HDP-103, a PSMA targeting amanitin-based ADC, is efficacious even in difficult to treat patient-derived xenograft models with heterogenous PSMA expression

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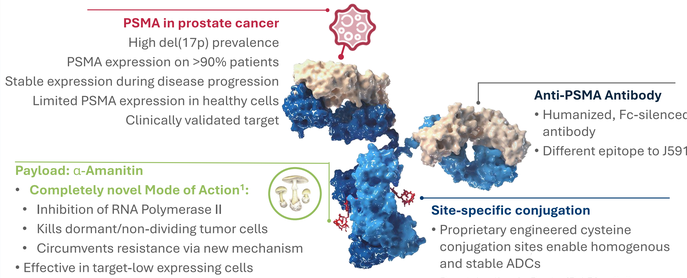
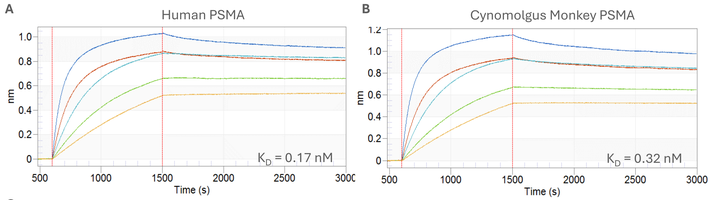
Background

Antibody-drug conjugates (ADCs) are increasingly used in the treatment of solid tumors. HDP-103 is an anti-PSMA amanitin-based ADC targeting metastatic castration-resistant prostate cancer (mCRPC). With amanitin as cytotoxic payload. HDP-103 deploys a novel mode of action that has the potential to overcome known limitations of common cytotoxic cancer agents (see picture below).

This study presents nonclinical data demonstrating efficacy of HDP-103 in difficult-to-treat mCRPC patient-derived xenograft models with heterogeneous PSMA expression, a manageable safety profile in cynomolgus monkeys and a favorable predicted therapeutic index (TI) in patients.



HDP-103 Specifically Binds to Human PSMA



C

Tissue	Cell type	Frequence and strength of binding
Breast	Glandular epithelial cells	~50% of cells, slight to moderate
Oviduct	Epithelial cells	<10% of cells, slight
Prostate	Glandular epithelial cells	>80% of cells, marked to strong
Small intestine	Interstitial cells in the submucosa/smooth muscle layers, suggestive of endothelial cells	Occasional, slight
Uterus	Spindle cells, suggestive of endothelial cells	Rare, minimal to slight

Fig. 1: HDP-103 specifically binds to human and cynomolgus monkey PSMA protein and demonstrates target specific binding in human tissues

A) Strong binding of HDP-103 to human PSMA was confirmed by BLI measurement.

B) HDP-103 binds to cynomolgus monkey PSMA with similar strength as compared to human PSMA, confirming the cynomolgus monkey as relevant toxicological species

C) A tissue cross reactivity study on 37 human tissues from healthy volunteers demonstrated target specific binding of HDP-103. As shown in the table, membranous binding was detected only in few tissues with strongest binding to the prostate.

