SOHO-01: Updated safety and efficacy of sevabertinib in patients with advanced *HER2*-mutant non-small cell lung cancer

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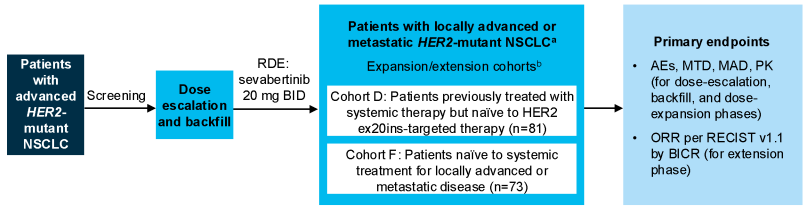
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INTRODUCTION

- Sevabertinib, a potent, reversible, oral tyrosine kinase inhibitor (TKI), received accelerated approval from the US Food and Drug Administration in November 2025 for the treatment of patients with locally advanced or metastatic *HER2*-mutant non-small cell lung cancer (NSCLC) harboring activating mutations in the tyrosine kinase domain (TKD) who had already received treatment[1-3]
- Sevabertinib demonstrated durable anti-tumor activity and manageable safety in patients with *HER2*-mutant NSCLC who had previously received treatment (Cohort D) or were naïve to systemic treatment for locally advanced or metastatic disease (Cohort F) in an ongoing Phase I/II, open-label, multicenter, multicohort study (SOHO-01) (NCT05099172)[1,4]
- Here, we report updated safety and efficacy data from Cohorts D and F

Figure 1. SOHO-01 study design (Cohorts D and F)



[a]Cohorts whose data are not presented in this poster are not included herein, including the *EGFR*-mutant NSCLC cohort; [b]Patients from dose escalation and expansion who were treated at the same dose level and who met the same eligibility criteria for an extension group were combined for the respective statistical analysis

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

METHODS

- Patients aged ⩾18 years with locally advanced, recurrent or metastatic HER2-mutant NSCLC received oral sevabertinib 20 mg twice daily
  - Key prespecified and secondary endpoints included duration of response (DoR) and progression-free survival (PFS) assessed by BICR per RECIST v1.1, and safety per Medical Dictionary for Regulatory Activities version 28.0 and National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0)
  - Area-under-the-curve analyses explored the longitudinal impact of diarrhea over the treatment duration in Cohort F

RESULTS

Patients and demographics

- As of the data cut-off of November 17, 2025, 154 patients had received sevabertinib (Table 1)

Table 1. Patient demographics and baseline cancer characteristics in Cohorts D and F

	Cohort D (*n*=81)	Cohort F (*n*=73)
Median age, years (range)	60 (29-82)	65 (31-82)
Female, *n* (%)	50 (62)	46 (63)
Never smoked, *n* (%)	50 (62)	57 (78)
Non-squamous histology, *n* (%)[a]	77 (95)	71 (97)
HER2 TKD mutation, *n* (%)	73 (90)	71 (97)
HER2 Y772_A775dupYVMA TKD mutation (YVMA), *n* (%)	49 (60)	57 (78)
Median follow-up, months (range)	19.5 (1-37)	15.0 (0-20)

[a]Squamous cell carcinoma was defined by squamous cell carcinoma (not otherwise specified), squamous carcinoma, or small cell non-keratinizing squamous cell carcinoma

Efficacy

- In patients with non-squamous histology and *HER2* TKD mutations at baseline treated in Cohorts D and F, ORRs were 73% and 75%, respectively (Table 2)
- In patients with *HER2* YVMA mutations at baseline in Cohorts D (*n*=49) and F (*n*=57), ORRs were comparable between cohorts (D, 78% [63, 88]; F, 74% [60, 85]); similar results were observed in the non-squamous subgroups (Table 2)
- ORR in all patients treated in Cohorts D and F, which included patients with non-squamous histology and *HER2* TKD mutations, was comparable, with an additional 2 and 3 patients, respectively, achieving an objective response on additional follow-up[1]

