Introduction of a Novel ADC Platform that Delivers Promising Physicochemical Properties and Preclinical Characteristics

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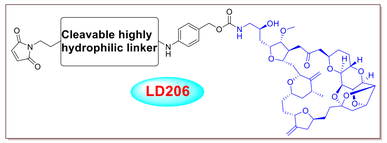
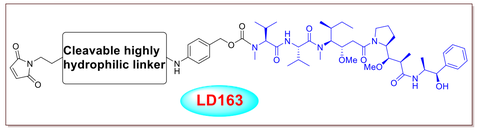
Introduction

• The physiochemical properties of an antibody-drug conjugate (ADC) are key design attributes that may significantly impact its stability and pharmacokinetics/ pharmacodynamics[1]. Typically, ADCs with better hydrophilicity are less prone to aggregation and have lower systemic clearance hence greater anti-tumor activities and a larger therapeutic index. However, the need for lipophilic payloads with enhanced bystander effects has posed significant challenges to ADC and linker design, especially at high drug-antibody ratios.

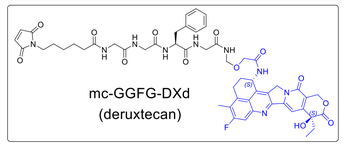
• Here we present a set of novel linker-drugs (LDs) that are composed of proprietary hydrophilic linkers (via introducing PEG, polyhydroxyl, and/or polycarboxyl groups) and lipophilic payloads (that carry established bystander effects and pharmacological characteristics, ie, exatecan, eribulin, and MMAE). These novel LDs were conjugated to a tool mAb[2], and evaluated for physicochemical properties as well as PK/PD, anti-tumor activity, and tolerability, in preclinical models.

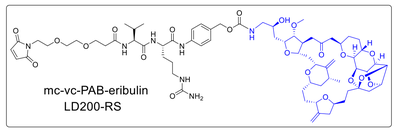
Structure of the Novel LDs

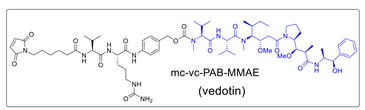




Structure of the Benchmarking LDs







LDs and ADCs Characterized in the Studies

Linker	Drug	LD	ADC (DAR)
proprietary	exatecan	LD038[3]	mAb-LD038(8)
proprietary	MMAE	LD163	mAb-LD163(8)
proprietary	eribulin	LD206	mAb-LD206(8)
mc-GGFG	DXd	deruxtecan	mAb-deruxtecan(8)
mc-vc-PAB	MMAE	vedotin	mAb-vedotin(4)
mc-vc-PAB	eribulin	mc-vc-PAB-eribulin (LD200-RS)	mAb-LD200-RS(4)

(all LDs were conjugated to the tool mAb[2], for head-to-head comparisons)

Characterization of the ADCs by HIC

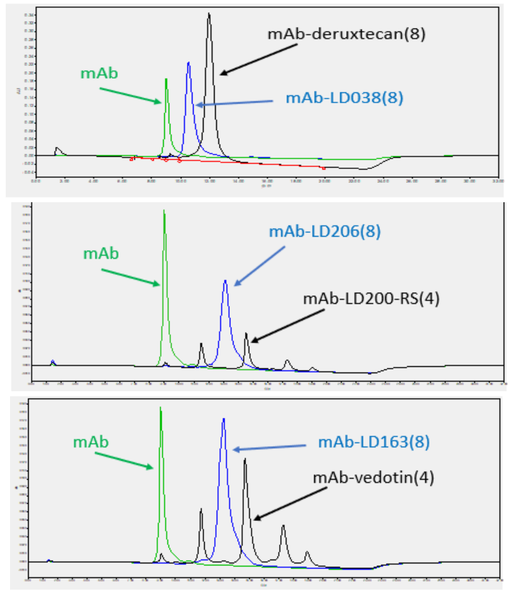
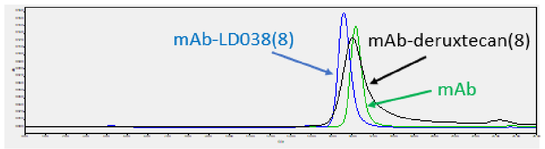


Fig. 1. Hydrophilicity of the ADCs were evaluated by standard hydrophobicity interaction chromatography (HIC)-HPLC methodologies.

