: 47.8 months

Repotrectinib
TRIDENT-1; N=71
Overall Efficacy

79%

ORR
Median DOR: 34.1 months
Median PFS: 35.7 months
Median OS: NE

Entrectinib
ALKA-372-001, STARTRK-1, STARTRK-2; N=168
Intracranial Efficacy, n=25 with measurable CNS

80%

IC-ORR
Median IC-DOR: 12.9 months
Median IC-PFS: 8.8 months

Repotrectinib
TRIDENT-1; N=71
Intracranial Efficacy, n=9 with measurable CNS Metastases

89%

IC-ORR
Median IC-DOR: NE
Median IC-PFS: NA

Drilon A, et al. JTO Clin Res Rep 2022; Drilon A, et al. N Engl J Med 2024. The medications and indications mentioned may not be authorized in all jurisdictions, including Spain.

TRUST-I & TRUST-II Clinical Trials

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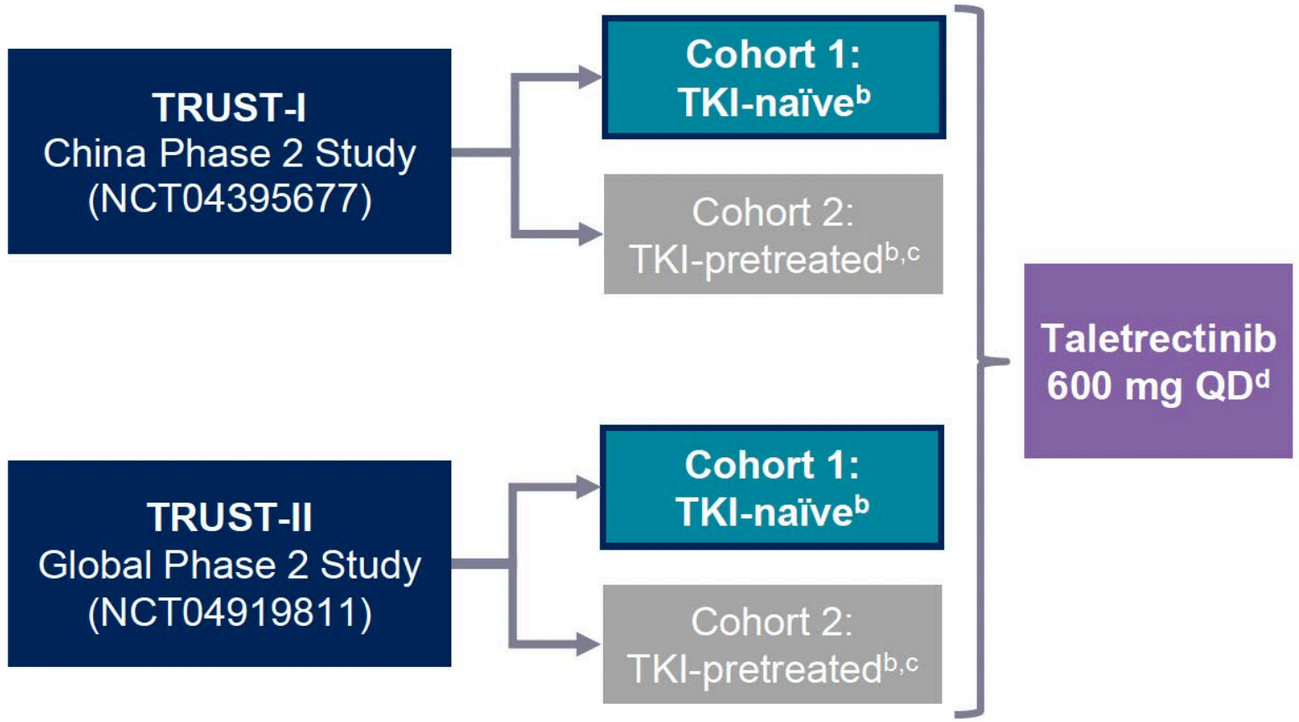

