464P Pharmacokinetic (PK) assessment of BT1718: A phase I/II a study of BT1718, a first in class bicycle toxin conjugate (BTC), in patients (pts) with advanced solid tumours

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Background: BT1718 contains a constrained bicyclic peptide with high affinity and selectivity for cell surface target MT1-MMP (MMP14) linked to a toxin (DM1) via a cleavable disulphide linker. BT1718 has demonstrated significant anti-tumor activity in preclinical studies in tumors that express MT1-MMP. Following intravenous (IV) administration to preclinical species, BT1718 exhibited PK typical of a BTC. We report clinical progress on QW and BIW dosing, plasma and tumor PK results.

Methods: This is a first in human, multicenter, dose escalation study in advanced solid tumor pts with the aims of establishing the recommended phase 2 dose (RP2D) for QW & BIW IV BT1718 dosing (3 out of every 4 weeks per cycle), and exploratory PK. Following determination of RP2Ds, expansion cohorts will enroll to further explore efficacy, tolerability and PD of BT1718 in ~70 pts with MT1-MMP expressing tumors such as NSCLC and TNBC.

Results: 24 pts were enrolled with various types of solid tumors across both dose escalation cohorts (see table). BIW RP2D was determined as 7.2 mg/m^2. The 2 pts with DLTs at 9.6 mg/m^2 BIW experienced grade 3 increased GGT or fatigue. QW dose escalation continues at 20 mg/m^2. Mean number of cycles received = 2.3 months (N = 24), with no objective responses observed to date in this unselected population. Consistent with preclinical data, preliminary clinical PK results with BT1718 confirm moderate plasma clearance (~10 mL/min/kg) linear with dose, a volume of distribution similar to extracellular fluid (~0.20 L/kg) and a $t_{1/2}$ of ~0.3 h. Analysis of pts biopsy samples confirms distribution of DM1 in tumors at similar concentrations observed in mouse xenograft models. Results will be updated at time of presentation.

Table: 464P

BT1718 Dose (mg/m^2)	Twice weekly schedule (BIW)		Once weekly schedule (QW)	
	DLT evaluable pts	DLTs	DLT evaluable pts	DLTs
0.6	1	0	NA	NA
1.2	1	0	NA	NA
2.4	1	0	NA	NA
4.8	1	0	NA	NA
7.2	6	0	NA	NA
9.6	4	2	3	0
15	NA	NA	3	0
20	NA	NA	2	0

Conclusions: BT1718 is a first in class BTC which is generally well tolerated at the present dose level. Current plasma and tumor PK data are consistent with proposed preclinical mechanism of tumor targeted toxin delivery.

Clinical trial identification: NCT03486730.

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