Characterization and management of sevabertinib-induced diarrhea in the SOHO-01 study

18P

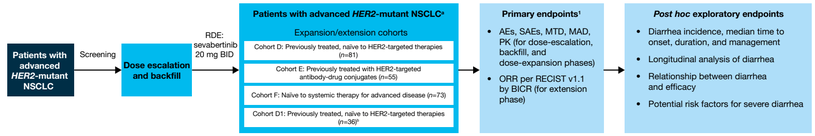
Nicolas Girard,[1] Tae Min Kim,[2] Herbert H Loong,[3,4] Arsela Prelaj,[5] Lin Li,[6,7] Yong Fang,[8] Shun Lu,[9] Xiaorong Dong,[10] Lin Wu,[11] Yuki Shinno,[12] Gennaro Daniele,[13] Tsung-Ying Yang,[14] Hye Ryun Kim,[15,16] Virginie Aris,[17] Mercedeh Ghadessi,[17] Paolo Grassi,[18] Vadim Bernard-Gauthier,[19] Xiuning Le[20]

[1]Institut Curie, Paris, France; [2]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; [3]Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong SAR, China; [4]Phase 1 Clinical Trial Center, Chinese University of Hong Kong, Hong Kong SAR, China; [5]Oncologia Medica Toracica Dipartimento, Fondazione IRCCS–Istituto Nazionale dei Tumori, Milan, Italy; [6]Department of Medical Oncology, Beijing Hospital, Beijing, China; [7]National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China; [8]Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; [9]Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [10]Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [11]Department of Thoracic Medical Oncology, Hunan Cancer Hospital, Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; [12]National Cancer Center Hospital, Tokyo, Japan; [13]Phase 1 Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [14]Department of Chest Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [15]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Seoul, South Korea; [16]Graduate School of Medical Science, Brain Korea 21 Project, Yonsei University College of Medicine, Seoul, South Korea; [17]Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA; [18]Bayer S.p.A., Milan, Italy; [19]Bayer Inc., Mississauga, Ontario, Canada; [20]MD Anderson Cancer Center, Houston, TX, USA

INTRODUCTION

- Sevabertinib is a potent, oral, reversible tyrosine kinase inhibitor that received accelerated US Food and Drug Administration (FDA) approval in November 2025 for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) with human epidermal growth factor receptor 2 (*HER2*) tyrosine kinase domain-activating mutations and who have previously received systemic therapy[1,2]
  - In January 2026, sevabertinib was granted Breakthrough Therapy Designation by the FDA in the USA and the Center for Drug Evaluation in China for the first-line treatment of patients with *HER2*-mutant NSCLC[3]
- SOHO-01 is a Phase I/II, open-label, multicenter, multicohort study evaluating sevabertinib in patients with advanced NSCLC with *HER2* or epidermal growth factor receptor mutations (NCT05099172)[4]
- Sevabertinib showed durable responses in patients with advanced *HER2*-mutant NSCLC who had not previously received HER2-targeted therapies (Cohort D, *n*=81), those previously treated with a HER2-targeted antibody-drug conjugate (Cohort E, *n*=55), and those naïve to systemic treatment for advanced disease (Cohort F, *n*=73)[1]
- Diarrhea is the most commonly reported adverse event associated with approved HER2 tyrosine kinase inhibitors (sevabertinib and zongertinib) in clinical trials for NSCLC, with approximately 32-91% of patients reporting drug-related diarrhea (0-23% grade ⩾3) across trial cohorts[1,5]
- Here, we report exploratory analyses to characterize the temporal evolution of sevabertinib-related diarrhea in the SOHO-01 trial as of the data cut-off date of August 7, 2025, with a focus on Cohorts D and F (Figure 1)

Figure 1. SOHO-01 study design



[a]Cohorts not included in this analysis are not shown; [b]Cohort D1 was not included in the extension phase and investigated sevabertinib at 10 mg BID