HDP-103 is Efficacious in mCRPC PDX Model with Heterogenous PSMA Expression

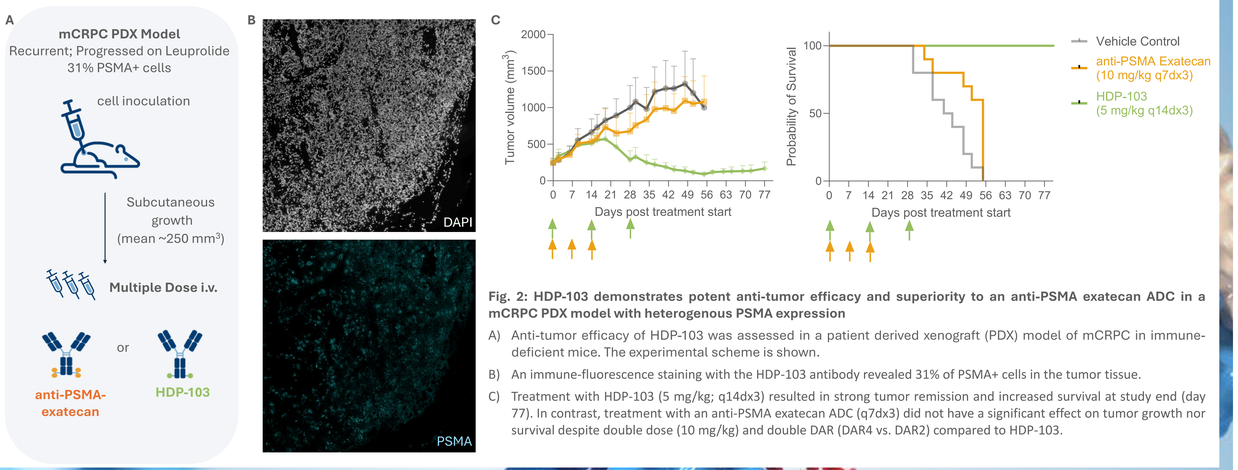


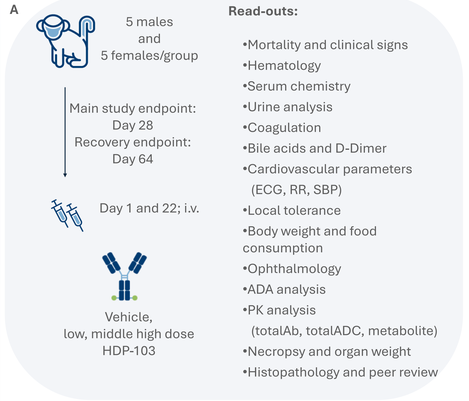
Fig. 2: HDP-103 demonstrates potent anti-tumor efficacy and superiority to an anti-PSMA exatecan ADC in a mCRPC PDX model with heterogenous PSMA expression

A) Anti-tumor efficacy of HDP-103 was assessed in a patient derived xenograft (PDX) model of mCRPC in immune-deficient mice. The experimental scheme is shown.

B) An immune-fluorescence staining with the HDP-103 antibody revealed 31% of PSMA+ cells in the tumor tissue.

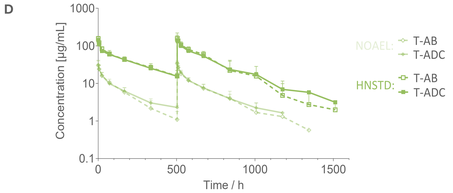
C) Treatment with HDP-103 (5 mg/kg; q14dx3) resulted in strong tumor remission and increased survival at study end (day 77). In contrast, treatment with an anti-PSMA exatecan ADC (q7dx3) did not have a significant effect on tumor growth nor survival despite double dose (10 mg/kg) and double DAR (DAR4 vs. DAR2) compared to HDP-103.

HDP-103 Demonstrates a Favorable PK and Safety Profile in Cynomolgus Monkeys



B

Parameter	HNSTD (high dose)
Clinical symptomes	Palor (1 male)
Local reaction	-
Body weight	-
Ophthalmology	-
Cardiovascular and respiratory	-
Hematology	• Transient moderate increase in WB cells and PLTs • Transient decrease in RBC parameters
Clinical chemistry	• Transient increase in AST, GGT and LDH • Transient slight increase in total protein due to globulin • Increased urea and/or creatinine in 1/10
Coagulation	• Transient slightly prolonged activated partial thromboplastin time
Urine analysis	-
Histopathology	• Minimal to marked increased cellularity in the thymus and the draining lymph node • Mild to moderate tubular degeneration/regeneration in the kidney • Minimally decreased cellularity of erythroid cells in the bone marrow



