Zidesamtinib efficacy and safety in patients with advanced *ROS1*-positive solid tumors other than NSCLC in the ARROS-1 study

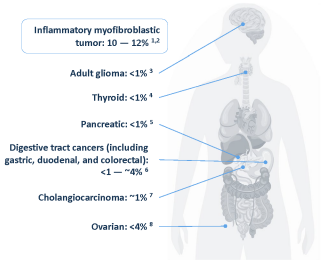
Benjamin J. Solomon[1], Sanjay Popat[2], Enriqueta Felip[3], Alexander Drilon[4], Benjamin Besse[5], Kiichiro Ninomiya[6], Hidetoshi Hayashi[7], Tatsuya Yoshida[8], Dwight H. Owen[9], Ramon Yarza[10], Ryo Ariyasu[11], Hiroaki Akamatsu[12], Marina Chiara Garassino[13], Christina S. Baik[14], Manoj Samant[15], Bo Zhang[15], Vivek A. Upadhyay[15], Jürgen Wolf[16]

[1]Peter MacCallum Cancer Centre, Melbourne, Australia; [2]Lung Unit, Royal Marsden Hospital, London, United Kingdom; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center, New York, NY, USA; [5]Paris Saclay University, Gustave Roussy, Villejuif, France; [6]Okayama University Hospital, Okayama, Japan; [7]Kindai University Hospital, Osaka, Japan; [8]National Cancer Center Hospital, Tokyo, Japan; [9]Ohio State University, Columbus, OH, USA; [10]START Madrid, Madrid, Spain; [11]Japanese Foundation for Cancer Research, Tokyo, Japan; [12]Wakayama Medical University Hospital, Wakayama, Japan; [13]University of Chicago, Chicago, IL, USA; [14]Fred Hutchinson Cancer Center, Seattle, WA, USA; [15]Nuvalent, Inc., Cambridge, MA, USA; [16]Center for Integrated Oncology, University Hospital, Köln, Germany

BACKGROUND

EVALUATION OF ZIDESAMTINIB FOR *ROS1*+ SOLID TUMORS

- *ROS1* fusions are oncogenic drivers in multiple tumor types (Figure 1)[1–8]
- Although several ROS1 TKIs are available for *ROS1*+ NSCLC, there are limited data on the activity of these agents in patients with other *ROS1*+ tumors
- Zidesamtinib, a ROS1 TKI designed to have activity against ROS1 resistance mutations, penetrate the CNS, and have selectivity for ROS1 over TRK,[9,10] 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.[11]
- ARROS-1 is a global, single-arm, first-in-human, phase 1/2 clinical trial (NCT05118789) of zidesamtinib in patients with advanced/metastatic *ROS1*+ NSCLC and other solid tumors[12]
  - Zidesamtinib has shown encouraging clinical activity in patients with advanced, TKI-pretreated and TKI-naïve *ROS1*+ NSCLC, including patients with CNS disease and/or *ROS1* resistance mutations, with a safety profile consistent with its ROS1-selective design[12]
- **Here, we report the first data on the activity of zidesamtinib in patients with advanced or metastatic *ROS1*+ solid tumors other than NSCLC**

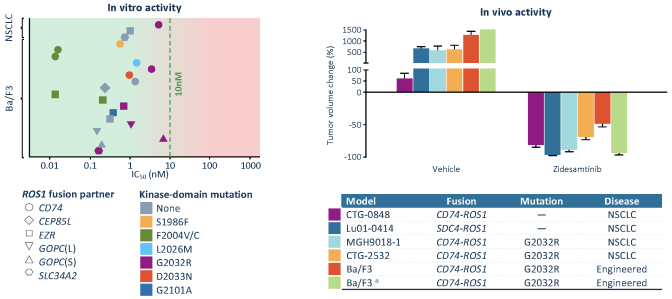


▲ Figure 1. Reported incidence of *ROS1* fusions across diverse solid tumors. [a]

[a]These estimates are based on published literature with limitations such as small sample sizes, varying patient populations, and differing methodologies.

ZIDESAMTINIB PRECLINICAL ACTIVITY

- Zidesamtinib has preclinical inhibitory activity against a wide variety of *ROS1* fusions and resistance mutations, in vitro and in vivo (Figure 2)
- The preclinical profile supports evaluation of zidesamtinib in patients with *ROS1*+ solid tumors in the ARROS-1 clinical trial



Model	Fusion	Mutation	Disease
CTG-0848	*CD74-ROS1*	—	NSCLC
Lu01-0414	*SDC4-ROS1*	—	NSCLC
MGH9018-1	*CD74-ROS1*	G2032R	NSCLC
CTG-2532	*CD74-ROS1*	G2032R	NSCLC
Ba/F3	*CD74-ROS1*	G2032R	Engineered
Ba/F3 [a]	*CD74-ROS1*	G2032R	Engineered

▲ Figure 2. Preclinical activity of zidesamtinib[a]. (Left) Potent in vitro activity observed in 21 cell lines harboring diverse *ROS1* fusions and resistance mutations. (Right) Regression observed in 6 xenograft models harboring diverse *ROS1* fusions and resistance mutations.

