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LUNG CANCER SYMPOSIUM

ROS-1 FUSIONS: Novel agents and new insights

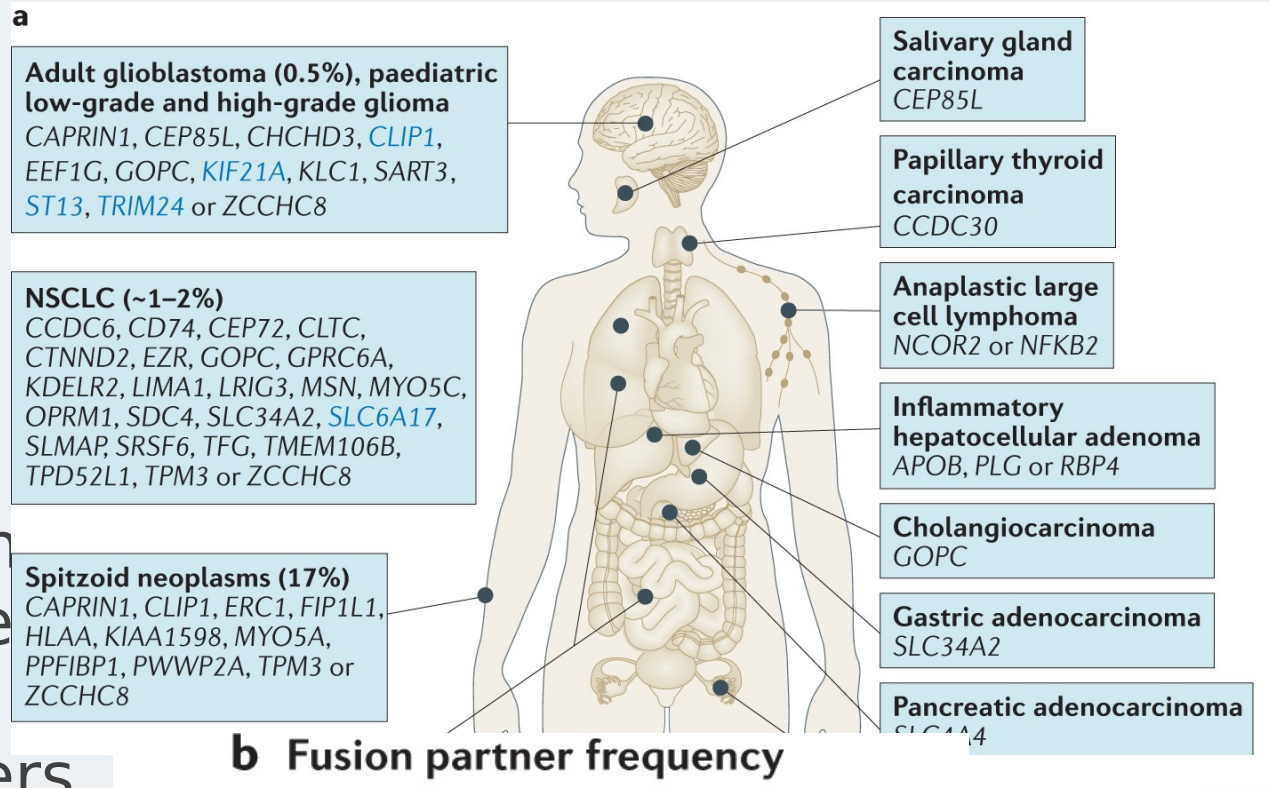
Jennifer Carlisle, MD

November 7, 2026

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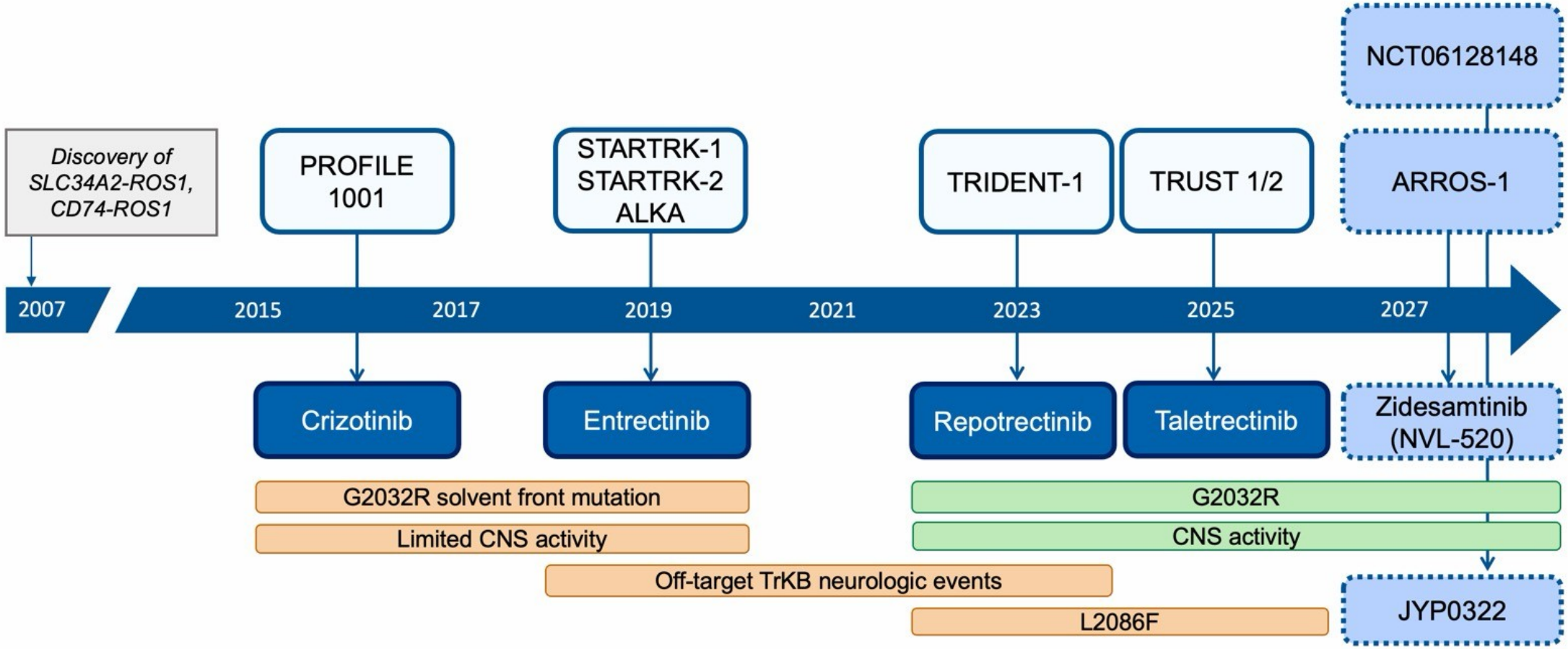
ROS-1 NSCLC

- Fusions seen in 1-2% NSCLC
- Typically adenocarcinoma, occasion large cell and squamous histologie
- Seen in younger, light/never smokers
- ~70% homology with ALK kinase domain



Drilon et al. *Nat Rev Clin Oncol* **18,** 35–55 (2021).

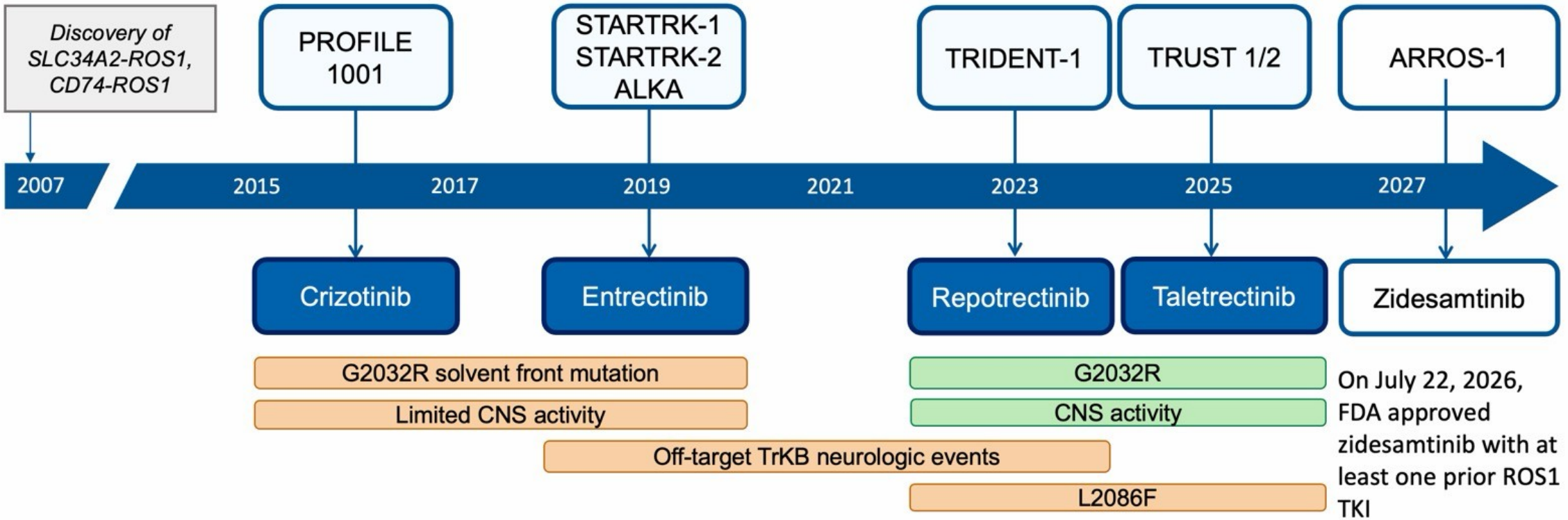
ROS1 NSCLC: Evolution in targeted treatment



