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

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Introduction
The vast majority of the ADCs in clinical use or in development are based on few toxic compounds, largely limited to microtubule- or DNA-targeting toxins, which are mainly active against proliferating cells and have limited efficacy in diseases with a low proliferative fraction such as multiple myeloma. Amanitin, the payload used in our ADCs, specifically inhibits RNA polymerase II thereby inhibiting the transcription process irrespective of the proliferation status of the target cell.

Clinical Study
HDP-101-01 is a first-in-human, open-label, non-randomized, multicenter, phase 1/2a trial in patients with multiple myeloma whose disease has progressed or is refractory. Dose escalation is guided by an adaptive Bayesian logistic regression model (BLRM) with overdose control.

Study Results
Preliminary data shows that the pharmacokinetics profile of HDP-101 aligns with expectations, and exposure to HDP-101 is dose proportional. Free payload was not detected in serum at a limit of detection of 30 ng/mL. 17 out of 18 patients were evaluable for dose limiting toxicities (DLT) in the 5 treatment cohorts. Initial 4 cohorts were well tolerated, without any DLTs, including no signs of hepatic and renal toxicities, infusion reactions, or ocular disorders.

All patients in Cohort 5 had Grade 1-4 transient thrombocytopenia with platelet reductions starting on Cycle 1/Day 2 (C1D2), a nadir on C1D5, and full recovery spontaneously by C1D15 at the latest without any clinical sequelae. Notably, subsequent dosing with HDP-101 did not produce similarly deep episodes of thrombocytopenia, supporting the theory that this event is not due to a direct cytotoxic effect against megakaryocytes. In Cohort 5 dose-limiting toxicities (DLT) were observed in 3 patients. After Cohort 5, based on SRC recommendation the DLT rules were modified for thrombocytopenia and dose optimization strategies were developed. For the new arms, the BLRM statistics will be reset. Mostly mild ALT and AST elevations were detected in Cohort 5 Cycle 1. Both transaminase levels returned to baseline spontaneously and elevations were not detected in further cycles.

No ocular disorders were seen in any study patients, including the responding patients.

Study Progress
As of November 2023, 18 patients (7 females, 11 males) were enrolled in 5 consecutive dose cohorts of 20, 30, 60, 80, and 100 µg/kg. Patients had a median age of 70 years (48-82), were heavily pretreated and multidrug-resistant, and had a median of 6.5 prior treatments (2-15).

Efficacy
Cohort 3 (60 µg/kg) includes a patient with sustained stable disease (SD) after 18 cycles, dose increased to 80 µg/kg from C12. In Cohort 5 (100 µg/kg), 3 patients achieved partial response (PR), and 3 patients showed progressive disease, one with dose reduced after C1. These encouraging results support the continuation with dose optimization.

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**Background**
HDP-101 is a new ADC targeting the B-cell maturation antigen (BCMA) that carries a synthetic amanitin payload. Amanitin inhibits RNA polymerase II, effectively shutting-down transcription and inducing apoptosis in tumor cells, regardless of their proliferation status.

**Anti-BCMA Antibody**

**Amanitin as Warhead**

**Site-specific Conjugation**

In murine xenograft models of human myeloma, HDP-101 caused dose-dependent tumor regression, including complete remissions, after a single dose in both subcutaneous and disseminated models.

**Timecourse of platelet counts in cohort 5 patients**

**Summary of responses in cohort 5 patients**