CONCLUSIONS

- In this updated analysis, sevabertinib demonstrated robust and consistent efficacy across treatment settings, with high response rates and prolonged PFS, particularly in treatment-naïve patients
  - Responses were higher in patients with non squamous histology and HER2 TKD mutations, reachiang an ORR of 78% in pretreated patients with HER2-activating YVMA mutations
- The safety profile was manageable and consistent with the TKI class, with low-grade diarrhea being the most frequently reported TRAE
  - Severity and burden of diarrhea decreased over time, with low rates of grade 3 events in the first-line setting and no grade 4 events or discontinuations due to diarrhea
- Overall, these data support a favorable benefit–risk profile and further development of sevabertinib in earlier lines of therapy for HER2-mutant NSCLC

Table 2. Efficacy per BICR (RECIST v1.1) in Cohorts D and F

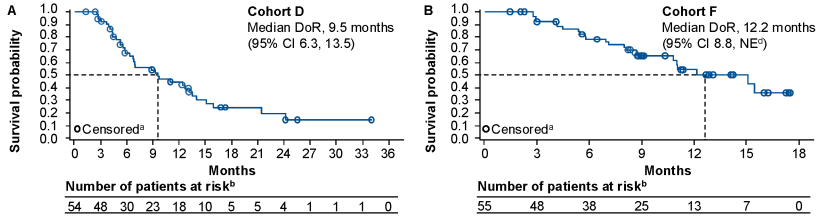
	Cohort D			Cohort F		
	Treated patients with non-squamous histology and HER2 TKD mutation (n=70)	Treated patients with non-squamous histology and HER2 YVMA mutation (n=49)	All treated patients (n=81)	Treated patients with non-squamous histology and HER2 TKD mutation (n=69)	Treated patients with non-squamous histology and HER2 YVMA mutation (n=55)	All treated patients (n=73)
ORR, % (95% CI)[a]	73 (61, 83)	78 (63, 88)	67 (55, 77)	75 (64, 85)	75 (61, 85)	75 (64, 85)
DCR, % (95% CI)[b]	84 (74, 92)	88 (75, 95)	81 (71, 89)	90 (80, 96)	89 (78, 96)	89 (80, 95)
mDoR, months (95% CI)	9.5 (6.3, 13.5)[c]	9.5 (6.3, 15.0)[d]	9.5 (6.3, 13.5)[e]	15.1 (8.8, NE)[c]	15.1 (8.8, NE)[d]	12.2 (8.8, NE)[e]
mPFS, months (95% CI)	9.6 (6.9, 14.5)	12.2 (6.9, 16.5)	8.3 (6.9, 12.3)	13.5 (10.0, NE[f])	16.4 (9.9, NE[f])	13.5 (10.0, NE[f])

[a]Patients with confirmed CR or PR; [b]Patients with confirmed CR or PR or stable disease for ⩾12 weeks; [c]Subset of patients with confirmed CR or PR (Cohort D, *n*=51; Cohort F, *n*=52); [d]Subset of patients with confirmed CR or PR (Cohort D, *n*=38; Cohort F, *n*=41); [e]Subset of patients with confirmed CR or PR (Cohort D, *n*=54; Cohort F, *n*=55); [f]Value cannot be estimated

CI, confidence interval; CR, complete response; DCR, disease control rate; mDoR, median duration of response; mPFS, median progression-free survival; NE, not estimable; PR, partial response

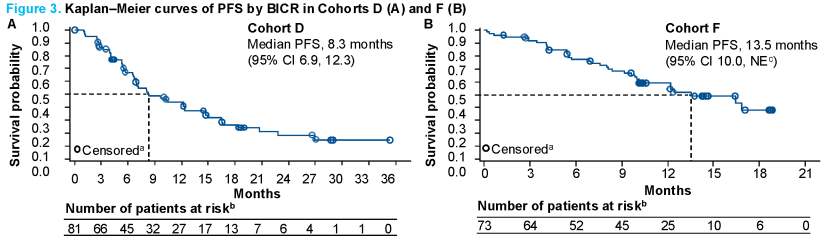
- Median DoR and median PFS were longer in treatment-naïve patients (Cohort F) than in patients who had previously received systemic treatment (Cohort D) in all treated patients (Table 2, Figures 2 and 3) and in treated patients with non-squamous histology and *HER2* TKD or *HER2* YVMA mutations (Table 2)

