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

Marc S. Raab, MD[123]; Jonathan Kaufman, MD[4]; Shambavi Richard MD[5]; Sebastian Grosicki, MD, PhD [6]; István Takács MD, PhD[7]; **András Strassz, MD[9]**; Andreas Pahl, PhD[10]; Thorsten Michael[9]; Anette Last[9]; Hajnalka Szabóki, MD[9]; Garrit Jentsch[11]; Oliver Schönborn-Kellenberger[12]; and Robert Z. Orlowski, MD, PhD[13]

[1]Department of Hematology, Oncology and Rheumatology, Heidelberg University Hospital, Heidelberg, Germany; [2]Clinical Cooperation Unit (CCU) Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Max-Eder-Group "Experimental Therapies for Hematologic Malignancies", German Cancer Research Center, Heidelberg, Germany; [4]Winship Cancer Institute, Emory University, Atlanta, GA; [5]Mount Sinai Hospital, New York, NY; [6]Medical University in Silesia, Katowice, Poland; [7]Semmelweis University, Ist Department of Medicine, Budapest, Hungary; [9]Heidelberg Pharma AG, Ladenburg, Germany; [10]Heidelberg Pharma, Ladenburg, Germany; [11]BAST GmbH Heidelberg; [12]Cogitars GmbH, Heidelberg, Germany; [13]Department of Lymphoma and Myeloma, MD Anderson Cancer Center, Houston, TX

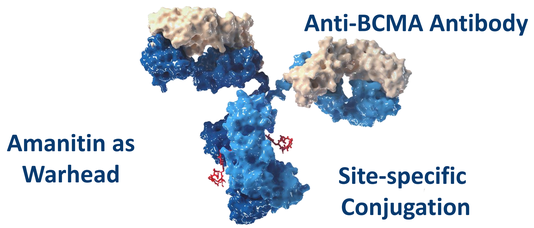
Poster #3334
ASH 2023

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. 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.

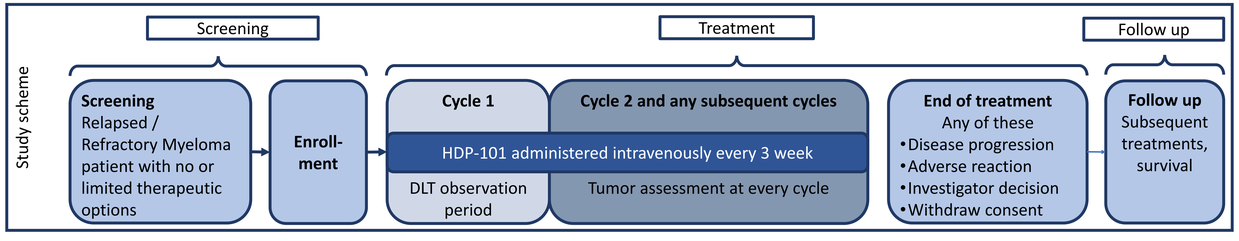
Background

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.

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.

Study Progress

The study started enrollment in February 2022. Cohort 4 was closed in September 2023.
Twelve (3 females and 9 males) patients were dosed in 4 consecutive dose cohorts.

The median age of the patients was 70 years, ranging between 50 and 82. All 12 patients were heavily pre-treated and multidrug-resistant. The median previous lines of treatment were 7 (4 to 15).

Cohort 1 20µg/Kg	Cohort 2 30µg/Kg	Cohort 3 60µg/Kg		Cohort 4 80µg/Kg	
101001 (m, 50) No DLT PD (3 doses)	101002 (f, 80) No DLT PD (3 doses)	102002 (m, 78) No DLT PD (2 doses)	102003 (m, 76) No DLT Ongoing SD **(14 doses)**	4815003 (m, 73) No DLT PD (3 doses)	3613001 (m, 65) No DLT PD (4 doses)
4904001 (m, 70) No DLT PD (1 dose)	4904002 (m, 52) No DLT PD (2 doses)	4904004 (m, 70) No DLT PD (2 doses)	103001 (f, 70) No DLT Not evaluable (1 dose)	4815004 (f, 57) No DLT PD (2 doses)	102004 (m, 82) No DLT PD (1 dose)

Study Results

Based on the limited data, the PK of HDP-101 was in line with our expectation based on the preclinical observations, exposure to HDP-101 is dose proportional. Anti-drug antibody (ADA) was not detected and there's no sign of immunogenicity.

Eleven of 12 patients were evaluable for dose limiting toxicities (DLT) in the first 4 treatment cohorts. The initial 4 cohorts were well tolerated, without any reports on DLTs, there were no signs of liver and kidney toxicity, no infusion reaction was detected. No reports of keratopathy or visual acuity loss were observed. Free payload was not detected in any of the available pharmacokinetic samples.

Objective responses were not reported in these four initial cohorts however in Cohort #3 (60µg/Kg) there was one patient ongoing after 14 cycles of treatment with SD, he did not receive any other anti-myeloma treatment since Jan 2023. This patient didn't have any long-term adverse events.