# TITLE: A Phase 1 Multicenter Dose Escalation and Dose Expansion Study of Antibody-Drug Conjugate MYTX-011 in Subjects with Non-Small Cell Lung Cancer – KisMET-01


**Sponsor:** Mythic Therapeutics, Inc.
100 Beaver Street
Waltham, MA 02453


**Protocol Number:** MYTX-011-01

**IND Number:** 159721

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**Study Drug(s):** MYTX-011


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**Version:** 7.0

**Date:** August 29, 2025

# SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol MYTX-011-01 for issuance.

**Protocol Title:** A Phase 1 Multicenter Dose Escalation and Dose Expansion Study of Antibody-Drug Conjugate MYTX-011 in Subjects with Non-Small Cell Lung Cancer – KisMET-01

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**SPONSOR CHIEF MEDICAL OFFICER, Mythic Therapeutics, Inc.**

| | | |
|---|---|---|
| Paul Basciano, MD | Signed by: Paul Basciano<br>Signer Name: Paul Basciano<br>Signing Reason: I approve this document<br>Signing Time: 9/2/2025 \| 2:01:59 PM PDT<br>FDF9A6288C264204A22D5AFAD7B97954 | 9/2/2025 |
| Print Name | Signature | Date |

**SPONSOR MEDICAL MONITOR, Mythic Therapeutics, Inc.**

| | | |
|---|---|---|
| Ting-Hui Wu, MD, MSc | Signed by:<br>Signer Name: Ting Wu<br>Signing Reason: I have reviewed this document<br>Signing Time: 9/2/2025 \| 3:08:17 PM PDT<br>034102BD6DA94A59B17ABFD1C22CBD5D | 9/2/2025 |
| Print Name | Signature | Date |

# PROTOCOL ACCEPTANCE FORM

**Protocol Title:** A Phase 1 Multicenter Dose Escalation and Dose Expansion Study of Antibody-Drug Conjugate MYTX-011 in Subjects with Non-Small Cell Lung Cancer – KisMET-01

**Protocol ID:** MYTX-011-01

**Version:** 7.0

**Final Date:** August 29, 2025

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and of the Investigator's Brochures to all members of the study team for whom I am responsible and who participate in the study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study.

Once the Institutional Review Board/Independent Ethics Committee (IRB/IEC) has approved the protocol, I will not modify this protocol without obtaining the prior approval of Mythic Therapeutics, Inc. and of the IRB/IEC. I will submit the protocol modifications and/or any informed consent modifications to Mythic Therapeutics, Inc. and the IRB/IEC, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (1964).

| Investigator - Print Name | Signature | Date |
|---|---|---|

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| Abbreviation | Definition |
|---|---|
| ADA | anti-drug antibodies |
| ADC | antibody-drug conjugate |
| ADCC | antibody-dependent cellular cytotoxicity |
| ADCP | antibody-dependent cellular phagocytosis |
| ADL | activities of daily living |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALK | anaplastic lymphoma kinase |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BAL | bronchoalveolar lavage |
| BOIN | Bayesian Optimal Interval |
| BOP2 | Bayesian Optimal Phase 2 |
| BoR | best observed response |
| BUN | blood urea nitrogen |
| BCVA | best corrected visual acuity |
| C, c | Cycle, cycle |
| CABG | coronary artery bypass graft |
| CDC | complement-dependent cytotoxicity |
| cfDNA | circulating free deoxyribonucleic acid |
| CFR | Code of Federal Regulations |
| CL | clearance |
| $C_{last}$ | last measurable concentration |
| $C_{max}$ | maximum concentration |
| cMET | protein product of the *MET* gene |
| CNS | central nervous system |
| COVID-19 | coronavirus disease 2019 |
| CR | complete response |
| CT | computed tomography |
| CTA | Clinical Trial Agreement |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumor deoxyribonucleic acid |
| CV | curriculum vitae |
| D, d | Day, day |

| Abbreviation | Definition |
|---|---|
| DAR | drug-to-antibody ratio |
| DCR | disease control rate |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| DSMB | Data Safety Monitoring Board |
| EC | Ethics Committee |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| eGFR | estimated glomerular filtration rate |
| *EGFR* | epidermal growth factor receptor [gene] |
| EOT | end of treatment |
| FDA | Food and Drug Administration |
| FIH | first in human |
| FISH | fluorescence in situ hybridization |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| HbA1c | hemoglobin A1c |
| HBcAb | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HCVAb | hepatitis C antibody |
| HED | human equivalent dose |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |
| HIV | human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IgG1 | immunoglobulin G1 |
| IHC | immunohistochemistry |
| ILD | interstitial lung disease |
| INR | international normalized ratio |
| IRB/IEC | Institutional Review Board (IRB) or Independent Ethics Committee (IEC) |
| IRR | infusion-related reaction |

