HDP-101: The Anti-BCMA Antibody-Drug Conjugate HDP-101 with a Novel Amanitin Payload Shows Promising Initial First in Human Results in Relapsed Multiple Myeloma

Poster 3381

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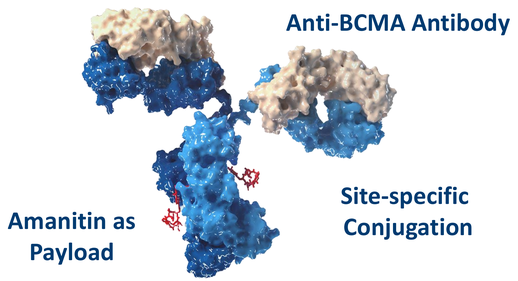
Introduction and Background

The vast majority of the ADCs in clinical use or in development are based on a few toxic compounds, largely limited to microtubule- or DNA-targeting toxins, which are mainly active against proliferating cells and have less efficacy in diseases with a low proliferative fraction such as multiple myeloma. Amanitin, the payload used in HDP-101, specifically inhibits RNA polymerase II thereby inhibiting the cellular transcription process irrespective of the proliferation status of the target cell. HDP-101 is a novel antibody-drug conjugate (ADC) that targets B-cell maturation antigen (BCMA) with a synthetic amanitin payload. HDP-101 has demonstrated cytotoxicity *in vitro* against BCMA-positive myeloma cell lines and non-proliferating primary CD138$^+$ cells from refractory myeloma patients, even those with low BCMA density.



Clinical Study

HDP-101-01 is a first-in-human, open-label, non-randomized, multicenter phase 1/2a clinical trial conducted in patients with relapsed or refractory multiple myeloma. The aim in Phase 1 is to determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D). Dose escalation is guided by an adaptive Bayesian logistic regression model (BLRM) with overdose control. The primary objective in Phase 2 is to assess the anti-tumor activity of HDP-101.

Study Progress

As of Nov, 2024, the study had enrolled 28 patients (8 females, 20 males) across six consecutive dose cohorts: 20, 30, 60, 80, and 100 µg/kg and the latest cohort which is a dose-optimization cohort including three different treatment arms at a dose of 90 µg/kg in various settings including premedication or split dosing. The median age of these patients was 69.5 years (range 48-82). They were heavily pre-treated and multidrug-refractory, with a median of 6 prior treatment regimens (range 2-15). Cohort 6 is fully enrolled and still ongoing.

Most Common Treatment-Emergent AEs (Cohort 1-5)

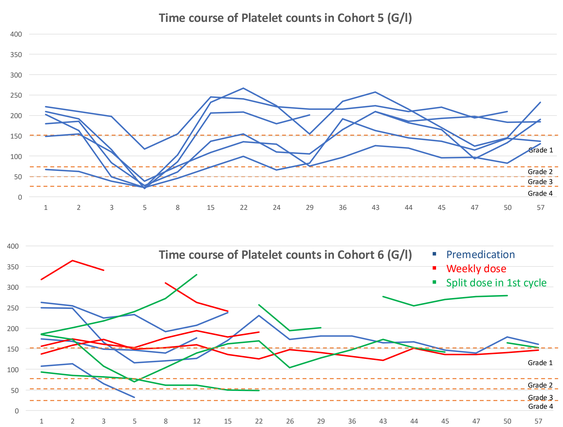
Preferred Term	Patients with any CTCAE grade (%) N=18	Patients with Grade 3-4 (%)
Thrombocytopenia	10 (56%)	7 (39%)
Arthralgia	6 (33%)	0 (0%)
Anaemia	6 (33%)	4 (22%)
Fatigue	5 (28%)	0 (0%)
Neutropenia	4 (22%)	3 (17%)
Hyperuricaemia	3 (17%)	0 (0%)
Nausea	3 (17%)	0 (0%)
White blood cell count decreased	3 (17%)	1 (6%)
Aspartate aminotransferase increased	3 (17%)	1 (6%)
Alanine aminotransferase increased	3 (17%)	1 (6%)
Hypercalcaemia	3 (17%)	1 (6%)
Constipation	3 (17%)	0 (0%)
Vomiting	3 (17%)	0 (0%)