Slide credit Dr. Cathleen Park

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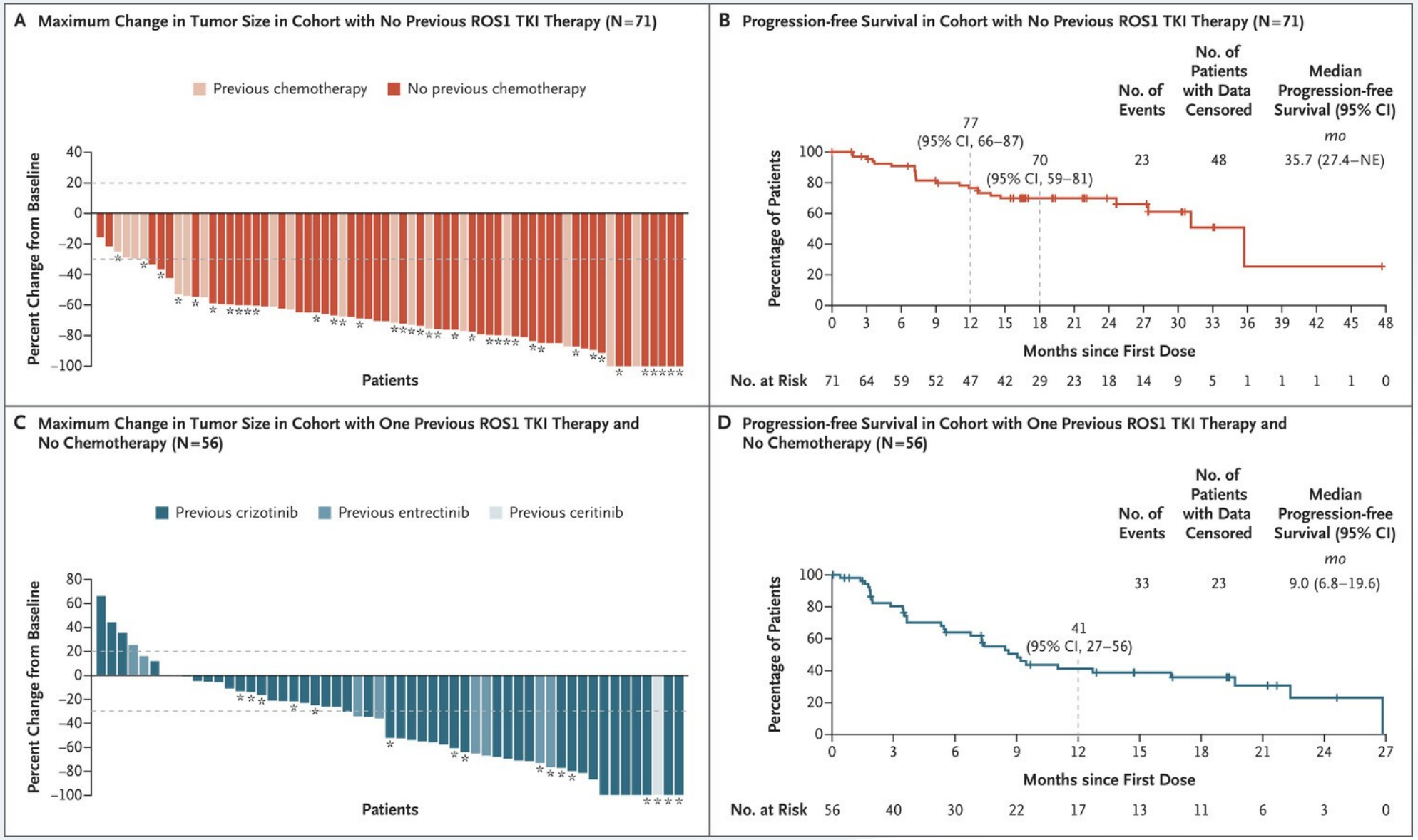
ROS1 NSCLC: Evolution in targeted treatment



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Repotrectinib: Trident 1



Drilon et al. NEJM 2024

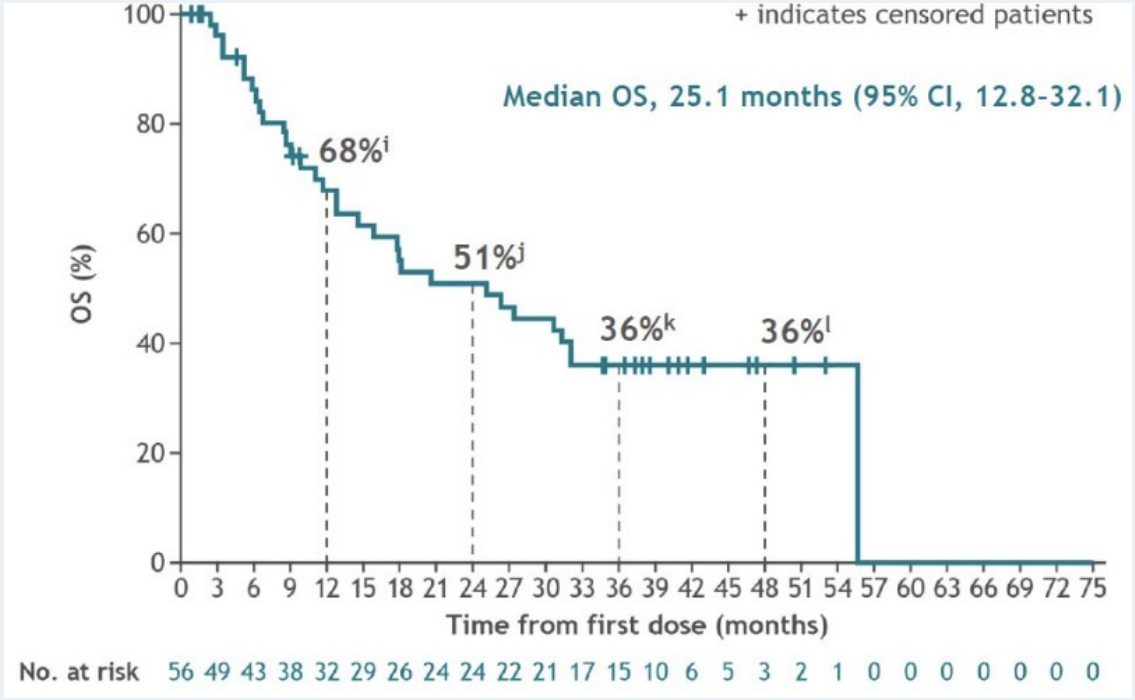
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Repotrectinib: Follow-up analysis

