Patient-reported outcomes and health-related quality of life of TKI pre-treated and TKI-naïve patients with advanced *ROS1*-positive NSCLC treated with zidesamtinib: Examination of ARROS-1 phase 2 trial data

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BACKGROUND

- *ROS1* fusions are detected in 1–3% of patients with NSCLC, and treatment with *ROS1* TKIs is standard of care.[1-3]
  - However, currently approved *ROS1* TKIs are limited by their ability to address drivers of disease progression and to support long-term tolerability at therapeutic doses.
  - Of note, CNS adverse events associated with off-target TRK inhibition and GI toxicities have been observed.
- Zidesamtinib, a ROS1 TKI designed to have activity against ROS1 resistance mutations, penetrate the CNS, and have selectivity for ROS1 over TRK, is approved by the FDA for the treatment of adult patients with locally advanced or metastatic *ROS1+* NSCLC who received a prior ROS1 kinase inhibitor.[4]

ARROS-1 STUDY DESIGN & POPULATIONS

ARROS-1 DESIGN AND PRO METHODS

- ARROS-1 is a global, single-arm, first-in-human Phase 1/2 clinical trial of zidesamtinib in advanced *ROS1*-positive (*ROS1+*) NSCLC and other solid tumors (NCT05118789).
- PRO data were collected using the EORTC QLQ-C30 questionnaire; analysis focused on scores for all functional, symptom, and global health domains and key neurocognitive (concentration, irritability, memory) and GI (nausea, vomiting, constipation, diarrhea) items.
- Score changes from baseline were summarized for 28-day cycles throughout the first year of treatment with zidesamtinib
- 327 patients with advanced *ROS1+* NSCLC treated with zidesamtinib contributed PRO data and were included in the analysis.

PATIENT CHARACTERISTICS & TREATMENT HISTORY

- 264 pts were *ROS1* TKI pretreated +/- chemo [range 1-5 prior *ROS1* TKIs], of which 133 had received only prior crizotinib or entrectinib (1 prior C/E) +/- chemotherapy. 63 additional patients were TKI-naïve +/- chemotherapy.

Patient characteristic	*ROS1* TKI Pre-Treated N = 264	1 Prior C/E N = 133	TKI-Naïve N = 63
Age, median (range)	57 (26 - 84)	58 (30 - 84)	58 (26 - 81)
Female	160 (60.6%)	82 (61.7%)	36 (57.1%)
Never smoker	175 (66.3%)	90 (67.7%)	36 (57.1%)
Geographic Region			
Asia Pacific	114 (43.2%)	66 (49.6%)	23 (36.5%)
Europe	92 (34.8%)	43 (32.3%)	15 (23.8%)
North America	58 (22.0%)	24 (18.0%)	25 (39.7%)
ECOG PS			
0	116 (43.9%)	60 (45.1%)	40 (63.5%)
1	148 (56.1%)	73 (54.9%)	22 (34.9%)
>1	0 (0%)	0 (0%)	1 (1.6%)
Brain metastases[a]	141 (53.4%)	73 (54.9%)	14 (22.2%)
Secondary *ROS1* G2032R mutation	51 (19.3%)	16 (12.0%)	0 (0.0%)

[a]Brain metastases at baseline per BICR

Treatment history	PRO Analysis Population N = 327
Prior anticancer therapy, median (range)	1 (1 - 6)
Prior chemotherapy	165 (50.5%)
TKI naïve	63 (19.3%)
Prior *ROS1* TKIs ± chemotherapy	264 (80.7%)
1 prior (crizotinib or entrectinib)	133 (40.7%)
Crizotinib	86 (64.7%)
Entrectinib	47 (35.3%)
1 prior (*lorlatinib, repotrectinib* or *taletrectinib*)	11 (3.4%)
≥ 2 prior	120 (36.7%)
Lorlatinib, repotrectinib,* or *taletrectinib	99 (75.6%)
Lorlatinib	66 (60.0%)
Repotrectinib	37 (33.6%)
Taletrectinib	18 (16.4%)

▲Table 1. ARROS-1 PRO Analysis Population All data shown as n (%) unless otherwise specified

› Data cut-off date: 21 March 2025

› Disclaimer: Content originally presented at the IASLC | ASCO 2025 North America Conference on Lung Cancer

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› Abbreviations: Δ = change; BL = Baseline; C = Cycle; CNS = central nervous system; C/E = crizotinib or entrectinib; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC = European Organisation for Research and Treatment of Cancer; GHS/QOL = Global Health Status / Quality of Life; GI = gastrointestinal; HRQoL = health-related quality of life; NSCLC, non-small cell lung cancer; PRO, patient-reported outcomes; TKI, tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.

