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Abstract CT009: SHR-A1811, a HER2-directed antibody-drug conjugate (ADC), in advanced *HER2*-mutant non-small cell lung cancer (NSCLC): Updated phase 2 results from HORIZON-Lung FREE

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Abstract

Background:

SHR-A1811 is a novel ADC consisting of a humanized HER2-directed monoclonal antibody, cleavable tetrapeptide-based linker, and DNA topoisomerase I inhibitor. We conducted a multicenter, open-label, phase 1/2 study to evaluate SHR-A1811 in HER2-altered NSCLC. In the registrational phase 2 portion in patients (pts) with *HER2-mutant NSCLC*, the primary endpoint of IRC-assessed ORR was met (DCO, Jun. 14, 2024). Here, we presented an updated analysis after an additional 6-mo follow-up, focusing on survival outcomes.

Methods:

Pts with advanced NSCLC and centrally confirmed *HER2* mutation, previously treated with (or intolerance to) platinum-based chemo and anti-PD-1/PD-L1 therapy, were enrolled. SHR-A1811 was administered at 4.8 mg/kg IV Q3W.

Results:

94 pts were enrolled and treated. Median prior lines of therapy was 2 (range 1-9); all received platinum-based chemo and anti-PD-1/PD-L1 therapy and 23.4% received anti-HER2 TKI. 25.5% had BM at baseline. The most common *HER2* mutation was exon 20 insertions (overall, 94.7%; A775_G776insYVMA, 72.3%). As of DCO (Dec. 14, 2024), median follow-up was 14.2 mo (range 4.7-18.2). Per IRC, ORR was 74.5% (95% CI 64.4-82.9); median DoR was 9.8 mo (95% CI 8.3-

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13.9). Median PFS was 11.5 mo (95% CI 9.7-15.2), with consistent benefits observed across baseline subgroups (**Table 1**). Efficacy per INV is shown in **Table 1**. Median OS was not reached; 12-mo OS rate was 88.2% (95% CI 79.8-93.3). Grade ≥3 TRAEs occurred in 63 (67.0%) pts; all with incidence ≥5% were haematological toxicities. ILD occurred in 8 (8.5%; grade 1-2, n=7; grade 3, n=1) pts. TRAEs led to dose discontinuation in 2 (2.1%) pts. There was no treatment-related death.

Conclusions:

At the updated analysis, SHR-A1811 continued to show clinically meaningful efficacy with a manageable safety profile in pts with previously treated *HER2*-mutant NSCLC, supporting it as a potential new treatment option for this population.

Table 1

Efficacy summary

	Patients (n=94)	
	IRC	**INV**
ORR, % (n/N; 95% CI)	74.5 (70/94; 64.4-82.9)	68.1 (64/94; 57.7-77.3)
Median DoR, mo (95% CI)	9.8 (8.3-13.9)	9.9 (7.2-11.5)
DCR, % (n/N; 95% CI)	98.9 (93/94; 94.2-100.0)	96.8 (91/94; 91.0-99.3)
Median PFS, mo (95% CI)	11.5 (9.7-15.2)	12.5 (9.9-15.1)
PFS by baseline subgroup, mo (95% CI)		
BM (n=24)	11.3 (9.5-NR)	-
No BM (n=70)	11.5 (8.5-15.2)	-
1 line of prior therapy (n=43)	9.9 (8.1-NR)	-
≥2 lines of prior therapy (n=51)	13.9 (9.7-16.8)	-
Prior anti-HER2 TKI (n=22)	9.7 (8.3-16.8)	-
No prior anti-HER2 TKI (n=72)	11.5 (9.9-NR)	-
A775_G776insYVMA (n=68)	15.2 (10.6-16.8)	-
Other mutations (n=26)	9.6 (7.1-11.1)	-

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BM, brain metastases; DCR, disease control rate; DoR, duration of response; INV, investigator; IRC, independent review committee; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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