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Safety, Tolerability and Preliminary Efficacy of Anti-PD-L1 ADC HLX43 in Advanced or Metastatic Non-small Cell Lung Cancer: A Phase 1 Study

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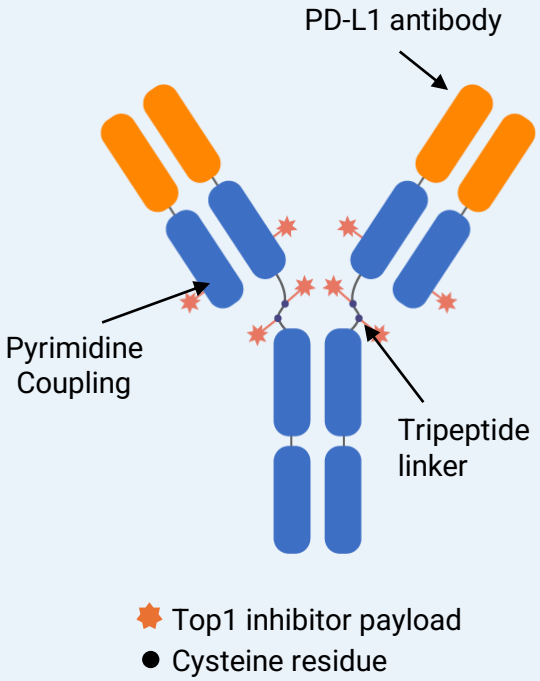
Background

- Despite the approval of multiple PD-1/PD-L1 inhibitors for advanced NSCLC, the majority of 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 is the second PD-L1-targeting ADC in global development.

Molecular components of HLX43



Key Features

- 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)

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.
DAR, drug-to-antibody ratio; NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death 1 ligand 1; PD-1, programmed cell death 1; TME, tumor microenvironment; Top1, topoisomerase 1.

Study design

An open-label, first-in-human, phase 1 clinical trial (NCT06115642)

Key inclusion criteria:

- Age ≥18 years;
- ECOG PS of 0 or 1;
- 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;
- Measurable disease according to RECIST v1.1.

Phase 1a dose escalation cohorts

HLX43
4.0 mg/kg
3.0 mg/kg
2.5 mg/kg
2.0 mg/kg
1.0 mg/kg
0.5 mg/kg
IV, Q3W

N = 3–6 for each cohort

Primary endpoints

- Proportion of patients with DLT
- MTD

Phase 1b dose expansion cohorts

Cohort 1	Cohort 2	Cohort 3
HLX43 2.0 mg/kg IV, Q3W	HLX43 2.5 mg/kg IV, Q3W	HLX43 3.0 mg/kg IV, Q3W
N = 20	N = 20	N = 20

Primary endpoints

- RP2D
- ORR as assessed by BICR per RECIST v1.1

DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; BICR, Blinded Independent Central Review; IV, intravenous; MTD, maximum tolerable dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; Q3W. every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase II dose.

Baseline demographic and disease characteristics

Here we present results in the NSCLC patients (phase 1a + phase 1b 2.0 and 2.5 mg/kg cohorts).

Data cutoff: Jun 28, 2025
Median follow-up:
9.0 months (95% CI 6.9–9.3)
ITT: N=56
SS: N=56
RES: N=54*

