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

#1865

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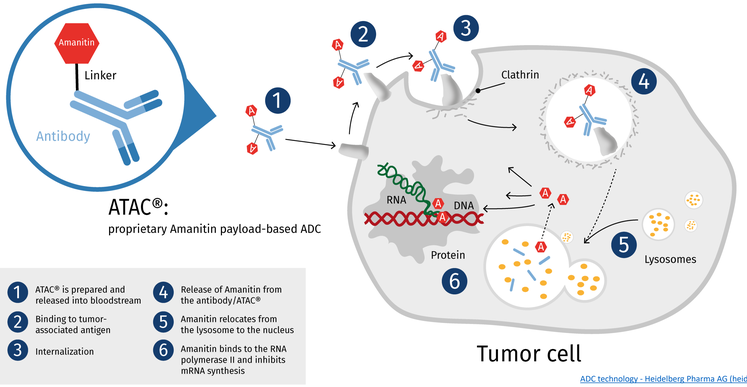
Heidelberg PHARMA
Focused Cancer Therapies

Background

Antibody-drug conjugates (ADC) are gaining importance as anti-cancer therapy. Most ADCs are based on cytotoxic warheads targeting only proliferating cells. In contrast, Heidelberg Pharma's proprietary ATAC® platform utilizes amatoxins as payload. Amatoxins are specific inhibitors of eukaryotic RNA polymerase II, suppressing a key function in the protein metabolism of cells not limiting their cytotoxicity to proliferating cells. Furthermore, there are no known resistance mechanisms against amatoxins in mammalian cells (i.e. multi drug resistance transporters), making ATAC®s 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 (THIOMAB® strategy) to cysteine-reactive amanitin-linker constructs via a non-cleavable linker, synthesized at Heidelberg Pharma. Drug-antibody ratio according to LC-MS analysis is ~2.0 amanitins per IgG (3).



ADC technology - Heidelberg Pharma AG (heidelberg-pharma.com)

Results *in vitro* and *in vivo*

1. HDP-102 specifically targets CD37 positive immune cells

A

Tissues	Cell Type Involved
Lymph node	B-lymphocytes mainly (T-lymphocytes to a lesser extent)
Spleen	B- and/or T-lymphocytes
Thymus	B-lymphocytes
Lymphatic tissue	B-lymphocytes mainly
Inflammatory cell infiltrates in different tissues	B- and/or T-lymphocytes

B

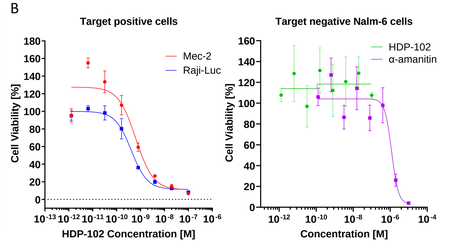
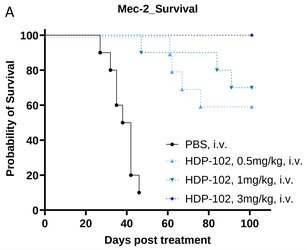


Figure 1: *HDP-102 specifically binds to human B- and T-lymphocytes and exhibited strong cytotoxicity exclusively on CD37 positive cells*
A) A tissue cross reactivity study revealed binding of HDP-102 exclusively to B- and T-lymphocytes. This staining pattern resembles the expression pattern of CD37.
B) HDP-102 shows cytotoxicity in the pM range on two different NHL cell lines (left panel) while HDP-102 was not cytotoxic on CD37 negative cells (right panel).

2. HDP-102 has strong anti-tumor efficacy on CD37 positive NHL CDX models

A



B

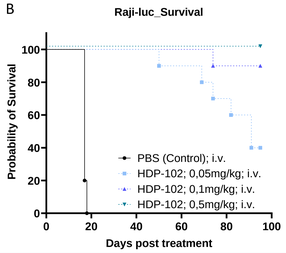
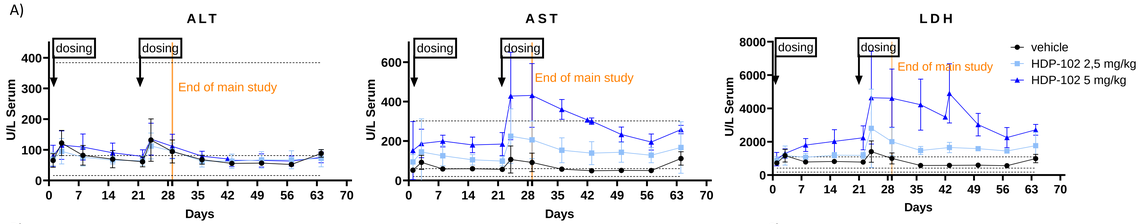


Figure 2: *HDP-102 has very strong anti-tumor efficacy in different disseminated NHL models*
Anti tumor efficacy of HDP-102 was evaluated upon single i.v. doses of 1 mg/kg and lower in tumor-bearing female CB17-SCID mice. Single dose treatment resulted in significantly extended survival in disseminated model of Mec-2 (A) and Raji-luc (B) NHL xenografts. In the Raji-luc model, tumor burden was followed by bioluminescence measurements.