› References: [1]Ou SI, Zhu VW. CNS metastasis in ROS1+ NSCLC: An urgent call to action, to understand, and to overcome. Lung Cancer. Apr 2019;130:201-207. [2]National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. 2025. [3]Patil T, Smith DE, Bunn PA, et al. The Incidence of Brain Metastases in Stage IV ROS1-Rearranged Non-Small Cell Lung Cancer and Rate of Central Nervous System Progression on Crizotinib. J Thorac Oncol. Nov 2018;13(11):1717-1726. [4]IDEYTRO (zidesamtinib) [prescribing information]. Cambridge, MA: Nuvalent, Inc.; 2026. [5]Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. Jan 1998;16(1):139-44.

QLQ-C30 GLOBAL HEALTH STATUS/QOL SCORES: CHANGE FROM BASELINE RESULTS

CHANGE IN QLQ-C30 GLOBAL HEALTH STATUS/QOL SCORES OVER TIME

Each of the TKI pre-treated, TKI pre-treated (1 prior C/E), and TKI-naïve populations demonstrated improvement from baseline in mean Global Health Status/QoL scores after one month of zidesamtinib treatment (Cycle 2) (Figure 1).

- Improved mean scores were seen through one year (Cycle 13) across each population – no worsening in QLQ-C30 Global Health Status/QoL was observed at the population level.
- The level of improvement seen in the TKI pre-treated (1 prior C/E) and TKI-naïve populations exceeded the established threshold (≥10 points) for clinically meaningful improvement at multiple monthly cycles throughout the first year of zidesamtinib treatment.
  - **TKI pre-treated (1 prior C/E) population** demonstrated clinically meaningful improvements in mean Global Health Status/QoL scores at Cycles 2, 3, 6, and 13.
  - **TKI-naïve population** demonstrated clinically meaningful improvements in mean Global Health Status/QoL scores at Cycles 2, 3, and 8 through 11.

SUMMARY OF CHANGE

Each of the TKI pre-treated, TKI pre-treated (1 prior C/E), and TKI naïve populations demonstrated moderately high baseline functioning and low symptom burden; these levels were generally maintained or improved during the first year of zidesamtinib treatment (Table 2).

- The **TKI pre-treated population** maintained a moderately high baseline GHS/QoL (60.4; range of mean change from baseline from Cycle 2 to Cycle 7: +7.3 to +10.1; range of mean change from baseline from Cycle 2 to Cycle 13: +5.1 to +10.1).
  - Functioning scores were high and largely maintained or improved across monthly cycles
  - Besides a slight increase in mean constipation levels at Cycle 7, levels of key symptoms were low at baseline and were further reduced across monthly cycles; mean improvement in appetite loss at Cycle 7 was clinically meaningful.
- The **TKI pre-treated (1 prior C/E) population** maintained a moderately high baseline GHS/QoL (61.3; range of mean change from baseline from Cycle 2 to Cycle 7: +8.6 to +11.9; range of mean change from baseline from Cycle 2 to Cycle 13 : +6.2 to +14.7).
  - Functioning scores were high and largely maintained or improved across monthly cycles
  - Besides a slight increase in mean constipation levels at Cycle 7, levels of key symptoms were low at baseline and were further reduced across monthly cycles; mean improvement in appetite loss at Cycle 7 was clinically meaningful.
- The **TKI naïve population** maintained a moderately high baseline GHS/QoL (64.3; range of mean change from baseline from Cycle 2 to Cycle 7: +7.0 to +11.4; range of mean change from baseline from Cycle 2 to Cycle 13: +5.0 to +12.8).
  - Functioning scores were high and largely maintained or improved across monthly cycles
  - Levels of key symptoms were low at baseline and were largely further reduced across monthly cycles; mean improvement in fatigue and appetite loss at Cycle 7 was clinically meaningful.