Figure 2. Kaplan–Meier curves of DoR by BICR in Cohorts D (A) and F (B)



[a]Patients censored: 19 (35%); [b]Patients with confirmed CR or PR; [c]Patients censored: 35 (58%); [d]Value cannot be estimated NE, not estimable

Figure 3. Kaplan–Meier curves of PFS by BICR in Cohorts D (A) and F (B)

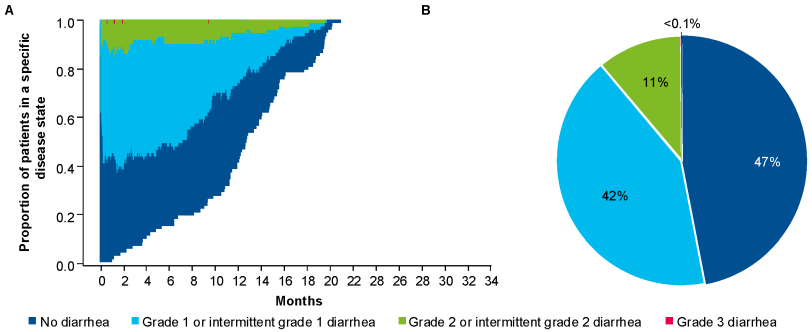


[a]Patients censored: 27 (33%); [b]Patients censored: 39 (53%); [c]Value cannot be estimated NE, not estimable

Safety

- The most common treatment-emergent AEs in Cohorts D and F combined were diarrhea (87%), rash (56%), and paronychia (29%), consistent with previous reports.[1] No cases of interstitial lung disease were reported
  - Treatment-emergent AEs led to dose modifications (delays, interruptions, and reductions) in 52% of patients in Cohort D and 55% of patients in Cohort F
  - 5% of patients in Cohort D and 3% in Cohort F discontinued treatment due to treatment-emergent AEs
- In Cohort F, the relative proportion of time spent with grade 2 or 3 treatment-emergent diarrhea decreased over time (Figure 4A), and the proportions of patient-days with grade 2 or 3 treatment-emergent diarrhea were 11% and <0.1%, respectively (Figure 4B)

Figure 4. Time–course analysis of treatment-emergent diarrhea by grade (A) and proportion of patient-days spent with diarrhea (B) in Cohort F[a]



[a]No competing risk or adjustments for confounding factors were completed

- The most common drug-related AE was diarrhea (Table 3)
  - No grade 4 diarrhea or discontinuations of sevabertinib due to diarrhea were reported

Table 3. Most common drug-related AEs occurring in >20% of patients in Cohort D or F

	Cohort D (*n*=81)		Cohort F (*n*=73)	
n (%)[a]	All grade	Grade 3	All grade	Grade 3
Diarrhea	70 (86)	19 (23)	62 (85)	4 (5)
Rash	42 (52)	1 (1)	41 (56)	0
Paronychia	23 (28)	1 (1)	20 (27)	1 (1)
Stomatitis	15 (19)	1 (1)	20 (27)	0
Anemia	15 (19)	1 (1)	19 (26)	1 (1)
Nausea	17 (21)	2 (2)	8 (11)	2 (3)

[a]Shown are drug-related AEs of any grade and grade 3 that occurred in >20% of patients from Cohort D or F. Relatedness of AEs to treatment was assessed by the investigator. Drug-related AEs were graded by the investigator based on CTCAE v5.0

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Acknowledgments

This study was supported by Bayer AG. Medical writing support, under the direction of the authors, was provided by Karishma Smart, PhD, 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

Disclosures

Dr Loong reports consultancy/advisory/speaker roles for Bayer, Boehringer Ingelheim, Celgene, Eisai, Eli Lilly, Guardant Health, MSD, and Novartis

Poster presented at NCODA 2026 International Fall Summit, October 28-30, 2026; Orlando, Florida; © 2026 American Society of Clinical Oncology, Inc. Reused with permission. Abstract was accepted and previously presented at the 2026 ASCO Annual Meeting. All rights reserved.

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