Phase 1a/1b first-in-human study of HLX316/E-688, a first-in-class B7-H3-targeted sialidase for advanced solid tumors

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Hypersialylation Drives Tumor Immune Evasion

Abstract

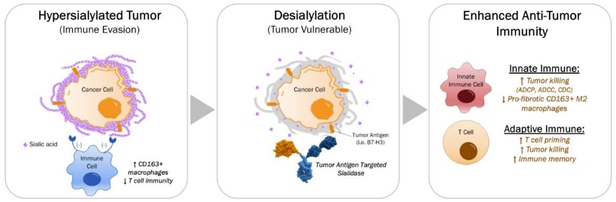
Tumor hypersialylation is an immune-evasion mechanism independent of the PD-1/PD-(L)1 axis: tumor sialoglycans engage multiple inhibitory receptors on immune cells, suppressing anti-tumor T cell immunity, and driving macrophages to pro-tumor phenotypes (CD163+). HLX316/E-688 is a first-in-class targeted sialidase, an engineered human sialidase fused to an anti-B7-H3 single-domain antibody via a functional IgG1 Fc, designed to remove immunosuppressive sialoglycans from the tumor while directing antibody-mediated tumor killing. In preclinical studies, B7-H3 targeting increased desialylation potency 5,000–10,000-fold and extended its durability relative to untargeted sialidase. NCT07541534 is a multicenter, open-label, first-in-human Phase 1a/1b study of HLX316/E-688 monotherapy in patients with platinum-resistant ovarian cancer or other B7-H3-expressing advanced solid tumors. Phase 1a uses accelerated titration followed by 3+3 dose escalation (1, 3, 10, 20, and 30 mg/kg IV once weekly), with backfill cohorts at two candidate recommended doses. Phase 1b will randomize approximately 40 patients with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer 1:1 to two candidate RP2Ds. Primary endpoints are DLT incidence and MTD (Phase 1a) and investigator-assessed ORR with RP2D selection (Phase 1b); secondary endpoints include safety, pharmacokinetics, desialylation pharmacodynamics, and B7-H3 and sialylation biomarkers. The first patient was dosed in May 2026, and enrollment is ongoing.

KEY POINTS

- First-in-class B7-H3-targeted sialidase: tumor-selective desialylation plus Fc-mediated tumor killing
- First-in-human Phase 1a/1b study (NCT07541534); first patient dosed May 2026
- Lead indication: platinum-resistant ovarian cancer, with high B7-H3 and hypersialylation co-expression

Hypersialylation: A Distinct, Addressable Axis of Immune Evasion

- Cancer cells upregulate surface sialoglycans, which engage multiple inhibitory receptors on immune cells, suppressing anti-tumor T cell immunity, and driving macrophages to pro-tumor phenotypes (CD163+)
- Tumor hypersialylation correlates with poor outcomes across >50 independent studies and drives resistance to IO, chemotherapy, and radiotherapy
- Siglec redundancy defeats single-receptor blockade; enzymatic desialylation disrupts all interactions at once

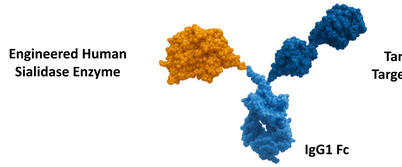


Abbreviations

ADA, anti-drug antibody; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; AE, adverse event; B7-H3, B7 homolog 3 (CD276); CA-125, cancer antigen 125; CI, confidence interval; CR, complete response; CRPC, castration-resistant prostate cancer; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; Fc, fragment crystallizable; GCP, Good Clinical Practice; GLP, Good Laboratory Practice; ICH, International Council for Harmonisation; IgG1, immunoglobulin G1; IO, immuno-oncology; iORR, immune ORR; iRECIST, immune RECIST; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; mpk, mg/kg; MTD, maximum tolerated dose; NAb, neutralizing antibody; NCI, National Cancer Institute; NHP, non-human primate; NOAEL, no-observed-adverse-effect level; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PI, principal investigator; PK, pharmacokinetics; PR, partial response; pt, patient; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SAE, serious adverse event; SCLC, small cell lung cancer; SD, stable disease; Siglec, sialic acid-binding immunoglobulin-like lectin; SRC, Safety Review Committee; TBD, to be determined; TTR, time to response.

