# Pivotal ARROS-1 Efficacy and Safety Data: Zidesamtinib in TKI Pretreated Patients with Advanced/Metastatic *ROS1*+ NSCLC

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## BACKGROUND

- Zidesamtinib is an investigational ROS1 TKI designed to be highly selective, have activity against diverse ROS1 fusions and ROS1 resistance mutations, be brain-penetrant, and avoid TRK inhibition
- 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
  - Pivotal data for TKI pre-treated *ROS1*+ NSCLC and preliminary data for TKI-naïve *ROS1*+ NSCLC are presented

## ARROS-1 STUDY DESIGN & POPULATIONS

- As of the data cut-off date of March 21, 2025, 514 patients with any *ROS1*+ solid tumor had been enrolled across Phase 1 and 2
  - The safety population included 432 patients with advanced *ROS1*+ NSCLC who received zidesamtinib 100 mg QD
  - The efficacy population included 117 ROS1 TKI pre-treated patients with measurable disease by BICR and ≥ 6 months duration of response follow-up
  - The TKI-naïve cohort included 35 patients with measurable disease by BICR treated by August 31, 2024

**PHASE 1:** Zidesamtinib dose escalation (25 – 150 mg QD) in ROS1 TKI pre-treated patients with advanced *ROS1*+ solid tumors

**PHASE 2: Zidesamtinib 100 mg QD (RP2D)**

| ARROS-1 PHASE 2 PATIENT POPULATION | PRIOR ROS1 TKI | PRIOR CHEMO/I-O |
|---|---|---|
| *ROS1*+ NSCLC | ROS1 TKI-naïve [a] | ≤ 1 |
| | 1 prior ROS1 TKI [b] | None |
| | | 1 [c] |
| | ≥ 2 Prior ROS1 TKIs [d] | ≤ 1 |
| Any *ROS1*+ Solid Tumor [e] | Any | Any |

**PHASE 2 OBJECTIVES**
- **Primary:** ORR by BICR
- **Secondary:** Additional efficacy measures (DOR, TTR, CBR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile, PROs

**Patient Populations**
*Data cut-off: March 21, 2025*

**Total Enrolled: N = 514**
Any *ROS1*+ solid tumor, any dose
Phase 1 + Phase 2 pooled

**Pivotal Safety Population: N = 432**
Advanced *ROS1*+ NSCLC
Received zidesamtinib at 100 mg QD

**Pivotal Efficacy Population: ROS1 TKI Pre-Treated**
with measurable disease by BICR
Treated by May 31, 2024 (≥ 6 months DOR follow up)
**n = 117**

***Preliminary Data* TKI-Naïve**
with measurable disease by BICR
Treated by August 31, 2024
**n = 35**

▲ Figure 1. ARROS-1: A Global First-in-Human Phase 1/2 Clinical Trial of Zidesamtinib in Advanced *ROS1*+ NSCLC and Other Solid Tumors (NCT05138789).
**Zidesamtinib is an investigational product and has not been approved by the FDA or any other health authority.**
[a]Open for enrollment; [b]Either crizotinib or entrectinib; [c]Platinum-based chemotherapy with or without immunotherapy; [d]With initial TKI of either crizotinib or entrectinib; [e]Exploratory cohort, currently enrolling; includes adolescents and patients with NSCLC who do not qualify for any of the other cohorts.

## PATIENT CHARACTERISTICS & TREATMENT HISTORY

- Patients had received a median of 2 prior lines of therapy (range 1 – 11)
  - 50% (58/117) had received ≥ 2 prior ROS1 TKIs, including 93% (54/58) who had received prior lorlatinib, repotrectinib, or taletrectinib; and 53% (62/117) had received prior chemotherapy
- 49% (57/117) had active CNS disease, including cases of disease progression following treatment with the brain-penetrant TKIs entrectinib, lorlatinib, repotrectinib and/or taletrectinib
- 36% (42/117) had a secondary *ROS1* mutation, with a secondary *ROS1* G2032R mutation in 26 patients

| Patient characteristic | ROS1 TKI pre-treated [a] pivotal efficacy population N = 117 |
|---|---|
| Age, median (range) | 57 (31 – 83) |
| Female | 66 (56%) |
| Never smoker | 80 (68%) |
| Geographic Region | |
| Asia Pacific | 30 (26%) |
| Europe | 38 (32%) |
| North America | 49 (42%) |
| ECOG PS | |
| 0 | 45 (38%) |
| 1 | 72 (62%) |
| Active CNS disease [b] | 57 (49%) |
| Secondary *ROS1* mutation [c] | 42 (36%) |
| G2032R | 26 (22%) |