Zidesamtinib: 1–5 mg/kg PO BID × 14–28 days; N = 4–10; mean ± SEM plotted.
[a]Intracranial model; measured by bioluminescence imaging, vehicle +1200000%.

ARROS-1 STUDY DESIGN

- Patients with advanced or metastatic *ROS1*+ solid tumors other than NSCLC were enrolled in the completed Phase 1 dose escalation and in one cohort within the ongoing Phase 2 study
- Key endpoints were ORR (per RECIST v1.1 by BICR), DOR, IC-ORR, and safety

PHASE 1

Zidesamtinib dose escalation (25 – 150 mg QD) in 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 [a]
ROS1+ NSCLC	ROS1 TKI-naïve	≤ 1
	1 prior ROS1 TKI [b]	None
		1
	≥ 2 Prior ROS1 TKIs [c]	≤ 1
Any *ROS1*+ Solid Tumor [d]	Any	Any

PHASE 2 ENDPOINTS

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

▲ Figure 3. ARROS-1: A global, first-in-human, Phase 1/2 clinical trial of zidesamtinib in advanced *ROS1*+ NSCLC and other solid tumors (NCT05118789).

Zidesamtinib is investigational for patients with advanced or metastatic *ROS1*+ solid tumors other than NSCLC.
[a]Platinum-based chemotherapy with or without immunotherapy. [b]Either crizotinib or entrectinib. [c]With initial TKI of either crizotinib or entrectinib.
[d]Exploratory cohort, currently enrolling: Includes patients with NSCLC who do not qualify for any of the other cohorts.

ZIDESAMTINIB FOR *ROS1*+ SOLID TUMORS OTHER THAN NSCLC: PRELIMINARY EFFICACY & SAFETY

PATIENT CHARACTERISTICS & TREATMENT HISTORY

Patients were enrolled across 10 tumor types other than NSCLC

- As of September 22, 2025, 15 efficacy-evaluable patients with advanced or metastatic *ROS1*+ solid tumors (excluding NSCLC) were treated with zidesamtinib across the Phase 1 and Phase 2 portions of ARROS-1 (Table 1)
- Patients had received a median of 2 prior anticancer therapies (range 1-6): 60% were ROS1 TKI-naïve, 40% were ROS1 TKI-pretreated (range 1-2), and 73% had prior chemotherapy (range 1-4)
- Overall, 10 different *ROS1*+ tumor types were enrolled, with the most common being glioma (n = 3), inflammatory myofibroblastic tumor (n = 2), ovarian cancer (n = 2), and pancreatic adenocarcinoma (n = 2)

▶ Table 1. ARROS-1 solid tumor cohort patient characteristics and treatment history.

All data shown as n (%) unless otherwise specified.
[a]Patients who received zidesamtinib at any dose with measurable disease by BICR at baseline and ≥1 post-treatment tumor assessment or discontinued treatment due to any reason.
[b]Enrolled by cfDNA; *ROS1* fusion partner not determined. [c]*ROS1* resistance mutations as per local or central testing of blood (ctDNA) or tissue NGS.

Patient Characteristic	*ROS1*+ Solid Tumor Population (N = 15) [a]
Age, median (range)	58 (19 – 80)
Female	8 (53%)
ECOG PS	
0	7 (47%)
1	8 (53%)
ROS1 fusion partner	
GOPC	7 (47%)
SLC4A4	3 (20%)
TFG	2 (13%)
DCPH1	1 (7%)
FN1	1 (7%)
Unknown [b]	1 (7%)
ROS1 resistance mutation(s) [c]	
G2032R	1 (7%)
F2004I; F2004V	1 (7%)

Treatment history	*ROS1*+ Solid Tumor Population (N = 15) [a]
Prior anticancer therapy	**14 (93%)**
Median (range)	2 (1 – 6)
Prior chemotherapy	**11 (73%)**
Median (range)	2 (1 – 4)
Prior ROS1 TKIs ± chemotherapy	**6 (40%)**
Median (range)	1 (1 – 2)
0	9 (60%)
1	4 (27%)
2	2 (13%)
Crizotinib	3 (20%)
Entrectinib	2 (13%)
Lorlatinib	2 (13%)
Repotrectinib	1 (7%)

