Hanjugator camptothecin platform: Effective, low-toxicity design maximizing antibody functionality and delivering potential best-in-class cMet/EGFR bispecific antibody-drug conjugate

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Background:

High toxin potency in antibody-drug conjugates (ADCs) limits clinical doses to those below optimal antibody levels, diminishing signal blockade potential and emphasizing chemotherapeutic effects. To address this, we developed Hanjugator, a modular camptothecin-based linker-payload platform with tunable potency—from threefold lower than deruxtecan to comparable with exatecan—broadening therapeutic window while preserving antibody functionality. We applied medium-potency payload to an EGFR/cMet bispecific ADC, a target combination requiring higher doses for optimal receptor occupancy and efficacy.

Methods:

Cytotoxicity of toxin candidates and ADCs was assessed by CTG in immortalized cell lines. ADC binding/internalization was evaluated by flow cytometry on cells with varying antigen levels. Pharmacokinetics of Hanjugator-based ADC were determined in rats after a single 5 mg/kg IV dose. Bystander killing was quantified by co-incubating antigen-positive and -negative (Jurkat) cells, with Jurkat viability measured by CTG. In vivo efficacy of EGFR/cMet ADC was tested in xenograft models (LU387, SW48, HT29, NCI-H1975). Preliminary toxicology in cynomolgus monkeys used doses of 30 or 60 mg/kg every three weeks.

Results:

The Hanjugator platform provides highly hydrophilic linker-payloads compatible with non-standard, hydrophobic antibodies and shows strong thermal, plasma, and freeze-thaw stability. These conjugates have over 10-fold stronger bystander killing than deruxtecan and outperform several clinical-stage linker-payload systems in efficacy, despite some having higher intrinsic payload potency. Its wide toxin potency range expands applications. Medium-potency linker-payload, conjugated to an EGFR/cMet bispecific antibody, induced significant tumor regression at a single 3 mg/kg dose in multiple xenograft models and outperformed AZD9592 in the HT29 CDX model. Preliminary toxicology showed our EGFR/cMet ADC was well tolerated in cynomolgus after 3 doses at 60 mg/kg Q3W.

Conclusion:

We developed Hanjugator, a modular camptothecin-based linker-payload platform with tunable potency for diverse targets and ADC programs, enabling optimized dosing and broader clinical use. Our EGFR/cMet bispecific ADC exhibits a superior therapeutic index, maximizing antibody-mediated signaling blockade, and positions as best-in-class molecule with Investigational New Drug submission in Q1 2026.

Maximizing Antibody Function of ADC by Fine Tune Payload potency

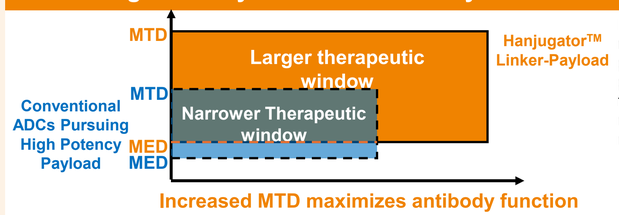


Figure 1. Schematic representation illustrating how precisely calibrated payload potency improves ADC therapeutic window by maximizing antibody-mediated pathway blockade.

Wide Range of Toxin Candidate Potency Levels for Diverse Applications

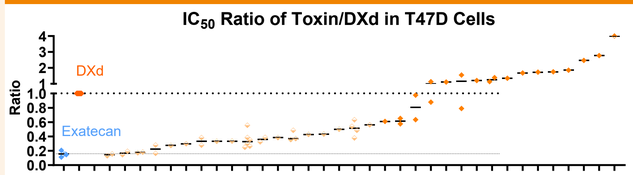


Figure 2. Cytotoxicity of Hanjugator candidate toxins on T47D cells assessed via 96-hour CTG assay. Y-axis: IC_{50} ratio of candidate toxin to that of DXd.