| Abbreviation | Definition |
|---|---|
| IRT | Interactive Response Technology |
| ISF | Investigator Study File |
| IV | intravenous(ly) |
| L858R | substitution of leucine (L) with arginine (R) at position 858 |
| LVEF | left ventricular ejection fraction |
| *MET* | *MET* proto-oncogene, receptor tyrosine kinase |
| mg | milligram |
| mL | milliliter(s) |
| MMAE | monomethyl auristatin E |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| MUGA | multigated acquisition scan |
| NCI | National Cancer Institute |
| NE | not estimable |
| NSCLC | non-small cell lung cancer |
| NYHA | New York Heart Association |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |
| PET | positron emission tomography |
| PFS | progression-free survival |
| P-gp | P-glycoprotein |
| PHI | protected health information |
| PK | pharmacokinetic(s) |
| PR | partial response |
| PT | prothrombin time |
| PTCA | percutaneous transluminal coronary angioplasty |
| Q3W | every 3 weeks |
| QTc | corrected QT interval |
| RBC | red blood cell |
| RECIST 1.1 | Response Evaluation Criteria in Solid Tumors 1.1 |
| RNA | ribonucleic acid |
| RP2D | recommended Phase 2 dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SCr | serum creatinine |
| SD | stable disease |
| SDV | source document verification |
| SEER | Surveillance, Epidemiology, and End Results |

| Abbreviation | Definition |
|---|---|
| SJS | Stevens-Johnson syndrome |
| SRC | Safety Review Committee |
| SSF | Site Study File |
| SUSAR | suspected unexpected serious adverse drug reaction |
| T790M | substitution of threonine (T) with methionine (M) at position 790 |
| TEAE | treatment-emergent adverse event |
| TEN | toxic epidermal necrolysis |
| TIA | transient ischemic attack |
| TKI | tyrosine kinase inhibitor |
| $T_{last}$ | time of last measurable concentration |
| $T_{max}$ | time to maximum concentration |
| TTR | time to response |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| vcMMAE | valine-citrulline-monomethyl auristatin E; linker/payload for MYTX-011 (mc-vc-PAB-MMAE), a monomethyl auristatin E derivative with valine-citrulline (vc) linker |
| Vd | volume of distribution |
| $V_{ss}$ | volume of distribution at steady state |

# 1. STUDY SYNOPSIS

**Name of Sponsor:** Mythic Therapeutics, Inc.

**Name of Investigational Product:** MYTX-011

**Product Identifier:** MYTX-011-01

**Title of Study:** A Phase 1 Multicenter Dose Escalation and Dose Expansion Study of Antibody-Drug Conjugate MYTX-011 in Subjects with Non-Small Cell Lung Cancer – KisMET-01

**Study Center(s):** Approximately 100 sites globally will participate. Initially approximately 10 sites will be selected, then upon expansion additional sites will be added.

**Enrollment Duration:** Enrollment is expected to last approximately 36 months.

**BACKGROUND AND RATIONALE**

MYTX-011 is a cMET-targeted valine-citrulline monomethyl auristatin E (vcMMAE) antibody-drug conjugate (ADC) with a fully humanized immunoglobulin (Ig)G1. The drug-to-antibody ratio (DAR) for MYTX-011 is 2:1. MYTX-011 binds to cMET with high affinity and specificity.

MYTX-011 has been engineered to have pH-dependent binding, which results in higher internalization and payload delivery to cMET+ tumor cells. This is manifested as increased internalization in cMET+ tumor cells in vitro compared to a non-engineered parent ADC and greater in vivo efficacy in murine non-small cell lung cancer (NSCLC) cMET+ tumor xenograft models compared to reference cMET-targeting ADCs with higher DAR values.

The linker/payload of MYTX-011 (vcMMAE) has been well-characterized nonclinically and/or clinically for several marketed monomethyl auristatin E (MMAE)-containing ADCs. The nonclinical and clinical toxicities of MMAE-containing ADCs also have been well described in the literature (Fisher 2021; Saber and Leighton 2015).

Preliminary safety and efficacy data from in vitro and in vivo nonclinical assessments of MYTX-011 further support development as a treatment for NSCLC in appropriately designed clinical research studies.

The study will be conducted in 2 parts. Part 1 will assess the safety and tolerability of MYTX-011 and identify the dose to be studied in Part 2. Part 2 will include subjects with NSCLC with cMET expression, a population with a current unmet medical need.