AE, adverse event; BICR, blinded independent central review; BID, twice daily; ex20ins, exon 20 insertion; MAD, maximum administered dose; MTD, maximum tolerated dose; ORR, objective response rate; PK, pharmacokinetics; RDE, recommended dose for expansion; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event

METHODS

- Patients aged ⩾18 years with locally advanced, recurrent or metastatic NSCLC harboring *HER2*-activating mutations received oral sevabertinib 20 mg twice daily (BID)[1]
- Diarrhea was assessed by investigators from the start of treatment until 30 days after the last dose, per Medical Dictionary for Regulatory Activities version 28.0, and graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0[1]
- Anti-diarrhea prophylaxis was not mandated in SOHO-01; however, prompt treatment with anti-diarrhea medication (eg, loperamide) after the first unformed stool was recommended and pre-medication was allowed after the first dose of study treatment
- Outcomes are described and included diarrhea incidence, median time to onset, duration, management, and its relationship with efficacy
  - Kaplan–Meier estimates were used to analyze time-to-event outcomes
- Area-under-the-curve (AUC) analyses explored the longitudinal impact of diarrhea over the treatment duration in Cohorts D, E, F, and D1; no competing risk or adjustments for confounding factors were completed
- Multivariate analysis, including penalized logistic regression, random forest, and extreme gradient boosting models, was used to identify risk factors for severe (grade ⩾3) diarrhea in Cohorts D, E, F, and D1

RESULTS

Participants and demographics

- In total, 81 patients in Cohort D and 73 patients in Cohort F were treated with sevabertinib 20 mg BID
- Patient demographics have previously been reported and were similar between cohorts.[1] At baseline:
  - Median age was 60 (Cohort D) and 65 (Cohort F) years
  - 62% (Cohort D) and 63% (Cohort F) were female
  - 62% (Cohort D) and 78% (Cohort F) had never smoked
- Median treatment duration was 9.9 (Cohort D) and 10.0 (Cohort F) months
- Median duration of follow-up was 16.2 (Cohort D) and 11.8 (Cohort F) months

Diarrhea events in SOHO-01

- Incidence of any-grade diarrhea was similar between cohorts, and grade 3 diarrhea was lower in patients who were naïve to systemic therapy *vs* those with previous systemic therapy (Cohort F: 5% *vs* Cohort D: 23%) (Table 1)
  - There were no reports of grade 4 diarrhea or discontinuations due to diarrhea
- Median time to onset of any-grade diarrhea was 4-6 days (interquartile range 2-11)
- Patients with grade 3 diarrhea had a median of 1 episode with a median duration of 2-4 days (Table 2)
- Loperamide use was not mandated and was reported in 69% (Cohort D) and 53% (Cohort F) of patients (Table 2)
- Time-course analyses of diarrhea by grade showed that the relative proportion of time with grade 2 or 3 diarrhea decreased over time in Cohorts D and F (Figure 2A-B)
- Overall patient-days with grade 3 diarrhea over the course of treatment were very low (<0.1-0.6%) (Figure 2C-D)

CONCLUSIONS

- This exploratory analysis suggests sevabertinib-associated diarrhea was common but manageable
  - In cases of severe diarrhea, episodes were generally not sustained or recurrent and were effectively managed with loperamide use and dose interruptions, delays, and/or reductions
- Higher sevabertinib exposure was associated with a higher risk of severe diarrhea
- Overall response rates were similar across cohorts irrespective of diarrhea occurrence
- Timing of previous PD-(L)1 therapy and platinum-based chemotherapy may affect the risk of diarrhea
- This longitudinal, exploratory assessment provides clinically relevant context beyond the standard analysis of adverse-event incidence
  - These data support the use of sevabertinib with appropriate strategies to manage diarrhea and guide physicians and patients on the importance of timely supportive measures

