

Efficacy and Safety of HLX43 (Anti-PD-L1 ADC) in Patients with Advanced Non-small Cell Lung Cancer

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Background

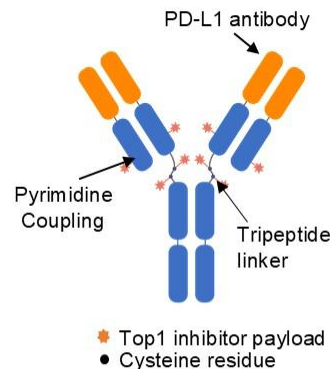


- The majority of NSCLC patients still face resistance, including both *de novo* and acquired resistance.^{1, 2}
- By specifically delivering cytotoxic payloads to tumor cells, antibody-drug conjugates (ADCs) represent an effective strategy for patients who are refractory to PD-1/PD-L1 therapies.³



- HLX43 demonstrated encouraging efficacy with a manageable safety in patients with advanced solid tumors, including CC, NPC, ESCC.

Molecular components of HLX43



- High-affinity, internalizable PD-L1 antibody
- Highly stable linker in circulating blood
- Cleavable and **TME-activatable tripeptide linker**
- Potent cytotoxic payload Top1 inhibitor (DAR=8)

Here, we present the pooled findings from the phase 1 (HLX43-FIH101) and the global phase 2 study (HLX43-NSCLC201) investigating HLX43 in patients with NSCLC.

CC, cervical cancer; DAR, drug-to-antibody ratio; ESCC, esophageal squamous cell carcinoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PD-1, programmed death-1; TME, tumor microenvironment; Top1, topoisomerase 1.

1. Sharma P, et al. Cell. 2023;186(8):1652-1669. 2. Doroshow DB, et al. Nat Rev Clin Oncol. 2021;18(6):345-362. 3. Fu Z, et al. Sig Transduct Target Ther. 2022;7(1):93.

Study design

HLX43-FIH101

Key inclusion criteria

- For **phase 1a**, histologically or cytologically confirmed advanced malignant **solid tumors**
- For **phase 1b**, histologically or cytologically confirmed advanced **NSCLC** refractory or not amenable to standard therapy

Screening

Phase 1a China only

4.0 mg/kg
3.0 mg/kg
2.5 mg/kg
2.0 mg/kg
1.0 mg/kg
0.5 mg/kg
HLX43, Q3W
n = 20

Phase 1b China only

3.0 mg/kg Q3W
n = 20

2.5 mg/kg Q3W
n = ~50

2.0 mg/kg Q3W
n = ~50

HLX43-NSCLC201

Key inclusion criteria

- Locally advanced or metastatic **NSCLC** confirmed by histology or cytology, and not suitable for radical treatment
- Has failed at least one prior line of standard therapy

R 1:1

Part A Global

2.5 mg/kg
HLX43, Q3W
n = 50

2.0 mg/kg
HLX43, Q3W
n = 50

Part B Global

Selected dose
HLX43, Q3W
n = 143

Pooled analysis to evaluate the efficacy in NSCLC patients

4.0 mg/kg HLX43, Q3W
n = 5

3.0 mg/kg HLX43, Q3W
n = 23

2.5 mg/kg HLX43, Q3W
n = 85

2.0 mg/kg HLX43, Q3W
n = 89

1.0 mg/kg HLX43, Q3W
n = 3

n, number; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; R, randomization.

Baseline characteristics

Data cutoff: Feb 28, 2026
Median follow-up: 7.5 months

Of the total patients, 5 were from the United States, 2 from Australia, and the remainder from China.

	NSCLC (n = 205) 1, 2, 2.5, 3, 4 mg/kg
Median age (range), years	60 (36–75)
Male, n (%)	147 (71.7)
ECOG PS, n (%)	
0	54 (26.3)
1	151 (73.7)
Smoking status, n (%)	
Never	90 (43.9)
Current	15 (7.3)
Former	100 (48.8)
NSCLC subtype	
Squamous	95 (46.3)
Non-squamous	110 (53.7)
EGFR wild type	63 (30.7)
EGFR mutant	47 (22.9)
Metastases, n (%)	
Bone	57 (27.8)
Liver	28 (13.7)
Brain	28 (13.7)

	NSCLC (n = 205) 1, 2, 2.5, 3, 4 mg/kg
PD-L1 expression by TPS [#] , n (%)	
TPS < 1%	85 (41.5)
1% ≤ TPS < 50%	66 (32.2)
TPS ≥ 50%	30 (14.6)
Not available	24 (11.7)
Prior lines of therapy, n (%)	
1	59 (28.8)
2	66 (32.2)
3	43 (21.0)
≥ 4	37 (18.0)
Median, (range)	2 (1–9)
Median, (range) for squamous	2 (1–7)
Median, (range) for non-squamous	2 (1–9)
EGFR wild type	2 (1–6)
EGFR mutant	3 (1–9)
Prior platinum-based chemo, n (%)	203 (99.0)
Prior immunotherapy, n (%)	168 (82.0)
Prior target therapy, n (%)	84 (41.0)
Prior docetaxel, n (%)	50 (24.4)