**OBJECTIVES AND ENDPOINTS**

| **Part 1: MYTX-011 Dose Escalation** | |
|---|---|
| **Objective** | **Endpoint** |
| *Primary* | |
| • To evaluate the safety and tolerability of MYTX-011<br>• To determine the RP2D and/or MTD of MYTX-011 | • Incidence and severity of TEAEs, AEs, and clinically significant changes from baseline in vital signs, ECGs, and laboratory parameters<br>• The RP2D will be selected as a biologically active dose at or below the MTD (or the highest dose tested if the MTD is not identified during the study)<br>• MTD will be determined by DLTs during Cycle 1. The observation period for DLTs is Cycle 1. |
| *Secondary* | |
| • To characterize the PK profile of MYTX-011, including total ADC, total antibody, and free MMAE | • PK values for MYTX-011 including but not limited to total antibody, conjugated payload, and free payload ($C_{max}$, $T_{max}$, $C_{last}$, $T_{last}$, AUC, half-life, CL, $V_{ss}$) |

| | |
|---|---|
| • To determine the optimal biological dose of MYTX-011 for use in Part 2 Cohorts A, B2, and E2 based on safety, PK, and preliminary anti-tumor activity<br>• To assess the incidence and persistence of ADAs to MYTX-011<br>• To determine preliminary anti-tumor activity of MYTX-011 | • Presence of ADAs at multiple timepoints during the study<br>• ORR (confirmed CR + confirmed PR) by RECIST 1.1<br>• DOR for subjects who achieve CR or PR<br>• DCR (CR+PR+SD), best overall response, and time to response<br>• PFS and OS |
| *Exploratory* | |
| • To measure the level of cMET expression in tumor tissue and presence of alterations in *MET* | • Levels of cMET expression<br>• Presence of alterations in *MET* |
| • To assess biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein) | • Biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein) |
| **Part 2: MYTX-011 Dose Expansion** | |
| **Objective** | **Endpoint** |
| *Primary* | |
| To evaluate preliminary anti-tumor activity of MYTX-011 in subjects with the following:<br>• Advanced non-squamous NSCLC without actionable *EGFR* mutations, with high cMET expression<br>• Advanced non-squamous NSCLC without actionable *EGFR* mutations, with intermediate cMET expression<br>• Advanced squamous cell NSCLC without actionable *EGFR* mutations, with cMET expression<br>• Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with low cMET expression<br>• Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression<br>• Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with ultra-low cMET expression | • ORR (confirmed CR+PR) in each expansion cohort according to RECIST 1.1 |
| *Secondary* | |
| • To evaluate the safety and tolerability of MYTX-011<br>• To characterize the PK profile of MYTX-011, including total ADC, total antibody, and free MMAE<br>• To characterize anti-tumor activity of MYTX-011<br>• To explore the optimal biological dose of MYTX-011 in various subgroups. | • Efficacy assessments according to RECIST 1.1 in each expansion cohort, including:<br>o DOR for subjects who achieve confirmed CR or PR<br>o Time to response<br>o Best overall response<br>o DCR (confirmed CR+PR+SD)<br>o PFS<br>o OS |

| | |
|---|---|
| • To assess the incidence and persistence of ADA to MYTX-011 | • Incidence and severity of TEAEs, treatment-related AEs, and clinically significant changes from baseline in vital signs, ECGs, and laboratory parameters<br>• PK values for MYTX-011 including but not limited to total antibody, conjugated payload, and free payload ($C_{max}$, $T_{max}$, $C_{last}$, $T_{last}$, AUC, half-life, CL, $V_{ss}$)<br>• Presence of ADA at multiple timepoints during the study |
| *Exploratory* | |
| • To measure the level of cMET expression in tumor tissue and presence of alterations in *MET* | • Levels of cMET expression<br>• Presence of alterations in *MET*<br>• Correlation to response |
| • To assess biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein) | • Biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein) |

ADA = anti-drug antibody; ADC = antibody-drug conjugate; AE = adverse event; AUC = area under the concentration-time curve; CL = total clearance; $C_{last}$ = last measurable concentration; $C_{max}$ = maximum concentration; cMET = protein product of the *MET* gene; CR = complete response; DCR = disease control rate; DLT = dose-limiting toxicity; DOR = duration of response; ECG = electrocardiogram; *EGFR* = epidermal growth factor receptor [gene]; *MET* = *MET* proto-oncogene, receptor tyrosine kinase; MMAE = monomethyl auristatin E; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SD = stable disease; TEAE = treatment-emergent adverse event; $T_{last}$ = time of last measurable concentration; $T_{max}$ = time to maximum concentration; $V_{ss}$ = volume of distribution at steady state

**METHODOLOGY**

**Part 1: Dose Escalation**

In Part 1, subjects will be enrolled to evaluate the safety of escalating doses of MYTX-011 and to establish the RP2D and/or maximum tolerated dose (MTD).

The dose escalation scheme is based on a 3-subject cohort minimum Bayesian Optimal Interval (BOIN) design (Yuan et al. 2016), a model-assisted design that employs an escalation/de-escalation procedure, similarly implemented as a classical 3 + 3 design, but optimized to minimize the probability of making an erroneous decision. Dose-limiting toxicities (DLTs) occurring during Cycle 1 (e.g., 21 days) will be considered when implementing the dosing algorithm and decisions. A Safety Review Committee (SRC) will review and assess data collected during the study to guide dose escalation and the determination of the RP2D.