| Treatment history | ROS1 TKI pre-treated [a] pivotal efficacy population N = 117 |
|---|---|
| Prior anticancer therapy, median (range) | 2 (1 – 11) |
| Prior chemotherapy | 62 (53%) |
| **Prior ROS1 TKIs ± chemotherapy** | |
| **1 prior (crizotinib or entrectinib)** | **55 (47%)** |
| *Crizotinib* | *28/55 (51%)* |
| *Entrectinib* | *27/55 (49%)* |
| 1 prior (repotrectinib or taletrectinib) | 4 (3%) |
| **≥ 2 prior** | **58 (50%)** |
| ***Lorlatinib, repotrectinib, or taletrectinib*** | ***54/58 (93%)*** |
| *Lorlatinib* | *43/58 (74%)* |
| *Repotrectinib* | *15/58 (26%)* |
| *Taletrectinib* | *5/58 (9%)* |

▲ Table 1. ARROS-1 Patient Population.
All data shown as n (%) unless otherwise specified. [a]Includes 4 patients with other oncogenic driver(s) in addition to *ROS1*. [b]By BICR; includes patients with untreated CNS lesions and patients with prior disease progression on the brain-penetrant TKIs entrectinib, lorlatinib, repotrectinib, and/or taletrectinib. [c]*ROS1* mutations as per local or central testing of blood (ctDNA) or tissue.

## ARROS-1 STUDY RESULTS

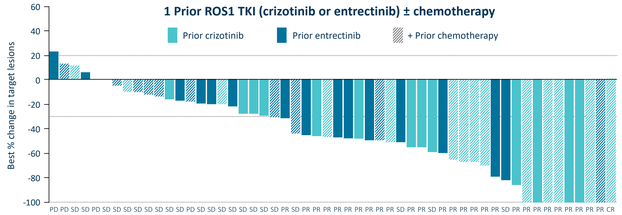
### OBJECTIVE RESPONSE RATE, DURABILITY OF RESPONSE, AND PROGRESSION-FREE SURVIVAL

- Among patients with any prior ROS1 TKI, the ORR by BICR was 44% (51/117)
- Among patients with 1 prior TKI of crizotinib or entrectinib, the ORR was 51% (28/55)
- 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

| 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) |

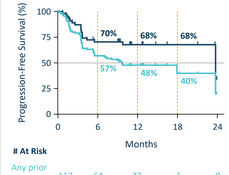
[a] Prior crizotinib only ± chemotherapy: ORR = 68% (19/28). Prior entrectinib only ± chemotherapy: ORR = 33% (9/27).

▶ Table 2 & Figure 2. Radiographic Tumor Response Across Previously Treated Patients with Advanced *ROS1*+ NSCLC.
Responses were observed after either prior TKI of crizotinib or entrectinib and in patients that received prior chemotherapy.




- Among the overall ROS1 TKI pre-treated population, the DOR rate was 84% at 6 months, 78% at 12 months, and 62% at 18 months; respective PFS rates were 57%, 48%, and 40%
  - Among patients with 1 prior TKI of crizotinib or entrectinib, the DOR rate was 93% at 6, 12, and 18 months; respective PFS rates were 70%, 68%, and 68%
  - In patients that received prior crizotinib only, there were no progression events among responders (DOR range: 7.3+ to 23.2+ months); the 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, the DOR rate was 71% [95% CI: 46, 86] at 6 months and 56% [95% CI: 29, 76] at 12 months
- Median DOR for each group continues to mature

| Advanced *ROS1*+ NSCLC Kaplan-Meier estimate | DURATION OF RESPONSE: Any prior ROS1 TKIs (range 1 – 4) ± chemotherapy [a] | DURATION OF RESPONSE: 1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy [b] | PROGRESSION-FREE SURVIVAL: Any prior ROS1 TKIs (range 1 – 4) ± chemotherapy [a] | PROGRESSION-FREE SURVIVAL: 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] |


▶ Figure 3 & Figure 4. Duration of Response and Progression-Free Survival.
[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).