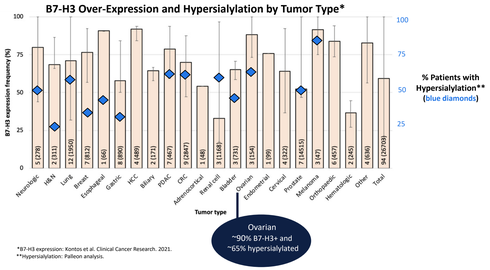
HLX316/E-688: a B7-H3 Targeted Sialidase

HLX316/E-688 Targets Sialidase Enzyme to B7-H3 Positive Tumors



- **Potency:** 5,000–10,000-fold greater desialylation than untargeted sialidase, lasting 5–7 days
- **Function:** IgG1 Fc drives ADCC and ADCP of B7-H3+ tumor cells
- **Efficacy:** 87.5% single-agent tumor growth inhibition in humanized A375 xenografts vs 38% (anti-PD-1) and 15% (untargeted sialidase)
- **Safety:** well-tolerated in GLP 1-month NHP toxicology; NOAEL 150 mg/kg/week

B7-H3 and Hypersialylation Are Broadly Co-Expressed



*B7-H3 expression: Kontos et al. Clinical Cancer Research. 2021.
**Hypersialylation: Palleon analysis.

- B7-H3 is broadly overexpressed across solid tumors; elevated expression correlates with advanced stage and metastatic disease
- Hypersialylation co-occurs with B7-H3 overexpression across multiple tumor types and independently correlates with poor clinical outcome in over a dozen indications
- Priority indications where both targets are highly co-expressed:
  - Ovarian cancer: ~90% B7-H3 expression; ~65% hypersialylated → first-in-human indication
  - Lung, prostate, and GI tumors: high co-expression rates → priority expansion indications

NCT07541534: First-in-Human Phase 1a/1b Study

Enrolling at Phase 1 Centers in Mainland China

Institution	City	Principal investigator(s)
Cancer Hospital of Shandong First Medical University (Shandong Cancer Institute, Shandong Cancer Hospital)	Jinan	Jinming Yu / Yuping Sun
Central Hospital Affiliated to Shandong First Medical University	Jinan	Qing Wen / Meili Sun
Obstetrics and Gynecology Hospital of Fudan University	Shanghai	Jiaqi Lu
Chongqing Cancer Hospital	Chongqing	Yongsheng Li

Key Eligibility: Platinum-Resistant Ovarian Cancer or B7-H3-Expressing Advanced Solid Tumors

Eligible tumor types

- Platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer (B7-H3 testing not required)
- Other advanced or metastatic solid tumors with B7-H3 expression by IHC

Ovarian cancer cohorts

- Epithelial histology (excludes non-epithelial, borderline, mucinous, malignant Brenner, undifferentiated)
- Progression ≤6 months after last platinum (CA-125, clinical, or radiographic)
- Received ≥2 prior lines of standard treatment for metastatic disease, including ≥1 platinum regimen, or were intolerant to such standard treatments

All patients

- Age ≥18 years; progressed on, intolerant of, or declined ≥1 standard therapy, or none available
- ≥1 measurable lesion (RECIST v1.1); ECOG PS 0–1; life expectancy >3 months
- Archival or fresh tumor tissue for B7-H3 testing

