BT1718, a novel Bicycle Drug Conjugate® shows potent anti-tumor activity in diverse cell-derived and patient-derived tumor xenograft models

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ABSTRACT

- Bicycle Therapeutics has developed a proprietary phage display technology which enables efficient identification of high affinity / high selectivity bicyclic peptides (Bicycles®)
- Bicycles can be efficiently linked to therapeutic payloads to produce Bicycle Drug Conjugates (BDC®) which enable antigen-mediated delivery of cytotoxins to tumors
- BT1718 is a BDC comprising a Bicycle binder of membrane type 1 matrix metalloprotease (MT1-MMP; MMP14) covalently linked through a hindered disulfide cleavable linker to the potent anti-tubulin agent DM1
- BT1718 demonstrated MT1-MMP-dependent cell killing of non-small cell lung cancer (NSCLC) cells in vitro and in vivo across a panel of human lung xenograft mouse models, including patient-derived xenograft models (PDX)

INTRODUCTION

BT1718 is a Bicycle Drug Conjugate (BDC) comprising a constrained bicyclic peptide that binds with high affinity and specificity (Table 1) to membrane type 1-matrix metalloprotease (MT1-MMP; MMP14) covalently linked through a hindered disulfide linker to the potent anti-tubulin agent DM1 (Figure 1).

METHODS & RESULTS

Figure 2: Efficacy of BT1718 in cell-derived NSCLC xenograft models. BT1718 was dosed at 1, 3, 10 mg/kg, twice weekly, i. v. (a) in EBC-1 xenografts, complete clearance of tumour was seen within 14 days at 10mg/kg & 5mg/kg, whilst a dose of 3mg/kg elicited tumour stasis. (b) in NCI-H1975 xenografts, complete clearance of tumour was seen by 28 days at 10mg/kg with lower doses being comparable to the vehicle control group. (c) in NCI-2031 xenografts, tumours were reduced to minimal volume within 28 days with bi-weekly dosing at 10mg/kg, with lower doses being partially efficacious. After the 8th dose, on day 28, dosing was ceased. In this model a rare relapse and re-growth of the tumour was observed and animals were subsequently re-dosed with BT1718 at 10mg/kg (when tumours had reached ~150mm3). The tumours were responsive to additional doses of BT1718 and the re-growth was successfully treated and tumour cleared.

Figure 3: Efficacy of BT1718 in patient-derived xenograft models. BT1718 was dosed at 3 or 10mg/kg twice weekly, i. v. Docetaxel was dosed at 20mg/kg once weekly, i. v. (a) in high MT1-MMP expressing PDXs, good efficacy was seen with 3 & 10mg/kg BT1718, with complete clearance of tumour within 20 days at the 10mg/kg dose and tumour stasis at the 3mg/kg dose. Docetaxel, as standard of care comparator, shows a small reduction in the growth of the tumour. (b) In high MT1-MMP expressing NCI-H1975, efficacy was seen at both 3 & 10mg/kg BT1718, with complete clearance of tumour within 20 days at 10mg/kg. Docetaxel, as standard of care comparator, shows comparable tumour clearance to BT1718 at 10mg/kg. However, at this dose significant weight loss (>10%) was seen in the Docetaxel group (see inset graph) and not in the BT1718 cohorts. (c) In low MT1-MMP expressing PDXs, efficacy was not observed with BT1718 at 3 or 10mg/kg, Docetaxel slowed the rate of tumour growth but again, exerted a significant effect on body weight (>10% loss in 20 days).

CONCLUSION/SUMMARY

- BT1718 has high affinity & selectivity for MT1-MMP, which is highly upregulated in NSCLC and other tumours
- BT1718 rapidly clears tumours in a range of lung cancer models in an MT1-MMP dependent manner
- Comparable efficacy in observed in cell-derived and patient-derived xenografts independent of sensitivity of the model to current standard of care therapies
- BT1718 is a first-in-class cytotoxic Bicycle Drug Conjugate with great potential for treatment of lung cancer and is progressing forward to clinical trials in collaboration with Cancer Research UK

REFERENCES

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