MYTX-011 in patients with previously treated locally advanced or metastatic NSCLC: Initial dose escalation results in the phase 1 KisMET-01 study

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Abstract #8558

BACKGROUND

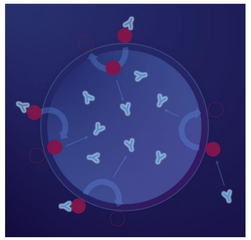


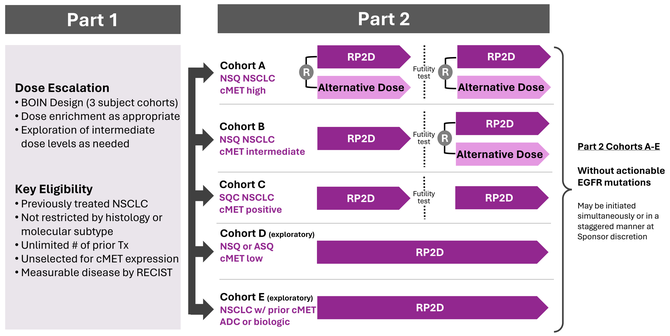
Figure 1. Illustration of MYTX-011 pH-dependent binding

- MYTX-011 is a novel cMET-targeted, DAR 2 vcMMAE antibody-drug conjugate (ADC) with a monoclonal antibody that has been engineered to have pH-dependent binding between the target and the ADC.[1]
- The pH-dependent binding allows MYTX-011 to dissociate from cMET in acidic endosomes, leading to higher net internalization and payload delivery.[2] (Figure 1)
- MYTX-011 demonstrated superior anti-tumor activity and more favorable pharmacokinetics (PK) compared to benchmark ADC and the non-engineered parent ADC. [1,2]

METHODS

- KisMET-01 (NCT05652868) is a multicenter, first-in-human study of MYTX-011 in patients with previously treated, locally advanced or metastatic NSCLC. The study is comprised of Part 1 dose escalation followed by Part 2 dose expansion (Figure 2).
- Part 1 enrolls patients with previously treated locally advanced or metastatic NSCLC without available standard of care. There is no limitation on histology, molecular subtype/actionable mutation, or number of prior lines of therapy (Tx) received. cMet expression by immuno-histochemistry (IHC) is not required for entry but analyzed retrospectively via a central lab whenever tumor tissue is available.
- Dose escalation follows the 3-subject cohort BOIN design. Enrichment of cleared dose levels and exploration of intermediate dose levels are allowed.
- Part 2 dose expansion includes five cohorts. Cohort A–D will enroll selected NSCLC patients defined by cMET expression levels and histology. Cohort E will enroll patients with prior exposure to cMET-targeted ADC/biologics, which not eligible for study entry in other cohorts.
- The primary objectives of Part 1 are to assess safety and tolerability and determine the recommended phase 2 dose (RP2D). Secondary objectives include assessment of PK and preliminary anti-tumor activity.

Figure 2. KisMET-01 Study Design



RESULTS

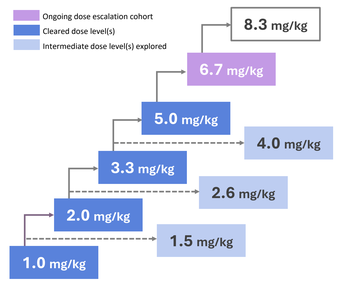
Table 1. Baseline Characteristics

Characteristics	N=41
Age, median [range]	65 [28–83]
Sex, n (%)	
Female	23 (56)
Male	18 (44)
Race, n (%)	
White	30 (73)
Asian	6 (15)
Black	3 (7)
Mixed-race	1 (2)
Not reported	1 (2)
ECOG, n (%)	
0	7 (17)
1	34 (83)
NSCLC histology, n (%)	
NSQ	30 (73)
SQ	10 (24)
ASQ	1 (2)
Actionable mutation, n (%)	
EGFR mutation	6 (15)
KRAS mutation	5 (12)
MET exon 14 skipping mutation	5 (12)
EML4-ALK fusion	3 (7)
cMET expression by IHC	
cMET expression available[1], n (%)	21 (51)
H-score, median [range]	190 [19–290]
High, n (%[2])	6 (29)
Intermediate, n (%[2])	2 (10)
Low, n (%[2])	8 (38)
Negative, (%[2])	5 (24)
Prior system anticancer Tx	
No. Tx, median [range]	3 [1–6]
Platinum-based	37 (90)
Immune checkpoint inhibitors	31 (76)
Taxane-based[3]	20 (49)
cMET TKI	6 (15)

1. All results were from central lab except for one patient
2. Percentage of patients with available cMET expression results
3. Prior exposure to docetaxel, paclitaxel, or nab-paclitaxel

cMET expression definition: High: ≥50% 3+; Intermediate: ≥25% to <50% 3+; Low: ≥25% 2+ and high and intermediate not met; Neg: high, intermediate, and low not met