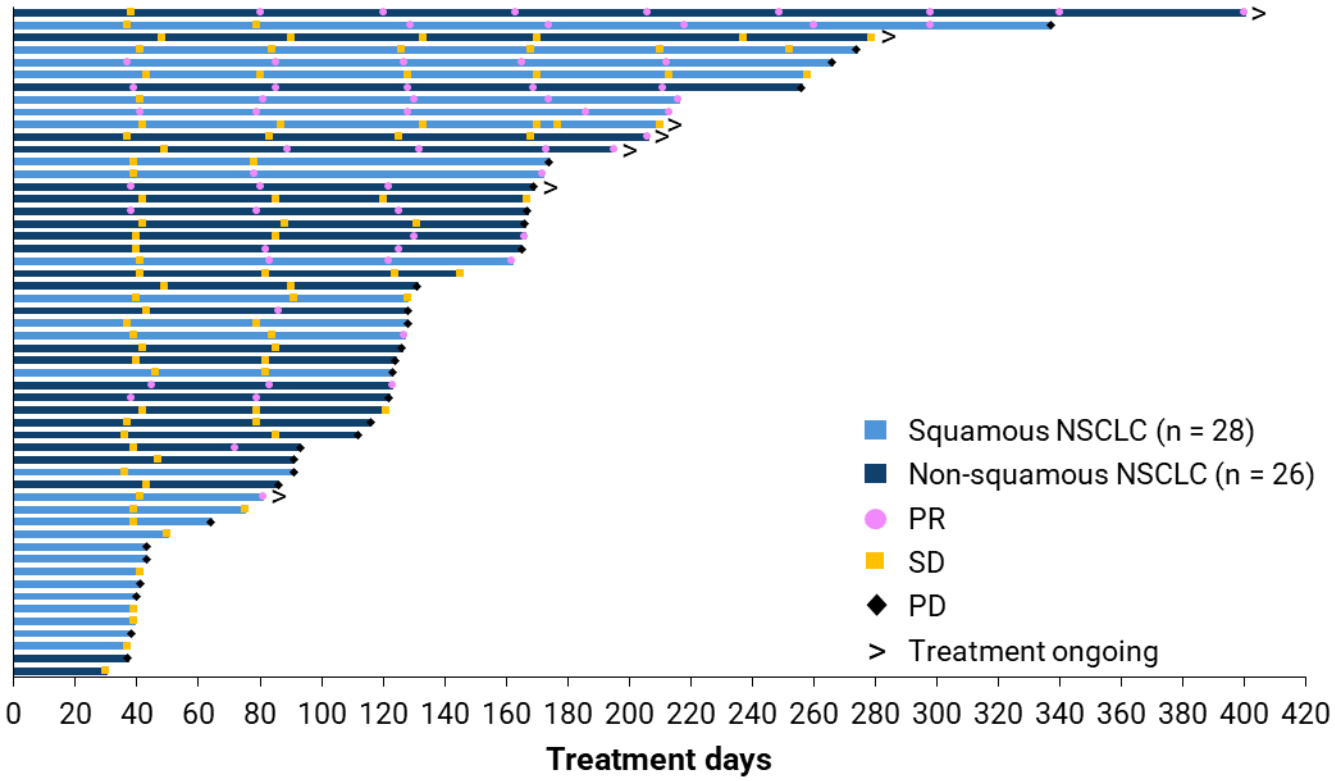
	NSCLC (n = 56)
Median age (range), years	60 (39–73)
Male, n (%)	38 (67.9)
ECOG PS, n (%)	
0	19 (33.9)
1	37 (66.1)
Smoking status, n (%)	
Never	31 (55.4)
Current	2 (3.6)
Former	23 (41.1)
NSCLC subtype	
Squamous	29 (51.8)
Docetaxel failed (≥ 3L)	10 (34.5)
Non-squamous	27 (48.2)
EGFR Wild type	15 (55.6)
EGFR Mutant	12 (44.4)
Metastases, n (%)	
Bone	14 (25.0)
Brain	11 (19.6)
Liver	4 (7.1)

	NSCLC (n = 56)
PD-L1 expression by TPS#, n (%)	
TPS ≥ 1%	32 (57.1)
TPS < 1%	23 (41.1)
Not available	1 (1.8)
Prior lines of therapy	
1	15 (26.8)
2	16 (28.6)
3	13 (23.2)
≥ 4	12 (21.4)
Median, range	2 (1–7)
Median, range for squamous	3 (1–7)
Median, range for non-squamous	2 (1–6)
EGFR Wild type	2 (1–6)
EGFR Mutant	2 (1–6)
Prior platinum-based chemo, n (%)	54 (96.4)
Prior immunotherapy, n (%)	50 (89.3)
Prior target therapy, n (%)	26 (46.4)
Prior docetaxel, n (%)	14 (25.0)

* Two patients without post-baseline tumor assessments were excluded from RES. # Detected with SP263.
CI, confidence interval; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; RES, response evaluable set; SS, safety set; TPS, tumor proportion score.