Long Term Analysis

ROS1 TKI-pretreated & chemotherapy naïve

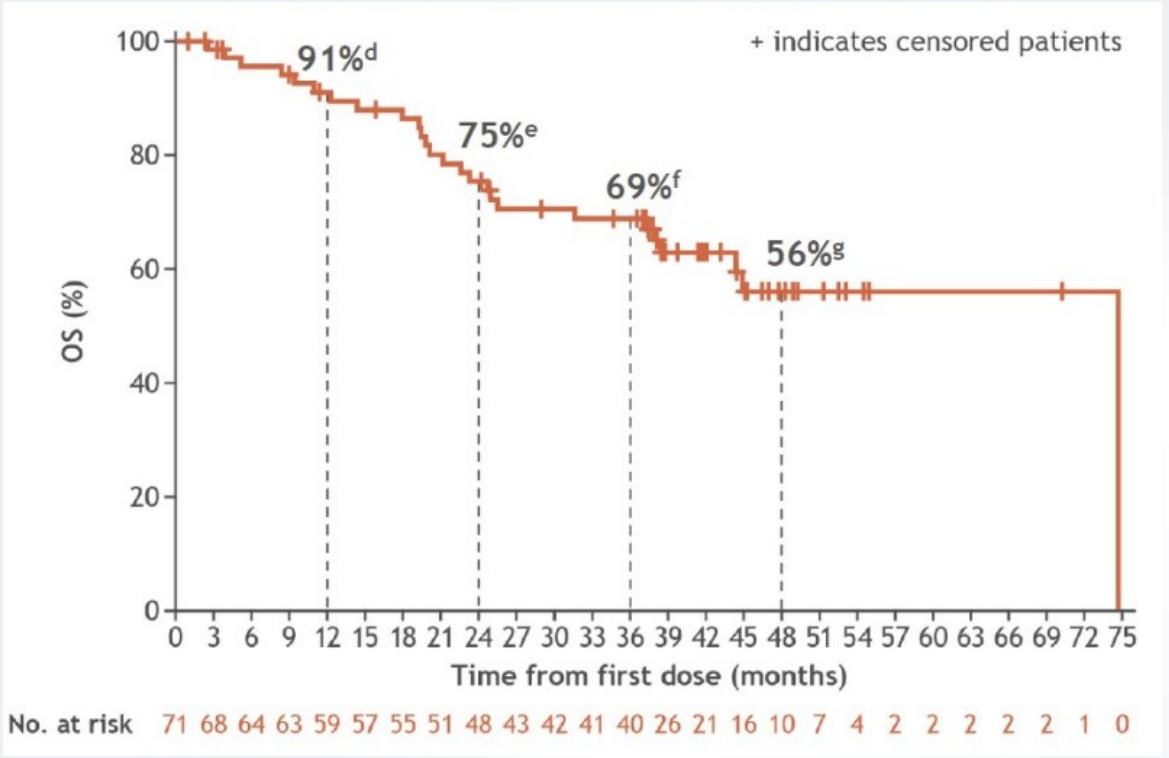
- 56 participants



mOS: **25.1 mo** (95% CI 13,32)

ROS1 TKI-naïve

- 71 participants



mOS: **NR**

Cho BC, et al. JTO October 2025;20 Abstract MA02.03

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Repotrectinib: Adverse events

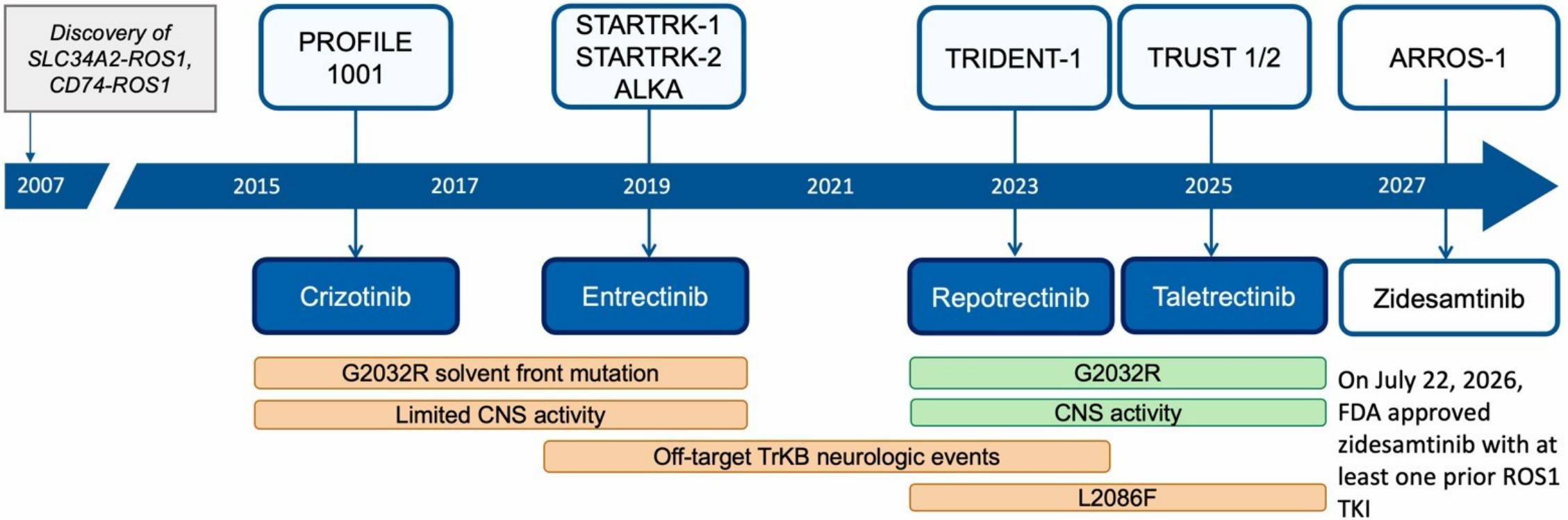
Table 3. Adverse Events in the 426 Patients Who Received the Phase 2 Dose of Repotrectinib.*

Event	During Treatment Period		Related to Treatment	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	422 (99)	216 (51)	409 (96)	122 (29)
Event occurring in ≥15% of patients				
Dizziness	264 (62)	11 (3)	245 (58)	11 (3)
Dysgeusia	224 (53)	0	213 (50)	0
Constipation	162 (38)	1 (<1)	111 (26)	0
Anemia	160 (38)	33 (8)	111 (26)	16 (4)
Paresthesia	143 (34)	3 (1)	126 (30)	3 (1)
Dyspnea	117 (27)	27 (6)†	36 (8)	2 (<1)
Increased alanine aminotransferase level	99 (23)	8 (2)	76 (18)	6 (1)
Fatigue	95 (22)	4 (1)	70 (16)	3 (1)
Ataxia	90 (21)	1 (<1)	87 (20)	0
Increased aspartate aminotransferase level	89 (21)	9 (2)	75 (18)	6 (1)
Nausea	85 (20)	3 (1)	51 (12)	2 (<1)
Muscular weakness	85 (20)	8 (2)	59 (14)	6 (1)
Headache	79 (19)	0	42 (10)	0
Increased blood creatine kinase level	75 (18)	15 (4)	72 (17)	15 (4)
Weight increase	67 (16)	11 (3)	49 (12)	7 (2)
Memory impairment	65 (15)	1 (<1)	54 (13)	1 (<1)
Cough	64 (15)	1 (<1)	10 (2)	0
Event that led to treatment discontinuation	31 (7)	0	14 (3)	0
Event that led to dose reduction	163 (38)	0	149 (35)	0
Event that led to dose interruption	213 (50)	0	150 (35)	0
Any serious event	147 (35)	0	38 (9)	0
Death	19 (4)	0	0	0

TRK side effects can be clinically significant

Dizziness
Dysgeusia
Ataxia
Muscular weakness
Memory impairment

ROS1 NSCLC: Evolution in targeted treatment



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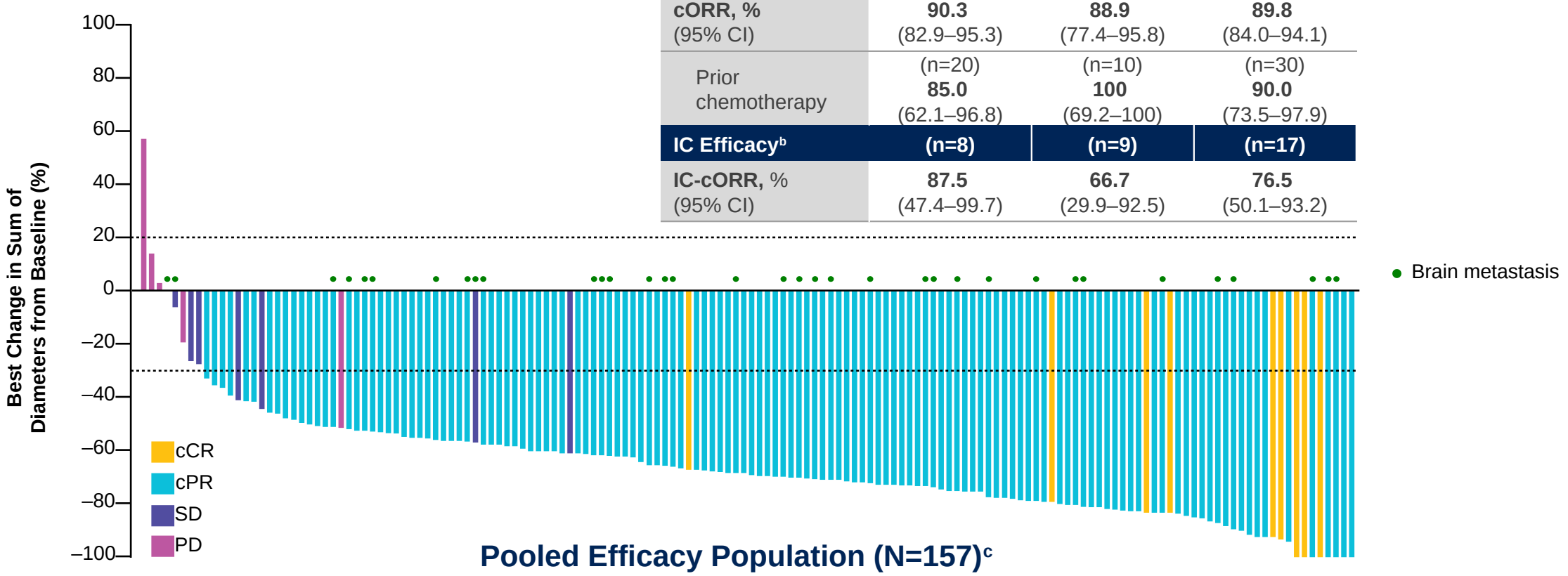
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Taltrectinib: Pooled analysis TRUST-1 TRUST-2

