HDP-101, an Anti-BCMA Antibody-Drug Conjugate with a Novel Payload Amanitin in Patients with Relapsed Multiple Myeloma, Initial Findings of the First in Human Study

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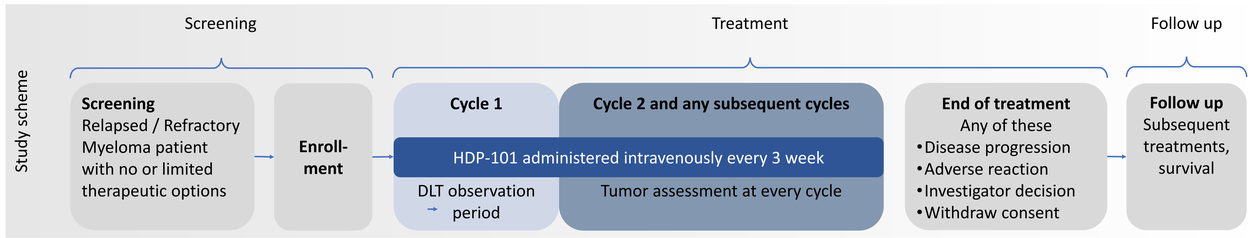
Introduction

Several antibody-drug conjugates (ADCs) are currently being evaluated in clinical trials in a variety of malignancies. Vast majority of these ADCs are based on a few toxic compounds, largely limited to microtubule- or DNA-targeting toxins target proliferating cells and have limited efficacy in diseases with a low proliferative fraction such as multiple myeloma. Thus, new compounds with alternative mode of actions and the ability to actively induce cell death in non-proliferating tumor cells could enhance the therapeutic potential of ADCs. We are currently developing amanitin based ADCs. Amanitin specifically inhibits RNA polymerase II thereby inhibiting the cellular transcription process at very low concentrations irrespective of the proliferation status of the target cell. Subsequently tumor cells enter apoptosis and are eliminated.

HDP-101-01 Clinical Study

HDP-101-01 is a first-in-human, open label, non-randomized, multicenter, phase 1/2a trial with HDP-101 in patients with multiple myeloma whose disease has progressed. The aim of the Phase 1 dose escalation part is to determine the Maximum Tolerated Dose and/or establish the Recommended phase 2 Dose. The primary objective of the phase 2 dose expansion phase is to assess the preliminary anti-tumor activity of HDP-101. An adaptive Bayesian logistic regression model with overdose control principle is used to guide the dose escalation steps. An Interim Analysis is planned after each cohort is completed. The design of the study ensures a safe and adaptive dose escalation to reach a potential clinical benefit in a patient who have limited or no therapeutic options.

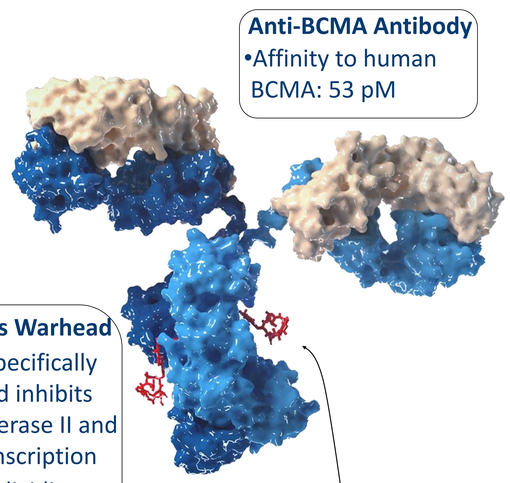


Study progress

The study started enrollment in February 2022. As of 12th of July 2022 four (1 female and 3 male) patients were dosed in 2 consecutive dose cohorts. The median age of the patients was 63.5 years, ranging between 51 and 80. All 4 patients were heavily pre-treated and multidrug-resistant. The median previous lines of treatment were 11 (5 to 16).

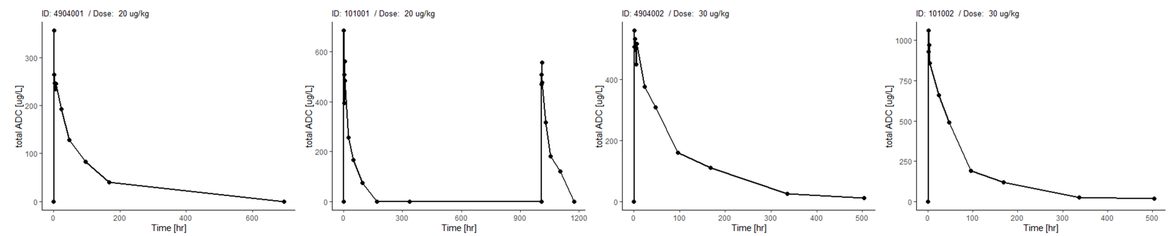
0101001 (m. 50 y.o.)	20µg/Kg	No DLT	PD (received 3 doses)
4904001 (m. 70 y.o.)	20µg/Kg	No DLT	PD (received 1 dose)
0101002 (f. 80 y.o.)	30µg/Kg	No DLT	PD (received 3 doses)
4904002 (m. 52 y.o.)	30µg/Kg	No DLT	PD (received 2 doses)

HDP-101 an Amanitin Based Antibody Drug Conjugate



HDP-101 is a new ADC targeting BCMA carrying a synthetic version of amanitin as a payload. In vitro cytotoxic potency of HDP-101 was demonstrated on BCMA-positive myeloma cell lines, as well as on non-proliferating primary CD138+ cells isolated from patients with refractory myeloma The cytotoxic effects of HDP-101 were seen even in non-proliferating myeloma cells with low BCMA density. Toxicity was observed neither in non-BCMA expressing control cells nor in myeloma cells exposed to an amanitin-loaded non-target control antibody. In murine xenograft models of human myeloma, HDP-101 caused dose-dependent tumor regression including complete remissions after a single dose in subcutaneous and as well as in disseminated models. Safety profiling in Cynomolgus monkeys revealed a good therapeutic index after repeated dosing.
Our non-clinical studies concluded that this amanitin-based ADC is a novel promising approach in the therapy of multiple myeloma to overcome drug resistance and improve patient outcome.

Results



Three of 4 patients were evaluable for dose limiting toxicities (DLT). The initial 2 cohorts were well tolerated, without any reports on DLTs. No reports of keratopathy or visual acuity loss were observed. Free payload was not detected in any of the available pharmacokinetic samples. Based on the limited data, the PK of HDP-101 was in line with our expectation based on the preclinical observations. Objective responses were not reported in these initial cohorts.

The initial dose cohorts showed good tolerability in late stage relapsed and/or refractory multiple myeloma patients. The study continues to enroll patient to higher dose cohorts at selected sites in US and Germany.