BT5528, a Bicycle Toxin Conjugate targeting EphA2: mechanism of action and clinical translation

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ABSTRACT

BT5528 is a Bicycle Toxin Conjugate (BTC) targeting the tumor expressed antigen EphA2. Increased EphA2 expression has been reported in multiple tumor types (including NSCLC, ovarian cancer, TNBC, gastric/upper GI, pancreatic and urothelial cancers) so represents an attractive tumor binding target. The identification, characterization and initial in vivo profiling of BT5528 has previously been described. This poster describes a more detailed analysis of the mechanism of action of BT5528.

RESULTS

Mechanism of action with BT5528

(a) Intravenous dosing of BT5528 provides short systemic exposure and limited systemic toxicity. MMAE payload. BT5528 efficiently delivers MMAE to tumor, with high concentrations measured in tumor doses to at least 48h post-dose. (b) Tumor cells show a pharmacodynamic response to BT5528 dosing, with a notable increase in cell numbers, staining positive for pHH3+, tumor volume decreases from 2d post-dose, indicating tumor death after dosing of BT5528. (c) Tumor killing with BT5528 requires expression of EphA2 receptor, shown by a clear relationship between EphA2 expression on cell surface (measured by FACS) and efficacy of BT5528. (d) Efficacy of BT5528 is independent of the rate of administration, with equivalent efficacy seen after administering the same dose as a bolus or as 1 or 2 24h infusions. (e) Efficacy can also be seen with dosing as infrequently as every 2 weeks. Compared to BT5528, reduced efficacy is seen with (f) antibodies either lacking a cleavable linker (g) or carrying the non-permeant toxin MMAE (h).

BT5528 toxicity

A preclinical Antibody Drug Conjugate targeting EphA2 (MEDI-547) showed good preclinical efficacy, but bleeding effects on liver enzymes were observed at the starting dose in a Ph1 clinical trial. The clinical events were prevented by nonclinical findings observed in toxicity studies in cynomolagus and rat. In preclinical toxicology with BT5528, no coagulopathy, DIC-like syndrome or bleeding events were seen, no changes were seen in measures of bleeding coagulation, and no increases seen in tests of liver enzymes in plasma (i).

CONCLUSION/SUMMARY

BT5528 is a Bicycle Toxin Conjugate targeting the tumor cell marker EphA2. Mechanism of action studies show that BT5528 has a limited systemic exposure but efficiently delivers toxin payload to tumor, resulting in extended pharmacodynamic effects and tumor regression. Efficacy can be seen across a range of dose rates and intervals, and requires target expression and in close proximity to a systemic bystander component. BT5528 maintains efficacy in a range of "hard to hit" models, including complex PDX models with very large tumor volumes, pancreatic tumors and metastatic models. Clear differentiation is seen from previous ADC approach to targeting EphA2 in terms of efficacy, but also importantly in terms of toxicity, with very little evidence of bleeding or liver toxicity in preclinical studies. BT5528 is currently progressing towards FIH clinical trials.

REFERENCES

Annunziata et al., Investigational New Drugs 31 (1): 77–84 (2013)