Phase 1 Multicenter Dose Escalation and Dose Expansion Study of Antibody-Drug Conjugate (ADC) MYTX-011 in Subjects with Non-Small Cell Lung Cancer

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KisMET-01

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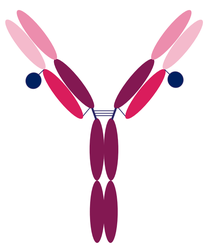
Alexander I Spira, Melissa Lynne Johnson, George R Blumenschein, Timothy F Burns, Jonathan Robert Thompson, Amit Deshpande, William C Comb, Brian Fiske, Gilles Gallant, Rebecca S Heist

NEXT Oncology - Virginia Cancer Specialists, Fairfax, VA; The Sarah Cannon Research Institute, Nashville, TN; University of Texas MD Anderson Cancer Center, Houston, TX; UPMC Hillman Cancer Center, Pittsburgh, PA; Medical College of Wisconsin, Milwaukee, WI; Mythic Therapeutics, Waltham, MA; Massachusetts General Hospital, Boston, MA

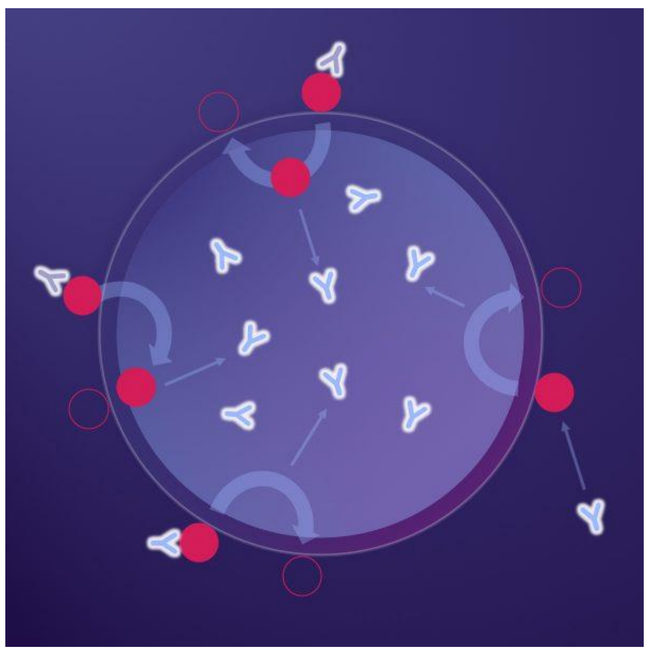
BACKGROUND

MYTX-011 Design



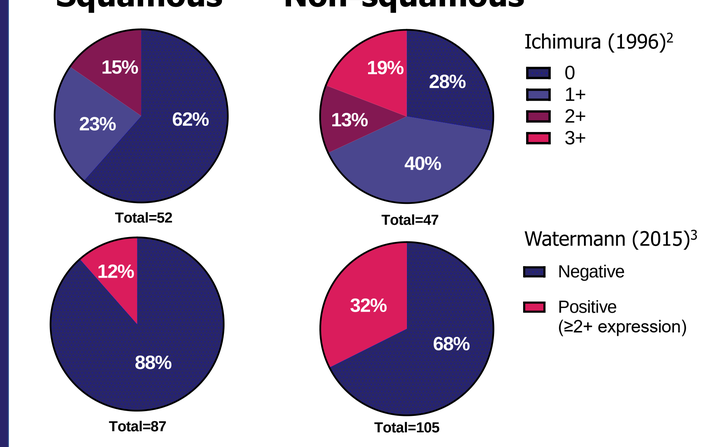
- Novel, pH-dependent anti-cMET IgG1 antibody that increases tumor internalization and ADC cytotoxicity
- Clinically validated vcMMAE linker-payload
- Conjugated at engineered cysteine residues (DAR 2)

MYTX-011 Mechanism



- A traditional ADC binds cell surface antigen, ADC-antigen complex internalizes and traffics to lysosomes where the linker is cleaved, and the payload is released. Destruction of mAb and antigen results.
- MYTX-011 binds with high affinity at neutral or slightly acidic pH representative of the tumor microenvironment but is engineered to quickly release from cMET antigen in the acidic endolysosomes.
  - The liberated MYTX-011 continues to lysosomal processing and linker cleavage, while the cMET antigen recycles to the surface for additional MYTX-011 binding. Non-productive recycling of the MYTX-011-antigen complex is prevented.
  - pH engineering results in increased internalization, in vitro cytotoxicity, in vivo efficacy, and improved PK compared to non-engineered controls or clinical benchmarks[1].

cMET Expression in NSCLC



Both IHC studies performed with SP44 anti-cMET antibody

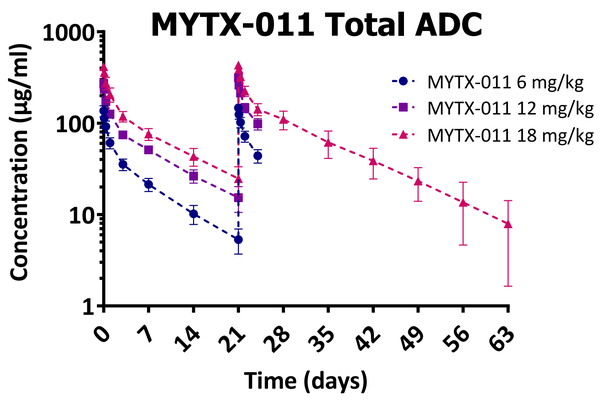
MYTX-011 Nonclinical Toxicity and Pharmacokinetics

- Repeat dose (day 1 and 21) GLP-toxicity study in cynomolgus monkeys*
- Toxicity profile was comparable to vcMMAE ADCs[3]
  - No adverse clinical observations or tolerability concerns were noted
  - Reversible neutropenia and mild bone marrow toxicity (with associated hematology changes) observed at ≥ 12mg/kg
- MYTX-011 levels in circulation increased in a dose proportional manner and no anti-drug antibodies were detected.