Characterization of the ADCs by SEC



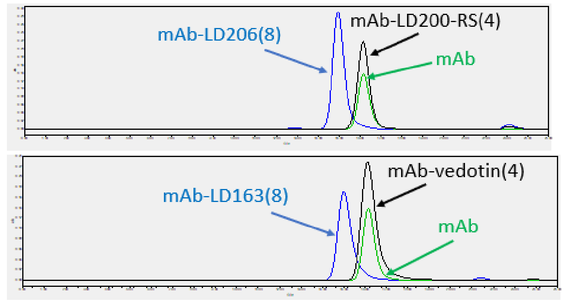
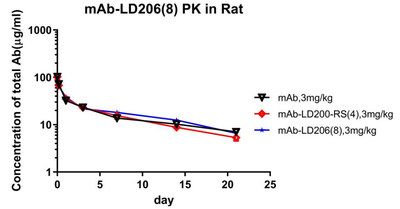
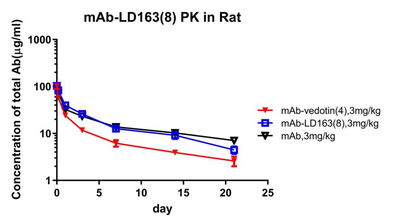


Fig. 2. Aggregation of ADCs were evaluated by standard size exclusion chromatography (SEC)-HPLC methodologies. In independent studies, there was no increased aggregation over free-thaw conditions, or over the time at 37°C for 30 days (not shown).

Plasma Pharmacokinetics of the ADCs





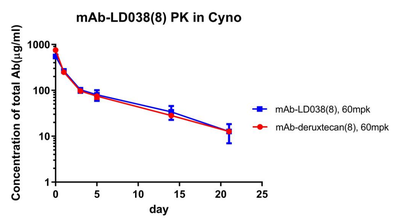


Fig. 3. Plasma PK of the ADCs were evaluated in rat (n=3 per group), rat (n=3 per group), cyno (n=2 per group), respectively. Concentrations of total antibodies were determined via an ELISA assay (2H6F5A5(anti-mAb idiotype antibody) as detection antibody and 2H6F5A5-Biotin as detection antibody). Additional DAR8 ADCs with this novel hydrophilic LD platform also displayed excellent PK in preclinical species[4,5].

In vivo Activity of the ADCs

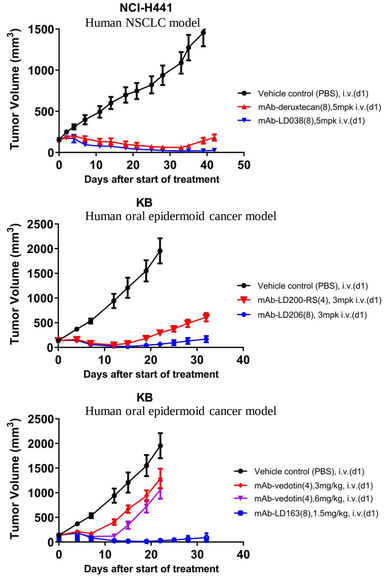


Fig. 4. Anti-tumor activity of the ADCs were examined in various cell-line derived xenograft (CDX) models. All studies were single-dose treatment at the specified doses (n=8 per treatment group). None of the ADC-treated animals exhibited appreciable weight loss or apparent distress (not shown). Additional studies also support the well-tolerated profile of the novel LDs[2,4,5].

Conclusions

• The novel LDs conjugated to a tool antibody at high DAR were more hydrophilic than the comparator ADCs with conventional linker-drugs and displayed minimal aggregation as well as excellent stability

• The novel LDs conferred excellent PK that is comparable to unconjugated parental mAb and strong anti-tumor activity in preclinical models

• Results in aggregate suggest that the novel hydrophilic LDs may be utilized for discovery and development of new ADCs with potentially expanded therapeutic index in the clinic to fulfill unmet medical need

References

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