Endpoints

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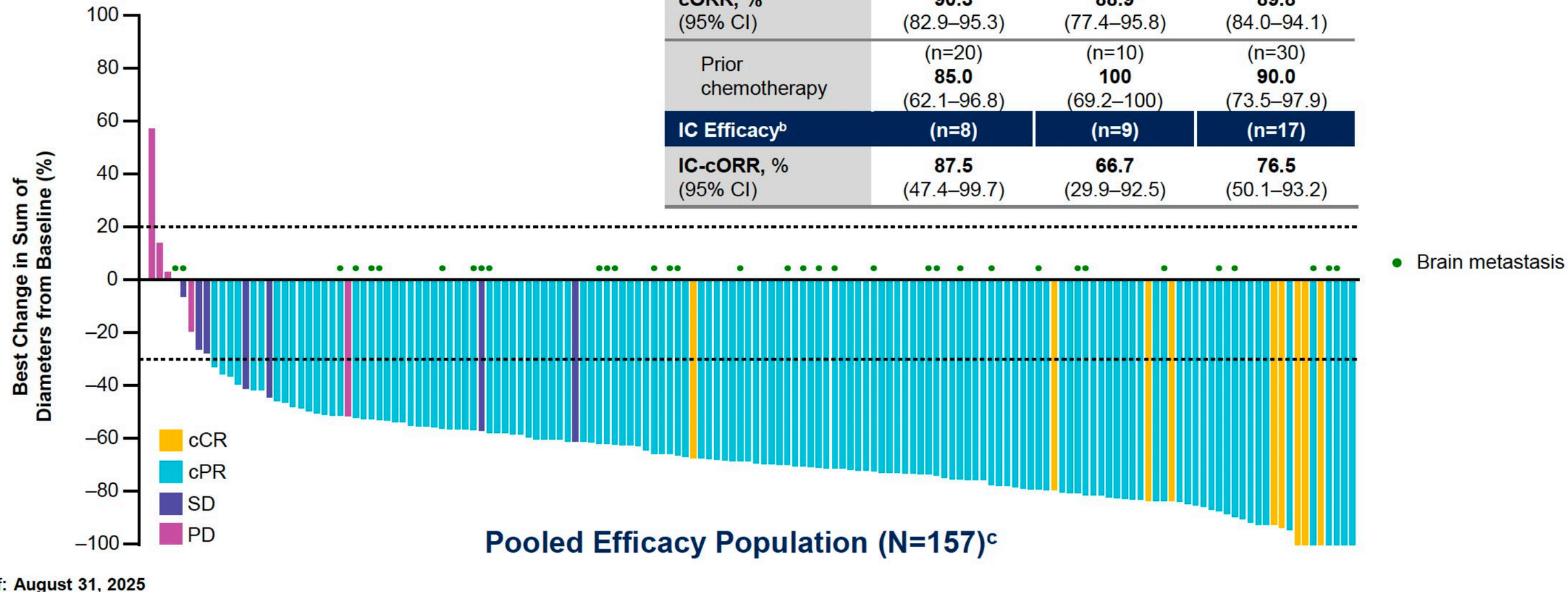
Tumor Response in TKI Naïve Patients

Efficacy[a]	TRUST-I (n=103)	TRUST-II (n=54)	Pooled (N=157)
cORR, % (95% CI)	**90.3** (82.9–95.3)	**88.9** (77.4–95.8)	**89.8** (84.0–94.1)
Prior chemotherapy	(n=20) **85.0** (62.1–96.8)	(n=10) **100** (69.2–100)	(n=30) **90.0** (73.5–97.9)
IC Efficacy[b]	**(n=8)**	**(n=9)**	**(n=17)**
IC-cORR, % (95% CI)	**87.5** (47.4–99.7)	**66.7** (29.9–92.5)	**76.5** (50.1–93.2)



