MYTX-011: A novel cMET-targeting antibody drug conjugate (ADC) engineered to increase on-target uptake in and efficacy against cMET expressing tumors

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**BACKGROUNd**

cMET alterations can act as an oncogenic driver in non-small cell lung cancer (NSCLC) and elevated cMET expression occurs in many cancers. Antibody drug conjugates targeting cMET (anti-cMET-ADCs) have been developed as a strategy to treat cMET positive (cMET+) tumors irrespective of dependency on cMET signaling.

- Anti-cMET-ADCs have shown promising clinical activity as a monotherapy in NSCLC, but activity was mostly limited to a subset of patients with high cMET expression, indicating cMET levels may be limiting for efficacy.
- We sought to create an ADC with the potential to benefit a broader population of patients including those expressing moderate cMET levels.
- We hypothesized that engineering the antibody to rapidly lose affinity at acidic extracellular pH would boost ADC uptake and efficacy in cMET+ tumor cells by avoiding non-productive ADC recycling.

Figure 1: MYTX-011 incorporates the clinically validated cMMAE linker-payload (Dab 2) conjugated to a novel, pH dependent anti-cMET IgG antibody.

**METHODS**

- We conducted mutageneis of anti-cMET antibodies, screening for variants that selectively lost binding under acidic conditions and assessed antibody internalization in cell-based assays.
- Binding to cMET was tested in basolateral interferometry (BLI) assays with antibody variants immobilized on the basolateral and concentric human cMET-hs in solution at pH 7.4, 6.4, or 5.4.
- Internalization assays were performed by incubating cMET+ cell lines with antibody variants and a secondary F(ab)² conjugated to phthalo dye.
- MYTX-011, non-hVMAE engineered Parent, Benchmark site specific ADCs were composed of antibody variable regions from clinical stage anti-cMET antibodies.
- Benchmark ADC (Dab 3) was built by hinge conjugation of a clinical stage anti-cMET ADC antibody to cMMAE, then HCl purification.
- Cytotoxicity assays in a large panel of cancer cell lines were performed at Crown Bioscience, IC₅₀ values (50% maximal inhibitory concentration) were determined from 8 point dose response curves; 96 hour incubation.
- For tumor xenograft studies, cancer cell lines were implanted in the flanks of SCID mice and animals were randomized into treatment groups (n/group) once tumors volumes reached 100-150 mm³. ADCs were administered intravenously as a single dose. cMET expression in tumors was assessed by immunohistochemistry (IHC) (SP4/Varian).

**CONCLUSIONS**

- MYTX-011 showed increased total mAb half life and reduced release of free MMAE compared to the non-pH engineered Parent and Benchmark ADCs due to reduced target mediated drug disposition.
- Total ADC levels for MYTX-011 were similar to total mAb confirming stability of the linker and the choice of conjugation site (data not shown).

**REFERENCES**


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