Table 1. Most common TEAEs occurring in >25% of patients in Cohorts D and F

n (%)	Cohort D (*n*=81)			Cohort F (*n*=73)		
	Any grade	Grade 1 or 2	Grade 3	Any grade	Grade 1 or 2	Grade 3
Diarrhea	**70 (86)**	**51 (63)**	**19 (23)**	**64 (88)**	**60 (82)**	**4 (5)**
Rash	43 (53)	42 (52)	1 (1)	43 (59)	43 (59)	0
Paronychia	24 (30)	24 (30)	0	19 (26)	19 (26)	0
Stomatitis	15 (19)	14 (17)	1 (1)	20 (27)	20 (27)	0
Anemia	23 (28)	21 (26)	2 (2)	24 (33)	21 (29)	3 (4)
Hypokalemia[a]	22 (27)	12 (15)	9 (11)	19 (26)	13 (18)	6 (8)
Nausea	20 (25)	18 (22)	2 (2)	11 (15)	9 (12)	2 (3)
Decreased weight	21 (26)	20 (25)	1 (1)	13 (18)	13 (18)	0

[a]1 grade 4 TEAE was reported in Cohort D

TEAE, treatment-emergent adverse event

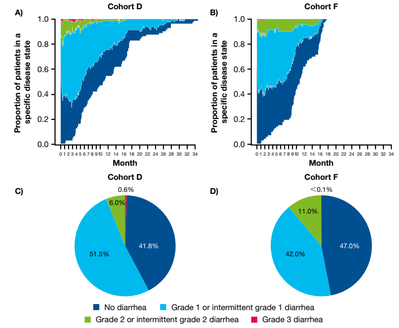
Table 2. Characterization and management of treatment-emergent diarrhea

	Cohort D (*n*=81)	Cohort F (*n*=73)
No diarrhea, *n* (%)	11 (14)	9 (12)
Treatment-emergent diarrhea (worst toxicity grade), *n* (%)	70 (86)	64 (88)
Grade 1	21 (26)	36 (49)
Grade 2	30 (37)	24 (33)
Grade 3	19 (23)	4 (5)
Grade 4	0	0
Onset at grade 3, *n* (%)	2 (2)	0
Action taken due to diarrhea, *n* (%)	70 (86)	64 (88)
Dose not changed	69 (85)	60 (82)
Dose interruptions or delays	12 (15)	3 (4)
Dose reductions[a]	10 (12)	6 (8)
Discontinuation	0	0
Loperamide use, *n* (%)	56 (69)	39 (53)
Loperamide started ⩽24 hours after first diarrhea event of any grade	30 (37)	13 (18)
Characteristics of grade 3 diarrhea events		
Patients with >1 episode, *n* (%)	3 (4)	0
Median episodes per patient (IQR)	1 (1-1)	1 (1-1)
Median duration of episodes, days (IQR)	4 (2-11)	2 (2-2)
Median time to first episode, days (IQR)	39 (15-123)	29 (14-50)
Median cumulative duration, days (IQR)	6 (3-14)	2 (2-2)

[a]Dose was not re-escalated after reduction for toxicity

IQR, interquartile range

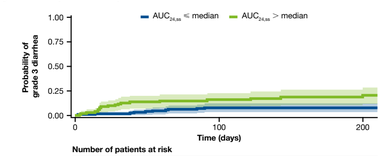
Figure 2. Time-course analysis of diarrhea by grade (A, B) and proportion of patient-days with diarrhea (C, D) in Cohorts D and F



Response among patients with and without diarrhea

- In Cohorts D and F, efficacy was generally similar among patients who did or did not experience grade ⩾2 diarrhea (Table 3)

Figure 3. Probability of grade 3 diarrhea during the first 200 days of treatment with sevabertinib in Cohorts D, E, F, and D1 stratified by median plasma exposure



Median $AUC_{24,ss}$ represents the median 24-hour AUC at steady state and was based on Cohorts D, E, and F who received sevabertinib 20 mg BID (12910 µg·h/L)

Figure 4. Diarrhea frequency by timing of previous anti-PD-(L)1 (A) and platinum-based chemotherapy (B) in Cohorts D, E, F, and D1

