HDP-102 - a CD37-targeting Amanitin-based ADC for the treatment of Non-Hodgkin Lymphoma (NHL) - non-clinical data package

Sarah-Jane Neubert, Kristin Decker, Christian Orlik, Irina Dronova, Anikö Pálfí, Torsten Hechler, Andreas Pahl, Michael Kulke

BACKGROUND

Antibody-drug conjugates (ADCs) are gaining importance as anti-cancer therapy. Most ADCs are based on cetuximab which targets the epidermal growth factor receptor (EGFR), a key factor in the protein metabolism of cells not limiting their cytotoxicity to proliferating cells. Furthermore, there are no known resistance mechanisms against amanitins in mammalian cells (e.g. multi drug resistance transporter), making HDP-102 a promising new class of anti-cancer ADCs (1,2). The current study presents pre-clinical data on the anti-CD37 ATAC® HDP-102. CD37 is a transmembrane protein expressed exclusively on immune cells, mainly mature B cells, and in many B-cell malignancies, including Non-Hodgkin Lymphoma (NHL). The anti-CD37 antibody is conjugated site-specifically. (THE)NAM® strategy to create reactive amanitin linker constructs uses a non-toxic linker, synthesized at Heidelberg Pharma. Drug-antibody ratio according to LC-MS analysis is ~2.0 amanitins per pIgG (3).

RESULTS IN CYMOLONUS MONKEYS

3. HDP-102 is well tolerated in Cynomolous monkeys

A) ALT / AST

B) LDH

C) Mec-2

D) Raji-Luc

4. HDP-102 is equally distributed in male and female monkeys with a half-life of approx. 10 days

5. HDP-102 has a favorable therapeutic index (TI)

6. HUMAN MODELING

HDP-102 predictions in human

Figure 6: Human predictions of HDP-102 plasma concentration based on selected pre-clinical cynomolous monkey popPK model coHDL. HDP-102 is administered as half-hour infusions of doses ranging from 0.03 mg/kg to 0.8 mg/kg. Predictions were generated for a human body of 70 kg of body weight and random effect parameters being set to zero. The highest dose is based is equal to the human equivalent dose of the HNSTD. This profile is emphasized by a stronger line width.

REFERENCES


ATTAC® is a registered trademark of Heidelberg Pharma Research GmbH, No US 7888594

CONTACT

Heidelberg Pharma Research GmbH
Gregor-Mendel-Straße 22
68256 Ladenburg
Germany
Phone: +49-6203-1009 0
Email: info@heidelberg-pharma.com
https://www.heidelberg-pharma.com

Figure 1: HDP-102 specifically binds to human B- and T-lymphocytes and ablated strong cytotoxicity exclusively on CD37 positive cells

A) A tissue cross reactivity study revealed binding of HDP-102 exclusively to B- and T-Lymphocytes. This starting pattern resembles the expression pattern of CD37.

B) HDP-202 shows cytotoxicity in the pIC50 range on two different NHL cell lines (left panel); within HDP-202 was not cytotoxic to CD37 negative right panel.

Figure 2: HDP-102 has very strong anti-tumor efficacy in different disseminated NHL models

Anti tumor efficacy of HDP-102 was evaluated upon single i.v. doses of 1 mg/kg and lower in tumor-bearing female C3H/SE-hCD (SE-hCD). Single dose treatment resulted in significantly extended survival in disseminated model of Mz-2 (A) and Raji (B) SE-hCD xenografts. In the Raji-hCD model, tumor burden was followed by haematology measurements.

Figure 3: HDP-102 is well tolerated in Cynomolous monkeys up to 2.5 mg/kg

A) Single intravenous dosing of HDP-102 on day 1 and 2 resulted in transient and dose dependent increases of the serum levels of liver damage markers aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH).

B) Intravenous dosing with HDP-102 results in dose-dependent depletion of lymphocytes that shows signs of recovery.

C) The HNSTD of HDP-102 at 0.5 mg/kg in limited number of necropsy findings in cynomolous monkeys. Animals were terminated on day 28 (end of treatment period) or after a recovery period of six weeks.

Figure 4: HDP-102 shows a dosedependent profile in Cynomolous monkeys

A) At the HNSTD of 2.5 mg/kg HDP-102 is equally distributed in male and female monkeys without signs of accumulation between the doses.

B) The half-life of HDP-102 in Cynomolous monkey serum is approximately 10 days.

Figure 5: TI of HDP-102

A) TI formula of the TI with HNSTD (the highest non-toxic dose) and NED converted (minimal effective dose; single dose that leads to haematopoiesis reduction below the start value for at least one week) in the mouse models, converted to monkey by the body surface area divided by 4.

B) TI of HDP-102 based on single dosing.

Figure 7: Plot of HDP-102

A) Data for the calculation of the TI with HNSTD (the highest non-toxic dose) and NED converted (minimal effective dose; single dose that leads to haematopoiesis reduction below the start value for at least one week) in the mouse models, converted to monkey by the body surface area divided by 4.

B) TI of HDP-102 based on single dosing.