Factors associated with clinical outcomes in patients with *HER2*-mutant NSCLC treated with sevabertinib (BAY 2927088)

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INTRODUCTION

- Mutations in human epidermal growth factor receptor 2 (*HER2*) occur in about 2-4% of patients with non-small cell lung cancer (NSCLC) and are associated with unfavorable outcomes[1,2]
- Pan-HER tyrosine kinase inhibitors (TKIs) have typically shown limited clinical efficacy in this population[3-5]; however, the novel HER2 TKI zongertinib has demonstrated promising efficacy in patients with *HER2*-mutated NSCLC who were naïve to HER2-targeted treatment (overall response rate [ORR] 71%),[6] leading to recent accelerated FDA approval[7]
- Sevabertinib (BAY 2927088) is a potent, reversible, oral TKI which inhibits growth of tumors with underlying *HER2* mutations, including exon 20 insertions (ex20ins) such as Y772_A775dup (YVMA; the most frequent alteration), and point mutations[8-10]
- Sevabertinib has demonstrated anti-tumor activity and a manageable safety profile in patients with advanced NSCLC harboring *HER2*-activating mutations in the Phase I/II SOHO-01 trial (NCT05099172)[11,12]
- Here, we report an exploratory analysis of the effect of baseline clinical and molecular characteristics on treatment outcomes in an expansion cohort of patients with previously treated, advanced NSCLC harboring *HER2*-activating mutations

METHODS

- Overall eligibility criteria included patients aged ⩾18 years with locally advanced or metastatic NSCLC harboring *HER2* or *EGFR* mutations who had relapsed or were refractory to ⩾1 systemic therapy
- Expansion Cohort D included patients with locally advanced or metastatic NSCLC harboring a *HER2*-activating mutation (including ex20ins) who were naïve to *HER2*-targeted therapies
- Patients received oral sevabertinib 20 mg twice daily
- Plasma ctDNA was assessed using the Thermo Fisher Scientific Oncomine™ Precision Assay
  - For the *TP53* co-alteration analysis, a *TP53* mutation was considered detected if any mutation with a variant allele frequency ⩾0.5 was reported; it was classified as "not detected" if valid sequencing showed no mutations at that threshold. Patients without detectable *HER2* ctDNA alterations at baseline were excluded from the co-alteration analysis
- Efficacy outcomes, including ORR, median duration of response (mDoR), and median progression-free survival (mPFS), were determined by investigator assessment
- The cut-off date for analysis was October 14, 2024

RESULTS

Patients and treatment

- Of the 44 patients treated in expansion Cohort D, 43 had a post-baseline tumor assessment and were included in the analysis
- At baseline, median age was 62.0 years, 65.1% were female, 72.1% had never smoked, and 46.5% had received <2 previous lines of therapy

Efficacy

Stratified by previous lines of therapy and Eastern Cooperative Oncology Group performance status (ECOG PS)

- Treatment with <2 *vs* ⩾2 previous lines of therapy was associated with improved mPFS (not reached [NR] *vs* 6.7 months), higher ORR (75.0% *vs* 69.6%), and longer mDoR (NR *vs* 5.2 months) (Figure 1 and Table 1)
- Efficacy outcomes were numerically higher for patients with a baseline ECOG PS of 1 *vs* those with a PS of 0 (Figure 2 and Table 1)

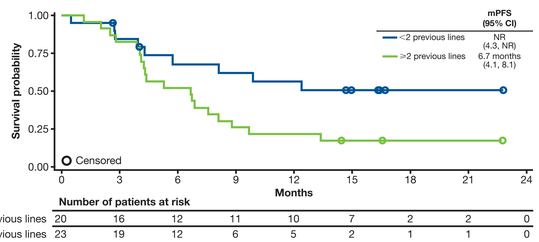
Stratified by baseline biomarker status

- Presence of the YVMA variant *vs* other *HER2* alterations (other ex20ins and *HER2* point mutations) was associated with improved mPFS (9.9 *vs* 3.9 months), higher ORR (86.7% *vs* 30.8%), and longer mDoR (9.7 *vs* 2.8 months) (Figure 3 and Table 2)
- In patients with detectable *HER2* ctDNA (*n*=37) at baseline, those without *TP53* co-alterations *vs* those with detectable *TP53* had improved outcomes, including longer mPFS (10.6 *vs* 6.7 months), higher ORR (79.2% *vs* 69.2%), and longer mDoR (NR *vs* 5.3 months) (Figure 4 and Table 2)