A sentinel dosing strategy will be used during Part 1 dose escalation for increasing doses (i.e., the dose level is the highest dose level that has been explored). A minimum of 24 hours must elapse between dosing of the first subject and subsequent subjects at each dose level. If no safety concerns are noted in the first subject at each dose level, subsequent subjects may be enrolled.

If a new dose level is opened at a lower/intermediate dose after exploring a higher dose level (i.e., de-escalation), sentinel dosing is not needed unless severe acute toxicities, e.g., Grade 3 or higher infusion-related reaction (IRR), occurred within 24 hours after study drug administration in higher dose levels, or the SRC recommends sentinel dosing for the lower dose level.

The first dose of study drug (this term is used interchangeably with “investigational product”) will be administered over 90 minutes or longer. Subjects will be observed closely for at least 2 hours following the initial dose for fever, chills, or other IRRs. Subsequent infusions may be administered over 60 minutes or longer if prior infusions were well tolerated. The average infusion rate must not exceed 1000 mg/hour. For active patients on the

study who receive MYTX-011 over 30-60 minutes regularly without experiencing IRR, the infusion duration of prior cycles may be maintained.

**Part 2: Dose Expansion**

The recommended Phase 2 dose (RP2D) and alternative dose for Part 2 randomized cohorts have been established based on Part 1 data assessed to date. These doses are as follows:

**RP2D is a 5 mg/kg dose break regimen**; dose every 21 days for 2 cycles, then 3-week dose break, i.e., 6 weeks between doses 2 and 3, then repeat this pattern of 2 cycles of treatment, followed by a 3-week dose break until end of treatment (this regimen is referred to as 5 mg/kg dose break regimen throughout the protocol).

**Alternative dose for randomized cohorts A, B2, E2** is 4 mg/kg every 21 days.

Cohorts for evaluation of efficacy in Part 2 of the study are:

- **Cohort A:** Advanced non-squamous NSCLC without actionable *EGFR* mutations, with high cMET expression by immunohistochemistry (IHC) (3+ with tumor cell positivity of ≥50%). Subjects will be randomized 1:1 to 1 of 2 dose levels. An interim analysis for futility will be performed.
- **Cohort B:** Advanced non-squamous NSCLC without actionable *EGFR* mutations, with intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25% to <50%). An interim analysis for futility will be performed.
- **Cohort B2:** Advanced non-squamous NSCLC without actionable *EGFR* mutations, with intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25% to <50%). Cohort B2 may open if Cohort B passes interim analysis for futility (i.e., futility criteria are not met). Subjects will be randomized 1:1 to 1 of 2 dose levels.
- **Cohort C:** Advanced squamous cell NSCLC without actionable *EGFR* mutations, with cMET expression by IHC (2+ with tumor cell positivity of ≥25%). An interim analysis for futility and efficacy will be performed.
- **Cohort D:** Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with low cMET expression by IHC (2+ with tumor cell positivity of ≥25%), that does not meet inclusion criteria for Cohorts A, B, or B2
- **Cohort E:** Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%).
- **Cohort E2:** Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%). Cohort E2 may open if Cohort E passes the interim analysis for futility (i.e., futility criteria are not met). Subjects will be randomized 1:1 to 1 of 2 dose levels.
- **Cohort F:** Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with ultra-low cMET expression by IHC (1+ with tumor cell positivity of ≥75%), that does not meet inclusion criteria for Cohorts A, B, B2, or D.

Cohorts A-E may be opened for enrollment simultaneously or in a staggered manner at the discretion of the Sponsor, with the exception of Cohorts B2 and E2, which may be opened if Cohorts B or E, respectively, pass interim analyses for futility (i.e., if futility criteria are not met). Subjects in Cohorts A, B2, and E2 may be randomized to receive 1 of 2 doses: either the RP2D selected at the end of dose escalation or an alternative dose that is at or below the MTD (or the highest dose tested during dose escalation if the MTD is not determined). Subjects in Cohorts B, C, D, E, and F will receive MYTX-011 at the RP2D determined at the end of Part 1. As noted in the paragraphs below, additional doses, based on emerging data, may be explored in these cohorts as well.

Cohort F will be opened on a country-by-country basis, with country-specific timing contingent upon Sponsor's meeting any necessary submission and approval requirements related to the specific IHC assay used to determine

cMET expression. Sites will only be permitted to enroll patients in Cohort F after all necessary country and site level diagnostic approvals are in place.

**Additional Doses in Part 2**

While the RP2D and Alternate doses have been identified based on initial data from Part 1, as additional safety and efficacy data are obtained from both Parts 1 and 2 of the study, other doses may be incorporated into one or more Part 2 cohorts to further guide dose selection for future evaluations. The dose(s) to be included will not exceed the MTD (or the highest dose tested and found not to exceed the MTD during dose escalation (Part 1) if the MTD is not determined).

