Development of BT1718, a novel Bicycle Drug Conjugate for the treatment of lung cancer

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ABSTRACT

- Bicycle® Therapeutics has developed a proprietary phage display platform technology allowing the selection of high affinity bicyclic peptide binding molecules (Bicycles®)
- BT1718 is a Bicycle Drug Conjugate (BDC®) comprising a constrained bicyclic peptide that binds with high affinity and specificity to membrane type 1-matrix metalloproteinase (MT1-MMP, MMP14) covalently linked through a hindered disulfide linker to the potent anti-tubulin agent DM1.
- BT1718 demonstrated MT1-MMP-target specific binding and MT1-MMP-dependent cell killing of lung tumor cells in vitro as well as efficacy across a panel of lung tumor xenograft mouse models.

INTRODUCTION

BT1718 is a Bicycle drug conjugate (BDC) comprising a constrained bicyclic peptide that binds with high affinity and specificity to membrane type 1-matrix metalloproteinase (MT1-MMP, MMP14) covalently linked through a hindered disulfide linker to the potent anti-tubulin agent DM1. MT1-MMP is naturally involved in tissue remodelling, however overexpression of the surface protease has been tied to tumor aggressiveness and invasiveness, as well as poor patient prognosis for many cancer indications. Expression of MT1-MMP is elevated in tissue culture models

METHODS & RESULTS

Figure 1. Expression of MT1-MMP in tissue sections, visualised by immunohistochemistry using anti-MT1-MMP antibody. Low expression of MT1-MMP is seen in normal lung tissue (a), with higher expression in NSCLC tumour sections (b) and in PDX xenograft sections (c).

Figure 2. Efficacy of BT1718 in NSCLC xenograft models. BT1718 was dosed at 1, 3, 10 mg/kg, twice weekly. iv. (a) EBC-1 xenograft, complete clearance of tumour was seen within 14 days, with partial efficacy seen at 3mg/kg & iv. (b) NC-1H1795 xenograft, complete clearance of tumour was seen by 28 days. (c) H23-292, tumours were reduced to minimal volume after 28 days, and dosing ceased. On relapse animals were re-treated (when tumours reached ~150mm3). Significant clearance of tumour was seen in mice following re-dosing. Figure 3. Efficacy of BT1718 in Patient-Derived Xenograft models. BT1718 was dosed at 3 or 10/30mg/kg twice weekly, iv. Docetaxel was dosed at 20mg/kg twice weekly, iv. (a) High MT1-MMP expressing sensitive BT1718, 3mg/kg & iv. BT1718, with complete clearance of tumour within 24/10kg. Docetaxel showed negligible effect on tumour. (b) High MT1-MMP expressing PDX, efficacy seen with 3 & 10mg/kg, with complete clearance of tumour within 28/10kg. Docetaxel shows complete clearance of tumor, though with significant weight loss (>10%). (c) Low MT1-MMP expressing PDX, efficacy not seen with BT1718 at 3 or 10/30mg/kg. Docetaxel shows negligible effect on tumour, with significant weight loss (>10%).

Figure 4. Using EBC-1 xenograft model, we investigated the target-dependence of BT1718 activity and evaluated a range of dose schedules. (a) Target dependence was evaluated by co-dosing unconjugated peptide binder. BT1718 efficacy was inhibited by co-injection of 150x excess of MT1-MMP binder, but not non-binder, peptide. (b) The same total dose of BT1718 (200ng) was equally efficacious when dosed in one, twice, three or seven injections.

CONCLUSION/SUMMARY

BT1718 is a first-in-class cytotoxic drug conjugate with great potential for treatment of lung cancer

- High affinity & selectivity for MT1-MMP. MT1-MMP is highly expressed in human lung tumours & xenografts, not in normal lung
- Rapid clearance of tumours in a range of MT1-MMP expressing lung cancer models
  - Comparable efficacy in cell line and patient-derived xenografts
  - Efficacy in lines sensitive or resistant to standard of Care treatment
- Efficacy dependent on binding to tumour-expressed MT1-MMP

BT1718 is progressing forward to clinical trials in collaboration with Cancer Research UK.

Bicycle Therapeutics will be presenting further data on posters 5144 / 16 & 3719/4

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