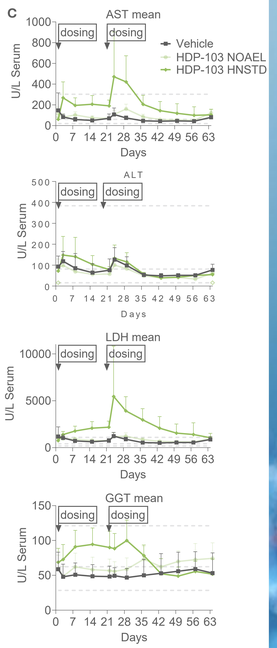


Fig. 3: HDP-103 demonstrates a well-manageable safety profile restricted to off-target effects and dose-dependent PK profile in cynomolgus monkeys

A) The safety profile of HDP-103 after two doses (q21dx2) was determined in a GLP toxicity study in cynomolgus monkeys at three dose levels.

B) No mortalities occurred in the study and adverse events at the HNSTD were restricted to transient changes in blood parameters as well as histopathological findings.

C) AST, ALT, LDH and GGT show transient, dose-dependent elevations.

D) PK analysis of total antibody (T-AB) and total ADC (T-ADC) demonstrate ADC stability in circulation as well as dose-linearity at a half-life of 6 – 10 days.

HDP-103 has Wide Predicted Therapeutic Index

A

	DS-7300[3]	Enhertu[4]	HDP-103	ARX517[5]
TI based on nonclinical data	13	12	**8**	5

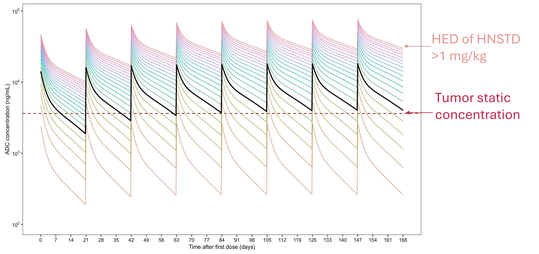


Fig. 4: Nonclinical data and an allometrically scaled PK/PD model predicts a comfortable TI for HDP-103 in prostate cancer patients

A) The TI of HDP-103 and other ADCs in development for solid tumors were calculated using a body surface area corrected dose-based approach. For other ADCs published and comparable efficacy and tolerability data was used.

B) Median predicted total ADC concentration-time profiles are shown, illustrating the typical HDP-103 exposure as described by the allometrically scaled model for a human of 70 kg. The highest dose is equal to the human equivalent dose (HED) of the HNSTD in monkeys. The tumor static concentration (TSC) was calculated based on efficacy studies in mouse models. The first dose exceeding the TSC 90% of the time is emphasized by the bold black line.

Conclusion

HDP-103, an anti-PSMA amanitin-based ADC for the treatment of mCRPC, demonstrates target specific binding in human tissues and robust and durable antitumor activity in PDX models representative of the target population, including tumors with heterogeneous PSMA expression and those harboring a del(17p). Despite maintained PSMA expression levels in the salivary gland of monkeys[6], adverse events with HDP-103 were restricted to known off-target effects of amanitin-based ADCs primarily in the liver and kidney. These effects are easily monitorable by AST and ALT elevations and are transient. HDP-103 serum levels demonstrate ADC stability in circulation as well as no drug accumulation, no difference between sexes and dose-linearity.

The potent anti-tumor efficacy of HDP-103 combined with a favorable half-life and a manageable safety togetprofile in cynomolgus monkeys, leads to a comfortable TI of HDP-103 that is well in the range of other ADCs that are approved or in development for solid tumor indications. Taken together, these data warrant further clinical development of HDP-103 as a novel treatment option for mCRPC. HDP-103´s unique mode of action gives it advantages over other treatment modalities in use or development for mCRPC including in patients with del(17p) who have a high unmet medical need.

References

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