[#] Detected with SP263. chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

BICR assessed confirmed tumor response

	2.0 mg/kg			2.5 mg/kg			3.0 mg/kg		
Tumor response ^a	Sq-NSCLC (n = 33)	Nsq-NSCLC EGFR wild type (n = 23)	Nsq-NSCLC EGFR mutant (n = 13)	Sq-NSCLC (n = 29)	Nsq-NSCLC EGFR wild type (n = 19)	Nsq-NSCLC EGFR mutant (n = 16)	Sq-NSCLC (n = 8)	Nsq-NSCLC EGFR wild type (n = 6)	Nsq-NSCLC EGFR mutant (n = 7)
Complete response	0	0	0	0	0	0	0	0	0
Partial response	11 (33.3)	1 (4.3)	2 (15.4)	4 (13.8)	7 (36.8)	6 (37.5)	1 (12.5)	2 (33.3)	0
Stable disease	16 (48.5)	15 (65.2)	7 (53.8)	20 (69.0)	11 (57.9)	8 (50.0)	5 (62.5)	3 (50.0)	3 (42.9)
Progressive disease	5 (15.2)	5 (21.7)	3 (23.1)	5 (17.2)	0	1 (6.3)	1 (12.5)	0	1 (14.3)
Not evaluable	1 (3.0)	2 (8.7)	1 (7.7)	0	1 (5.3)	1 (6.3)	1 (12.5)	1 (16.7)	3 (42.9)
Objective response rate, % (95% CI)	33.3 (18.0, 51.8)	4.3 (0.1, 21.9)	15.4 (1.9, 45.4)	13.8 (3.9, 31.7)	36.8 (16.3, 61.6)	37.5 (15.2, 64.6)	12.5 (0.3, 52.7)	33.3 (4.3, 77.7)	0
Disease control rate, % (95% CI)	81.8 (64.5, 93.0)	69.6 (47.1, 86.8)	69.2 (38.6, 90.9)	82.8 (64.2, 94.2)	94.7 (74.0, 99.9)	87.5 (61.7, 98.4)	75.0 (34.9, 96.8)	83.3 (35.9, 99.6)	42.9 (9.9, 81.6)

Data are in n (%), unless specified.

^a as assessed by BICR according to RECIST v1.1 in response-evaluable patients;

BICR, blinded independent central review; CI, confidence interval; NSCLC, non-small cell lung cancer; Nsq, nonsquamous; sq, squamous.

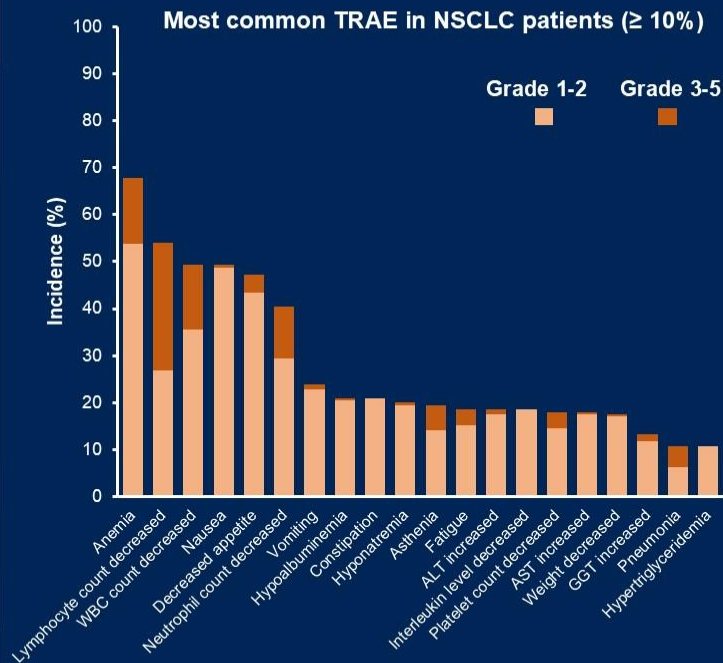
BICR assessed efficacy at the potential RP3D and in subgroups

