elcc European Lung Cancer Congress 2025

TALETRECTINIB VS CRIZOTINIB IN *ROS1*-POSITIVE NON-SMALL CELL LUNG CANCER: A MATCHING-ADJUSTED INDIRECT COMPARISON

Misako Nagasaka,[1] Geoffrey Liu,[2] Nathan A. Pennell,[3] Maurice Pérol,[4] Wenfeng Chen,[5] Lyudmila Bazhenova,[6] Caicun Zhou[7]

[1]University of California Irvine School of Medicine and Chao Family Comprehensive Cancer Center, Orange, CA, USA; [2]Princess Margaret Cancer Centre, Temerty School of Medicine, University of Toronto, Toronto, Canada; [3]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [4]Léon Bérard Cancer Center, Lyon, France; [5]Nuvation Bio, New York, NY, USA; [6]University of California San Diego Moores Cancer Center, San Diego, CA, USA; [7]Shanghai Pulmonary Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China

Presented by Misako Nagasaka

27 March 2025

Organisers: ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE; IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Partners: ESTRO; ETOP·IBCSG PARTNERS FOUNDATION

DISCLOSURES

Misako Nagasaka: Advisory Board: AstraZeneca, Daiichi Sankyo, Takeda, Novartis, EMD Serono, Pfizer, Lilly, Regeneron, Genentech; Consultancy: Caris Life Sciences (virtual tumor board); Speaker: Blueprint Medicines, Janssen, Mirati, Takeda; Travel Support: Nuvation Bio Inc.

Geoffrey Liu: Nonfinancial Interests, Personal, Other – Honorarium: Takeda, Amgen, AstraZeneca, Roche, Novartis, Merck, Pfizer, Jazz Pharmaceuticals; Financial Interests, Institutional, Funding, Research Grants: Takeda, AstraZeneca, Amgen, Boehringer Ingelheim

Nathan A. Pennell: Advising/Consulting: Merck, BMS, Pfizer, Genentech, Sanofi Genzyme, Novartis, Bayer, Summit Therapeutics, AnHeart Therapeutics, Takeda, J&J, Lilly/Regeneron, Iovance

Maurice Pérol: Invited Speaker: Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Janssen-Cilag, Medscape, MSD, Roche, Sanofi, Pfizer, Takeda; Expert Testimony: BMS, Roche; Advisory Board: Amgen, AnHeart Therapeutics, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Esai, GlaxoSmithKline, Gritstone, Ipsen, Janssen-Cilag, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi, Takeda; Principal Investigator: AbbVie, Amgen, AnHeart Therapeutics, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda; Sponsor/Funding: AstraZeneca, Boehringer Ingelheim, Chugai, Roche, Takeda; Advisory Role: AnHeart Therapeutics, AstraZeneca, Bristol Myers Squibb, Dohme, Eli Lilly, GlaxoSmithKline, Ipsen, Pfizer, Merck Sharp & Roche, Takeda

Wenfeng Chen: Employment: Nuvation Bio Inc.

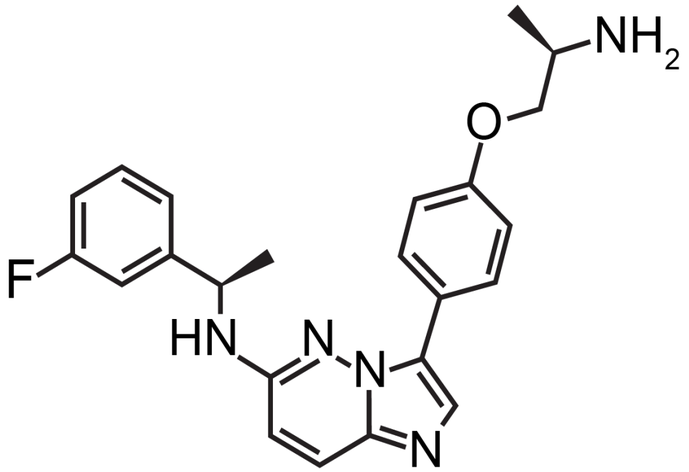
Lyudmila Bazhenova: Advisory Board: Nuvation Bio Inc., Bayer, Daiichi Sankyo, Genentech, Gilead Sciences, Janssen/J&J, Novocure, ORIC, Regeneron, Pfizer, Sanofi, Teligene, Boehringer Ingelheim