CLINICALLY MEANINGFUL CHANGE IN QLQ-C30 GLOBAL HEALTH STATUS/QOL

In each of the TKI pre-treated, TKI pre-treated (1 prior C/E), and TKI naïve populations, the majority of patients maintained or improved baseline score at each monthly cycle during the first year of treatment (Figure 2).

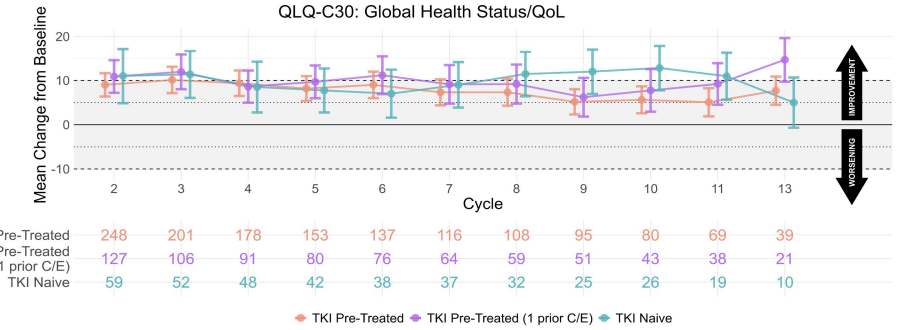
- A ≥10-point change in a score was used as the threshold for clinical meaningfulness, as defined by Osoba et al.[5]
- Higher scores on the Global Health Status/QoL scale reflect better quality of life
  - ≥10-point increase in score indicates meaningful improvement in global health status/QoL
  - ≥10-point decrease in score indicates meaningful worsening in global health status/QoL
  - A change in score <10-points indicates no change or maintenance in global health status/QoL
- In the **TKI pre-treated population**, 30.2-41.6% of patients demonstrated clinically meaningful improvement in their Global Health Status/QoL scores; 40.2-48.2% had no change, and 12.9-23.1% experienced worsening.
- In the **TKI pre-treated (1 prior C/E) population**, 32.2-46.1% of patients demonstrated clinically meaningful improvement in their Global Health Status/QoL scores; 38.1-50.9% had no change, and 10.4-21.6% experienced worsening.
- In the **TKI naïve population**, 30.0-47.5% of patients demonstrated clinically meaningful improvement in their Global Health Status/QoL scores; 36.8-50.0% had no change, and 6.3-20.0% experienced worsening.

CONCLUSIONS

Patients treated with zidesamtinib maintained or improved their relatively high baseline levels of functioning and low symptom burden, without experiencing worsening neurocognitive or GI adverse events, as measured by the QLQ-C30

- No consistent worsening was observed with zidesamtinib treatment for all key neurocognitive and GI symptoms and aspects of HRQoL.
- A higher proportion of patients consistently showed clinically meaningful improvement (≥10 points; 30.0-50.0%) than deterioration (6.3%-23.1%) in Global Health Status/QoL scores in each PRO analysis population across each monthly cycle during the first year of treatment.
- TKI pre-treated (1 prior C/E) patients demonstrated clinically meaningful improvements in mean Global Health Status/QoL scores at Cycles 2, 3, 6, and 13.
- TKI-naïve patients demonstrated clinically meaningful improvements in mean Global Health Status/QoL scores at Cycles 2, 3, and 8 through 11.

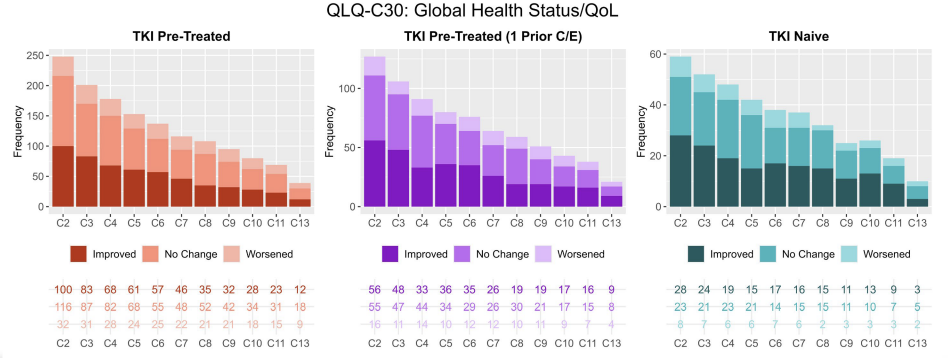
▼Figure 1. Descriptive Mean Change from Baseline in QLQ-C30 Global Health Status/QoL Score Across First Year of Zidesamtinib Treatment
For the Global Health Status/QoL scale, higher scores indicate better quality of life and function. Dashed horizontal lines reflect thresholds of clinically meaningful change (≥10-point change); dotted horizontal lines reflect thresholds of minimal change (5-10-point change)/ At Cycle 7, approximately 50% of each baseline sample remained on-study and had available PRO data.