Topoisomerase I Inhibition of Hanjugator Toxin *in vitro*

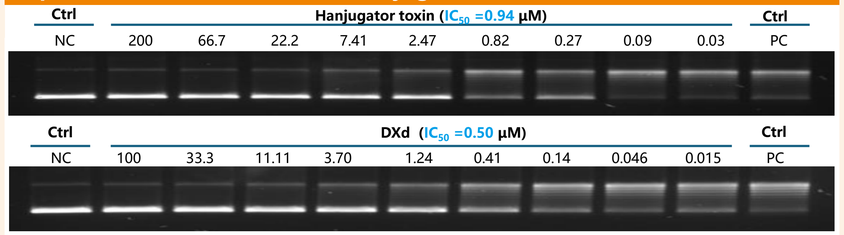
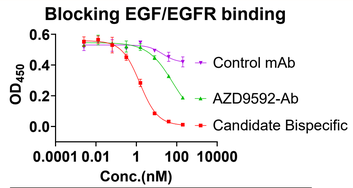
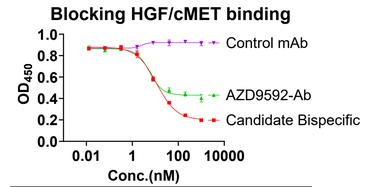


Figure 3. *In vitro* inhibition of topoisomerase I by Hanjugator toxin compared to DXd. It exhibited nearly two-fold weaker enzymatic inhibition than that of DXd.

Superior Ligand-Blocking Potency of an Anti-EGFR/cMet Bispecific Relative to Benchmark



Ligand: EGF	Candidate Bispecific	AZD9592 Ab	Control mAb
IC_{50} (nM)	1.5	61.9	-



Ligand: HGF	Candidate Bispecific	AZD9592 Ab	Control mAb
IC_{50} (nM)	11.4	5.6	-

Figure 4. Ligand-blocking activity of the cMET/EGFR bispecific antibody was evaluated by ELISA and compared head-to-head with an AZD9592 analog. The bispecific antibody showed stronger inhibition of both EGFR–EGF (A) and HGF–cMET (B) interactions than AZD9592.

cMET/EGFR Bispecific ADC Exhibited Enhanced Target-Mediated Cytotoxicity and Bystander Killing

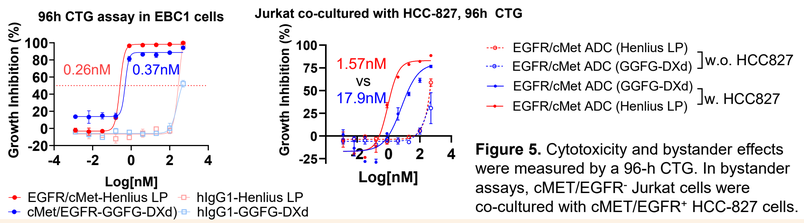


Figure 5. Cytotoxicity and bystander effects were measured by a 96-h CTG. In bystander assays, cMET/EGFR⁻ Jurkat cells were co-cultured with cMET/EGFR⁺ HCC-827 cells.

cMET/EGFR ADC Exhibited Excellent Plasma, Accelerated, and Freeze–Thaw Stability

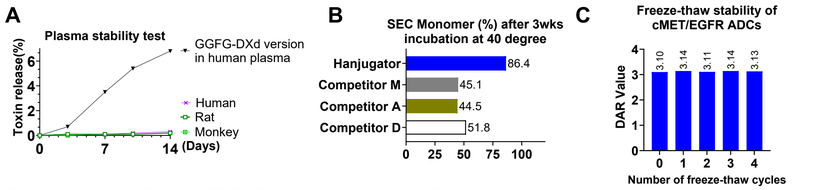


Figure 6. Bystander effect of cMET/EGFR ADC was quantified by CTG-based viability of target-negative Jurkat cells after 96 h co-culture with EGFR/cMet-positive HCC-827 cells