Caicun Zhou: Honoraria: Amoy Diagnostics, Boehringer Ingelheim, CStone Pharmaceuticals, Hengrui Pharmaceutical, Innovent Biologics, Lilly China, LUYE Pharma, MSD, QiLu Pharmaceutical, Roche, Sanofi, TopAlliance Biosciences Inc.; Consulting or Advisory Role: Amoy Diagnostics, Boehringer Ingelheim, CStone Pharmaceuticals, Hengrui Pharmaceutical, Innovent Biologics, Lilly China, Luye Pharma, MSD, QiLu Pharmaceutical, Roche, Sanofi, TopAlliance Biosciences Inc.

MAIC: Taletrectinib vs Crizotinib in TKI-Naive Patients With *ROS1*+ NSCLC

- For patients with *ROS1*-positive (*ROS1*+) NSCLC, ROS1 tyrosine kinase inhibitors (TKIs) are the current standard of care[1]
  - However, most patients progress within 2 years due to acquired resistance mutations (ie, G2032R) or brain metastases[1]
- Taletrectinib is an oral, CNS-active, next-generation, and selective ROS1 TKI specifically designed to[2-4]:
  - Improve efficacy and safety in *ROS1*+ NSCLC
  - Effectively treat CNS metastases
  - Overcome acquired resistance
  - Reduce neurological side effects with selectivity for *ROS1* over tyrosine receptor kinase B (TrkB)