CONCLUSIONS

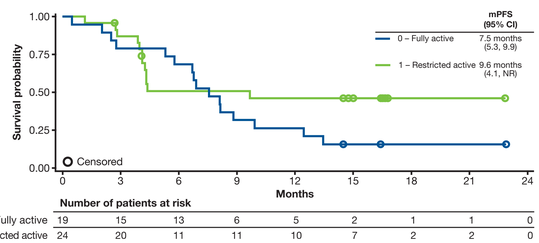
- In patients with pretreated *HER2*-mutant NSCLC, treatment with sevabertinib 20 mg twice daily resulted in rapid, substantial, and durable responses
- Treatment with <2 previous lines of therapy was associated with improved treatment efficacy compared with patients who had received ⩾2 previous lines
- Presence of the YVMA variant was associated with enhanced treatment efficacy compared with other *HER2* alterations, whereas *TP53* co-alterations were linked to reduced treatment efficacy
- MVA indicated that both *TP53* and *HER2* YVMA provide independent prognostic information when adjusted for clinical factors
- This exploratory analysis of clinical and molecular characteristics in patients with *HER2*-mutant NSCLC indicates favorable ORR, mDoR, and mPFS among those who had received only 1 previous line of therapy or who had specific molecular characteristics
- The findings underscore the importance of integrating clinical and molecular features to identify potential prognostic or predictive markers
- As these results are limited to a single expansion cohort in an ongoing trial, further validation in larger studies is required

Figure 1. Kaplan–Meier curves of PFS by number of previous lines of systemic anti-cancer therapy



Determined by investigator assessment
CI, confidence interval; NR, not reached

Figure 2. Kaplan–Meier curves of PFS by ECOG PS at baseline



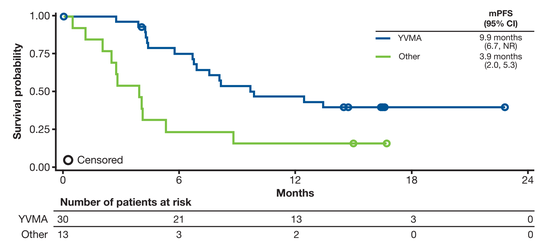
Determined by investigator assessment
CI, confidence interval; NR, not reached

Table 1. Investigator-assessed efficacy by previous lines of therapy and ECOG PS status

	Previous lines of therapy		Baseline ECOG PS	
	<2 lines (*n*=20)	⩾2 lines (*n*=23)	PS 0 (*n*=19)	PS 1 (*n*=24)
ORR, *n* (%) [95% CI]	15 (75.0) [50.9, 91.3]	16 (69.6) [47.1, 86.8]	12 (63.2) [38.4, 83.7]	19 (79.2) [57.8, 92.9]
mDoR, months[a] [95% CI]	NR [6.8, NR]	5.2 [2.8, 12.2]	7.7 [4.5, 12.2]	NR [2.8, NR]
mPFS, months [95% CI]	NR [4.3, NR]	6.7 [4.1, 8.1]	7.5 [5.3, 9.9]	9.6 [4.1, NR]

[a]mDoR data from a subset of patients with confirmed partial response or complete response (<2 lines, *n*=15; ⩾2 lines, *n*=16; PS 0, *n*=12; PS 1, *n*=19)
CI, confidence interval; NR, not reached

Figure 3. Kaplan–Meier curves of PFS by *HER2* mutation group (YVMA *vs* Other)