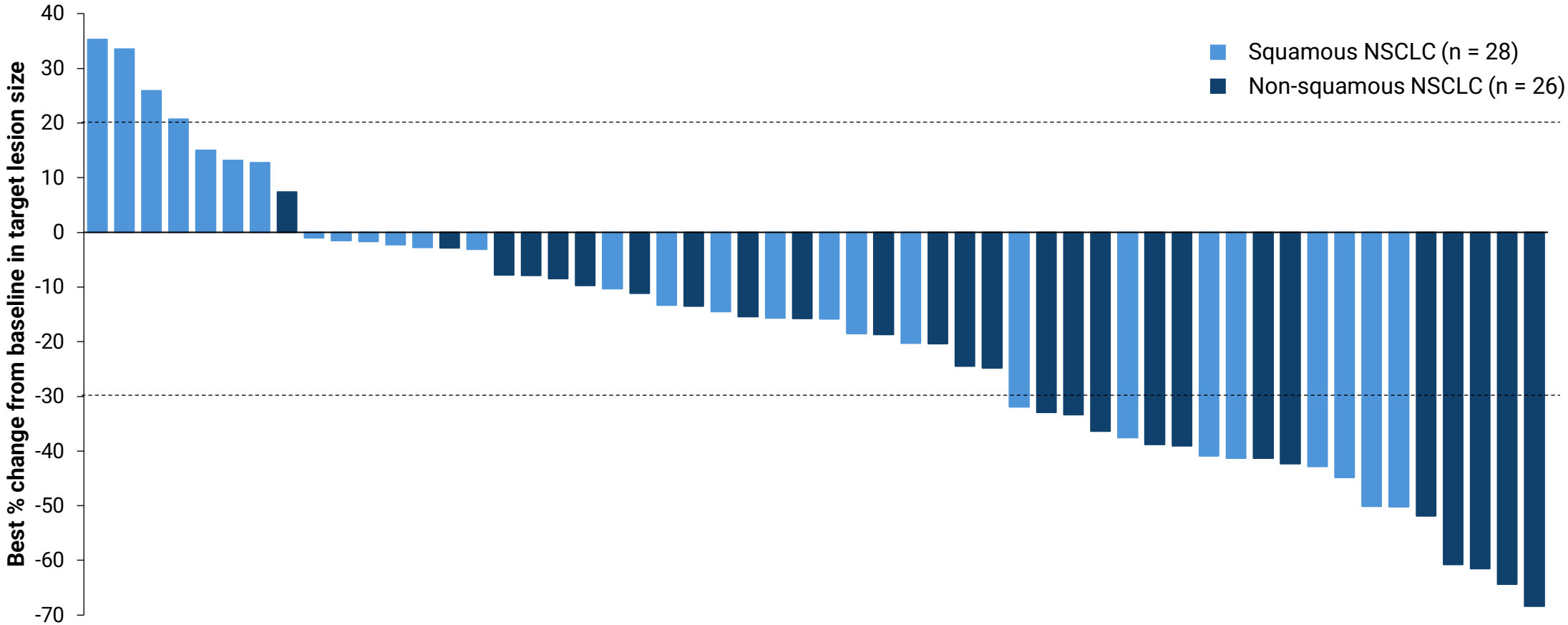
Efficacy in NSCLC patients per RECIST v1.1.

Efficacy*	NSCLC (n = 54)
CR, n (%)	0
PR, n (%)	20 (37.0)
SD, n (%)	27 (50.0)
PD, n (%)	6 (11.1)
NE, n (%)	1 (1.9)
ORR, % (95% CI)	37.0 (24.3–51.3)
DCR, % (95% CI)	87.0 (75.1–94.6)
mPFS, months (95% CI)	5.4 (4.0–5.8)
With brain metastasis (n=11)	5.4 (4.0–9.0)



*Unconfirmed tumor response among the 54 response-evaluable patients as assessed by investigator; 2 patients did not have post-baseline tumor assessment and were excluded in efficacy analysis.
CI, confidence interval; CR, complete response; DCR, disease control rate; mPFS, median progression-free survival; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Tumor response in NSCLC patients per RECIST v1.1.