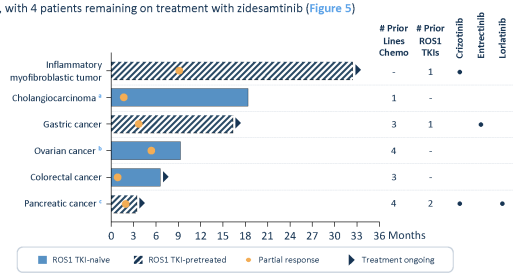
PRELIMINARY ACTIVITY

Encouraging preliminary activity was observed in patients with diverse *ROS1*+ solid tumors other than NSCLC

- Among all patients with *ROS1*+ solid tumors treated with zidesamtinib, the ORR was 40% (6/15; Table 2)
- Responses were seen across multiple tumor types and in patients that were ROS1 TKI-naïve and ROS1 TKI-pretreated (Figure 4)
- Median time to response was 8.4 weeks (range 3.7 – 23.4), with DOR ranging from 3.9+ to 22.8+ months
- As of the data cut-off, there was no disease progression by BICR among the 6 responders, with 4 patients remaining on treatment with zidesamtinib (Figure 5)

ROS1+ Solid Tumor Type	ORR per RECIST v1.1 by BICR
All patients	**6/15 (40%)**
Inflammatory myofibroblastic tumor	1/2
Ovarian cancer	1/2
Pancreatic adenocarcinoma	1/2 [b]
Cholangiocarcinoma	1/1
Colorectal cancer	1/1
Gastric cancer	1/1
Other [a]	0/6

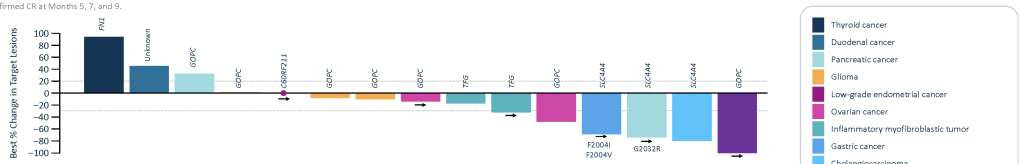
▲ Table 2. Tumor response to zidesamtinib.
[a]Glioma (n = 3) and duodenal cancer, thyroid cancer, and low-grade endometrial cancer (n = 1 each).
[b]Includes one single timepoint PR pending confirmation at data cutoff; patient subsequently experienced confirmed CR at Months 5, 7, and 9.



▲ Figure 5. Duration of treatment among responders with *ROS1*+ solid tumors other than NSCLC.
[a]Reason for discontinuation of study treatment was symptomatic deterioration. [b]Reason for discontinuation of study treatment was patient withdrawal. [c]Single timepoint PR pending confirmation at data cut-off; patient subsequently experienced confirmed CR at Months 5, 7, and 9.

▼ Figure 4. Radiographic tumor response across patients with *ROS1*+ solid tumors other than NSCLC.

Patients received zidesamtinib 100 mg QD unless otherwise noted. [a]Received 50 mg QD with dose escalation to 75 mg QD. [b]Received 75 mg QD. [c]Single timepoint PR pending confirmation at data cut-off; patient subsequently experienced confirmed CR at Months 5, 7, and 9.



[a]Data cut-off date: September 22, 2025

[b]Disclaimer: © 2026 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting. All rights reserved.

[c]Abbreviations: AE, adverse event; ALT, alanine aminotransferase increased; BICR, blinded independent central review; BID, twice daily; BOR, best overall response; CAPOX, capecitabine and oxaliplatin; CBR, clinical benefit rate; chemo, chemotherapy; CI, confidence interval; CNS, central nervous system; CPK, creatine phosphokinase; CR, complete response; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, United States Food and Drug Administration; FOLFIRINOX, folinic acid (leucovorin), fluorouracil, irinotecan, oxaliplatin; FOLFOX, folinic acid (leucovorin), fluorouracil, oxaliplatin; IC, intracranial; IC_{90}, half-maximal inhibitory concentration; 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; PO, orally; PR, partial response; PRO, patient-reported outcome; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ROS1, c-ros oncogene 1; RP2D, recommended phase 2 dose; SD, stable disease; SEM, standard error of the mean; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event; TRK, tropomyosin-related kinase; TTR, time to response.