cMET/EGFR ADC Outperformed Comparators in HT29 and SW48 CDX Models

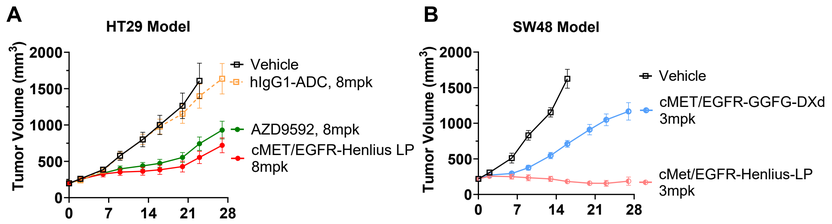


Figure 7. Characterization of EGFR/cMet-LPA003. (A) Toxin release kinetics in human plasma after 14-day incubation; (B) Pharmacokinetics following a single IV administration (5 mg/kg) in SD rats.

cMet/EGFR ADC Achieves Comparable or Superior Antitumor Efficacy vs. Competitors in three PDX models

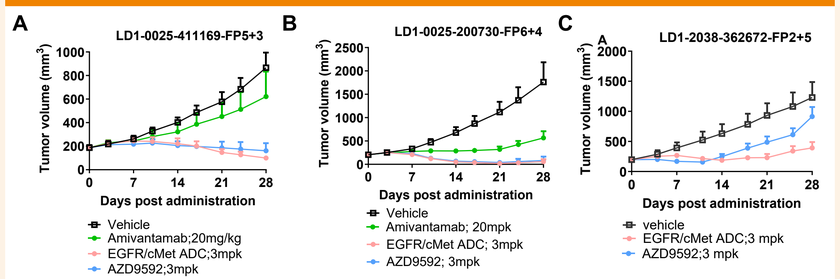


Figure 8. The antitumor efficacy of the cMET/EGFR bispecific ADC was compared head-to-head with AZD9592 in three PDX models refractory to standard therapies, all exhibiting high EGFR (3+) and cMET (3+) expression.(A) LD1-0025-411169-FP5+3, an osimertinib-resistant NSCLC model.(B) LD1-0025-200730-FP6+4, an additional osimertinib-resistant NSCLC model.(C) LD1-2038-362672-FP2+5, a cetuximab-resistant colorectal cancer model, with microsatellite stability, and wild-type KRAS and BRAF. All ADCs were administered as a single intravenous dose on day 0.

Hanjugator-Based cMET/EGFR ADC Was Well Tolerated at 60 mpk Q3W×3 in Cynomolgus Monkeys, Outperforming Comparator Linker-Payloads

Toxicity	Hanjugator (DAR 4)	Competitor M (DAR 2)	Competitor S (DAR 4)
Mortality	0/4	0/4	1/2 (D21)
Skin toxicity	3/4	3/4	1*/2
Gastrointestinal toxicity	1/4	3/4	1*/2
↓WBC	-13%	-43%	-26%
↓NEUT	-30%	-43%	-47%
↓LYMP	6%	-40%	-19%
↑RET	2%	-2%	4%
↓RBC	-3%	-13%	-15%
↑PLT	12%	49%	69%
Macroscopic Examinations#	skin	skin, thymus	TBD
HE^	skin	skin, thymus, bone marrow	TBD
HNSTD	60mpk	60mpk	30mpk

Table 1. The same bispecific antibody was conjugated to the in-house Hanjugator™ linker-payload or two comparator linker-payloads to generate ADCs for a pilot toxicology study in cynomolgus monkeys. ADCs were evaluated head-to-head following Q3W×3 dosing. The Hanjugator-based ADC was well tolerated at 60mpk Q3W x 3 dose levels, demonstrating an improved tolerability profile relative to comparator linker-payloads.

Disclosures: LR, SG, CY, ZL, YF, ZJ, GB, HC, ZX, YW, CX, YX, ZY, LZ, ZQ, YH, HC and are employees of Henlius.

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