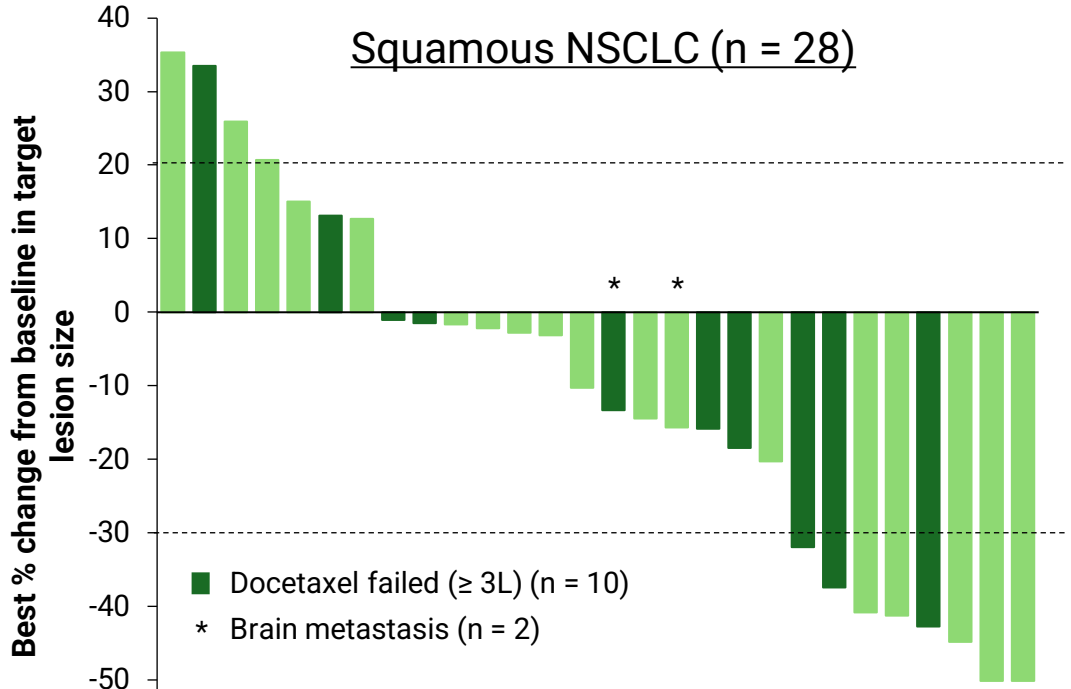
Tumor response among the 54 response-evaluable patients as assessed by investigator; 2 patients did not have post-baseline tumor assessment and were excluded in efficacy analysis.
NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Subgroup analysis of tumor response per RECIST v1.1.

