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Pooled Efficacy and Safety From 2 Pivotal Phase 2 Trials of Taletrectinib in Patients With Advanced or Metastatic ROS1+ Non–Small Cell Lung Cancer

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Objectives

This integrated analysis of the registrational cohorts of patients from the regional TRUST-I and global TRUST-II studies assessed the efficacy and safety of taletrectinib in people living with advanced ROS1+ NSCLC

Background

- Taletrectinib is an oral, selective, CNS-active, next-generation ROS1 TKI with selectivity over TrkB[1-3]
  - Potent against ROS1 and acquired-resistance mutations, such as G2032R
  - Clinical exposures at steady state sufficient to inhibit both ROS1 and ROS1^{G2032R}
- Taletrectinib demonstrated high and durable overall responses, intracranial activity, prolonged PFS, activity against G2032R, and had a favorable safety profile in the regional TRUST-I study (NCT04395677)[2]
- Previously, data from TRUST-I[2] and TRUST-II[4] were presented individually; we now present a more mature integrated analysis from the largest efficacy population (N=273) of people living with advanced ROS1+ NSCLC from pivotal studies

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOR, best overall response; C, crizotinib; cORR, confirmed objective response rate; CPK, creatinine phosphokinase; CR, complete response; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; E, entrectinib; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IRC, independent review committee; mRECIST, modified Response Evaluation Criteria in Solid Tumors v1.1; NR, not reached; NSCLC, non–small cell lung cancer; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors v1.1; REP, response evaluable population; SD, stable disease; TEAE, treatment-emergent adverse event; TrkB, tropomyosin receptor kinase B; TKI, tyrosine kinase inhibitor; WBC, white blood cell.

References

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3. Papadopoulos KP, et al. *Clin Cancer Res*. 2020;26(18):4785-4794.
4. Perol M, et al. *Ann Oncol*. 2023;34(supp 2):S788-S789.

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Methods

Study Design

- TRUST-I (NCT04395677): Regional phase 2, multicenter, open-label, single-arm trial of taletrectinib in patients with ROS1+ NSCLC in China (cohort 1: ROS1 TKI naive; cohort 2: ROS1 TKI pretreated)
- TRUST-II (NCT04919811): Global phase 2, multicenter, open-label, single-arm trial of taletrectinib in patients with ROS1+ NSCLC and other solid tumors (cohort 1: ROS1 TKI naive; cohort 2: ROS1 TKI pretreated; cohorts 3–5: exploratory cohorts included in safety analyses)

Key Eligibility Criteria for Pivotal Cohorts

- Locally advanced or metastatic NSCLC
- Age ≥18 years[a]
- ECOG PS 0–1
- Evidence of ROS1 fusion
- Stable CNS involvement allowed
- At least 1 measurable lesion per RECIST v1.1

ROS1 TKI naive | **ROS1 TKI pretreated[b]**

Taletrectinib 600 mg QD[c]

Study Endpoints

Primary
- IRC-assessed cORR per RECIST v1.1

Key Secondary
- IC-cORR per mRECIST v1.1
- DOR
- PFS
- Safety

Study Populations
- Efficacy[c]: Response evaluable population (REP) included patients with ROS1+ NSCLC with ≥1 measurable lesion at baseline per RECIST V1.1 by IRC and who received ≥1 dose of taletrectinib; TKI naive (n=160) and TKI pretreated (n=113)
- Safety[c]: Patients with ROS1+ NSCLC who received ≥1 dose of taletrectinib 600 mg (n=337)

[a]Or ≥20 years, as required by local regulations. [b]One prior ROS1 TKI (crizotinib [C] or entrectinib [E]). [c]Three patients in TRUST-I started taletrectinib 400 mg and of these, 2 escalated to 600 mg.