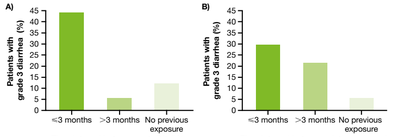


Table 3. Response per BICR (RECIST v1.1) by presence of grade ⩾2 diarrhea

	Cohort D (*n*=81)		Cohort F (*n*=73)	
	Grade ⩾2 diarrhea (*n*=49)	No grade ⩾2 diarrhea (*n*=32)	Grade ⩾2 diarrhea (*n*=28)	No grade ⩾2 diarrhea (*n*=45)
ORR, *n* (%)	34 (69)	20 (63)	20 (71)	33 (73)
Median DoR, months (min, max)[a]	7 (2, 30)	6 (1, 15)	9 (2, 13)	7 (1, 13)
Median PFS, months (min, max)	8 (1, 31)	5 (0, 16)	9 (0, 15)	8 (0, 15)

[a]Based on patients with an objective response

BICR, blinded independent central review; DoR, duration of response; max, maximum; min, minimum; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Cohorts D, E, F, and D1: Potential contributors to incidence of severe (grade 3) diarrhea

- Sevabertinib exposure above the median 24-hour AUC at steady state ($AUC_{24,ss}$) was associated with higher rates of grade 3 diarrhea during the first 200 days of treatment compared with lower exposure ($AUC_{24,ss}$ below the median) (Figure 3)
- Exploratory multivariate analyses identified that shorter time since last exposure to anti-programmed cell death protein 1/programmed death (ligand) 1 (PD-[L]1) therapy and/or platinum-based chemotherapy may be associated with a higher risk of grade 3 diarrhea (Figure 4)
  - Patients who received their last dose of anti-PD-(L)1 therapy within 3 months before the first dose of sevabertinib were approximately 8 times more likely to have grade 3 diarrhea than patients who were treated more than 3 months before and approximately 4 times more likely than patients with no previous exposure (Figure 4A)
  - Among those who received platinum-based chemotherapy, grade 3 diarrhea was more likely if last exposure was 3 months or less *vs* more than 3 months before the first dose of sevabertinib and almost 6 times more likely than in patients with no previous exposure (Figure 4B)

References

1. Le X *et al. N Engl J Med* 2025; 393: 1819-1832
2. HYRNUO (sevabertinib). Highlights of prescribing information. https://labeling.bayerhealthcare.com/html/products/pi/HYRNUO_PI.pdf
3. Bayer AG. https://www.bayer.com/media/en-us/bayer-receives-breakthrough-therapy-designation-in-the-us-and-china-for-sevabertinib-as-a-first-line-treatment-for-patients-with-her2-mutant-non-small-cell-lung-cancer/
4. ClinicalTrials.gov. NCT05099172. https://clinicaltrials.gov/study/NCT05099172
5. Heymach JV *et al. N Engl J Med* 2025; 392: 2321-2333

Disclosures

Nicolas Girard reports: consultancy, advisory, speaker role for AbbVie, Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Janssen, LEO Pharma, Lilly, MSD, Mirati, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, and Takeda; research funding from AstraZeneca, Bristol Myers Squibb, and Sivan; travel, accommodation, and expenses provided by Janssen; stock options in Incendia and Owkin

Acknowledgments

This study was supported by Bayer AG. Medical writing support, under the direction of the authors, was provided by Jenifer Li, MSc, of the Publications Division of Omnicom Health Medical Communications, funded by Bayer AG, in accordance with Good Publication Practice (GPP 2022) guidelines. Editorial support was provided by Rachel Fairbanks, BA (Hons), of the Publications Division of Omnicom Health Medical Communications, funded by Bayer AG

Poster presented at the European Lung Cancer Congress (ELCC), 25-28 March 2026, Copenhagen, Denmark

Presenting author: Nicolas Girard (nicolas.girard2@curie.fr)