Determined by investigator assessment
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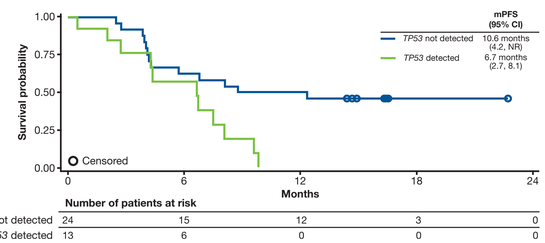
Figure 4. Kaplan–Meier curves of PFS by *TP53* mutation status



Determined by investigator assessment
CI, confidence interval; NR, not reached

Table 2. Investigator-assessed efficacy by YVMA variant and *TP53* co-alteration status at baseline

	YVMA variant		*TP53* co-alteration	
	Present (*n*=30)	Other (*n*=13)	Not detected (*n*=24)	Detected (*n*=13)
ORR, *n* (%) [95% CI]	26 (86.7) [69.3, 96.2]	4 (30.8) [9.1, 61.4]	19 (79.2) [57.8, 92.9]	9 (69.2) [38.6, 90.9]
mDoR, months[a] [95% CI]	9.7 [5.3, NR]	2.8 [2.7, NR]	NR [3.1, NR]	5.3 [2.8, 6.8]
mPFS, months [95% CI]	9.9 [6.7, NR]	3.9 [2.0, 5.3]	10.6 [4.2, NR]	6.7 [2.7, 8.1]

[a]mDoR data from a subset of patients with confirmed partial response or complete response (YVMA variant present, *n*=26; Other, *n*=4; *TP53* co-alteration not detected, *n*=19; Detected, *n*=9)
CI, confidence interval; NR, not reached

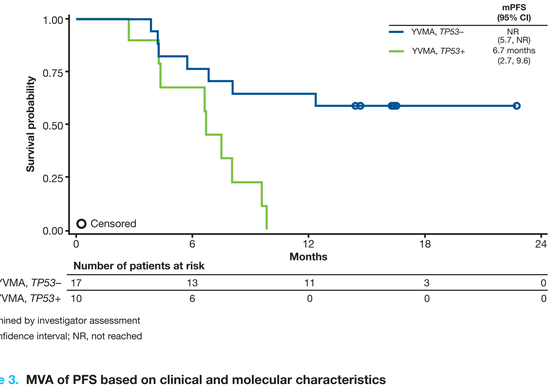
Patients with HER2 YVMA at baseline, stratified by TP53- status

- In 27 patients with the YVMA variant, those without *TP53* co-alterations *vs* those with detectable *TP53* had better outcomes, with longer mPFS (NR *vs* 6.7 months), higher ORR (94.1% *vs* 80.0%), and longer mDoR (NR *vs* 5.3 months) (Figure 5)

Multivariate analysis (MVA)

- MVA showed that YVMA and *TP53* status were both significantly associated with PFS when adjusted for previous treatment lines and ECOG PS (Table 3)
- Figure 5 illustrates the improved treatment outcome when both positive features (presence of YVMA, absence of *TP53*) are combined

Figure 5. Kaplan–Meier curves of PFS by *TP53* mutation status in patients with the YVMA variant



Determined by investigator assessment
CI, confidence interval; NR, not reached

Table 3. MVA of PFS based on clinical and molecular characteristics

Parameter[a]	Hazard ratio [95% CI]	*p* value
ECOG PS (1 – Restricted active [ref = 0 – Fully active])	0.7 [0.3, 1.7]	0.43
Number of previous treatment lines (⩾2 lines [ref = <2 lines])	1.6 [0.7, 3.8]	0.28
HER2 mutation group (Other [ref = YVMA present])	7.1 [2.5, 20.8]	<0.001
TP53 mutation status (*TP53* detected [ref = *TP53* not detected])	4.9 [1.7, 13.9]	0.003

[a]MVA is based on a Cox proportional hazards regression
CI, confidence interval

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