Results

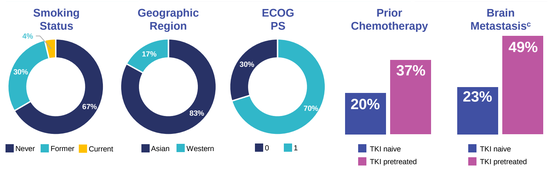
Patient Demographics and Baseline Characteristics[a]

273[b] patients enrolled as of June 7, 2024

Median age: **56 y** Range: 26-82

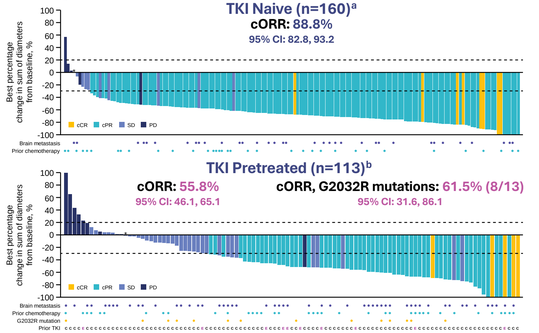
156 (57%) of patients were female

256 (94%) of patients had **stage IV disease**



[a]Patients in REP. [b]Overall, 172 (63%) patients from TRUST-I and 101 (37%) from TRUST-II were enrolled. [c]Assessed by an IRC per mRECIST version 1.1.

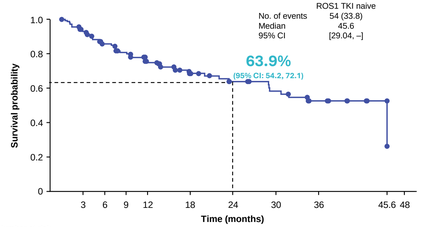
cORR by IRC



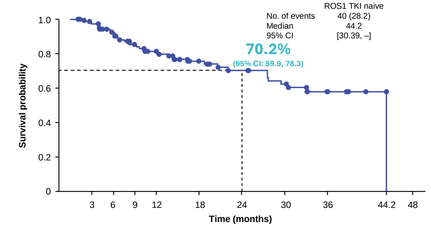
[a]Three patients with confirmed BOR as not evaluable are not displayed in the waterfall plot. [b]Six patients with confirmed BOR as not evaluable are not displayed in the waterfall plot. *One patient had a best percentage change of 0 and BOR as SD.

Efficacy in TKI-Naive Patients

Median PFS: **45.6 months**
95% CI: 29.0, NR



Median DOR[a]: **44.2 months**
95% CI: 30.4, NR

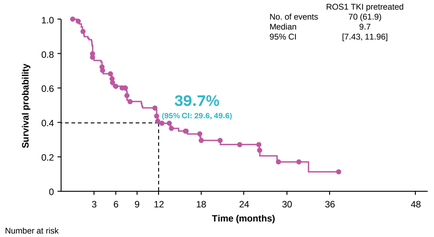


Median follow-up: **21.2 months**
(Range: 3.6–46.6)

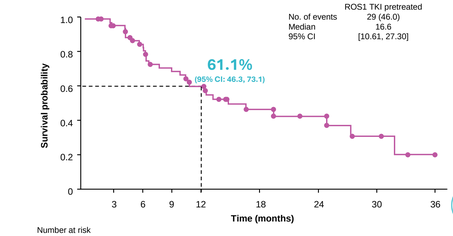
[a]REP patients with a confirmed objective response.

Efficacy in TKI-Pretreated Patients

Median PFS: **9.7 months**
95% CI: 7.4, 12.0



Median DOR[a]: **16.6 months**
95% CI: 10.6, 27.3



Median follow-up: **21.0 months**
(Range: 3.9–45.4)

[a]REP patients with a confirmed objective response.

Conclusions

Integrated analysis from the TRUST-I and TRUST-II studies establishes taletrectinib as a potential best-in-class ROS1 TKI for people living with advanced ROS1+ NSCLC

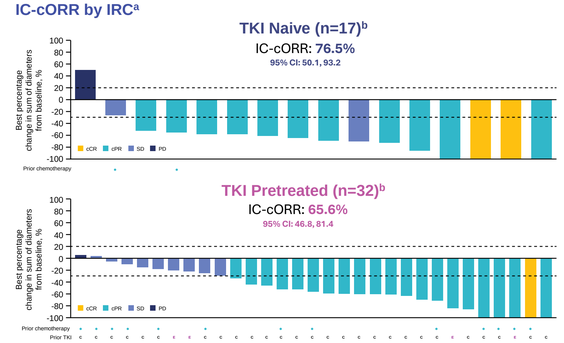
- **High and durable overall response rates were observed in both cohorts**
- **In TKI-naive patients, median DOR and median PFS were 44.2 months and 45.6 months, respectively**
- **In TKI-pretreated patients, median DOR and median PFS were 16.6 months and 9.7 months, respectively**
- **IC responses were robust in both cohorts, and G2032R response rates were high in TKI-pretreated patients**
- **Response rates were consistent among the subgroups analyzed**