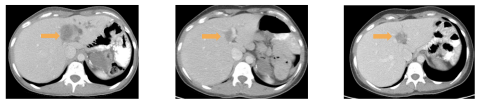
[c]References: 1. Lovly CM, et al. *Cancer Discov*. 2014;4:889–95. 2. Antonescu CR, et al. *Am J Surg Pathol*. 2015;39:957–67. 3. Davare M, et al. *Clin Cancer Res*. 2018; 24 (24):6471-6482. 4. Chu YH, et al. *Mod Pathol*. 2020;33:2458–72. 5. Gkountakos A, et al. *Trends Cancer*. 2024;10:430–43. 6. Lim SM, et al. *Cancer Res Treat*. 2017;49:185–92. 7. Lee J, et al. *Cancer*. 2013;119:3627–35 8. Aydin HA, et al. *Pathol Res Pract*. 2018;214:1868–72. 9. Drilon A, et al. *Cancer Discov*. 2023;13:598–615. 10. Tangpeerachaikul A, et al. *Mol Cancer Ther*. 2025;24:1005–19. 11. ZYKTRO [zidesamtinib] [prescribing information]. Cambridge, MA: Nuvalent, Inc.; 2026. 12. Drilon AE, et al. *J Thoracic Oncol*. 2025;20(10 Suppl_1):S3.

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CASE STUDIES

Zidesamtinib response in 30-year-old female patient with inflammatory myofibroblastic tumor and *TFG-ROS1* fusion

- Prior treatment with crizotinib, best response of SD for 15 months, discontinued for PD
- PR on zidesamtinib (-32% by BICR per RECIST v1.1), with ongoing response after 42+ months of therapy



▲ Figure 6. Response in patient with *ROS1*+ inflammatory myofibroblastic tumor.
Images courtesy of Drs Alexander E. Drilon and Jaime Rubio-Perez, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Zidesamtinib response in 41-year-old female patient with metastatic colorectal cancer and *GOPC-ROS1* fusion

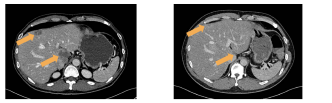
- Previously treated with CAPOX (discontinued for AE), FOLFOX, FOLFIRINOX (discontinued for PD)
- PR on zidesamtinib (-100% by BICR per RECIST v1.1), with ongoing response after 13+ months of therapy



▲ Figure 7. Response in patient with *ROS1*+ metastatic colorectal cancer.
Images courtesy of Drs Alexander E. Drilon and Jaime Rubio-Perez, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Zidesamtinib response in 47-year-old male patient with cholangiocarcinoma and *SLC4A4-ROS1* fusion

- Previously treated with first-line FOLFOX (discontinued for PD)
- PR on zidesamtinib (-80% by BICR per RECIST v1.1), with ongoing response after 19+ months of therapy



▲ Figure 8. Response in patient with *ROS1*+ metastatic cholangiocarcinoma.
Images courtesy of Dr Benjamin Solomon, Peter MacCallum Cancer Centre, Melbourne, Australia

Treatment duration presented in case studies is based on data after the September 22, 2025 cut-off date

PRELIMINARY SAFETY PROFILE

In these patients with *ROS1*+ solid tumors, the overall safety profile of zidesamtinib was consistent with previously reported safety results from ARROS-1 for patients with advanced *ROS1*+ NSCLC[12]

- TRAEs in ≥15% of patients were increased ALT, increased blood CPK, and dysgeusia (n = 3 patients each)
- 1 patient (7%) had a dose reduction (Grade 4 TRAE of increased blood CPK)
- No patients discontinued treatment due to TEAEs or TRAEs

▼ Table 3. All TRAEs in ≥15% of patients treated with zidesamtinib (N = 15). [a]

[a]No TEAEs or TRAEs leading to death.

Preferred Term	Any Grade	Grade ≥3 [a]
ALT increased	3 (20%)	-
Blood CPK increased	3 (20%)	1 (7%)
Dysgeusia	3 (20%)	-

SUMMARY

- **In a preliminary analysis of the ARROS-1 clinical trial, responses to zidesamtinib were observed in patients with diverse *ROS1*+ solid tumors other than NSCLC**
  - **An ORR of 40% (6/15) was observed across patients with *ROS1*+ solid tumors**
  - **Responses were seen for patients refractory to standard-of-care therapies, and for those who had received a prior ROS1 TKI**
- **Zidesamtinib was generally well tolerated with low rates of dose reduction and no treatment discontinuations in patients with *ROS1*+ solid tumors**
- **Evaluation of zidesamtinib in patients with advanced or metastatic *ROS1*+ solid tumors continues in the ARROS-1 clinical trial; enrollment is ongoing**

Correspondence: medinfo@nuvalent.com