Additional dose(s) for evaluation in Part 2 may be added in two ways:

- As a substitute for the RP2D or Alternative dose
- As an additional dose level beyond the RP2D and Alternative doses

When added as a substitute for the RP2D or Alternative dose, the interim and final cohort sizes and rules for futility and efficacy will be applied to this new dose as described for the RP2D or Alternate dose in each cohort as described in Section 8.2.2; enrollment will be re-initiated to account for the additional dose. If added as an additional dose beyond the RP2D and Alternative dose, the rules governing the RP2D for futility, efficacy, and cohort size will be applied. If the RP2D has been evaluated and not found to meet rules for futility, the additional doses may enroll without futility assessment.

Any randomization (in Cohorts A, B2, or E2) already underway may be re-initiated with the additional dose level(s) for evaluation as a substitute for the RP2D or Alternative dose. Randomization may also be added to Cohorts C, D, and F to evaluate additional doses versus RP2D (provided the RP2D has not been found to be futile). Randomization is not required for the evaluation of additional dose(s) and its implementation will be determined by the Sponsor based on the current status of doses evaluated within those cohorts.

**STUDY DRUG AND TREATMENT REGIMEN**

MYTX-011 will be administered by intravenous (IV) infusion in 21-day cycles, or in a dose break regimen. Dose levels are summarized below. The SRC may recommend changing the frequency of the dosing regimen if the emerging data suggest that the current regimen is not optimal (e.g., to every 2 or 4 weeks). Additionally, intermediate dose levels and/or different dosing schedules may be implemented by the Sponsor or recommended by the SRC and will be communicated to clinical study sites via administrative memorandum.

**Planned Dose Levels**

| Dose Level | Dose (mg/kg)[1,2] |
|---|---|
| -1[3] | 0.3 |
| 1 | 1.0 |
| 2 | 2.0 |
| 3 | 3.3 |
| 4 | 5.0 |
| 5 | 6.7 |
| 6 | 8.3 |
| 7 | 10.0 |

[1] Subjects weighing >100 kg will receive a fixed dose, whereas subjects weighing up to 100 kg will receive the mg/kg dose specified. Based on emerging PK, safety, and preliminary anti-tumor activity data during the study, the SRC may recommend changing the fixed dose to a mg/kg dose for subjects who weigh >100 kg.

[2] Intermediate dose level/s and/or different dosing schedule may be implemented by the Sponsor or recommended by the SRC to assess the safety, PK, and preliminary anti-tumor activity data.

[3] If a dose de-escalation is needed at dose level 1 based on the BOIN design, the SRC will review the emerging data and determine if the study should be amended, terminated, or a lower dose explored. The lowest dose to be explored may be 0.3 mg/kg, but SRC may recommend a different dose based on emerging data.

**ELIGIBILITY**

**Inclusion Criteria**

Subjects must meet all the following inclusion criteria to be eligible for participation in this study.

1. Part 1
   a. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic NSCLC and have received available standard of care therapy.
   b. There is no limit on the number of prior therapies that can have been received.
2. Part 2 (Cohorts A-D, F)
   a. Known to *not* have an actionable *EGFR* mutation. Subjects with or without other driver mutations are permitted to enroll.
   b. Must have received (or be ineligible for) available standard of care therapy.
   c. Must have progressed on at least 1 line of prior systemic therapy in the locally advanced/metastatic setting.

      Note: multiple tyrosine kinase inhibitor (TKI) for the same actionable mutation count as 1 line of therapy. Maintenance therapy is not considered a separate line of therapy. Rechallenge of the same therapy regimen, or part of the regimen within 6 months of discontinuation date of the therapy is not considered a separate line of therapy. Adjuvant and neoadjuvant therapies count as 1 line of therapy if given within 6 months of study entry. The same rules above apply to all inclusion/exclusion criteria regarding prior lines of therapy.
   d. Subjects *without any actionable gene alteration*: must have progressed on (or be considered ineligible for), or be intolerant to, platinum-based chemotherapy and immune checkpoint inhibitor (as monotherapy or in combination with chemotherapy), and have not received more than 2 lines of prior systemic therapy in the locally advanced/metastatic setting.
   e. Subjects *with actionable gene alterations (other than* EGFR*) for which immune checkpoint inhibitor therapy is not standard of care* (e.g., anaplastic lymphoma kinase [ALK] translocation): must have progressed on (or be considered ineligible for), or be intolerant to, anticancer therapy targeting driver gene alterations and platinum-based chemotherapy, and have not received more than 3 lines of prior systemic therapy in the locally advanced/metastatic setting.
   f. Subjects *with actionable gene alterations (other than MET* exon 14 skipping mutation*) for which immune checkpoint inhibitor is standard of care*: must have progressed on (or be considered ineligible for), or be intolerant to, anticancer therapy targeting driver gene alteration and platinum-based chemotherapy, and also progressed on (or be considered ineligible for), or be intolerant to, immune checkpoint inhibitor (as monotherapy or in combination with platinum-based chemotherapy), and have not received more than 3 lines of prior systemic therapy in the locally advanced/metastatic setting.
   g. Subjects with *MET* exon 14 skipping mutation must have progressed on, or be intolerant to, at least one MET TKI if available, and have not received more than 2 lines of prior systemic therapy in the locally advanced/metastatic setting.
3. Part 2
   a. Cohort A
      i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic non-squamous NSCLC.