	Confirmed ORR % (95% CI)	Confirmed DCR % (95% CI)	Median PFS (95% CI), month
NSCLC subtype			
Squamous 2.0 mg/kg (n = 33)	33.3 (18.0, 51.8)	81.8 (64.5, 93.0)	6.34 (4.07, 7.13)
Docetaxel failed ($\geq$ 3L) (n = 15)	46.7 (21.3, 73.4)	80.0 (51.9, 95.7)	6.90 (1.35, 8.28)
Non-squamous 2.5 mg/kg (n = 35)			
<i>EGFR</i> wild type (n = 19)	36.8 (16.3, 61.6)	94.7 (74.0, 99.9)	6.67 (4.14, 8.25)
<i>EGFR</i> mutant (n = 16)	37.5 (15.2, 64.6)	87.5 (61.7, 98.4)	5.55 (4.04, NE)
Brain metastasis			
Yes (n = 10)	20.0 (2.5, 55.6)	90.0 (55.5, 99.7)	5.36 (1.18, NE)
No (n = 58)	37.9 (25.5, 51.6)	86.2 (74.6, 93.9)	6.34 (4.30, 7.16)
PD-L1 expression by TPS			
TPS $\geq$ 1% (n = 29)	37.9 (20.7, 57.7)	89.7 (72.6, 97.8)	6.80 (4.04, 7.13)
TPS < 1% or NE (n = 39)	33.3 (19.1, 50.2)	84.6 (69.5, 94.1)	5.49 (4.76, 8.25)

BICR, Blinded Independent Central Review; CI, confidence interval; DCR, disease control rate; EGFR, epidermal growth factor receptor; L, line; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Safety and tolerability

Event, n (%)	1.0 mg/kg (n = 3)	2.0 mg/kg (n = 89)	2.5 mg/kg (n = 85)	3.0 mg/kg (n = 23)	4.0 mg/kg (n = 5)	NSCLC (n = 205)
Any TRAE	3 (100.0)	85 (95.5)	83 (97.6)	23 (100.0)	5 (100.0)	199 (97.1)
Grade ≥ 3	0	37 (41.6)	46 (54.1)	14 (60.9)	3 (60.0)	100 (48.8)
Most common Grade ≥ 3 ($\geq 10\%$) [#]						
Lymphocyte count decreased	0	18 (20.2)	29 (34.1)	8 (34.8)	1 (20.0)	56 (27.3)
Anemia	0	7 (7.9)	17 (20.0)	2 (8.7)	3 (60.0)	29 (14.1)
WBC count decreased	0	3 (3.4)	17 (20.0)	5 (21.7)	3 (60.0)	28 (13.7)
Neutrophil count decreased	0	2 (2.2)	13 (15.3)	6 (26.1)	2 (40.0)	23 (11.2)
TRAE leading to Tx interruption	0	27 (30.3)	37 (43.5)	9 (39.1)	5 (100.0)	78 (38.0)
TRAE leading to Tx discontinuation	0	5 (5.6)	7 (8.2)	4 (17.4)	0	16 (7.8)
TRAE leading to Tx reduction	0	3 (3.4)	13 (15.3)	4 (17.4)	5 (100.0)	25 (12.2)
TRAE leading to death	0	0	1 (1.2)	1 (4.3)	0	2 (1.0) *



[#] Occurring in at least 10% of all the 205 patients. * Due to respiratory failure (n = 1 in the 2.5 mg/kg group), and pneumonia (n = 1 in the 3.0 mg/kg group).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; NSCLC, non-small cell lung cancer; TRAE, treatment-related adverse event; Tx, treatment; WBC, white blood cell.

Conclusions

- **Efficacy at RP3D dose**

- ✓ **IO- and chemo-treated Squamous NSCLC**

- ✓ cORR: 33.3%; mPFS: 6.34 months

- ✓ Docetaxel failed ($\geq 3L$) cORR: 46.7%; mPFS: 6.90 months

- ✓ **IO- and chemo-treated, *EGFR* WT Non-squamous NSCLC**

- ✓ cORR: 36.8%; mPFS: 6.67 months

- **Biomarker independent:** efficacy observed irrespective of *EGFR* mutation status or PD-L1 expression level
- **Favorable safety profile with low hematologic toxicities**

**HLX43 demonstrated promising efficacy along with manageable safety in advanced NSCLC.
Further investigation of HLX43 for this disease indication is warranted.**

chemo, chemotherapy; cORR, confirmed objective response rate; DCR, disease control rate; EGFR, epidermal growth factor receptor; IO, immunotherapy; L, line; NSCLC, non-small-cell lung cancer; mPFS, median progression-free survival; PD-L1, programmed death-ligand 1; RP3D, recommended phase 3 dose; WT, wild type.

Lay Summary

What did this research tell us?

- HLX43 (an antibody-drug conjugate) provided promising clinical and survival benefits in patients with heavily pretreated advanced NSCLC, regardless of subtypes, brain metastasis, and PD-L1 expression
- HLX43 was well tolerated

Who does this research impact?

- People with advanced NSCLC, their caregivers and clinicians treating NSCLC

What does this mean for patients right now?

- HLX43 may potentially be a broad-spectrum treatment option for patients with previously treated advanced NSCLC regardless of subtypes, presence of brain metastasis and PD-L1 expression level.

Where can I access more information?

- Information on the medicine used in this study and the people who could participate can be found here: <https://clinicaltrials.gov/study/NCT06115642>; <https://clinicaltrials.gov/study/NCT06907615>

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