SHR-4849 (IDE849), an ADC targeting delta-like ligand 3 (DLL3), in relapsed small cell lung carcinoma (SCLC) and other neuroendocrine carcinomas (NECs): long-term results from the phase 1 study

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BACKGROUND

- **Delta-like ligand 3 (DLL3)**, a protein that inhibits Notch signaling, is an attractive therapeutic target in small cell lung cancer (SCLC) and other neuroendocrine carcinomas (NECs) due to high expression in tumors of neuroendocrine lineage.[1-4]
- **SHR-4849 (IDE849*)** is an antibody-drug conjugate comprising a humanized anti-DLL3 IgG1 monoclonal antibody, linked to a DNA topoisomerase I inhibitor payload by a cleavable linker.
- We initiated a **first-in-human study** of SHR-4849 in relapsed or metastatic SCLC and other NECs. SHR-4849 at doses ranging from 0.8 to 4.2 mg/kg showed **a tolerable and manageable safety profile, favorable pharmacokinetic profile, and promising anti-tumor activity**.[5]

METHODS

- **Study design**: a multicenter, phase 1 study (NCT06443489).
- **Key eligibility criteria**:
  - Histologically or cytologically confirmed relapsed or metastatic SCLC and other DLL3-expressing NECs.
    DLL3 positivity was defined as H-score >0.
  - Had progressive or recurrent disease after standard treatment(s).
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
  - Stable CNS metastases following local therapy.
- **Treatment**: Eligible patients received intravenous SHR-4849 at 0.8, 1.8, 2.4, 3.0, 3.5, and 4.2 mg/kg every 3 weeks.
- This report presents the **updated efficacy and safety data**.
  - Data cutoff: Aug 21, 2026.
  - Median follow-up duration: 12.1 months (IQR, 8.2–16.0).

RESULTS

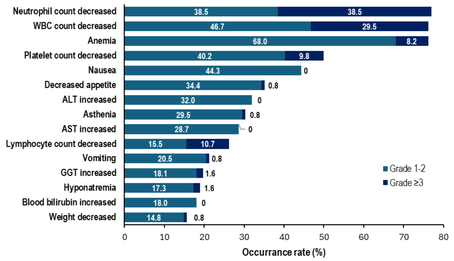


Figure 1. TRAEs occurring in ≥15% of patients

Table 1. Patient characteristics

	SCLC (N=103)	Other NECs (N=19)	Total (N=122)
Sex			
Male	79 (76.7)	9 (47.4)	88 (72.1)
Female	24 (23.3)	10 (52.6)	34 (27.9)
Age, years	60 (36–75)	59 (28–70)	60.0 (28–75)
ECOG performance status			
0	5 (4.9)	2 (10.5)	7 (5.7)
1	98 (95.1)	17 (89.5)	115 (94.3)
Clinical stage IV	89 (86.4)	18 (94.7)	107 (87.7)
Brain metastases	27 (26.2)	0	27 (22.1)
Liver metastases	32 (31.1)	9 (47.4)	41 (33.6)
Prior lines of therapy			
1	51 (49.5)	12 (63.2)	63 (51.6)
2	35 (34.0)	7 (36.8)	42 (34.4)
≥3	17 (16.5)	0	17 (13.9)
Prior immunotherapy	81 (78.6)	11 (57.9)	92 (75.4)

Data are n (%) or median (range).
One (0.8%) patient had previously received T-cell-engaging therapy targeting DLL3.

Table 2. Safety summary

	Total (N=122)
Any TRAE	121 (99.2)
Grade ≥3	73 (59.8)
Leading to dose reduction	23 (18.9)
Leading to treatment discontinuation	3 (2.5)
Serious	26 (21.3)
Leading to death	1 (0.8)

Patients

- A total of 122 patients were enrolled, including 103 (84.4%) with SCLC and 19 (15.6%) with other NECs (**Table 1**).

Safety

- The most common grade ≥3 treatment-related adverse events (TRAEs) were hematological toxicities (**Figure 1**).
- Occurrence of grade ≥3 TRAEs and serious TRAEs increased with dose; the rates in the 2.4, 3.0, and 3.5 mg/kg cohorts were:
  - Grade ≥3 TRAEs: 33.3%, 70.3%, and 76.2%;
  - Serious TRAEs: 15.2%, 24.3%, and 26.2%.
- Treatment-related interstitial lung disease occurred in 9 (7.4%) patients (grade 1–2: 8 [6.6%]; grade ≥3: 1 [0.8%]).
- Only 2.5% of patients discontinued SHR-4849 due to TRAEs (**Table 2**).
- One patient died due to TRAE (pneumonia).