Data cutoff: August 31, 2025

**Updated Data presented at AACR 2026 – Bazhenova L et al, Zhou et al, JCO, 2026

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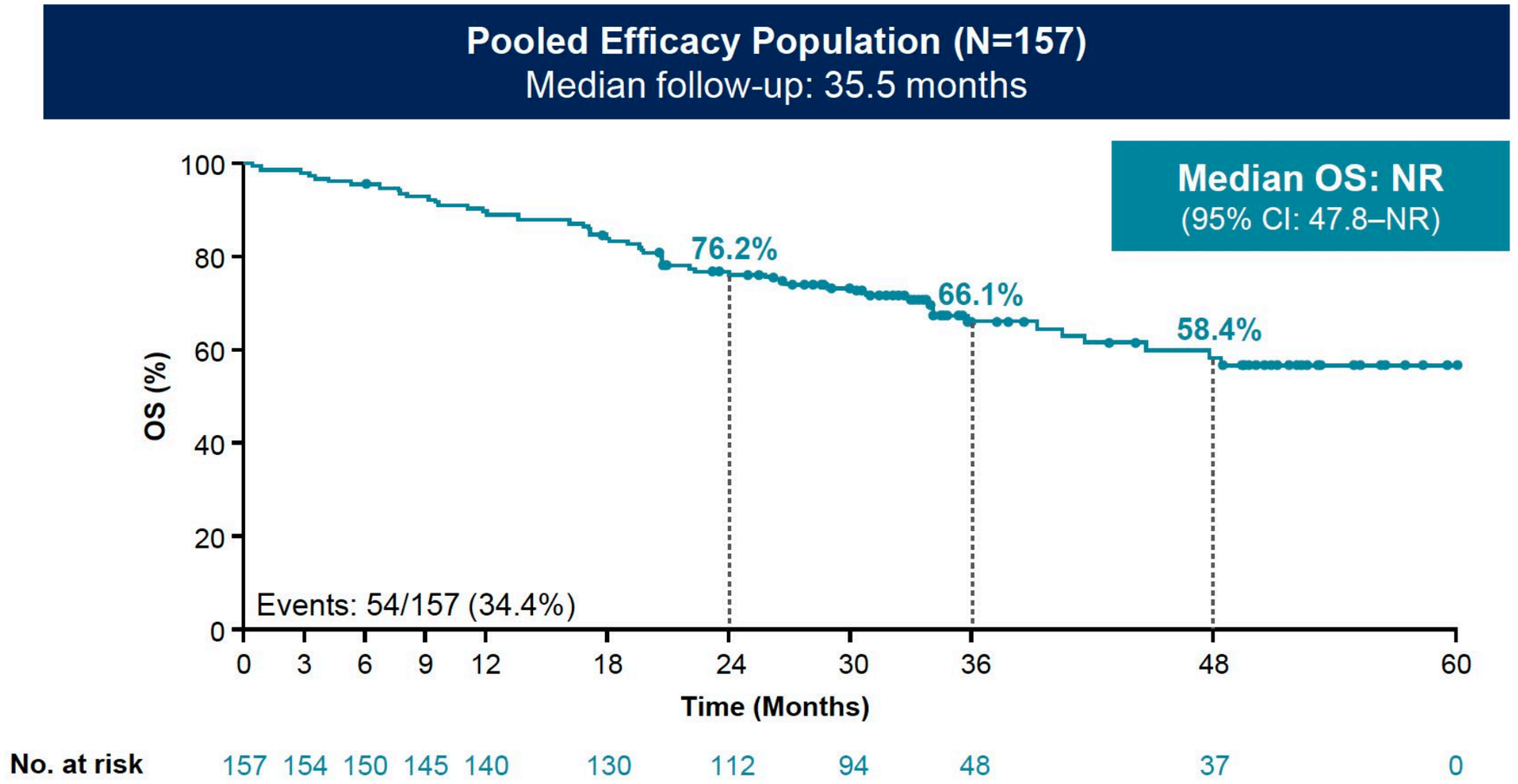
Summary of Efficacy Data in TKI-naïve Advanced ROS1+ NSCLC

	Crizotinib (N=53)	Entrectinib (N=168)	Repotrectinib (N=71)	Taletrectinib (N=157)
Study	**PROFILE 1001** (Phase 1)	**ALKA-372-001, STARTRK-1, STARTRK-2** (Phase 1/2)	**TRIDENT-1** (Phase 1/2)	**TRUST-I and TRUST-II** (Phase 2)
EFFICACY	**N=53**	**N=168**	**N=71**	**N=160**
ORR, %	**72**	**68**	**79**	**89.8****
Median DOR, months	24.7	20.5	34.1	**49.7****
Median PFS, months	**19.3**	**15.7**	**35.7**	**46.1****
INTRACRANIAL EFFICACY	**NA**	**n=25**	**n=9[b]**	**n=17**
IC-ORR, %	-	80	89	76.5
IC-DOR, months	-	12.9	NR	14.7

**Updated Data presented at AACR 2026 – Bazhenova L et al, Zhou et al, JCO, 2026

Overall Survival in TKI Naïve Patients



Median OS was **NR** (95% CI: 41.6–NR) for TRUST-I and **NR** (95% CI: NR–NR) for TRUST-II

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Emerging Next-Gen TKIs: Zidesamtinib Ph1/2 ARROS-1

ARROS-1 STUDY DESIGN & POPULATIONS

- At the data cut-off (September 22, 2025), 570 patients with any *ROS1*+ solid tumor had been enrolled, including 481 patients with advanced *ROS1*+ NSCLC who received zidesamtinib 100 mg once daily; 46 and 19 patients had received prior treatment with repotrectinib and taletrectinib, respectively (3 of whom had previously received both)
- Key endpoints were ORR (RECIST v1.1 by BICR), DOR, IC-ORR, and safety

