#CO151

Taletrectinib vs Entrectinib in *ROS1*-Positive Non-Small Cell Lung Cancer: A Matching-Adjusted Indirect Comparison

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Objective

To conduct a matching-adjusted indirect comparison (MAIC) of taletrectinib and entrectinib in TKI-naive patients with *ROS1+* NSCLC

Background

- For patients with *ROS1+* NSCLC, ROS1 tyrosine kinase inhibitors (TKIs) are the current standard of care[1]
- Entrectinib was approved by the US Food and Drug Administration in 2019 and crosses the blood-brain barrier, but overall responses were marginal in patients with prior CNS progression (IC-ORR: 11%) [2,3]
- Taletrectinib is an oral, potent, CNS-active, selective, next-generation, ROS1 inhibitor [4-6]
  - Taletrectinib has demonstrated high and durable overall and IC response rates, activity against G2032R, and a favorable safety profile in the pivotal regional TRUST-I (NCT04395677) and global TRUST-II (NCT04919811) studies [6,7]
  - In December 2024, the US FDA granted priority review to the NDA for seeking the approval of taletrectinib for the treatment of advanced *ROS1+* NSCLC (PDUFA goal date of June 23, 2025)
- In the absence of head-to-head trials in TKI-naive patients with *ROS1+* NSCLC, we compared taletrectinib with the first-generation TKI, entrectinib, using a MAIC analysis

Abbreviations

CNS, central nervous system; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; MAIC, matching-adjusted indirect comparison; NA, not available; NDA, New Drug Application; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PDUFA, Prescription Drug User Fee Act; PFS, progression-free survival; PR, partial response; PT, preferred term; *ROS1+*, *ROS1*-positive; SAE, serious adverse events; SD, stable disease; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event; US FDA, US Food and Drug Administration.

References

1. Gendarme S, et al. *Curr Oncol*. 2022;29:641-658. **2.** Rozlytrek [package insert]. San Francisco, CA: Genentech USA, Inc; October 2023. **3.** Drilon A, et al. *JTO Clin Res Rep*. 2022;3:100332. **4.** Nagasaka M, et al. *Future Oncol*. 2023;19:123-135. **5.** Katayama R, et al. *Nat Comm*. 2019;10:3604. **6.** Li W, et al. *J Clin Oncol*. 2024;42:2660-2670. **7**. Liu, et al. *JTO*. 2024;10:S72-S73. **8.** Drilon A, et al. *Lancet Oncol*. 2020;21:261-270. **9.** Fan Y, et al. *Clin Lung Cancer*. 2024;25:e81-e86.e4. **10.** Perol M, et al. *JCO*. 2025.

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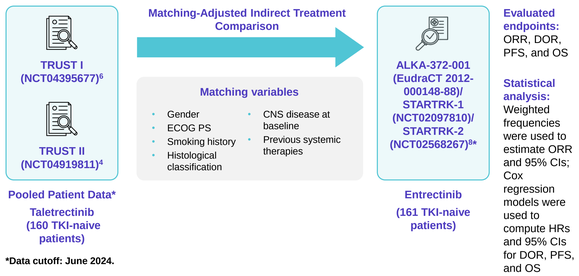
Methods

Study Design



*Data cutoff: June 2024.

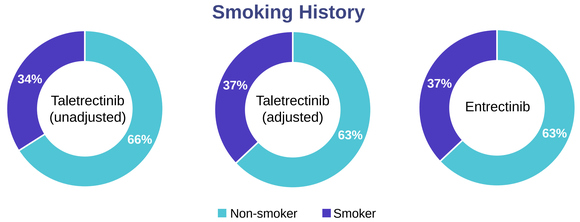
Results

Baseline Comparison in *ROS1+* TKI-Naive NSCLC

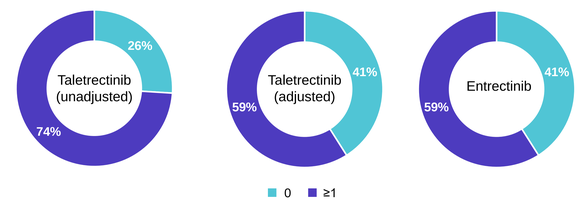
Gender, Female
Taletrectinib (unadjusted) – 56%
Taletrectinib (adjusted) – 65%
Entrectinib – 65%

Adenocarcinoma
Taletrectinib (unadjusted) – 97%
Taletrectinib (adjusted) – 98%
Entrectinib – 98%