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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

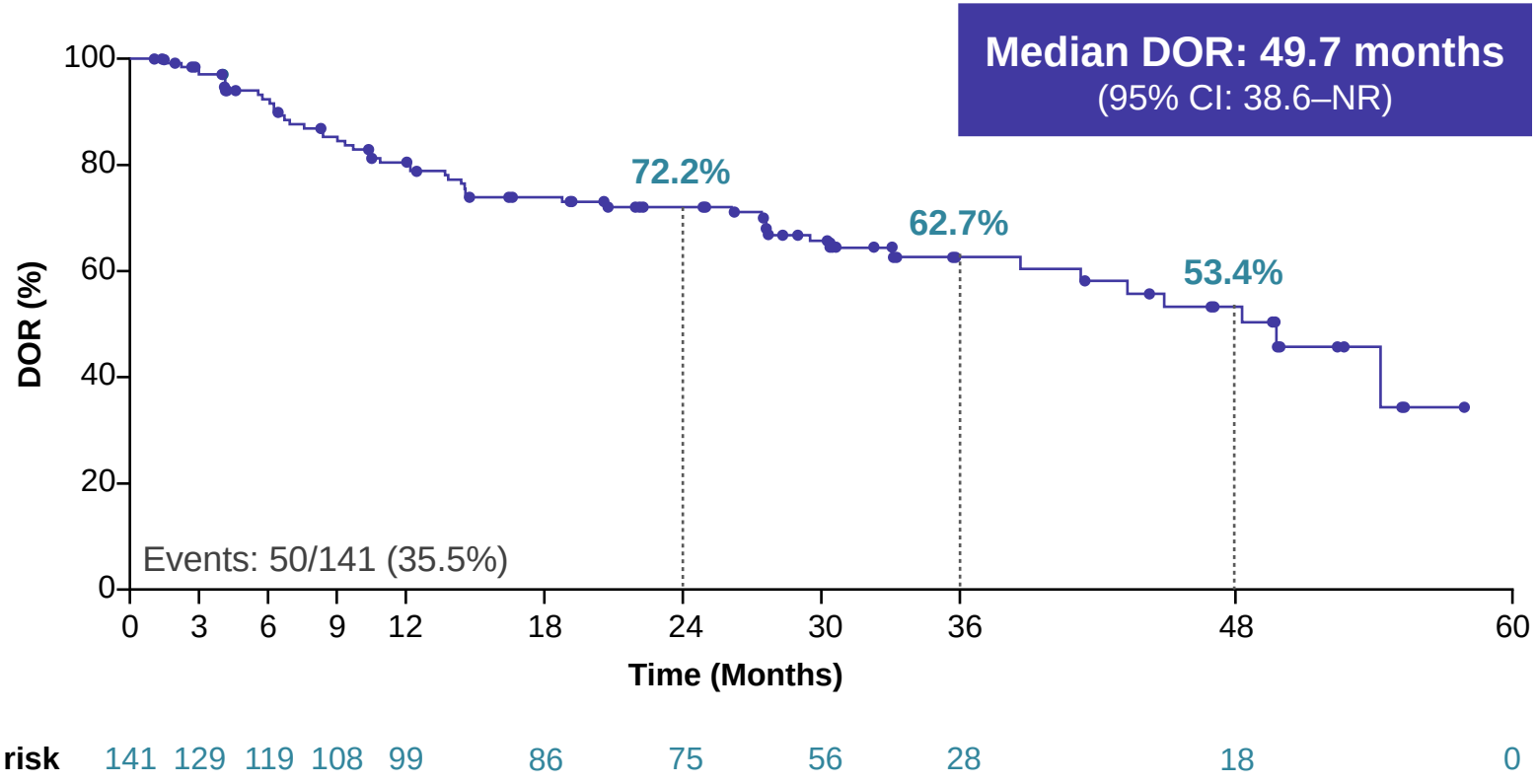
[a]Patients with ≥1 measurable baseline lesion per RECIST v1.1 by IRC who started treatment on taletrectinib 600 mg QD. [b]Assessed by IRC per mRECIST v1.1 in patients with ≥1 measurable baseline brain metastasis. Among these, three patients from TRUST-II had been previously treated with IC radiotherapy. [c]Three patients with cBOR of NE are not shown in the figure. One patient with cBOR of SD had a best % change of 0%.

BOR, best overall response; c, confirmed; CI, confidence interval; CR, complete response; IC, intracranial; IRC, independent review committee; (m)RECIST v1.1, (modified) Response Evaluation Criteria in Solid Tumors version 1.1; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; TKI, tyrosine kinase inhibitor.

Taltrectinib: Pooled analysis TRUST-1 TRUST-2 TKI-Naïve

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Pooled Efficacy Population (N=141)[a]
Median follow-up: 35.5 months



Data cutoff: August 31, 2025

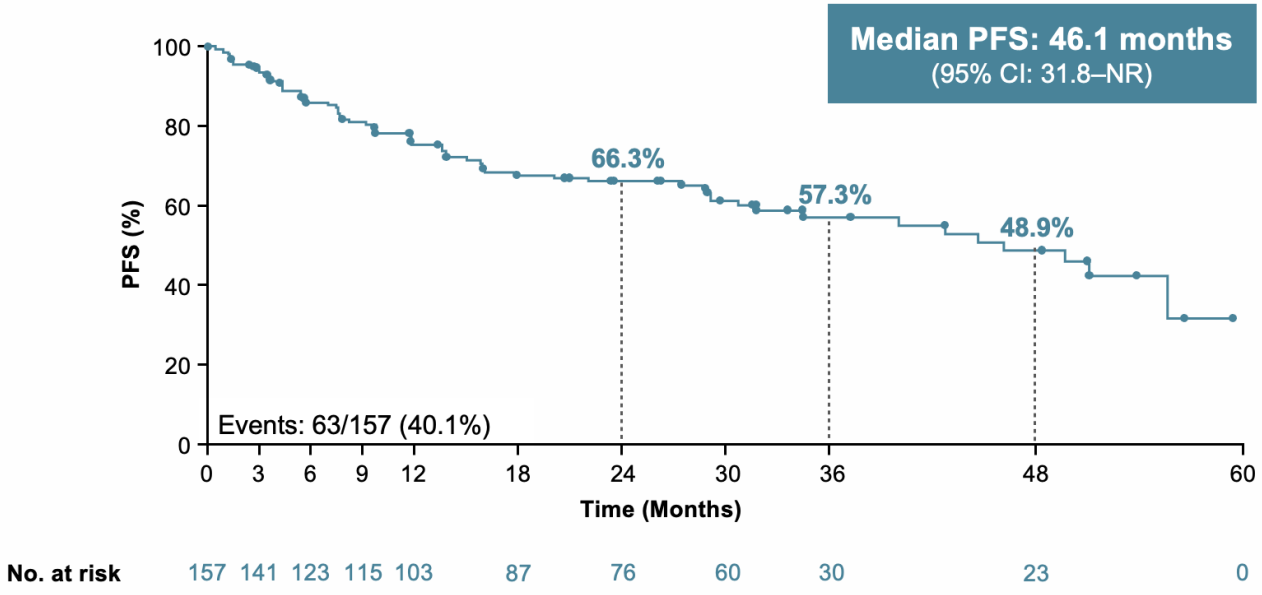
[a]DOR reported only for patients with a complete or partial tumor response.

CI, confidence interval; DOR, duration of response; NR, not reached; TKI, tyrosine kinase inhibitor.