Endpoints are Safety, RP2D, and Antitumor Activity

- **Phase 1a: escalation and backfill**
- **Primary:** DLTs (21-day window); MTD
- **Secondary:** safety (AEs, SAEs, labs, ECG, vital signs, physical examination); investigator-assessed ORR, DCR, DOR, TTR, PFS; OS; iORR (iRECIST); PK; immunogenicity (ADA/NAb); PD biomarkers (cytokine profiling, immune/tumor cell desialylation, TME modulation, etc.)
- **Phase 1b: randomized expansion**
- **Primary:** investigator-assessed ORR (RECIST v1.1); RP2D selection integrating safety, PK/ADA profiles, and potential clinical efficacy (including ORR and PFS, etc.)
- **Secondary:** DCR, DOR, TTR, PFS, OS; safety (AEs, SAEs, labs, ECG, vital signs, physical examination); PK; immunogenicity (ADA/NAb); PD biomarkers (cytokine profiling, immune/tumor cell desialylation, TME modulation, etc.)
- **Potential Biomarker (both phases):** baseline tumor B7-H3 expression by IHC

Statistical Methods

- **Sample size:** up to ~93 patients (Phase 1a escalation, 13–30; backfill, 12–18; Phase 1b, ~40). Phase 1b is not powered for formal hypothesis testing and is sized to inform dose selection.
- **MTD:** highest dose level with ≤1 DLT among 6 DLT-evaluable patients.
- **Efficacy:** ORR (confirmed CR/PR) and DCR (confirmed CR, PR, or SD) per RECIST v1.1 and iRECIST, with 95% Clopper-Pearson CIs; PFS, OS, DOR, and TTR by Kaplan-Meier.
- **Safety:** AEs coded by MedDRA, graded per NCI CTCAE v6.0, and summarized by dose level.

Study Design and Trial Status

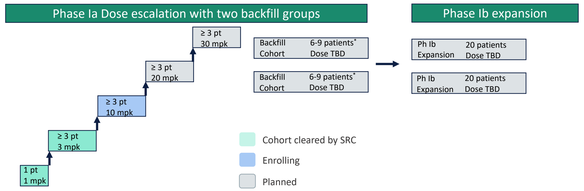
Study Design: Escalation, Backfill, and Randomized Expansion

Phase 1a: Dose escalation with backfill at two highest tolerated dose groups

- 1 mg/kg sentinel, then 3+3 escalation through 3, 10, 20, and 30 mg/kg once weekly
- backfill (6–9 patients each) at two candidate RP2Ds* based on MTD

Phase 1b: Randomized dose expansion of selected dose groups with a focus on ovarian cancer

- Up to 40 patients with platinum-resistant ovarian cancer randomized 1:1 to two RP2Ds;
- Each arm initially enrolls 10 patients with option to expand to 20 patients after confirmed ORR



*May increase to 20 patients or initiate a randomized trial if efficacy signals are observed in the first 12 patients

Trial Status: Dose Escalation Ongoing

- First patient dosed May 2026; 6 patients dosed as of October 23, 2026
- 4 sites active; more to open for backfill and expansion
- Safety, PK, and efficacy data will be reported as escalation matures

Conclusions

- HLX316/E-688 pairs tumor-selective desialylation with Fc-mediated killing, overcoming the potency and durability limits of untargeted sialidase
- Escalation with backfill and a randomized two-dose expansion selects the RP2D on safety and activity, not MTD alone
- Enrolling since May 2026 in mainland China, with platinum-resistant ovarian cancer as the lead indication

Ethics, Funding, Disclosures, and References

Ethics: approved by the ethics committees of all participating institutions; conducted per the Declaration of Helsinki and ICH-GCP. All patients provided written informed consent.
Investigational status: HLX316/E-688 is an investigational agent not approved by any regulatory authority.
Funding: sponsored by Shanghai Henlius Biotech, Inc.; the sialidase fusion component is licensed from Palleon Pharmaceuticals.
Disclosures: authors affiliated with Palleon Pharmaceuticals and Shanghai Henlius Biotech are employees of those companies.
Acknowledgments: we thank the patients, their families, and the investigators and site staff.

References

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