### SAFETY

- TEAEs that occurred in ≥ 15% of patients comprised peripheral edema, constipation, blood CPK increased, fatigue, and dyspnea
  - The only TRAE in ≥ 15% of patients was peripheral edema (29%)
- Dose reductions due to TEAEs occurred in 10% (43/432) of patients, most commonly (> 2 patients) for peripheral edema (n = 8), blood CPK increased (n = 4), peripheral sensory neuropathy (n = 4), arthralgia (n = 3), and paresthesia (n = 3)
- Discontinuations due to TEAEs occurred in 2% (10/432) of patients, most commonly (> 2 patients) for pneumonia (n = 3)

▶ Table 7. All TEAEs in ≥ 15% of Patients Treated with Zidesamtinib 100 mg QD (N = 432).
Data pooled for patients in the Phase 1 or Phase 2 portion of ARROS-1 with a data cut-off of March 21, 2025. Patients received ≥ 1 dose of zidesamtinib at 100 mg QD with median duration of exposure of 5 months (range 0 – 32).

| Preferred or grouped term | Any Grade (N = 432) | Grade ≥ 3 (N = 432) |
|---|---|---|
| **Peripheral edema** [a] | 36% | 0.7% |
| **Constipation** | 17% | 0% |
| **Blood CPK increased** | 16% | 3.5% |
| **Fatigue** [b] | 16% | 0.7% |
| **Dyspnea** [c] | 15% | 3.0% |

[a] Includes terms peripheral edema, peripheral swelling, edema, generalized edema.
[b] Includes terms fatigue, asthenia, malaise.
[c] Includes terms dyspnea, dyspnea exertional, orthopnea

❯ **Data cut-off date:** March 21, 2025
❯ **Disclaimer:** Content originally presented at the IASLC 2025 World Conference on Lung Cancer (WCLC 2025)
❯ **Acknowledgments:** We thank the participating patients and their families, the ARROS-1 study team, and the study investigators and staff.
❯ **Abbreviations: BICR**, blinded independent central review; **C**, crizotinib; **CBR**, clinical benefit rate; **CI**, confidence interval; **CNS**, central nervous system; **CPK**, creatine phosphokinase; **CR**, complete response; **DOR**, duration of response; **E**, entrectinib; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **FDA**, United States Food and Drug Administration; **IC**, intracranial; **I-O**, immuno-oncology; **NE**, not estimable; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PK**, pharmacokinetics; **PR**, partial response; **PRO**, patient reported outcome; **QD**, once daily; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **RP2D**, recommended phase 2 dose; **SD**, stable disease; **TEAE**, treatment-emergent adverse event; **TKI**, tyrosine kinase inhibitor; **TRAE**, treatment-related adverse event; **TRK**, tropomyosin-related kinase; **TTR**, time to response.

### ACTIVITY IN KEY SUBGROUPS

- Responses to zidesamtinib were observed in patients with the *ROS1* G2032R resistance mutation and in patients with CNS disease

| *ROS1* G2032R resistance mutation: Advanced *ROS1*+ NSCLC Analysis by BICR | Any prior ROS1 TKI ± chemotherapy | 1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy [a] |
|---|---|---|
| **ORR, %** (n/N) [95% CI] | **54%** (14/26) [33, 73] | **83%** (5/6) [36, 100] |
| **% DOR ≥ 6 months** [95% CI] [b] | **79%** [47, 93] | **80%** [c] [20, 97] |
| **% DOR ≥ 12 months** [95% CI] [b] | **60%** [28, 81] | **80%** [c] [20, 97] |

Responses were also observed in patients with:
- *ROS1* G2032R mutation following ≥ 2 prior ROS1 TKIs ± chemotherapy, including lorlatinib or repotrectinib
- Other *ROS1* resistance mutations, including G1957A, L1982V, S1986F, F2004C/V, G2032K, and D2033N

[a] Patients received zidesamtinib as their first TKI designed with activity against *ROS1* G2032R.
[b] Analyses of DOR based on Kaplan-Meier estimates.
[c] One progression event among responders.

| Measurable CNS lesions by BICR at baseline: Advanced *ROS1*+ NSCLC Analysis by BICR | Any prior ROS1 TKI ± chemotherapy | Prior crizotinib only ± chemotherapy |
|---|---|---|
| **IC-ORR, %** (n/N) [95% CI] | **48%** (27/56) [a] [35, 62] | **85%** (11/13) [55, 98] |
| **IC-CR,** % (n/N) | **20%** (11/56) | **54%** (7/13) |
| **% IC-DOR ≥ 6 months** [95% CI] [b] | **79%** [56, 91] | **91%** [c] [51, 99] |
| **% IC-DOR ≥ 12 months** [95% CI] [b] | **71%** [46, 87] | **91%** [c] [51, 99] |

- CNS responses also observed in patients who had received ≥ 1 prior brain-penetrant TKI, including prior entrectinib, lorlatinib, repotrectinib, or taletrectinib: IC-ORR: 37% (16/43 [a]; [95% CI: 23, 53]), including 4 IC-CRs
- No CNS progression was observed among patients who entered the study without brain metastases at baseline per BICR

[a] Includes 2 unconfirmed intracranial PR.
[b] Analyses of DOR based on Kaplan-Meier estimates.
[c] One CNS progression event among CNS responders (n=11).