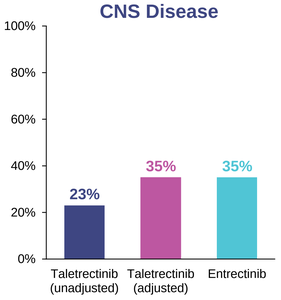
Smoking History



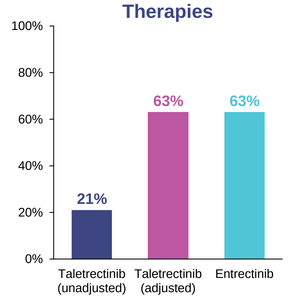
ECOG PS



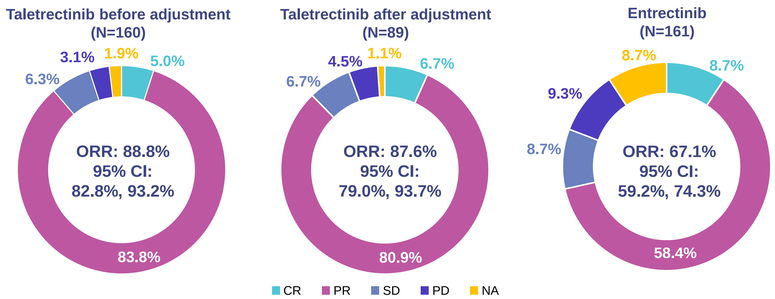
Baseline CNS Disease



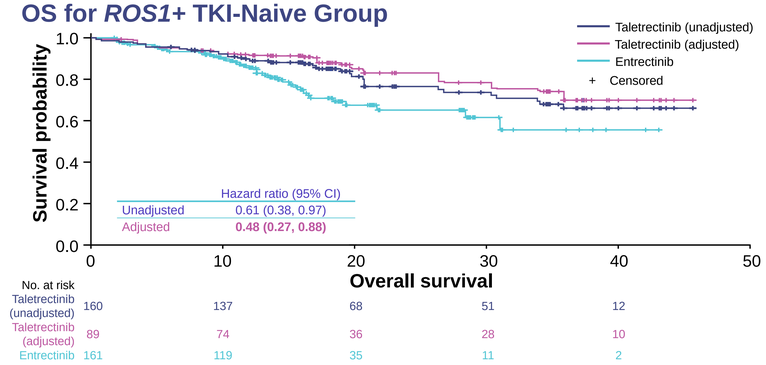
Previous Systemic Therapies



ORR in *ROS1+* TKI-Naive NSCLC



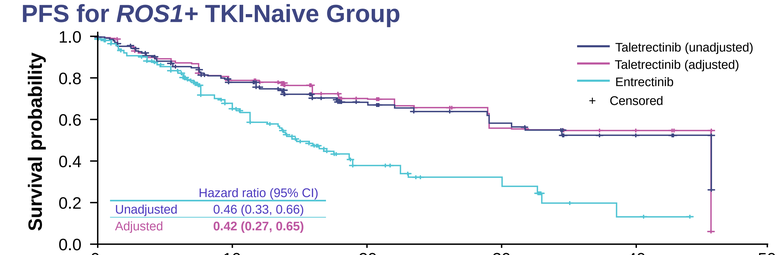
OS for *ROS1+* TKI-Naive Group



No. at risk

Taletrectinib (unadjusted)	160	137	68	51	12
Taletrectinib (adjusted)	89	74	36	28	10
Entrectinib	161	119	35	11	2

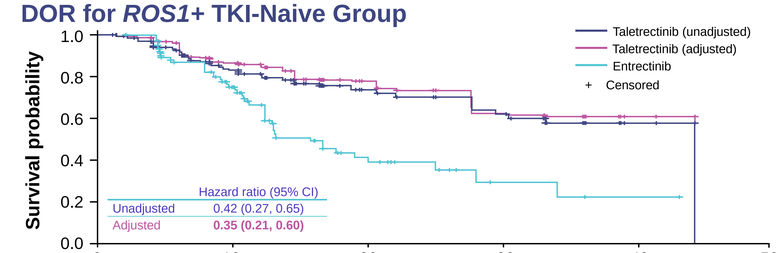
PFS for *ROS1+* TKI-Naive Group



No. at risk

Taletrectinib (unadjusted)	160	105	48	32	8
Taletrectinib (adjusted)	89	62	28	20	6
Entrectinib	161	79	23	14	2

DOR for *ROS1+* TKI-Naive Group



No. at risk

Taletrectinib (unadjusted)	142	100	41	31	6	0
Taletrectinib (adjusted)	78	60	27	20	4	0
Entrectinib	108	58	19	4	1	

Safety in *ROS1+* NSCLC

TRAEs	Taletrectinib (N=352)* n (%)	Entrectinib[9] (N=247) n(%)
TRAEs leading to permanent discontinuation	9 (2.6)	17 (6.9)
TRAEs leading to treatment interruption	96 (27.3)	89 (36.0)
TRAEs leading to dose modification	97 (27.6)	86 (34.8)
Any grade 3/4 TRAEs	116 (33.0)	107 (43.3)
Treatment-related SAEs	27 (7.7)	35 (14.2)
Treatment-related deaths	3 (0.9)	1 (0.4)

* Pooled safety population included all patients receiving taletrectinib 600 mg once daily until disease progression or unacceptable toxicity across the safety population[10]

- TRAE rates are summarized for taletrectinib and entrectinib
- Due to the inconsistent definition of TRAEs, as well as lack of availability of baseline patient characteristics of comparable safety population, these estimates are unadjusted and not designed for drawing comparisons between agents

Limitations

- Indirect treatment comparison studies are subject to bias due to variations in patient populations, study designs, and outcome measures across the included trials, leading to uncertain comparisons

Strength

- Given the available evidence, the described comparative analysis is a transparent and methodologically sound approach to compare taletrectinib and entrectinib

Conclusions

Taletrectinib showed significantly improved efficacy outcomes vs entrectinib in TKI-naive patients with *ROS1+* NSCLC in the MAIC analysis, including

- **Higher ORR and a significant 65% improvement in the likelihood of maintaining a response**
- **Significant 52% reduction in the risk of death and a 58% reduction in the risk of progression/death**

TRAEs are summarized as unadjusted estimates, since the lack of comparable baseline characteristics limits comparison across treatments

These findings underscore the therapeutic benefits of taletrectinib over entrectinib outside of head-to-head randomized controlled trials

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