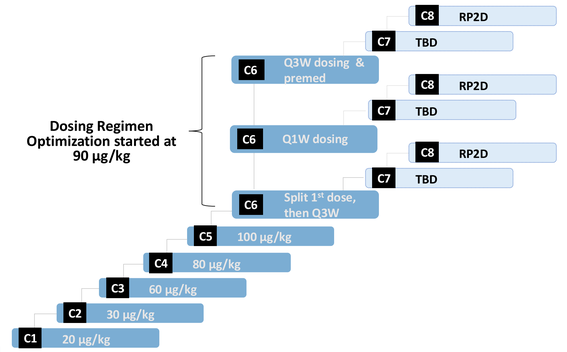
Study Results

Data indicate that the pharmacokinetics of HDP-101 are consistent with non-clinical data and pharmacometric simulations, showing dose-proportional exposure. The free amanitin payload was not detected in serum at the detection limit of 30 ng/mL, and there were no occurrences of anti-drug antibodies or immunogenic reactions. The treatment in general was well tolerated, with the absence of hepatic and renal serious adverse events, infusion reactions, or ocular disorders. Mild elevations in Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were observed in Cohort 5 during Cycle 1, which resolved spontaneously, returned to baseline and did not recur in subsequent cycles.

All patients in Cohort 5 experienced transient thrombocytopenia, characterized by platelet reductions starting on Cycle 1 Day 2 (C1D2), reaching a nadir on C1D5, and fully recovering by C1D15 without clinical sequelae or interventions. Three of these events fulfilled the criteria of a dose limiting toxicity (DLT).

Subsequent dosing did not result in similarly profound thrombocytopenia episodes, suggesting this effect was not due to direct cytotoxicity against megakaryocytes or platelets. Consequently, based on Safety Review Committee (SRC) recommendations after Cohort 5, the DLT criteria were revised for thrombocytopenia, and dose optimization strategies were developed to continue dose escalation. Cohort 6 is currently ongoing with 10 patients enrolled, where all patients completed the 21-day DLT observation period without any reported DLTs as of 10th of November, though the full assessment of the cohort is still pending. Initial results from Cohort 6 suggest that the dose distribution strategies might mitigate toxicity as first cycle thrombocytopenia is modest or absent compared to cohort 5. Patients will be monitored further.

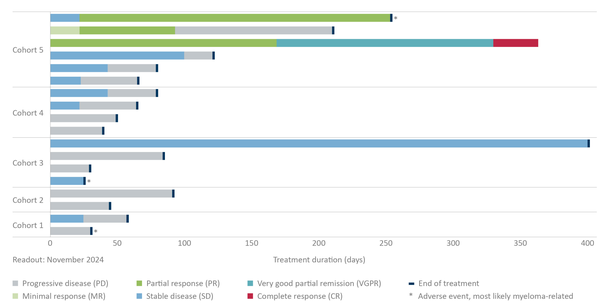




Efficacy

In Cohort 3 (60 µg/kg), one patient achieved stable disease (SD) over 17 cycles. In Cohort 5 (100 µg/kg), two patients achieved partial response (PR), one patient is currently in complete response (CR) after 15 cycles of treatment, while three exhibited progressive disease, one of whom required a dose reduction after Cycle 1. The patient who is in CR had a prior BCMA-targeting CAR-T cell therapy and a GPRC5D/CD3 bispecific. Efficacy results from Cohort 6 are still pending. These promising findings support the continuation and further optimization of dosing strategies, and future combinations.

IMWG Response Over Time Cohort 1-5



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