BT5528, a Bicycle Toxin Conjugate (BTC) targeting EphA2 has potent anti-tumour activity without bleeding or coagulation abnormalities in animal models

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WHY BICYCLES

- Bicycle® are novel therapeutic agents: bicycle peptides constrained via a chemical scaffold, which confer structural stability leading to high affinity and selectivity comparable with antibodies.
- The small size of Bicycle (1.5-3 kDa) allows rapid tissue penetration and extravasation.
- Bicycles are fully synthetic, allowing simple conjugation to form a Bicycle Toxin Conjugate, allowing targeted delivery of a cytotoxic payload.
- Ephrin receptor A2 (EphA2) is a member of the Ephrin receptor family of cell-cell junction proteins highly overexpressed in several solid tumours and associated with poor prognosis in patients. This profile has made EphA2 an attractive drug target for antibody-based therapies, including Antibody Drug Conjugates (ADCs).
- One such ADC, MEDI-547, showed good efficacy in preclinical models (Jackson et al, 2008) and was progressed into clinical trials. As described in Annizuela et al (2013), the clinical trial was terminated early, due to the reagent-related bleeding and coagulation events (hemorrhagic related, n=3, epistaxis, n=2) occurring in 5/6 patients receiving the dose. The bleeding and coagulation events observed in humans showed some similarities to those evident in rats and monkeys. In all three species, increased activated partial thromboplastin time (APTT) and increased fibrin D-dimer were reported, together with changes in liver function parameters (ALT, AST, AUF, serum albumin). Toxicology studies in the monkey identified disseminated intravascular coagulation (DIC) as the DII. The events observed in humans were considered to be consistent with the preclinical findings, in particular to the observation of DIC.

ABSTRACT

- BT5528 is a Bicycle Toxin Conjugate targeting EphA2-positive tumours.
- BT5528 shows profound efficacy in a range of EphA2-expressing tumour models.
- BT5528 maintains efficacy even in patients with relapsed or refractory solid tumours.

RESULTS

As shown in Figure 1, BT5528 binds to EphA2 with high affinity, across a range of relevant species (a). There is no significant binding to other related receptors.

In EphA2-expressing cells, BT5528 shows high affinity binding (b), against activity on EphA2 (c) and cell cytotoxicity (d). As shown in Figure 2, in vivo models, BT5528 shows target-mediated efficacy after intravenous administration, with significant effects seen in the high EphA2-expressing NCI-H1975 NSCLC xenograft (a) and MDA-MB-231 TNBC (b), but no significant effects seen in the low EphA2-expressing MDOI-8 Mucule Myeloma xenograft (c).

Figure 3 shows comparative efficacy in xenograft models between BT5528 and the ADC MEDI-547. Comparable efficacy is seen at 3mg/kg qw for the two agents in HT-1080 fibrosarcoma (a) and PC-3 prostate cancer (b) xenografts (though (c) BT5528 is also fully efficacious at 1mg/kg qw in PC3). In a larger, more heterogenous xenograft (NSCLC PDX), BT5528 maintains efficacy, while MEDI-547 fails to show efficacy (c). This probably reflects the greater capacity for BT5528 to penetrate solid tumours, as illustrated by PET imaging (d).

Figure 4 shows the lack of effect of BT5528 on toxicological parameters described for MEDI-547. In NHP exploratory toxicity studies BT5528 at doses ~MTO does not produce changes in D-Dimer (a), APTT (b) or liver enzymes (c). Additionally, no signs of bleeding were observed in any pre-clinical or micro-sopic pathology analysis.

CONCLUSION/SUMMARY

- BT5528 shows profound efficacy in a range of EphA2-expressing tumour models, comparable to that described for previous ADCs including MEDI-547.
- Unlike MEDI-547, BT5528 maintains efficacy even in large (>1000mm3), heterogeneous PDX tumours, reflecting the rapid and complete penetration of Bicycle Toxin Conjugates into solid tumours.
- BT5528 shows no bleeding or coagulation toxicity in preclinical species.
- IND-enabling studies for BT5528 are currently underway.

REFERENCES


REMARKS: Bicycle® is a registered trademark of Bicycle Therapeutics Limited. Bicycle Therapeutics Ltd, Cambridge, United Kingdom.