ii. Tumor sample with high cMET expression by IHC (3+ with tumor cell positivity of ≥50%) confirmed by central laboratory testing.

b. Cohorts B and B2 (Cohort B2 may be opened if Cohort B passes interim analysis for futility)

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic non-squamous NSCLC.

ii. Tumor sample with intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25% to <50%) confirmed by central laboratory testing.

c. Cohort C

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic squamous NSCLC.

ii. Tumor sample with cMET expression by IHC (2+ with tumor cell positivity of ≥25%) confirmed by central laboratory testing.

d. Cohort D

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic non-squamous or adenosquamous NSCLC.

ii. Have low cMET expression on tumor biopsy confirmed centrally by IHC (2+ with tumor cell positivity of ≥25%) that does not meet inclusion criteria for Cohorts A, B, or B2.

e. Cohorts E and E2 (Cohort E2 may be opened if Cohort E passes interim analysis for futility)

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic NSCLC.

ii. Have high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%) confirmed by central laboratory testing.

iii. Harbors actionable EGFR mutations, including exon 21 substitution of leucine with arginine at position 858 (L858R), exon 19 deletions, exon 20 variation, and other uncommon sensitizing EGFR mutations.

iv. Have previously received and had disease progression following at least 1 EGFR TKI or discontinued treatment due to intolerable toxicity (does not apply to subjects with exon 20 insertion), and have progressed on, intolerable to, or ineligible for platinum-based chemotherapy. Subjects with exon 21 L858R, exon 19 deletions, or substitution of threonine with methionine at position 790 (T790M) should have received osimertinib or other 3rd generation EGFR TKI if available. Subjects with exon 20 insertion should have received amivantamab if available.

v. Must have received an available standard of care therapy and have progressed on at least 1 line and no more than 3 lines of prior systemic therapy in the locally advanced/metastatic setting.

vi. Prior exposure to cMET-targeted antibody (either monoclonal, bi-specific, tri-specific)/bicycle/small peptide therapies is allowed. Prior cMET-targeted ADC or ADC that contains antitubulin payload are not allowed.

f. Cohort F

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic non-squamous or adenosquamous NSCLC.

ii. Have ultra-low cMET expression on tumor biopsy confirmed centrally by IHC (1+ with tumor cell positivity of ≥75%) that does not meet inclusion criteria for Cohorts A, B, B2, or D.

**For All Subjects Enrolled in Part 1 and Part 2**

4. Subject has at least 1 measurable lesion per RECIST 1.1(Appendix C)

5. ECOG performance status 0 or 1; see Appendix D
6. Adults aged ≥18 years at time of informed consent
7. Resolution of acute effects of prior therapy or surgical procedures to ≤Grade 1 or baseline (except alopecia, stable immune related toxicity such as hypothyroidism on hormone replacement, adrenal insufficiency on ≤10 mg daily prednisone [or equivalent], or anemia)
8. Cardiac left ventricular ejection fraction (LVEF) ≥50% by either echocardiogram or MUGA scan
9. Adequate organ function as defined as:
    a. Absolute neutrophil count (ANC) ≥1500 cells/$mm^3$ (without growth factors within 1 week of first dose of study drug administration)
    b. Platelet count ≥75,000/mm3 (Platelet transfusion not allowed within 1 week prior to first dose of study drug administration)
    c. Hemoglobin ≥9 g/dL (red blood cell [RBC] transfusion not allowed within 1 week prior to first dose of study drug administration)
    d. International normalized ratio (INR) activated partial thromboplastin time (aPTT) and prothrombin time (PT) ≤1.5 × institution's ULN unless the subject is receiving anticoagulants. Subjects on stable anticoagulant dose are permitted to enroll
    e. Calculated creatinine clearance >30 mL/min as calculated by the Modified Cockcroft-Gault formula. Refer to Appendix E and Section 5.1
    f. Total bilirubin ≤1.5 × ULN, ≤2.0 × ULN for subjects with Gilbert syndrome
    g. AST and ALT ≤2.5 × ULN for subjects without liver metastases. For subjects with liver metastases, AST and ALT ≤5 × ULN
    h. Alkaline phosphatase ≤1.5 × ULN for subjects without liver and/or bone metastases.
    i. Serum albumin ≥3.0 g/dL
    j. Hemoglobin A1c <7.5%. Diabetic subjects must be on a stable dose of antidiabetic medications (for ≥4 weeks prior to first dose of study drug)
10. For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly effective method of birth control for the duration of the study treatment and for at least 6 months after the last dose of study drug. See Appendix A.
11. Able to provide informed consent, and willing and able to comply with study protocol requirements.