▲ Table 3 & Table 4. Activity in Patients with *ROS1* G2032R Resistance Mutation and Measurable CNS lesions by BICR at Baseline.

### PRELIMINARY DATA IN TKI-NAÏVE PATIENTS

- The ORR was 89% (31/35), and the 12-month DOR rate was 96%
- An intracranial-ORR of 83% was observed in 6 patients with measurable intracranial lesions, including 4 intracranial CRs
- Intracranial-DOR ranged from 4.6 to 11.1 months, with no CNS progression among intracranial responders

| TKI-naïve advanced *ROS1*+ NSCLC Analysis by BICR | Response-evaluable n = 35 |
|---|---|
| **ORR, %** (n/N) | **89%** (31/35) |
| **CR, %** (n/N) | **9%** (3/35) [a] |
| **% DOR ≥ 6 months** [95% CI] [b] | **96%** [76, 99] |
| **% DOR ≥ 12 months** [95% CI] [b] | **96%** [76, 99] |
| **DOR range** | 1.9+ to 13.9+ months |

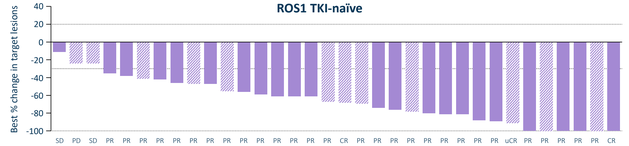
[a] Includes 1 unconfirmed CR following confirmed PR.
[b] Analyses of DOR based on Kaplan-Meier estimates.

| TKI-naïve advanced *ROS1*+ NSCLC Analysis by BICR | Measurable intracranial lesions n = 6 |
|---|---|
| **IC-ORR, %** (n/N) | **83%** (5/6) |
| **IC-CR, %** (n/N) | **67%** (4/6) |
| **IC-DOR** | **No CNS progression events among intracranial responders** |
| **IC-DOR range** | 4.6+ to 11.1+ months |

▲ Table 6. Preliminary Data in TKI-Naïve Patients with Advanced *ROS1*+ NSCLC and Measurable Intracranial Lesions.
Data for patients treated with zidesamtinib 100 mg QD by August 31, 2024, in the Phase 2 portion of ARROS-1 with a data cut-off of March 21, 2025. Patients may have received up to 1 prior line of chemotherapy.

▲ ▶ Table 5 & Figure 5. Preliminary Data in TKI-Naïve Patients with Advanced *ROS1*+ NSCLC.
Data for patients treated with zidesamtinib 100 mg QD by August 31, 2024, in the Phase 2 portion of ARROS-1 with a data cut-off of March 21, 2025. Patients may have received up to 1 prior line of chemotherapy.

No prior chemotherapy
1 prior line of chemotherapy




## ARROS-1 SUMMARY

- **In the pivotal dataset for TKI pre-treated patients with advanced *ROS1*+ NSCLC, zidesamtinib demonstrated a clinical profile consistent with its preclinical design goals**:
  - Durable activity, including in heavily pre-treated patients that have exhausted available options (including prior repotrectinib or taletrectinib) and patients with the *ROS1* G2032R resistance mutation
  - Durable activity in a population of patients receiving 1 prior ROS1 TKI of crizotinib or entrectinib. This population was distinct from those studied with other approved ROS1 TKIs; 51% of patients had received prior crizotinib or 49% prior entrectinib, and approximately half had also received prior chemotherapy
  - Durable intracranial responses, including in patients who previously received the brain-penetrant TKIs entrectinib, lorlatinib, repotrectinib, or taletrectinib
  - Generally well-tolerated with low rates of dose reduction (10%) and treatment discontinuation (2%), and a safety profile consistent with its ROS1-selective, TRK-sparing design
- **Encouraging preliminary data in a TKI-naïve population support ongoing investigation in the front-line setting**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