▼ Table 2. Mean Baseline Scores and Mean Change from Baseline in Select QLQ-C30 Scores
All Scores are mean or mean change from BL. All scores range from 0-100. For Functional scales, higher scores indicate better quality of life and function, and positive change scores indicate improvement. For Symptom scales, lower scores indicate lower symptom levels and negative change scores indicate improvement. A change of 10 points or more is considered the threshold for clinical meaningfulness.

	TKI Pre-treated (N = 264)				TKI Pre-Treated (1 prior C/E) (N = 133)				TKI-Naïve (N = 63)			
	BL Score (N = 263)	Change from BL @ C7 (N = 116)	Change from BL, Range (C2-C7)	Change from BL, Range (C2-C13)	BL Score (N = 132)	Change from BL @ C7 (N = 64)	Change from BL, Range (C2-C7)	Change from BL, Range (C2-C13)	BL Score (N = 63)	Change from BL @ C7 (N = 37)	Change from BL, Range (C2-C7)	Change from BL, Range (C2-C13)
FUNCTIONAL SCALES												
GHS/QoL	60.4	7.3	7.3, 10.1	5.1, 10.1	61.3	9.1	8.6, 11.9	6.2, 14.7	64.3	9.0	7.0, 11.4	5.0, 12.8
Physical	77.0	4.2	4.0, 4.9	2.0, 6.7	78.9	5.1	3.3, 5.9	-0.0, 9.0	80.1	3.8	1.9, 9.4	-0.7, 9.4
Role Functioning	70.6	4.1	4.1, 7.6	2.8, 7.6	74.0	5.6	5.3, 6.4	1.3, 9.9	75.1	8.1	3.5, 11.5	-5.0, 11.5
Cognitive Functioning	84.0	-1.7	-1.7, -0.6	-4.9, -0.6	85.0	-0.5	-0.5, 0.5	-0.7, 4.0	86.2	-2.3	-2.3, 3.2	-2.3, 3.2
SYMPTOM SCALES												
Fatigue	35.2	-7.4	-9.5, -7.4	-9.5, -2.7	32.0	-7.1	-8.9, -6.3	-8.9, -1.7	32.6	-13.8	-14.5, -11.3	-17.5, -11.3
Nausea	12.2	-6.3	-7.4, -6.1	-7.4, -1.0	9.1	-5.2	-6.7, -5.0	-6.7, 0.8	10.1	-4.5	-7.0, -4.5	-7.0, 0.0
Vomiting	4.8	-3.7	-4.1, -1.3	-4.1, 0.9	2.8	-2.6	-2.6, -1.3	-2.6, 1.6	3.2	0.0	-3.5, -0.0	-3.5, 1.0
Appetite Loss	18.9	-14.4	-14.6, -12.4	-14.6, -10.5	18.2	-15.1	-16.2, -12.0	-16.2, -11.4	20.6	-14.4	-15.4, -9.7	-15.4, -6.7
Constipation	19.7	2.6	-0.2, 2.6	-0.2, 2.9	18.6	2.1	-1.6, 2.1	-1.6, 3.3	11.6	-0.9	-4.4, 10.7	-4.4, 10.7
Diarrhea	8.7	-3.2	-5.4, -0.5	-5.4, 1.2	6.1	-0.5	-2.5, 0.8	-2.5, 3.2	5.3	0.9	-2.3, 0.9	-10.0, 0.9

▼ Figure 2. Proportion of Patients with Clinically Meaningful Change on the QLQ-C30 Global Health Status/QoL in the TKI Pre-Treated, TKI Pre-Treated (1 Prior C/E), and TKI Naive Populations



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