Taletrectinib

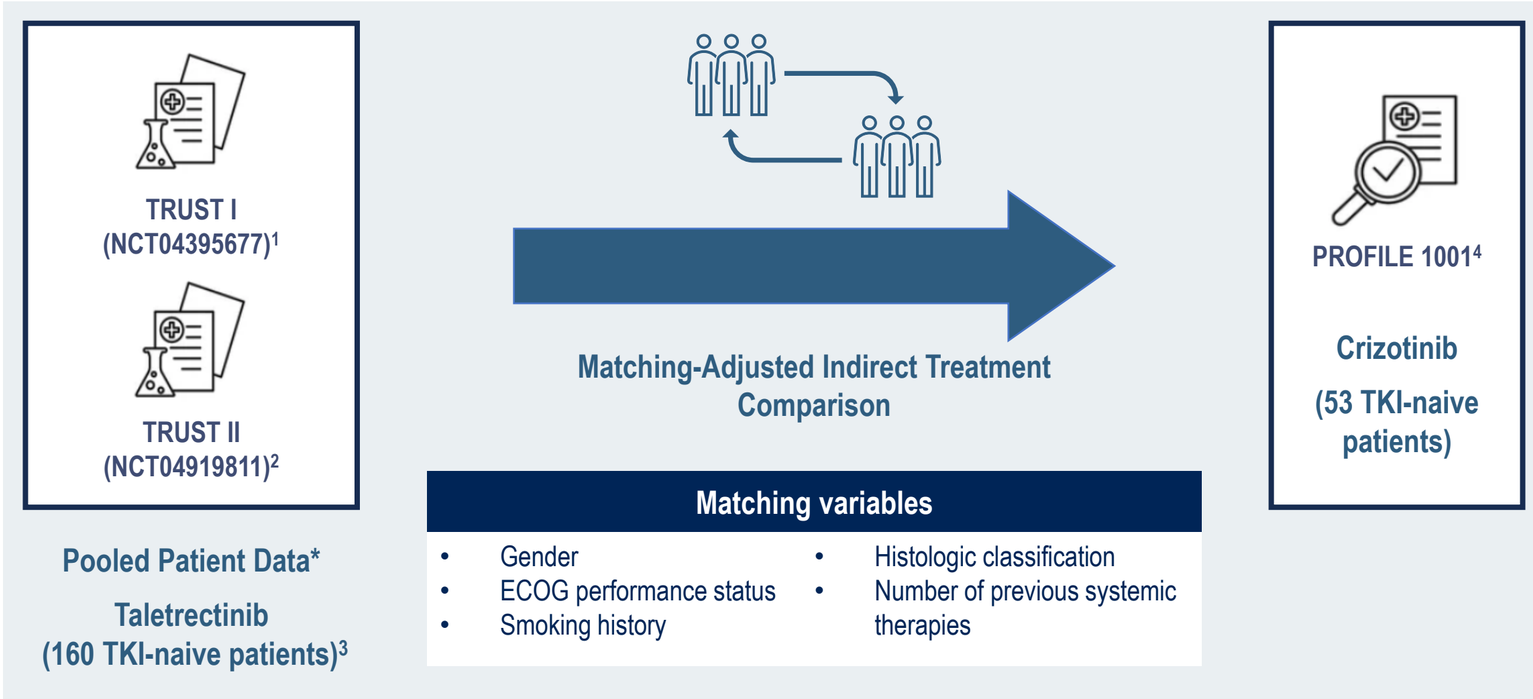


- In the absence of head-to-head trials in TKI-naive patients with *ROS1*+ NSCLC, we compared taletrectinib with the first-generation TKI, crizotinib, using a matching-adjusted indirect comparison (MAIC)

CNS, central nervous system; MAIC, matching-adjusted indirect comparison; NSCLC, non-small cell lung cancer; ROS1+, ROS1 positive; TKI, tyrosine kinase inhibitor; TrkB, tyrosine receptor kinase B.

1. Gendarme S, et al. *Curr Oncol.* 2022;29:641-658. **2.** Nagasaka M, et al. *Future Oncol.* 2023;19:123-135. **3.** Katayama R, et al. *Nat Comm.* 2019;10:3604. **4.** Li W, et al. *J Clin Oncol.* 2024;42:2660-2670.

MAIC: Taletrectinib vs Crizotinib in *ROS1*+ TKI-Naive NSCLC



- Evaluated endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and grade 3 treatment-related adverse event (TRAE) rates
- Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using adjusted Cox regression models

***Data cutoff: June 2024.**

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; ROS1+, ROS1 positive; TKI, tyrosine kinase inhibitor; TRAEs, treatment-related adverse events.

1. Li W, et al. *J Clin Oncol.* 2024;42:2660-2670. **2.** Liu G, et al. World Conference on Lung Cancer. San Diego, USA. September 7-10, 2024. Oral Presentation. **3.** Perol M, et al. European Society for Medical Oncology. Barcelona, Spain. September 13-17, 2024. Poster #1289P. **4.** Shaw AT, et al. *Ann Oncol.* 2019;30:1121–1126.