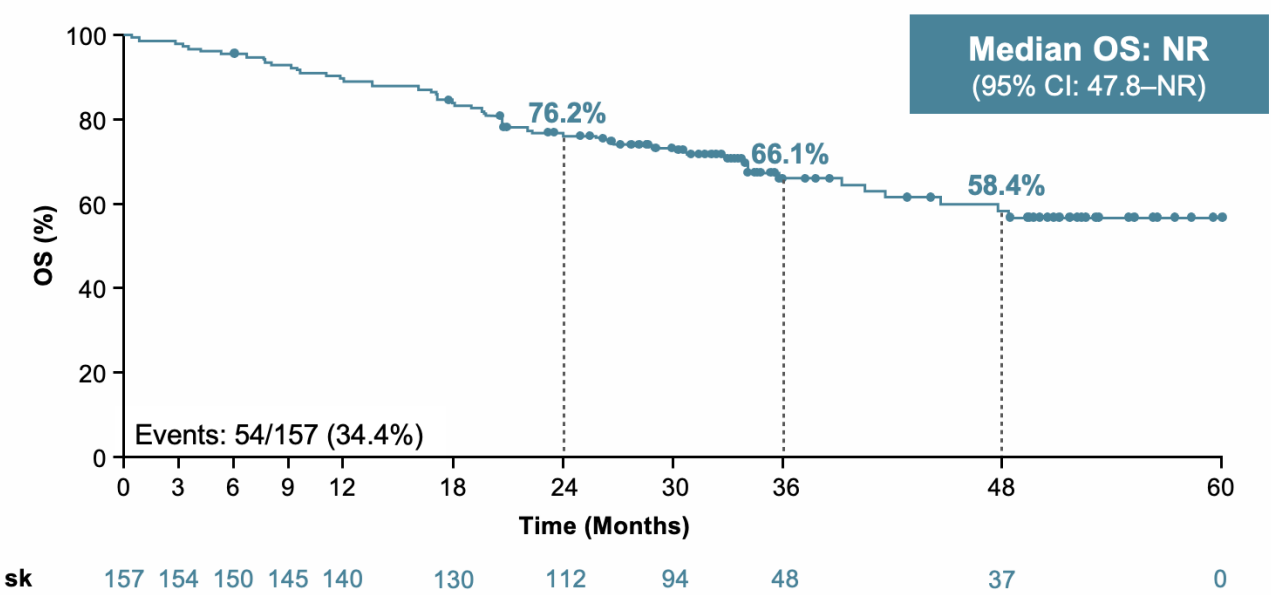
Taltrectinib: Pooled analysis TRUST-1 TRUST-2 TKI-Naïve

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Pooled Efficacy Population (N=157)
Median follow-up: 35.5 months



Pooled Efficacy Population (N=157)
Median follow-up: 35.5 months



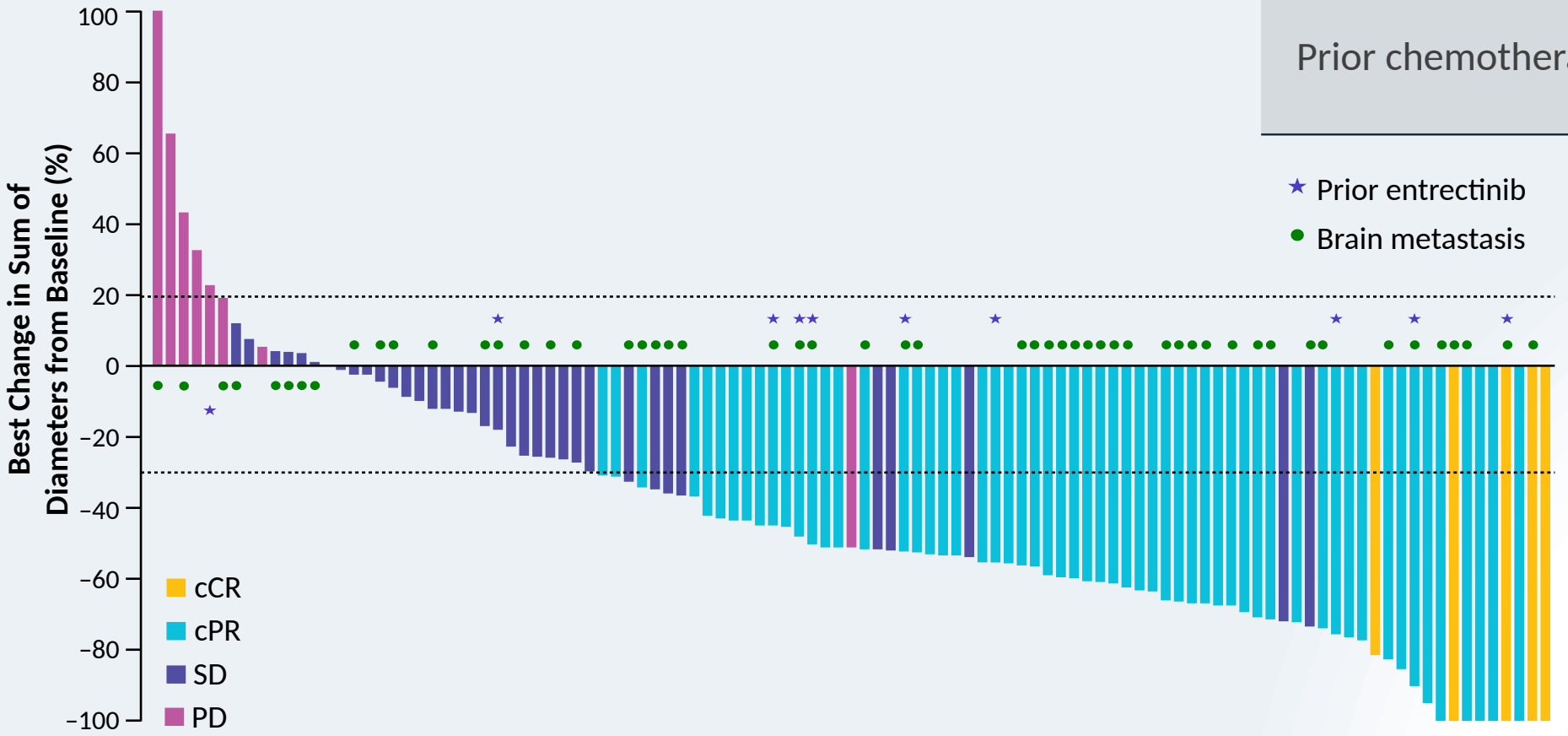
Median OS was **NR** (95% CI: 41.6–NR) for TRUST-I and **NR** (95% CI: NR–NR) for TRUST-II

Data cutoff: August 31, 2025
CI, confidence interval; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Taltrectinib: Pooled analysis TRUST-1 TRUST-2

TKI pre-treated (n=113)

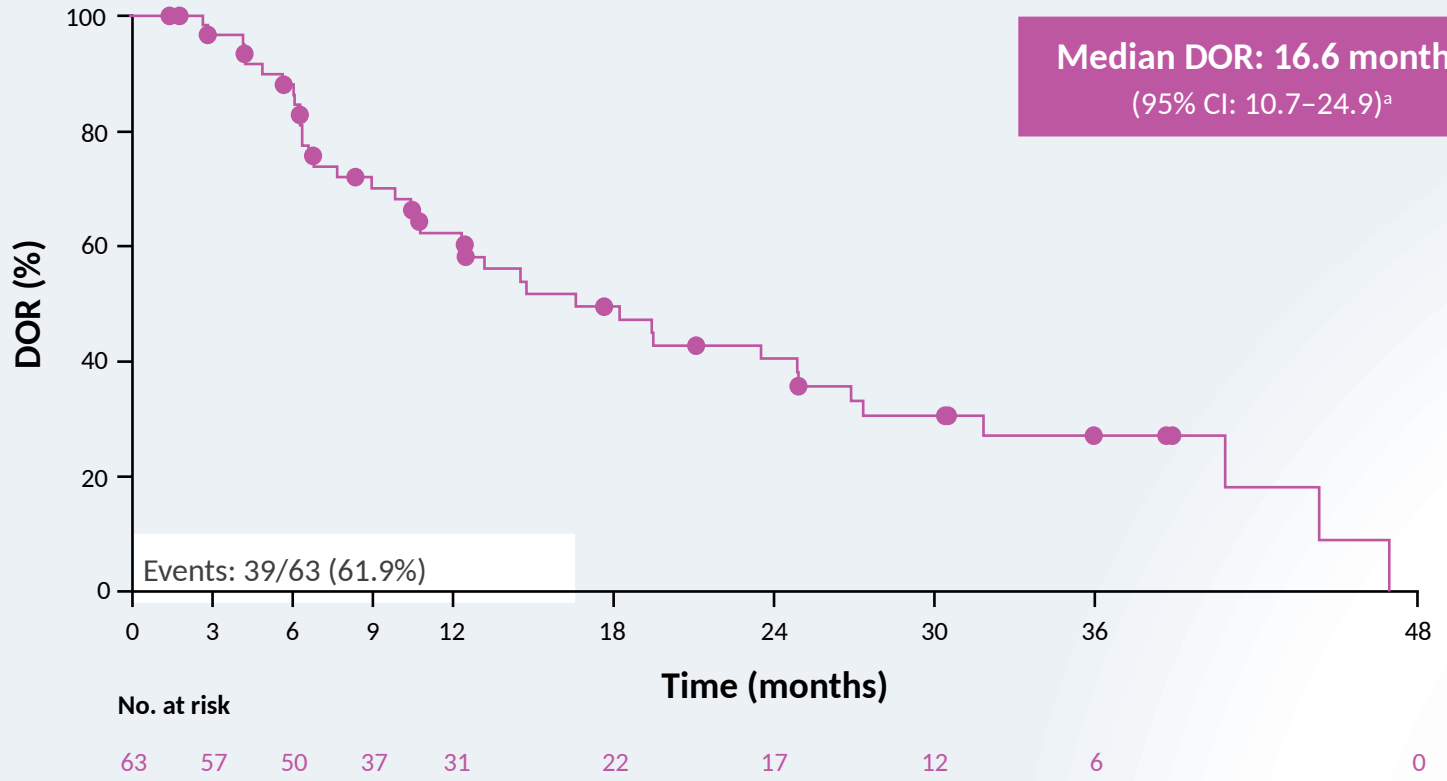
cORR, % (95% CI)	**55.8** (46.1–65.1)
Prior chemotherapy	(n=42) **59.5** (43.3–74.4)