Results in cynomolgus monkeys

3. HDP-102 is well tolerated in Cynomolgus monkeys

A)



B)

Organ	2.5 mg/kg HDP-102		5 mg/kg HDP-102	
	End of main study	End of recovery	End of main study	End of recovery
Spleen	4/6	3/4	4/5	3/3
Lymph nodes	2/6	4/4	2/5	3/3
Thymus	3/6	2/4	4/5	1/3

No Change
Minimal
Mild
Moderate
Marked

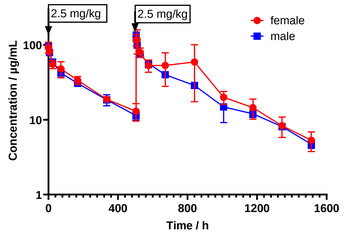
C)

Results	Following Administration of HNSTD 2.5 mg/kg HDP-102
Mortality	0/10
Test item related clinical symptoms	Hunched Posture (1/10) (Day 23 and 24)
Body weight/ food consumption	No changes
ophthalmology changes	No changes
Hematology	End of treatment period Changes in RBC mass parameters and reticulocyte counts, one animal
	End of recovery period **No changes**
Clinical chemistry parameters	End of treatment period Changes in AST, LDH, CK, cholesterol, globulin
	End of recovery period Changes in AST, LDH, CK
Organ weight	End of treatment period Decreased thymus weight.
	End of recovery period **No changes.**
Macroscopic observations	End of treatment period No changes
	End of recovery period Decreased thymus size in one female.
Cardiovascular and respiratory changes and parameter	**End of treatment period** **No changes**
	End of recovery period **No changes.**

Figure 3: *HDP-102 is well tolerated in Cynomolgus monkeys up to 2.5 mg/kg*
A) Single intravenous doses of HDP-102 on day 1 and 22 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 of 2.5 mg/kg results in limited number of necropsy findings in cynomolgus monkeys. Animals were terminated on day 28 (end of treatment period) or after a recovery period of six weeks.

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

A)



B)

Dose (mg/kg)	2.5	
Gender	M	F
Day	Day 1	
C_{max} (µg/mL)	97	94
AUC_{last} (µg/mL*h)	11655	12360
$T_{1/2}$ (days)	9.13	8.70
Day	Day 22	
C_{max} (µg/mL)	130	136.6
AUC_{last} (µg/mL*h)	24317	31441
$T_{1/2}$ (days)	10.43	9.94

Figure 4: *HDP-102 shows a favorable PK profile in Cynomolgus 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 Cynomolgus monkey serum is approximately 10 days.

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

A)

$$TI = \frac{HNSTD_{monkey}}{MED_{mouse}converted}$$

B)

Test item	TI
HDP-102	200

Figure 5: *TI of HDP-102*
A) Formula for the calculation of the TI with $HNSTD_{monkey}$ (the highest non-severely toxic dose) and MED_{mouse}converted (minimal effective dose; single dose that leads to Bioluminescence 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.

Human Modeling

6. HDP-102 predictions in human

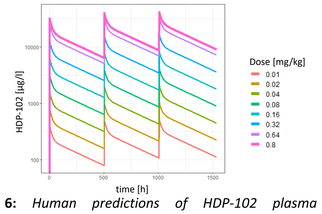


Figure 6: *Human predictions of HDP-102 plasma concentration based on selected pre-clinical cynomolgus monkey popPK model run011.* HDP-102 is administered as half hour infusions of doses ranging from 0.01 mg/kg to 0.8 mg/kg. Predictions were generated for a human of 70 kg of body weight and random effect parameters being set to zero. The highest dose studied is equal to the human equivalent dose of the $HNSTD_{cyno}$. This profile is emphasized by a stronger line width.

Conclusion

- HDP-102 shows target-specific cytotoxicity on CD37⁺ cells and no activity on target-negative cells
- HDP-102 specifically binds to B- and T-lymphocytes
- HDP-102 shows strong anti-tumor efficacy in disseminated CD37⁺ tumor models
- HDP-102 shows good tolerability in cynomolgus monkeys with limited number of necropsy findings
- The therapeutic index is 200 based on the HNSTD of 2.5 mg/kg
- HDP-102 human predictions suggest that a dose of 0.01 mg/kg will show anti-tumor efficacy in patients

References

(1) Pahl A *et al.* in Cytotoxic Payloads for Antibody–Drug Conjugates Chapter 19; The Royal Society of Chemistry 2019
(2) Li Y. *et al.* J Sci Transl Med. 2021; 13(580):eabc6894
(3) Vaisitti T *et al.,* Blood 2022; 140 (13):1565-1569

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