MAIC Taletrectinib vs Crizotinib: Baseline Comparison in *ROS1*+ TKI-Naive NSCLC

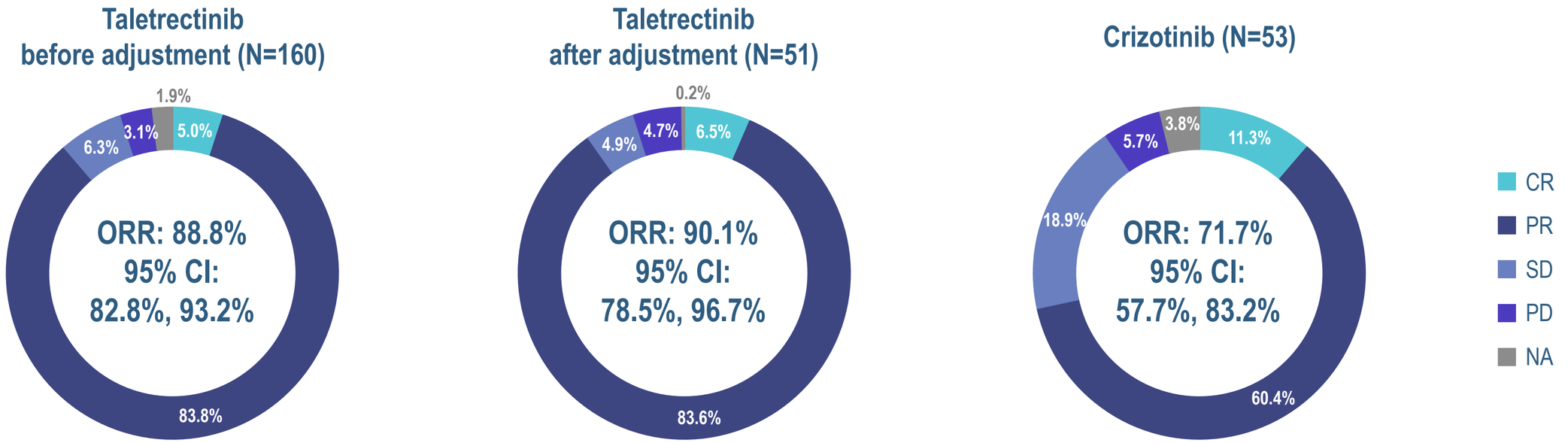
TKI-naive populations were well balanced on measured covariates, and the effective sample size for taletrectinib was 51

Variables		Taletrectinib before adjustment (N=160), n (%)	Taletrectinib after adjustment (N=51), n (%)	Crizotinib (N=53), n (%)
Gender	Male	71 (44)	22 (43)	23 (43)
	Female	89 (56)	29 (57)	30 (57)
ECOG PS	0	41 (26)	23 (45)	23 (43)
	≥1	119 (74)	28 (55)	30 (57)
Smoking history*	Non-smoker	105 (66)	38 (75)	40 (75)
	Smoker	55 (34)	13 (25)	13 (25)
Histologic classification	Adenocarcinoma	155 (97)	49 (96)	51 (96)
	Other	5 (3)	2 (4)	2 (4)
Number of previous systemic therapies	No	127 (79)	7 (13)	7 (13)
	Yes	33 (21)	44 (87)	46 (87)

*The smoking status and lines of prior therapies were transferred to binary variables (smoker vs nonsmoker; with/without previous therapies).
ECOG PS, Eastern Cooperative Oncology Group Performance Status; MAIC, matching-adjusted indirect comparison; NSCLC, non-small cell lung cancer; ROS1+, ROS1 positive; TKI, tyrosine kinase inhibitor.

MAIC Taletrectinib vs Crizotinib: ORR in *ROS1*+ TKI-Naive NSCLC

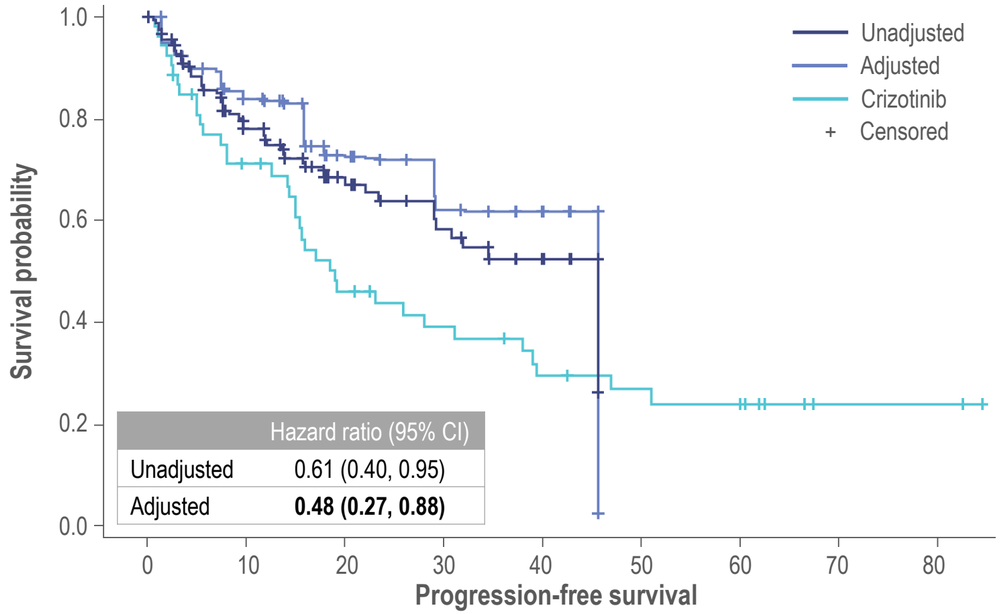
After adjustment, ORR for taletrectinib was approximately 20% higher vs crizotinib