Taltrectinib: Pooled analysis TRUST-1 TRUST-2

TKI pre-treated (n=113)

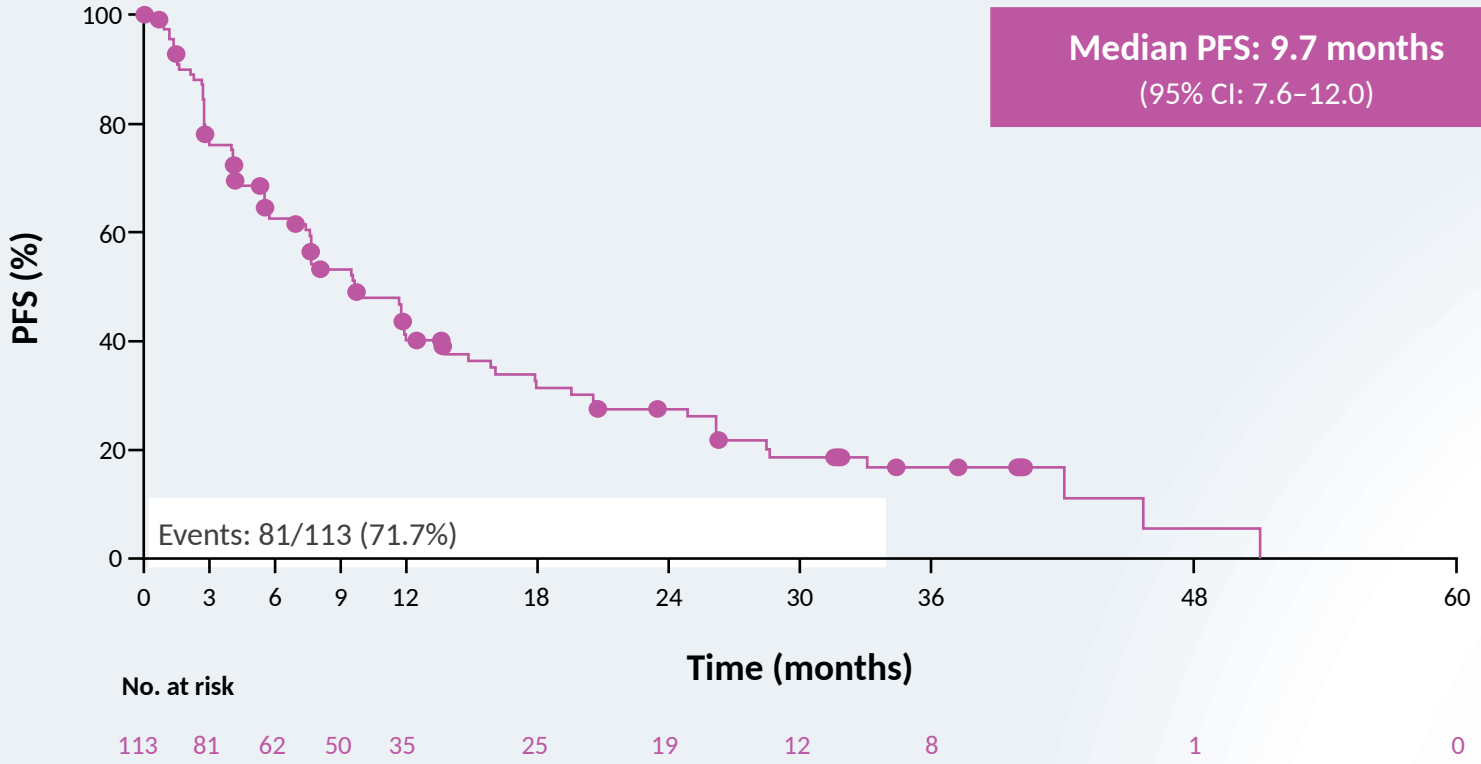
Pooled (N=113)
Median follow-up: 35.8 months



Data cutoff: August 31, 2025.
[a]DOR reported only for patients with a CR or PR.
CI, confidence interval; CR, complete response; DOR, duration of response; PR, partial response.

Taltrectinib: Pooled analysis TRUST-1 TRUST-2
PFS in TKI-Pretreated

Pooled (N=113)
Median follow-up: 35.8 months



Data cutoff: August 31, 2025.
CI, confidence interval; PFS, progression-free survival.

Taletrectinib Safety Profile in the Integrated Safety Analysis (N=363)[a]

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Most frequent TEAEs (≥20% of patients), n (%)	Any grade	Grade 1	Grade 2	Grade ≥3
AST increased	261 (71.9)	166 (45.7)	65 (17.9)	30 (8.3)
ALT increased	248 (68.3)	143 (39.4)	65 (17.9)	40 (11.0)
Diarrhea	234 (64.5)	181 (49.9)	44 (12.1)	9 (2.5)
Nausea	174 (47.9)	131 (36.1)	38 (10.5)	5 (1.4)
Vomiting	164 (45.2)	127 (35.0)	32 (8.8)	5 (1.4)
Anemia	139 (38.3)	80 (22.0)	44 (12.1)	15 (4.1)
Dizziness	78 (21.5)	67 (18.5)	10 (2.8)	1 (0.3)
Electrocardiogram QT prolonged	76 (20.9)	52 (14.3)	11 (3.0)	13 (3.6)
Constipation	74 (20.4)	62 (17.1)	12 (3.3)	0
Blood creatinine increased	73 (20.1)	62 (17.1)	11 (3.0)	0

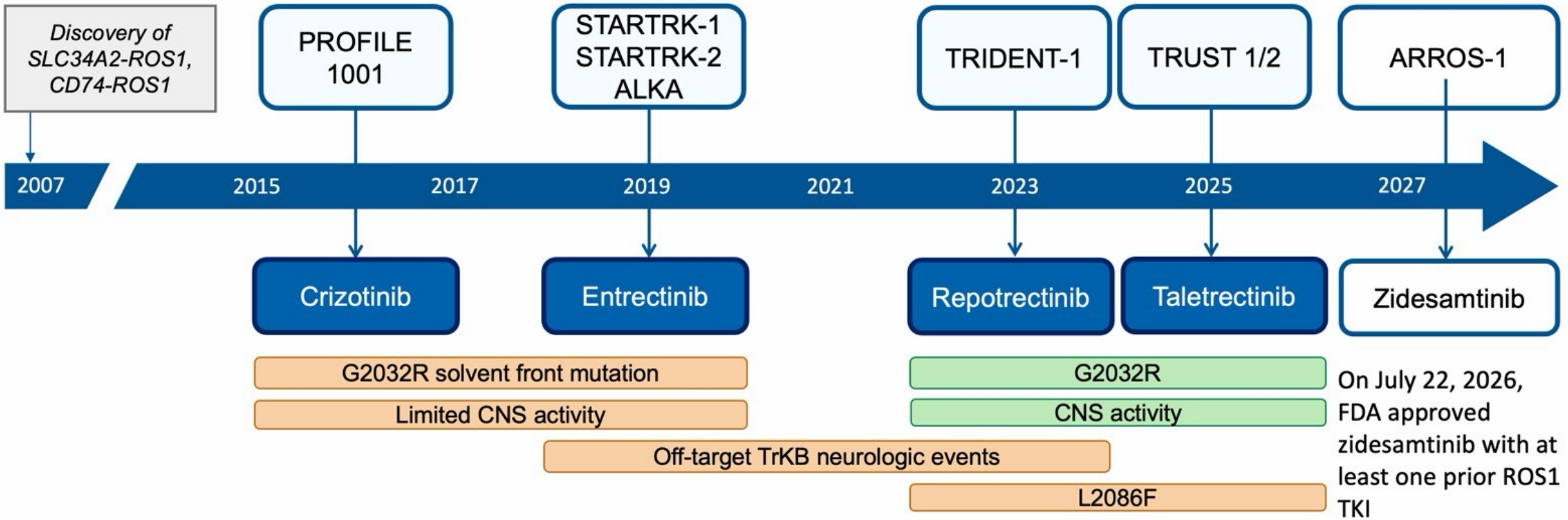
- With longer follow-up, no new safety signals were identified, and safety was consistent between the integrated safety population and TKI-naïve patients
- The most common (any grade) TEAEs were increased AST, increased ALT, diarrhea, nausea, and vomiting
- Rates of neurologic TEAEs were low and mostly Grade 1 or 2
  - **Dizziness**: 18.5% Grade 1; 2.8% Grade 2
  - **Dysgeusia**: 13.2% Grade 1; 2.2% Grade 2
- TEAEs led to dose interruptions in 42.7% of patients, dose reductions in 31.3%, and treatment discontinuations in 8.5%

Data cutoff: August 31, 2025

[a]The integrated safety population includes TKI-naïve and TKI-pretreated patients with ROS1+ NSCLC who received ≥1 dose of taletrectinib 600 mg QD from Phase 2 trials (TRUST-I and TRUST-II) and a Phase 1 trial (J102).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, ROS proto-oncogene 1; TEAE, treatment-emergent adverse event, TKI, tyrosine kinase inhibitor.