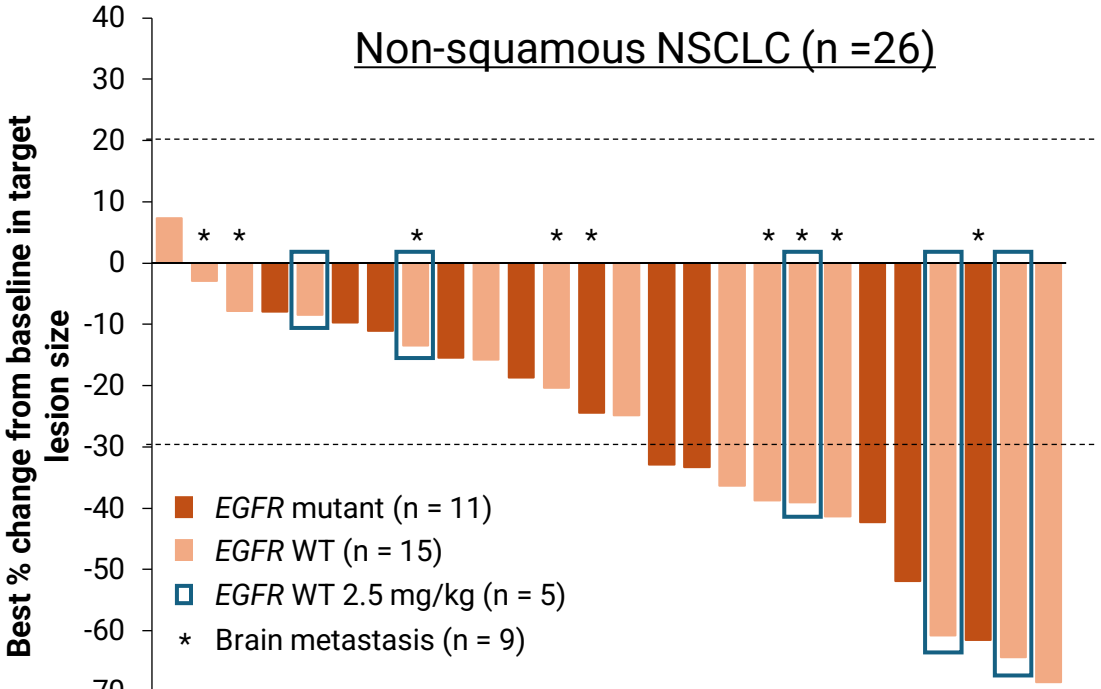
Tumor response*	ORR % (95% CI)	DCR % (95% CI)
NSCLC subtype		
Squamous (n = 28)	28.6 (13.2–48.7)	82.1 (63.1–93.9)
Docetaxel failed (≥ 3L) (n = 10)	30.0 (6.7–65.3)	80.0 (44.4–97.5)
2.0 mg/kg dose level (n = 15)	40.0 (16.3–67.7)	73.3 (44.9–92.2)
Non-squamous (n = 26)	46.2 (26.6–66.6)	96.2 (80.4–99.9)
EGFR Wild type (n = 15)	46.7 (21.3–73.4)#	93.3 (68.1–99.8)
2.5 mg/kg dose level (n = 5)	60.0 (14.7–94.7)#	80.0 (28.4–99.5)
EGFR Mutant (n = 11)	45.5 (16.7–76.6)	90.9 (58.7–99.8)
Brain metastasis		
Yes (n = 11)	36.4 (10.9–69.2)#	100 (71.5–100)
No (n = 43)	37.2 (23.0–53.3)	83.7 (69.3–93.2)
PD-L1 expression by TPS‡		
TPS ≥ 1% (n = 32)	34.4 (18.6–53.2)	87.5 (71.0–96.5)
TPS < 1% (n = 21)	38.1 (18.1–61.6)	85.7 (63.7–97.0)

* Unconfirmed tumor response assessed by investigator. # Confirmed tumor response as assessed by investigator. ‡ PD-L1 expression in one patient was not evaluable and was not included in the analysis.
CI, confidence interval; DCR, disease control rate; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed cell death 1 ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.

Subgroup analysis of tumor response per RECIST v1.1.



Docetaxel failed(≥ 3L): ORR 30.0% (95 CI 6.7–65.3)
DCR 80.0% (95 CI 44.4–97.5)