**Exclusion Criteria**

Subjects who meet any of the following exclusion criteria will be excluded from this study:

1. NSCLC with adenosquamous histology (for Cohorts A, B, B2, and C only; subjects with advanced NSCLC with adenosquamous histology are allowed in Cohorts D, E, E2, and F).
2. Radiation to the lung within 6 weeks prior to screening. For all other sites (except lung), therapeutic or palliative radiation within 2 weeks prior to the first dose of study drug. Must have recovered from all radiation-related toxicity.
3. Major surgery within 28 days prior to first dose of study drug administration. This 28-day washout period also applies to any surgical intervention that involves the eye or orbital region.
4. Systemic anticancer therapy including investigational drugs, within the lesser of 28 days or 5 half-lives of the prior therapy before starting study drug (14 days or 5 half-lives for small molecule targeted therapy).

    Concurrent use of hormonal therapy for breast cancer or prostate cancer is permitted.
5. Previously received cMET-targeted antibody or ADC, bicycle, or small peptide therapies targeting cMET.

    Note: For Cohort E: Prior exposure to cMET-targeted antibody/bicycle/small peptide therapies is allowed, but subjects who have previously received cMET-targeted ADC will be excluded.

6. Previously received ADC that contains antitubulin (e.g., MMAE, MMAF) payload, regardless of ADC target.
7. Use of any concomitant or prohibited therapies outlined in Section 7.6
8. Untreated, uncontrolled central nervous system (CNS) metastases and/or leptomeningeal disease. Subjects with CNS metastases (not applicable for leptomeningeal disease) who have had surgical resection at least 4 weeks prior to first dose of study drug or who have received radiation therapy to all known sites of CNS disease ending at least 2 weeks prior to first dose of study drug are eligible if:
    a. There is no evidence of disease progression after at least 2 weeks after the end of definitive therapy; **and**
    b. The subject is neurologically stable and either off or on a non-increasing dose (in the past 2 weeks) of systemic steroids.
9. Untreated or uncontrolled human immunodeficiency virus (HIV) infection. For HIV treatments, anti-viral therapies must not be strong CYP3A4 inhibitors or inducers while receiving MYTX-011. The subject must receive/switch to anti-viral therapy that does not interfere with CYP3A4 at least 4 weeks prior to first dose of study drug. For a subject with HIV to be considered controlled, they must:
    a. Have a consistent CD4 count of at least 350/$mm^3$ and undetectable viral load within 3 months before first dose of study drug. If the patient switched to a different anti-viral regimen prior to first dose of study drug, one serology test that meets the above qualification must be performed at least 3 weeks after starting new anti-HIV regimen.
    b. Have no history of opportunistic infection within 3 months before first dose of study drug.
10. Untreated hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
    a. HBV: Subjects with serological evidence of chronic HBV infection should have an HBV viral load below the limit of quantification to be eligible. In addition, subjects with positive HBsAg should be on anti-HBV therapy at enrollment and while receiving MYTX-011.
    b. HCV: Subjects with history of HCV infection should have completed curative antiviral treatment and have HCV viral load below the limit of quantification.
11. Myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) or cerebrovascular event (stroke or transient ischemic attack [TIA]) within 6 months of first dose of study drug, symptomatic congestive heart failure (New York Heart Association [NYHA] >Class II; see Appendix B), or ventricular arrhythmias requiring treatment.
12. Elevated corrected QT interval (QTc) >480 ms based on Fridericia's correction formula.
13. History of interstitial lung disease or pneumonitis that required treatment with systemic steroids or evidence of active interstitial lung disease or pneumonitis. A history of prior radiation pneumonitis in the radiation field (fibrosis) is permitted, but the radiation pneumonitis must have resolved to Grade 1 no less than 6 months prior to study entry.
14. Subject requires systemic steroid therapy: prednisone 10 mg daily or equivalent. Inhaled steroids or topical steroid use is permitted.
15. Clinically significant systemic illness that could pose undue risk to the subject or confound the ability to interpret study results.
16. Active infection requiring IV antibiotics, antivirals, or antifungal medication within 14 days of Cycle 1 Day 1.
17. Neuropathy > Grade 1 for any reason.
18. History of cirrhosis, hepatic fibrosis, esophageal or gastric varices, or other clinically significant liver disease.
19. Active or chronic eye disorders specified below:
    a. Severe ocular surface/corneal disorder, such as primary or secondary Sjögren's syndrome, severe dry eye disease (any cause), history of corneal transplantation, ocular chronic graft-versus-host

disease, active corneal infection (including herpetic keratitis), neurotrophic keratopathy, or other forms of severe ocular surface disease.