Taletrectinib demonstrated a favorable tolerability and safety profile in people living with advanced ROS1+ NSCLC

- **TEAEs were mostly grade 1-2**
- **Rates of neurologic TEAEs were low (dizziness: 21.1%; dysgeusia: 14.5%), and most were grade 1**
- **Low incidence of discontinuations (6.5%) due to TEAEs**

Overall, taletrectinib demonstrated a favorable benefit risk profile at the recommended phase 2 dose of 600 mg QD

IC-cORR by IRC[a]



[a]REP patients with measurable brain metastases and a confirmed response. [b]One patient with confirmed BOR as not evaluable is not displayed in the waterfall plot.

cORR by Subgroup in REP

TKI Naive

Subgroup	No. of subjects	No. of responses	ORR (95% CI)
Overall	160	142	88.8 (82.80, 93.19)
Region category 1			
Western	21	17	81.0 (58.09, 94.55)
Asian	139	125	89.9 (83.68, 94.38)
Brain metastasis by IRC at baseline (mRECIST v1.1)			
Yes	37	32	86.5 (71.23, 95.46)
No	123	110	89.4 (82.60, 94.25)
Prior chemotherapy			
Yes	32	28	87.5 (71.01, 96.49)
No	128	114	89.1 (82.33, 93.89)

TKI Pretreated

Subgroup	No. of subjects	No. of responses	ORR (95% CI)
Overall	113	63	55.8 (46.11, 65.09)
Region category 1			
Western	26	17	65.4 (44.33, 82.79)
Asian	87	46	52.9 (41.87, 63.67)
Brain metastasis by IRC at baseline (mRECIST v1.1)			
Yes	55	31	56.4 (42.32, 69.70)
No	58	32	55.2 (41.54, 68.26)
Prior chemotherapy			
Yes	42	25	59.5 (43.28, 74.37)
No	71	38	53.5 (41.29, 65.45)

Safety

TEAEs in ≥15% of Patients With ROS1+ NSCLC Treated With Taletrectinib 600 mg QD (N=337)[a]

TEAE, n (%)	Any grade	Grade 1	Grade 2	Grade ≥3[b]
Patients with ≥1 TEAE	336 (99.7)	30 (8.9)	132 (39.2)	174 (51.6)
Increased AST	243 (72.1)	161 (47.8)	56 (16.6)	26 (7.7)
Increased ALT	229 (68.0)	135 (40.1)	60 (17.8)	34 (10.1)
Diarrhea	213 (63.2)	168 (49.9)	38 (11.3)	7 (2.1)
Nausea	159 (47.2)	123 (36.5)	31 (9.2)	5 (1.5)
Vomiting	146 (43.3)	114 (33.8)	27 (8.0)	5 (1.5)
Anemia	126 (37.4)	75 (22.3)	39 (11.6)	12 (3.6)
Constipation	71 (21.1)	61 (18.1)	10 (3.0)	0
Dizziness	71 (21.1)	64 (19.0)	6 (1.8)	1 (0.3)
QT prolongation	65 (19.3)	44 (13.1)	9 (2.7)	12 (3.6)
Increased blood creatinine	61 (18.1)	50 (14.8)	11 (3.3)	0
Increased blood bilirubin	59 (17.5)	43 (12.8)	12 (3.6)	4 (1.2)
Increased blood CPK	56 (16.6)	36 (10.7)	13 (3.9)	7 (2.1)
Decreased neutrophil count	56 (16.6)	28 (8.3)	14 (4.2)	14 (4.2)
Decreased appetite	53 (15.7)	38 (11.3)	14 (4.2)	1 (0.3)
Decreased WBC count	53 (15.7)	31 (9.2)	17 (5.0)	5 (1.5)

- Median duration of exposure was 11.1 months (range: 0.1–64.1)
- Most common TEAEs were elevated liver enzymes and gastrointestinal events
- Neurologic TEAEs were low (dizziness: 21.1%; dysgeusia: 14.5%), most were grade 1
- 28.8% of patients had a TEAE leading to a dose reduction (abnormal liver function tests accounted for 12.5%)
- 6.5% of patients had a TEAE leading to treatment discontinuation

[a]Worst grade per patient reported. [b]3 patients reported grade 5 AEs that were possibly treatment-related: hepatic failure, hepatic function abnormal, and pneumonia; n=1 each.