RESULTS

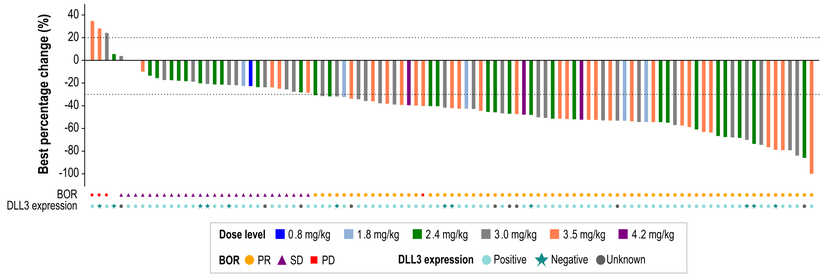


Figure 2. Best percentage change in target lesions in SCLC patients

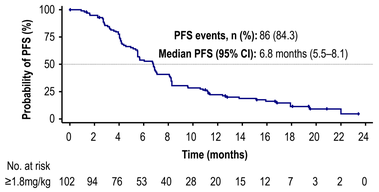


Figure 3. PFS in SCLC

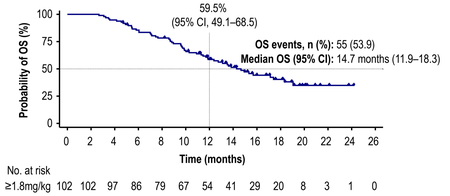


Figure 4. OS in SCLC

Table 3. Antitumor activity

	SCLC (≥1.8 mg/kg)				Other NECs (n=19)
	All (n=101)	2L Setting (n=51)	3L Setting (n=34)	With brain metastases (n=26)	
ORR, n (%; 95% CI)	69 (68.3%; 58.3–77.2)	37 (72.5%; 58.3–84.1)	21 (61.8%; 43.6–77.8)	20 (76.9%; 56.4–91.0)	10 (52.6%; 28.9–75.6)
Confirmed ORR, n (%; 95% CI)	55 (54.5%; 44.2–64.4)	31 (60.8%; 46.1–74.2)	17 (50.0%; 32.4–67.6)	17 (65.4%; 44.3–82.8)	7 (36.8%; 16.3–61.6)
DCR, n (%; 95% CI)	94 (93.1%; 86.2–97.2)	50 (98.0%; 89.6–100.0)	32 (94.1%; 80.3–99.3)	26 (100.0%; 86.8–100.0)	16 (84.2%; 60.4–96.6)

ORR, objective response rate. DCR, disease control rate.

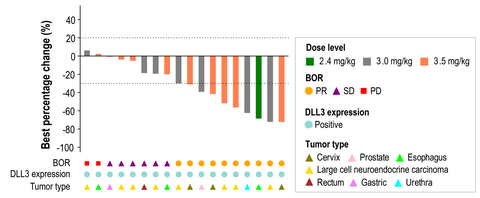


Figure 5. The best percentage change in target lesions in other NECs

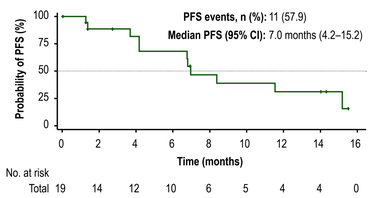


Figure 6. PFS in other NECs

Efficacy in SCLC (Table 3; Figures 2-5)

- **In patients receiving SHR-4849 at ≥1.8 mg/kg**:
  Confirmed ORR was 54.5%, and DCR was 93.1%;
  Median PFS was 6.8 months;
  Median OS was 14.7 months, and 12-month OS rate was 59.5%.
- **In patients in the 2L setting receiving SHR-4849 at ≥1.8 mg/kg:**
  Confirmed ORR was 60.8%, and DCR was 98.0%;
  Median PFS was 6.9 months (95% CI, 5.5–8.3);
  Median OS was 17.4 months (95% CI, 9.9–not reached), and 12-month OS rate was 60.0 (95% CI, 45.1–72.1).
- **In patients with brain metastases receiving SHR-4849 at ≥1.8 mg/kg:**
  Confirmed ORR was 65.4%, and DCR was 100.0%.

Efficacy in other NECs (Table 3; Figures 5-6)

- Confirmed ORR was 36.8%, and DCR was 84.2%;
- Median PFS was 7.0 months;
- 9-month OS rate was 82.4% (95% CI, 54.7–93.9).

CONCLUSIONS

- SHR-4849 (IDE849) has promising efficacy in patients with relapsed SCLC and other NECs, with clinically meaningful ORR and DCR and encouraging PFS and OS results.
- The safety profile is favorable, with few treatment discontinuations.
- Registrational studies are planned in SCLC and other NECs.

Acknowledgment: We would like to thank all patients and their families participating in the study, all investigators and research personnel who conducted the study, and the sponsor, Jiangsu Hengrui Pharmaceuticals, China.

Note: *SHR-4849 is being developed as IDE849 by IDEAYA Biosciences, worldwide outside of greater China.

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