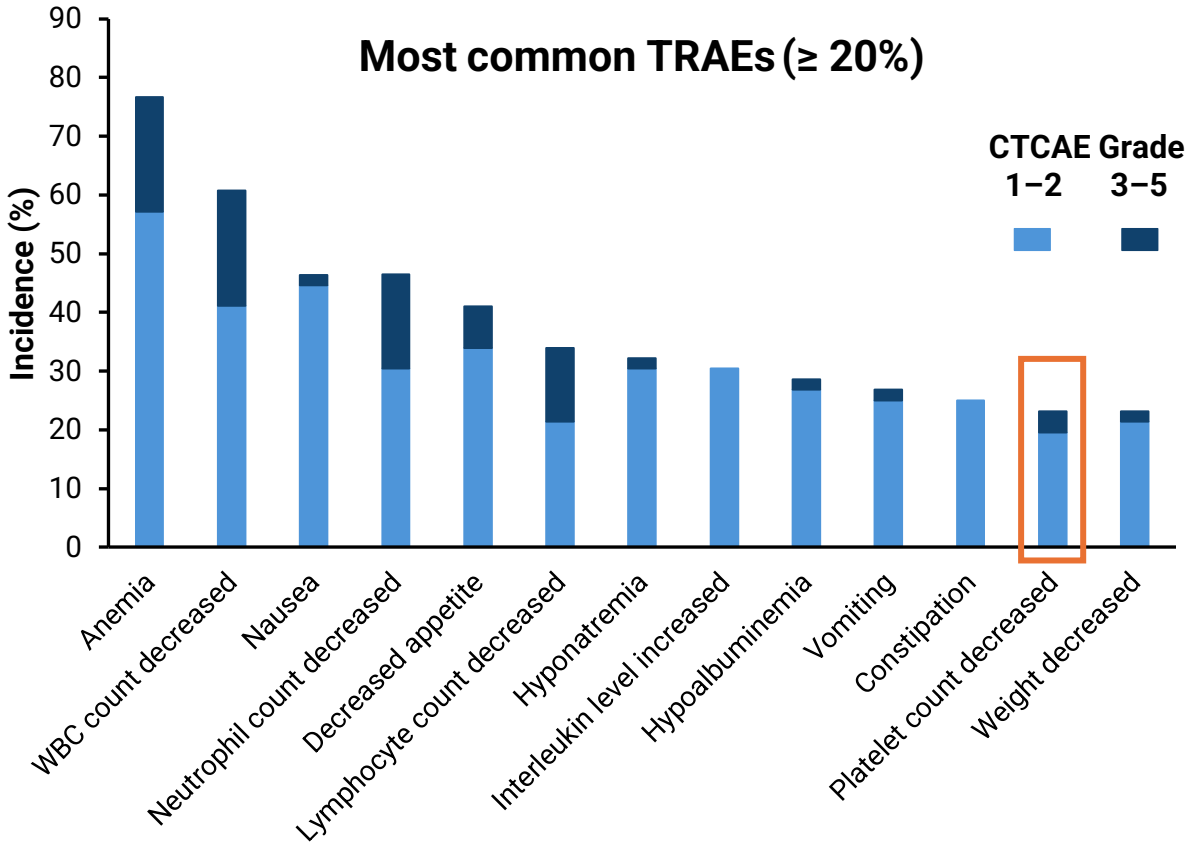


EGFR WT 2.5 mg/kg: cORR 60.0% (95 CI 14.7–94.7)
DCR[#] 80.0% (95 CI 28.4–99.5)

Tumor response among the 54 response-evaluable patients as assessed by investigator; 2 patients did not have post-baseline tumor assessment and were excluded in efficacy analysis.
[#] 1 case of stable disease did not meet the requirement of minimum evaluation duration and was counted as not evaluable in tumor assessment.
cORR, confirmed objective response rate; DCR, disease control rate; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; WT, wild type.

Safety and tolerability

Safety*	NSCLC (n = 56)
Any TRAE, n (%)	56 (100)
Grade ≥3	26 (46.4)
Most common Grade ≥3 (≥ 10%)	
Anemia	11 (19.6)
WBC count decreased	11 (19.6)
Neutrophil count decreased	9 (16.1)
Lymphocyte count decreased	7 (12.5)
TRAE leading to Tx interruption, n (%)	24 (42.9)
TRAE leading to Tx discontinuation, n (%)	5 (8.9)
TRAE leading to Tx reduction, n (%)	10 (17.9)
TRAE leading to death, n (%)	1 (1.8)#