ROS1 NSCLC: Evolution in targeted treatment



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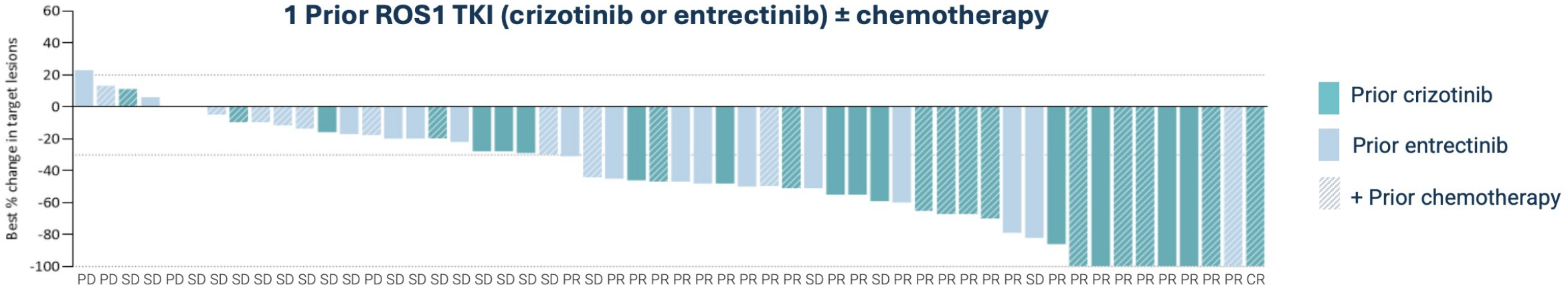
ARROS-1: Objective Response in ROS1 TKI Pre-treated Patients

Advanced *ROS1*+ NSCLC RECIST 1.1 by BICR	Any prior ROS1 TKI (range 1 – 4) ± chemotherapy	1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy
ORR, % (n/N) [95% CI]	**44%** (51/117) [34, 53]	**51%** (28/55) [a] [37, 65]
CR, % (n/N)	1% (1/117)	2% (1/55)

[a] Prior crizotinib only ± chemotherapy: ORR = 68% (19/28). Prior entrectinib only ± chemotherapy: ORR = 33% (9/27).

Responses were also observed in patients previously treated with:

- **≥2 prior ROS1 TKIs ± chemotherapy**: ORR = 38% (22/58; 95% CI: [26, 52])
- **Prior repotrectinib: ORR = 47% (8/17),** DOR range 3.5 to 17.2 months
- **Prior taletrectinib: ORR = 43% (3/7),** DOR range 5.2 to 7.0+ months



Data cut-off: March 21, 2025. CI, confidence interval; CR, complete response. PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease.

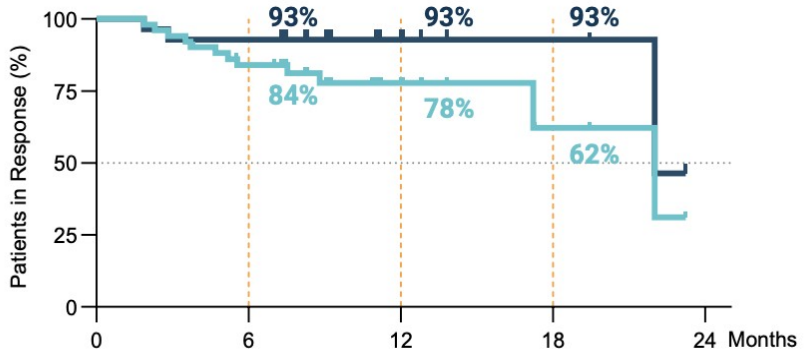
ARROS-1: Duration of Response and Progression-Free Survival

Advanced *ROS1*+ NSCLC Kaplan-Meier Estimate	Duration of Response		Progression-Free Survival	
	Any prior ROS1 TKIs (range 1-4) ± chemotherapy [a]	1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy [b]	Any prior ROS1 TKIs (range 1-4) ± chemotherapy [a]	1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy [b]
% ≥ 6 months [95% CI]	**84%** [71, 92]	**93%** [74, 98]	**57%** [47, 66]	**70%** [56, 81]
% ≥ 12 months [95% CI]	**78%** [62, 88]	**93%** [74, 98]	**48%** [38, 57]	**68%** [53, 79]
% ≥ 18 months [95% CI]	**62%** [28, 84]	**93%** [74, 98]	**40%** [24, 55]	**68%** [53, 79]

Data cut-off: March 21, 2025

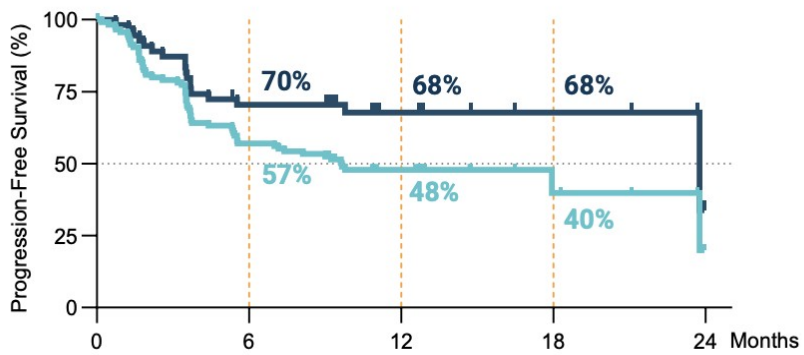
[a] Any prior ROS1 TKI: Emerging median DOR of 22 months [95% CI: 17, NE] continues to mature. Median PFS was 9.7 [5.5, NE] months with median follow-up of 11.1 months (range 0.2-25.6).

[b] 1 prior ROS1 TKI (crizotinib [C] or entrectinib [E]): Emerging median DOR of 22 months [95% CI: 22, NE] and median PFS of 23.8 months [95% CI: 23.8, NE] continue to mature; median follow-up was 11.8 months (range 1.2-25.6).



At Risk

Any prior ROS1 TKIs	51	40	10	3	0
Prior C or E only	28	26	6	3	0



At Risk

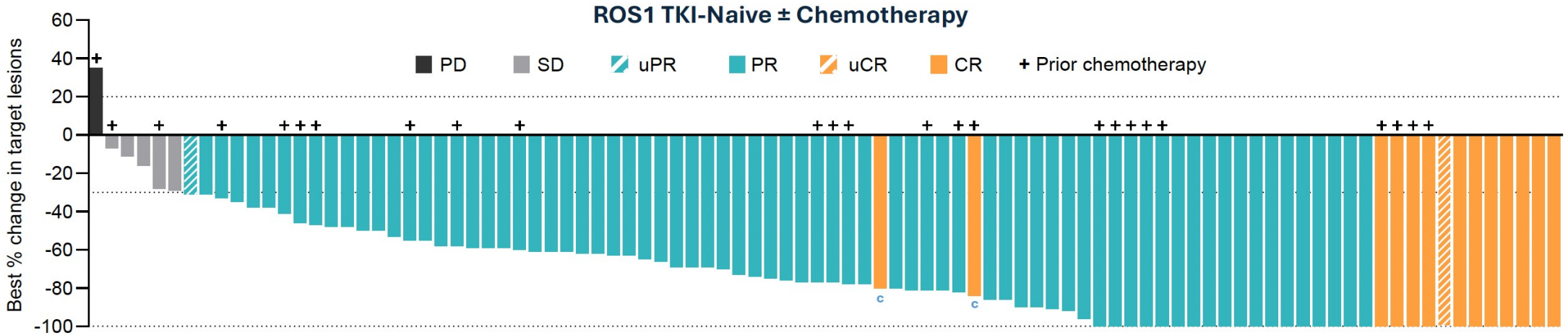
Any prior ROS1 TKIs	117	64	27	5	0
Prior C or E only	55	37	14	4	0