Incidence of Neutropenia

Sex	Control	6mg/kg	12mg/kg	18mg/kg*
Males	0/5	0/3	1/3	5/5
Females	0/5	0/3	0/3	4/5

Neutropenia = Neutrophils < $1*10^3$/ul



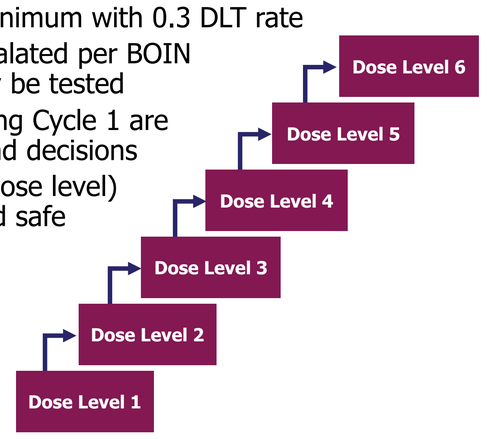
* 3 animals per sex per dose level were sacrificed 3 days after the second dose. 4 animals (2 per sex) in control and 18mg/kg group underwent 6-week recovery, represented in PK traces Day 28-63.

METHODS

Two-Part (Dose Escalation and Dose Expansion) Phase 1 First-in-Human Study

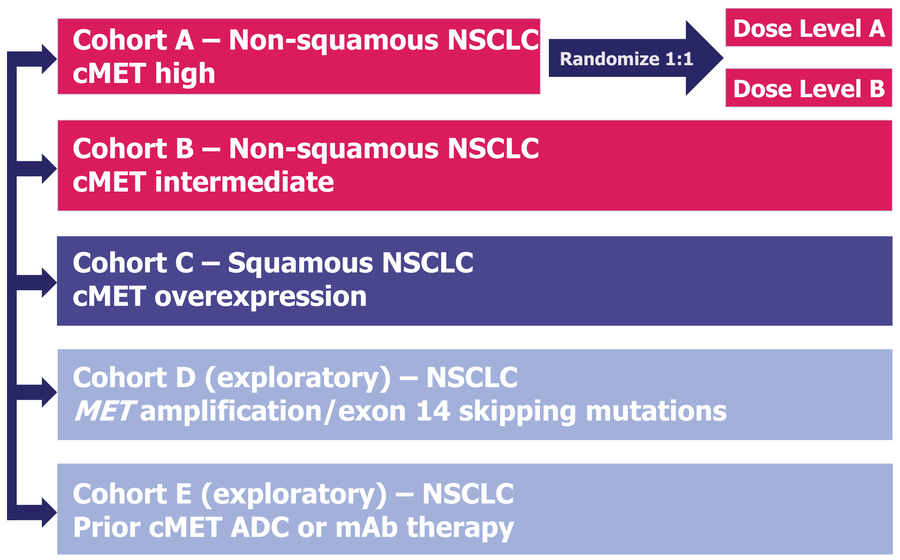
Part 1 – Dose Escalation

- BOIN[4] Design: 3-subject cohort minimum with 0.3 DLT rate
- Doses may be escalated or de-escalated per BOIN algorithm, intermediate doses may be tested
- Dose-limiting toxicities (DLTs) during Cycle 1 are considered for dosing algorithm and decisions
- Additional subjects (up to 10 per dose level) may be backfilled at doses deemed safe



Key Eligibility:
- Previously treated, locally advanced or metastatic NSCLC
- Unlimited prior therapy
- Unselected for cMET expression
- Measurable disease (RECIST 1.1)

Part 2 – Dose Expansion



Key Eligibility:
- No actionable EGFR mutations
- Cohorts A-C enrolled based on cMET expression (IHC)
- Measurable disease (RECIST 1.1)

KisMET-01 Objectives

Primary Objectives

Part 1:
- Evaluate the safety and tolerability of MYTX-011
- Determine the recommended Phase 2 dose (RP2D) and/or maximum tolerated dose (MTD)

Part 2:
- Evaluate the safety and tolerability of MYTX-011
- Evaluate the overall response rate based on the number of complete responses and partial responses

Secondary Objectives (Part 1 and Part 2)
- Characterize the pharmacokinetic (PK) profile of MYTX-011
- Assess the incidence and persistence of anti-drug antibodies to MYTX-011
- Determine preliminary anti-tumor activity of MYTX-011 (ORR, DOR, TTR, DCR, PFS, OS)

KisMET-01 is Currently Enrolling

References

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2. Ichimura E, Maeshima A, Nakajima T, Nakamura T. Expression of c-met/HGF receptor in human non-small cell lung carcinomas in vitro and in vivo and its prognostic significance. Jpn J Cancer Res. 1996;87(10):1063-1069. doi:10.1111/j.1349-7006.1996.tb03111.x
3. Watermann I, Schmitt B, Stellmacher F, et al. Improved diagnostics targeting c-MET in non-small cell lung cancer: expression, amplification and activation?. Diagn Pathol. 2015;10:130. Published 2015 Jul 28. doi:10.1186/s13000-015-0362-5
4. Junutula JR, Raab H, Clark S, et al. Site-specific conjugation of a cytotoxic drug to an antibody improves the therapeutic index. Nat Biotechnol. 2008;26(8):925-932. doi:10.1038/nbt.14804.
5. Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. *Clin Cancer Res*. 2016;22(17):4291-4301. doi:10.1158/1078-0432.CCR-16-0592