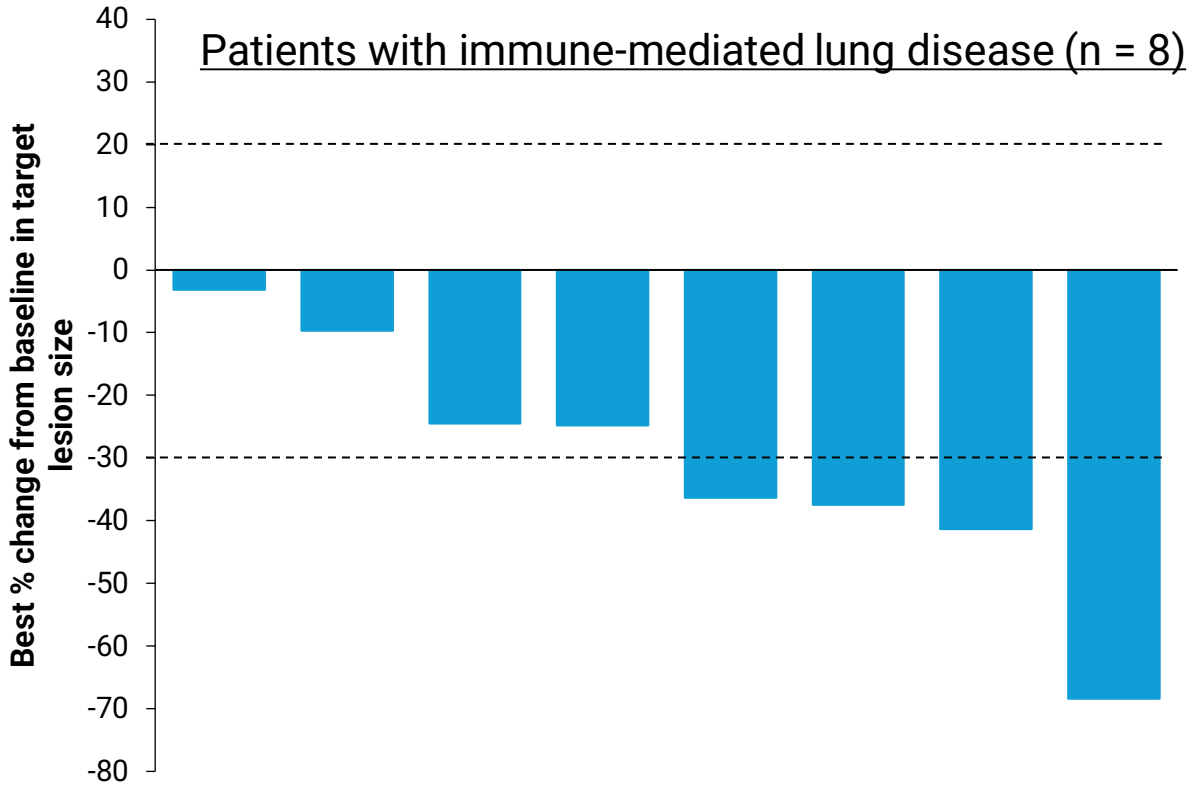


* Interstitial lung disease was reported in 2 patients as grade 3; both are in recovery. # From 2.5 mg/kg cohort (squamous NSCLC): respiratory failure.
CTCAE, Common Terminology Criteria for Adverse Events; TRAE, treatment-related adverse event; Tx, treatment; WBC, white blood cell.

Immune-related adverse events

	NSCLC (n = 56)
Any irAE, n (%)	12 (21.4)
Most common irAEs (≥ 10%)	
Immune-mediated lung disease	8 (14.3)
Grade 2	3 (5.4)
Grade 3	4 (7.1)
Grade 4	1 (1.8)
Grade 5	0

Confirmed ORR of 50% and 100% tumor shrinkage in patients with immune-mediated lung disease indicated that **HLX43 is capable of eliciting immunotherapeutic effects** in addition to payload-mediated cytotoxic tumor cell killing.



irAE, immune-related adverse event; ORR, objective response rate.

Conclusions

- **Outstanding efficacy in NSCLC**
  - ✓ **IO- and chemo-treated Squamous NSCLC (≥ 4L)**
    - ✓ ORR: 28.6%
    - ✓ Docetaxel failed (≥ 3L) ORR: 30%
  - ✓ **IO- and chemo-treated, *EGFR* WT Non-squamous NSCLC (≥ 3L)**
    - ✓ cORR: 46.7%
    - ✓ 2.5 mg/kg cORR: 60%
  - ✓ **NSCLC with brain metastasis:** cORR 36.4% (4/11); DCR 100%
- **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 or metastatic 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; ORR, objective response rate; PD-L1, programmed cell death 1 ligand 1; WT, wild type.

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Thank You

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