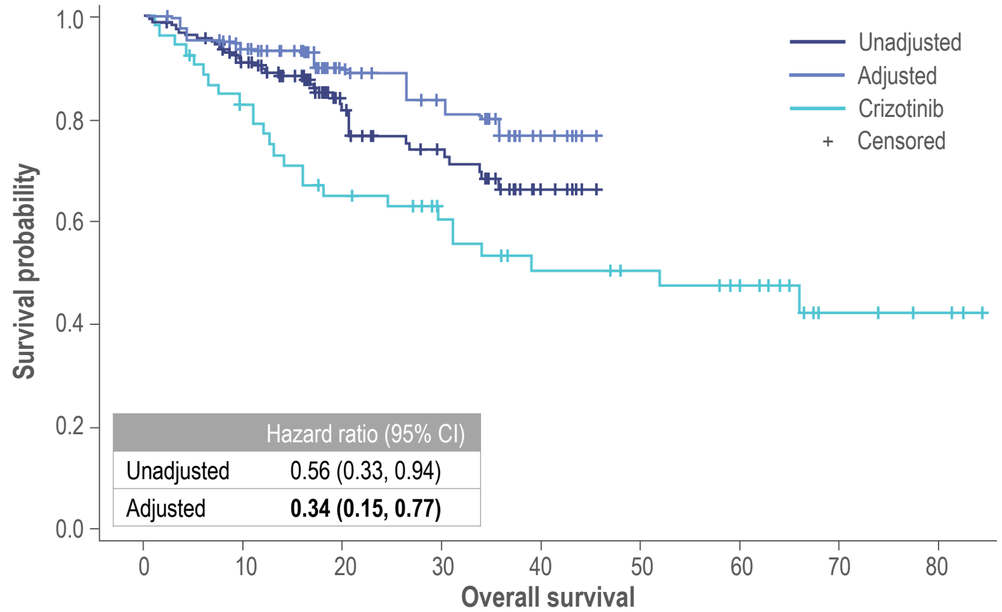
CR, complete response; MAIC, matching-adjusted indirect comparison; NA, not available; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progression disease; PR, partial response; ROS1+, ROS1 positive; SD, stable disease; TKI, tyrosine kinase inhibitor.

MAIC Taletrectinib vs Crizotinib: Progression-Free Survival and Overall Survival

The adjusted HRs for PFS and OS indicated a statistically significant 52% reduction in the risk of disease progression or death and a 66% reduction in the risk of death with taletrectinib vs crizotinib



Unadjusted	160	105	48	32	8				
Adjusted	51	37	18	15	5				
Crizotinib	53	35	22	17	12	10	9	2	2



Unadjusted	160	137	68	51	12				
Adjusted	51	44	24	18	9				
Crizotinib	53	42	32	25	19	17	14	5	3

MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

MAIC Taletrectinib vs Crizotinib: Safety in ROS1+ TKI-Naive Patients

	Taletrectinib before adjustment (N=160)		Taletrectinib after adjustment (N=51)		Crizotinib (N=53)	
	Any grade n (%)	Grade 3 n (%)	Any grade n (%)	Grade 3 n (%)	Any grade n (%)	Grade 3 n (%)
Any TRAE	159 (99)	62 (39)	51 (99)	23 (45)	53 (100)	19 (36)
Vision disorder	9 (6)	1 (1)	5 (10)	0.02 (<0.1)	46 (87)	0 (0)
Nausea	66 (41)	2 (1)	26 (51)	3 (6)	27 (51)	1 (2)
Edema*	16 (10)	0 (0)	4 (8)	0 (0)	25 (47)	0 (0)
Diarrhea*	103 (64)	5 (3)	34 (67)	0.4 (1)	24 (45)	0 (0)
Vomiting*	66 (41)	1 (1)	23 (46)	0.1 (0.2)	20 (38)	2 (4)
Constipation*	25 (16)	0	5 (9)	0	18 (34)	0 (0)
Fatigue	9 (6)	0	1 (3)	0	11 (21)	0 (0)
Dizziness*	35 (22)	1 (1)	9 (18)	0.1 (0.2)	10 (19)	0 (0)
Dysgeusia	32 (20)	0	9 (18)	0	10 (19)	0 (0)
Decreased appetite*	28 (18)	0	8 (17)	0	8 (15)	1 (2)
Neutropenia*	33 (21)	8 (5)	10 (21)	2 (3)	8 (15)	5 (9)
Rash	25 (16)	4 (3)	6 (12)	0.1 (0.2)	7 (13)	0 (0)

The incidence of grade 3 TRAEs was comparable between taletrectinib and crizotinib (45% [95% CI: 31.2%, 59.8%] vs 36% [95% CI: 23.1%, 50.2%], respectively)

For crizotinib, “Elevated transaminases” refers to a clustered term comprising adverse events that represent similar clinical symptoms/syndromes,[1] while for taletrectinib, alanine aminotransferase and aspartate aminotransferase elevations were reported separately,[2] and therefore have been excluded from this table.
“Vision disorder” was a group term for crizotinib, while “Vision blurred” was a preferred term for taletrectinib.
For “Neutropenia,” the preferred term “Decreased neutrophil count” was used for taletrectinib.
Preferred terms were used for taletrectinib (except for edema, dizziness, and neutropenia) and for crizotinib (except where indicated with an *).
*Group terms were used for both crizotinib and taletrectinib.
MAIC, matching-adjusted indirect comparison; TRAE, treatment-related adverse event.
1. Shaw AT, et al. *Ann Oncol*. 2019;30:1121-1126. **2.** Perol M, et al. European Society for Medical Oncology. Barcelona, Spain. September 13-17, 2024. Poster #1289P.

Conclusions

- In this cross-trial MAIC analysis, taletrectinib demonstrated significantly improved outcomes compared with crizotinib in TKI-naive patients with *ROS1*+ NSCLC
  - Higher ORR was observed
  - Statistically significant 52% reduction in the risk of disease progression or death and a 66% reduction in the risk of death with taletrectinib vs crizotinib
- Taletrectinib and crizotinib demonstrated similar overall safety profiles
  - The incidence of grade 3 TRAEs was comparable between taletrectinib and crizotinib
- These findings underscore the therapeutic benefits of taletrectinib over crizotinib outside of head-to-head randomized controlled trials
  - A phase 3 head-to-head trial (NCT06564324) comparing taletrectinib with crizotinib in patients with *ROS1*+ NSCLC is planned

MAIC, matching-adjusted indirect comparison; NSCLC, non-small cell lung cancer; ORR, objective response rate; ROS1+, ROS1 positive; TKI, tyrosine kinase inhibitor, TRAEs, treatment-related adverse events.

Acknowledgments

- We would like to thank all patients who participated in this study, the study investigators, and their staff

- This study was sponsored by Nuvation Bio, Inc. Writing support was provided by Tulika Bhushan Bahukhandi, RPh, MS, and Aeja Jackson, PhD, MS, of Peloton Advantage, LLC, an OPEN Health company, and funded by Nuvation Bio