- **In patients that received prior crizotinib only, there were no progression events among responders (DOR range: 7.3+ to 23.2+ months). PFS rate was 89% (95% CI: 70, 96) at 6, 12, and 18 months with median not reached.**
- **In patients that received ≥2 prior ROS1 TKIs ± chemotherapy, DOR rate was 71% (95% CI: 46, 86) at 6 months and 56% (95% CI: 29, 76) at 12 months.**

ARROS-1: Objective Response in ROS1 TKI-Naive Patients with NSCLC

Advanced *ROS1*+ NSCLC RECIST v1.1 by BICR	**ROS1 TKI-Naive ± Prior Chemotherapy (n = 94)**
ORR, % (n/N) [a] [95% CI]	**94%** (88/94) [87, 98]
CR, % (n/N) [b]	**15%** (14/94)

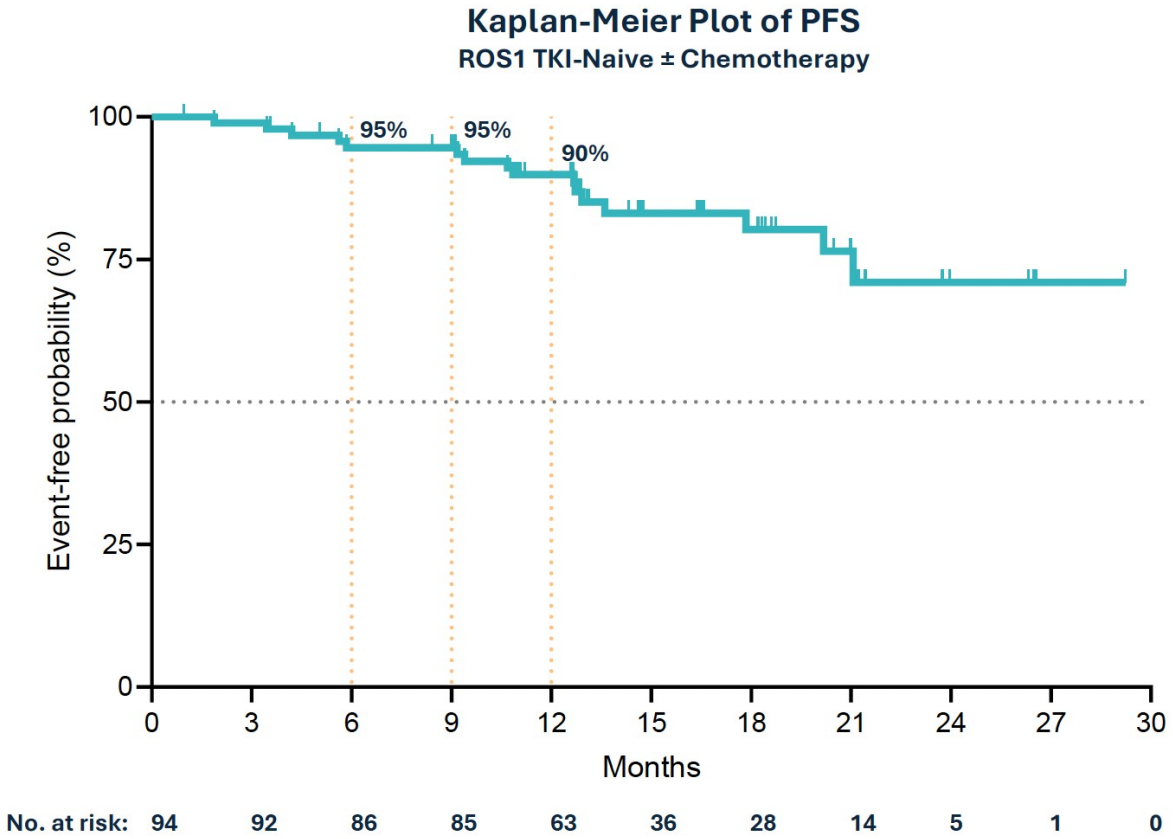
[a] Includes 1 single-timepoint PR pending confirmation in ongoing patient.
[b] Includes 1 single-timepoint CR pending confirmation in ongoing patient with prior confirmed PR.



[c] CR with <100% shrinkage due to residual non-pathologic lymph node.
BICR, blinded independent central review; **CR**, complete response; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumor; **ROS1**, c-ros oncogene 1; **SD**, stable disease; **TKI**, tyrosine kinase inhibitor; **uCR**, unconfirmed CR (single-timepoint CR pending confirmation in ongoing patient with prior confirmed PR); **uPR**, unconfirmed PR (single-timepoint PR pending confirmation in ongoing patient).

ARROS-1: Progression-Free Survival in ROS1 TKI-Naive Patients with NSCLC

Advanced *ROS1*+ NSCLC Kaplan-Meier Estimate	**ROS1 TKI-Naive ± Prior Chemotherapy n = 94**
% PFS ≥ 6 months [95% CI]	**95%** [87, 98]
% PFS ≥ 9 months [95% CI]	**95%** [87, 98]
% PFS ≥ 12 months [95% CI]	**90%** [81, 95]
Median PFS, months [95% CI]	**NR** [NE, NE]



NE, not estimable; **NR**, not reached; **NSCLC**, non-small cell lung cancer; **PFS**, progression-free survival; **ROS1**, c-ros oncogene 1; **TKI**, tyrosine kinase inhibitor.

ARROS-1: Safety in Advanced *ROS1*+ NSCLC

TEAEs in ≥ 15% of TKI-Naive or TKI-Pretreated Patients with Advanced *ROS1*+ NSCLC Receiving Zidesamtinib 100 mg QD (N = 532)

Preferred Term	Any Grade	Grade ≥3
Peripheral edema	42%	1%
Blood CPK increased	23%	5%
Constipation	23%	<1%
Weight increased	22%	7%
AST increased	19%	1%
ALT increased	18%	2%
Dysgeusia	18%	0
Dyspnea	17%	4%
Arthralgia	17%	1%
Peripheral sensory neuropathy	17%	1%
Hypertriglyceridemia	16%	3%
Headache	15%	<1%

- **Treatment-related AEs in ≥15% of patients (any grade; grade ≥3):**
  - Peripheral edema (34%; 0.6%)
  - Weight increased (18%; 4%)
  - Blood CPK increased (18%; 3%)
  - Dysgeusia (17%; 0%)
  - AST increased (15%; 1%)
- **Dose reduction due to TEAE: 12%; TRAE: 11%**
  - TEAEs leading to dose reduction in ≥1% of patients: peripheral edema (2.4%), peripheral sensory neuropathy (1.5%), blood CPK increased (1.1%), weight increased (1.1%)
- **Discontinuation due to TEAE: 4%; TRAE: 1%**
  - TEAEs leading to discontinuation in ≥2 patients: pneumonia (n=3), pneumonitis (n=3), weight increased (n=2)

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **CPK**, creatine phosphokinase; **NSCLC**, non-small cell lung cancer; **QD**, once-daily; **ROS1**, c-ros oncogene 1; **TEAE**, treatment emergent adverse event; **TKI**, tyrosine kinase inhibitor.

CNS efficacy

Reprotrectinib

	Prior ROS1 TKI (N=13)	ROS1 TKI-naïve (N=9)
IC-ORR (95% CI)	**38%** (14,68)	**89%** (52,100)
≥12mo DOR (95% CI)	**60%** (17,100)	**83%** (54,100)

Drilon A, et. al NEJM January 2024;390(2):118-131

Taltrectinib

	Prior ROS1 TKI (N=32)	ROS1 TKI-naïve (N=17)
IC-ORR (95% CI)	**65.6%** (47,81)	**76.5%** (50,93)
IC-DOR (95% CI)	**11.9 mo** (7,24)	**14.7 mo** (4,30)

Perol M et. al, JCO June 2025;42(16):1920-1929

Zidesamtinib

	Any prior ROS1 TKI (N=56)	ROS1 TKI-naïve (N=10)
IC-ORR (95% CI)	**48%** (35,62)	**100%** (69,100)
≥12mo DOR (95% CI)	**71%** (46,87)	**78%** (36,94)

Drilon A et. al, WCLC September 2025. Abstract PL02.15

Drilon A et. al, WCLC September 2026. Abstract PL03.06

Multiple new options in ROS-1 targeted therapy

Frontline:

Taltrectinib – note taken daily on empty stomach; avoid PPIs

_ decreased TRK mediated neurotoxicity

Repotectinib

Next Line:

Zidesamtinib

Questions remain:

Sequencing, use in early stage adjuvant or post CRT