**INTRODUCTION**

Amitoxin-based antibody-drug conjugates (so called ATACs) are a new class of ADCs that are based on the principle of two targets at once – the intended target and a bystander target (BTD). Only AMT has been approved by the FDA for use in patients with advanced epithelial ovarian cancer. ATACs are built on the fact that both targets are present in the tumor. This dual targeting concept, also known as the bystander effect (BTE), allows for the release of payload in the bystander area, thereby increasing the therapeutic index and avoiding unwanted side effects.

**METHODS**

ATACs: anti-CD7, anti-CD37 and anti-PSMA antibodies, produced by Heidelberg Pharma (HPD) were conjugated to a class specific DTH-PAMC linker. DTH-PAMC linker is known for its stable coupling and ease of conjugation. The conjugation was performed by the procedure patented and described in US patent 10,033,043. The conjugate was formed by irradiation, at 50 Mrad, of a mixture of anti-PSMA, anti-CD7 and anti-CD71 antibodies with acidic conjugates of methotrexate and doxorubicin. The conjugates were isolated by size exclusion chromatography. The conjugate was analyzed for its purity, as well as its conjugation ratio and payload. The conjugate was then formulated in a saline vehicle and administered to mice by s.c. or i.v. routes.

Mouse tolerability study: male C57BL/6 mice were treated with two single doses of ATAC or s.c. or i.v. Blood samples were taken on days 0, 1 and 4. Doses were adjusted until the maximal tolerated dose (MTD) was reached. In all studies, Cynomolgus monkeys were treated with a single dose of ATAC or s.c. or i.v. Blood samples were taken on days 0, 1, 4, 7, 10, 15, 20, 25, 30, 50, 70 and 90. Doses were adjusted until the maximal tolerated dose (MTD) was reached, and ADC levels were measured by LC-MS/MS.

Efficacy studies: prostate model: 2x10^6 PC3 cells were implanted subcutaneously into 8 mouse. After 4 weeks, a mean tumor volume of 150 mm^3 was measured, on day 10 and treated with a single dose of anti-PSMA-ADC (HPD-103) or PBS. B-cell leukemia model: 2x10^6 MEL-2 cells were injected i.c. into female C57BL/6 mice. On day 3 the mice were treated with a single s.c. or i.v. dose of anti-CD71-ADC or PBS.

2-4 year old monkeys were treated with a single s.c. or i.v. dose of Antibody-PSMA in an escalating dose regimen. AST and ALT levels were measured before and after dosing. Doses were adjusted until the MTD was reached, and ADC levels were measured by LC-MS/MS.

**RESULTS**

1. s.c. administration changes the pharmacokinetic profile and improves the tolerability of ATAC-based ADCs in mice

The PK profile directly influences the tolerability and efficacy of a drug it determines the maximal serum levels (Cmax), its serum half-life, and the dose available over time (AUC). Therefore, the effect of s.c. dosing on the PK profile of an ADC-based drug was investigated after a single s.c. or i.v. dose in mice (Figure 1).

2. The potential anti-tumor efficacy of ATAC-based ADCs is maintained after s.c. administration

The effect of s.c. dosing on the anti-tumor efficacy of ATAC-based drugs was investigated in human cancer cell xenograft models as previous results suggested that the efficacy of ATAC is driven by a bystander effect (AUC (Figure 2)).

3. s.c. administration improved the MTD of a single dose of ATAC-based ADCs by 30 to 50% as compared to i.v. treatment independent of the antibody-drug conjugate (ADC) used for non-targeting ATAC and the amatoxin (Amato) or AMD used as payload (Figure 3).

**CONCLUSION**

ATAC-based ADCs are a novel and promising class of ADCs with a new mode of action. Currently, HPD-103 is being tested in a clinical trial in patients with advanced epithelial ovarian cancer.

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