PHASE 1

Zidesamtinib dose escalation (25 – 150 mg QD) in ROS1 TKI-pretreated patients with advanced *ROS1*+ solid tumors

PHASE 2: Zidesamtinib 100 mg QD (RP2D)

ARROS-1 PHASE 2 PATIENT POPULATION	PRIOR ROS1 TKI	PRIOR CHEMO/I-O [a]
***ROS1*+ NSCLC**	ROS1 TKI-naïve	≤ 1
	1 prior ROS1 TKI [b]	None
		1
	≥ 2 prior ROS1 TKIs [c]	≤ 1
Any *ROS1*+ Solid Tumor [d]	**Any**	**Any**

PHASE 2 ENDPOINTS

- **Primary:** ORR by BICR
- **Secondary:** Additional efficacy measures (DOR, TTR, CBR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile, PROs

Patient population

Data cut-off: September 22, 2025

Total enrolled: N = 570
Any *ROS1*+ solid tumor, any dose
Phase 1 + Phase 2 pooled

Advanced *ROS1*+ NSCLC: n = 481
Received ≥1 dose of zidesamtinib at 100 mg QD

Prior repotrectinib [e] n = 46

Prior taletrectinib [e] n = 19

▲ **Figure 1. ARROS-1: A global, first-in-human, phase 1/2 clinical trial of zidesamtinib in advanced *ROS1*+ NSCLC and other solid tumors (NCT05118789).**

Zidesamtinib is an investigational product and has not been approved by the FDA or any other health authority.

[a] Platinum-based chemotherapy with or without immunotherapy. [b] Either crizotinib or entrectinib. [c] With initial TKI of either crizotinib or entrectinib. [d] Exploratory cohort, currently enrolling; includes patients with NSCLC who do not qualify for any of the other cohorts. [e] Patients with TKI-pretreated *ROS1*+ NSCLC with measurable disease by BICR at baseline, who received ≥1 dose of zidesamtinib at the RP2D and have ≥1 post-treatment tumor assessment or discontinued treatment due to any reason; 3 patients received both prior repotrectinib and prior taletrectinib.

Liu G, et al. Presented at AACR Annual Meeting 2026; April 17-22 2026, San Diego, CA; CT248

Zidesamtinib: ARROS-1 Results

Advanced *ROS1+* NSCLC (BICR analysis)	Prior Repotrectinib N=46	Prior Taletrectinib N=19
ORR, %	41%	47%
Median DOR, months	15.7	Not reached
DOR ≥6 months, %	67%	83%
INTRACRANIAL EFFICACY	N=18	N=7
IC-ORR, %	44%	71%
Median IC-DOR, months	Not reached	Not reached
IC-DOR ≥6 months, %	86%	80%
ROS1 G2032R Resistance Mutation	N=12	N=4
ORR, %	67%	50%
Median DOR, months	15.7	Not reached
DOR ≥6 months, %	69%	100%
Safety		
TRAEs leading to dose reduction, %	5%	
TRAEs leading to treatment discontinuation	0%	
TRAE experienced by ≥15% of patients	Peripheral edema (26%, no Grade ≥3)	

Liu G, et al. Presented at AACR Annual Meeting 2026; April 17-22 2026, San Diego, CA; CT248.

Key Takeaways in ROS1+ NSCLC Treatment

A comprehensive overview of treatment decisions, agent profiles, and clinical considerations for patients with ROS1-positive non-small cell lung cancer.

First-Line Treatment & Agents

- ROS1 TKIs are the established first-line treatment for ROS1+ NSCLC.
- Four agents are currently approved:
- Crizotinib,
- Entrectinib,
- Repotrectinib, and
- Taletrectinib

Next-Gen TKI Advantages

Newer TKIs (Entrectinib, Repotrectinib, Taletrectinib) demonstrate

- Superior intracranial activity and
- Superior efficacy against common resistance mutations like G2032R

Efficacy & Safety Profiles

Next-generation TKIs show

- Improved ORRs and PFS in TKI-pretreated settings and
- In TKI-naïve setting.
- Each agent has a distinct safety profile, requiring careful consideration for patient-specific tolerance.

Clinical Implications

Patient selection should account for

- Baseline CNS involvement
- Risk of CNS progression
- Potential resistance mechanisms.