Figure 3. Part 1 Dose Escalation Schema



Study Population

- As of April 30, 2024, 42 patients had been enrolled and received ≥1 dose of MYTX-011 [dose range 1.0– 6.7 mg/kg] in Part 1. Data from 41 pts was available by data cutoff. Median follow-up was 15 weeks [range 1– 49].
- The proportion of patients with non-squamous cell (NSQ), squamous cell carcinoma (SQ), and adenosquamous (ASQ) histology were 73%, 24%, and 2%, respectively.
- 46% of patients had actionable mutations, including *EGFR* mutation (15%), *KRAS* mutation (12%), *MET* exon 14 skipping mutation (12%), and *EML4-ALK* fusion (7%).
- Patients had a median of 3 [range 1– 6] prior lines of systemic anticancer Tx (Table 1). Majority of patients had received platinum-based therapy (90%) and immune checkpoint inhibitors (76%). 49% of the patients had prior exposure to at least one taxane-based therapy, and 15% had received a cMET tyrosine kinase inhibitor (TKI).
- cMET IHC results were available in 51% of patients with a median H-score of 190 [range 19– 290]. Among patients with available cMET expression, the proportion of high (≥50% tumor cells with 3+), intermediate (≥25% to <50% tumor cells with 3+), low (≥25% tumor cells with 2+, and criteria of high and intermediate not met), and negative (criteria of high, intermediate, and low not met) expression were 29%, 10%, 38%, and 24%, respectively.

Pharmacokinetics

- As of data cutoff, PK data was available in patients who received doses 1.0 to 5.0 mg/kg.
- PK of MYTX-011 showed nearly dose proportional exposure up to 5.0 mg/kg.
- Little separation of ADC and total mAb concentration was noted, suggesting good stability of MYTX-011.
- Unconjugated MMAE dose-normalized average C_{max} of MYTX-011 was less than 50% of the dose-normalized average C_{max} from 8 literature reported MMAE ADCs.[3]
- Overall PK profile supports the current Q3W dosing schedule.

Safety

- 90% of patients experienced at least one treatment-emergent adverse event (TEAE). Grade ≥ 3 TEAE occurred in 32% of patients. 5% of patients discontinued MYTX-011 due to AE.
- TEAEs reported in >10% of patients are listed in Table 2. The most frequent TEAEs were fatigue (34%), corneal changes (29%), and blurred vision (29%). Fatigue (5%) was the most frequent Grade ≥ 3 TEAE.
- Incidences of common AEs associated with MMAE or cMET-targeted Tx, including peripheral neuropathy, hematologic toxicities, hypoalbuminemia, peripheral edema, and elevated liver function tests were low or absent, and predominantly low grade (Table 3).

RESULTS (continued)

Figure 4. ADC and Total mAb Concentration

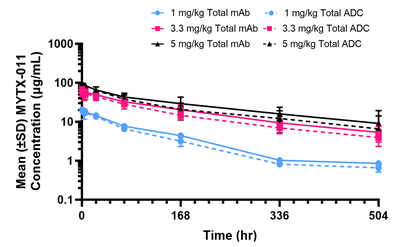
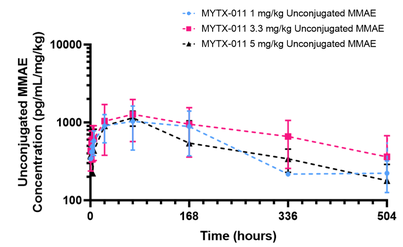


Figure 5. Unconjugated MMAE Concentration



- All ocular AEs (corneal changes, blurred vision, dry eye) were reversible. 24% of patients had dose delay due to ocular AE, and 17% had dose reduction. No worsening or recurrence of ocular AE was reported in patients who resumed dosing after dose delay and/or dose reduction. None of the ocular AEs led to discontinuation of MYTX-011. A protocol amendment that includes similar ocular AE mitigation measures taken by approved ADCs is being implemented in Q2 2024.[4,5]
- 1.0, 2.0, 3.3, and 5.0 mg/kg have been cleared in dose escalation (Figure 3). No dose-limiting toxicity was reported. Intermediate dose levels of 1.5, 2.6, and 4.0 mg/kg were explored. Dose escalation (Part 1) is ongoing.

Table 2. TEAEs reported in >10% of patients

Adverse Event	All Grade n (%)	≥ Grade 3 n (%)
Fatigue	14 (34)	2 (5)
Corneal changes[1]	12 (29)	1 (2)
Blurred vision	12 (29)	1 (2)
Dry eye	10 (24)	1 (2)
Nausea	10 (24)	1 (2)
Cough	7 (17)	0 (0)
Dyspnea[2]	7 (17)	1 (2)
Peripheral edema	5 (12)	0 (0)
Vomiting	5 (12)	0 (0)

1. Includes keratopathy, keratitis, microcystic lesions
2. None of the cases were pneumonitis or ILD

Table 3. Selected TEAEs: common AEs associated with MMAE or cMET-targeted Tx

Adverse Event	All Grade n (%)	≥ Grade 3 n (%)
Peripheral neuropathy	4 (10)	0 (0)
Anemia	2 (5)	1 (2)
Thrombocytopenia	0 (0)	0 (0)
Neutropenia	0 (0)	0 (0)
Hypoalbuminemia	1 (2)	1 (2)
Peripheral edema	5 (12)	0 (0)
AST/ALT elevation	3 (7)	1 (2)

CONCLUSIONS

- MYTX-011 has been well tolerated with low incidence of common AEs associated with MMAE or cMET targeted Tx.
- PK of MYTX-011 reflects good stability, supports dosing every 3 weeks, and translates into favorable safety profile.
- Given that dose escalation is ongoing and the overall median follow-up as of the data cutoff was 15 weeks, efficacy data will be presented in a future conference/publication.
- Preliminary profile supports development of MYTX-011 in multiple subsets of NSCLC.

REFERENCES

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