b. Conditions that may interfere with assessment of vision, such as
   - Monocular status (functional vision in only one eye)
   - Severe visual impairment in one or both eyes (from any cause)
   - Active ocular conditions requiring ongoing procedural intervention (e.g., intravitreal injections for wet age-related macular degeneration).

c. Uncontrolled glaucoma.

d. Patients with best-corrected visual acuity (BCVA) worse than 20/50 (Snellen) or logMAR >0.4 in either eye at baseline are excluded.

   This means:

   **Eligible**: 20/50 or better (≤0.4 logMAR)

   **Not eligible**: Worse than 20/50 (>0.4 logMAR, e.g., 20/60, 20/70, etc.).

20. History of another malignancy within the past 3 years prior to screening except adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the breast or cervix, or organ-confined prostate cancer. Subjects with another malignancy must have completed definitive treatment (e.g., surgery, radiation, chemoradiation, or chemotherapy depending on standard of care of the specific malignancy) more than 3 years prior to screening; subjects may receive adjuvant therapy within 3 years of screening. **For all regions except the United Kingdon (UK):** Patients with other indolent in situ cancers may be permitted to enroll, contingent upon approval by the Sponsor Medical Monitor.
21. Known active coronavirus disease 2019 (COVID-19) infection determined by positive COVID-19 antigen test or polymerase chain reaction (PCR) test, or has signs and symptoms associated with COVID-19 within 14 days prior to first dose of study drug. Subjects must have a negative test and/or no further signs and symptoms associated with COVID-19 within 14 days of administration of first dose of study drug. Subjects who screen fail due to COVID-19 may be rescreened after they have recovered from COVID-19 after discussion with the Sponsor Medical Monitor.
22. Known hypersensitivity to monoclonal antibodies.
23. Pregnant (positive pregnancy test at screening) or lactating female.
24. Known hypersensitivity to MYTX-011 or any of its excipients

# 2. INTRODUCTION

## 2.1. BACKGROUND

### 2.1.1. Overview of MYTX-011

MYTX-011 is a cMET-targeted val-cit-monomethyl auristatin E (vcMMAE) antibody-drug conjugate (ADC) with a fully humanized immunoglobulin (Ig)G1. The drug-to-antibody ratio (DAR) for MYTX-011 is 2:1. MYTX-011 binds to cMET with high affinity and specificity. MYTX-011 has been engineered to have pH-dependent binding, which results in higher internalization and payload delivery to cMET+ tumor cells.

The linker/payload of MYTX-011 (vcMMAE) has been well-characterized nonclinically and/or clinically for several marketed monomethyl auristatin E (MMAE)-containing ADCs.
The nonclinical and clinical toxicities of MMAE-containing ADCs also have been well described in the literature (Fisher 2021; Saber and Leighton 2015).

Initial dose escalation data from this ongoing MYTX-011-01 study (KisMET-01) were presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting (Johnson et al. 2024). Data were included from 41 patients who had received ≥1 dose of MYTX-011, with doses ranging from 1.0-6.7 mg/kg (in Part 1); dose escalation was ongoing.

Subsequent dose escalation data was presented at the 2025 ASCO Annual Meeting (Heist et al. 2025). Data were included from 92 patients who had received ≥1 dose of MYTX-011, with doses ranging from 1.0-8.3 mg/kg in Part 1. Preliminary efficacy data demonstrated the anti-tumor activity of MYTX-011 across a range of cMET-expressing NSCLC patients, regardless of cMET level, histology and molecular subtype.

### 2.1.2. Summary of Nonclinical Studies

MYTX-011 binds human and cynomolgus monkey cMET with high affinity. Binding of MYTX-011 to cMET is pH dependent. MYTX-011 has been engineered to enhance the internalization and delivery of the cytotoxic payload to cancer cells. MYTX-011 can cause cell cycle arrest and cytotoxicity in cMET+ human lung cancer cell lines. The anti-cMET monoclonal antibody (mAb) component of MYTX-011 did not show agonist activity (e.g., cellular proliferation or cell signaling) in cMET+ cancer cells. The anti-cMET mAb component of MYTX-011 showed no (or limited) antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, or cell-mediated cytotoxicity Fc effector functions.

MYTX-011 has potent in vitro activity in cMET+ human lung cancer cell lines and in vivo activity in murine xenograft models of non-small cell lung cancer (NSCLC).

Based on electrocardiograms (ECGs), heart rate, blood pressure, and daily and detailed weekly clinical observations, there were no cardiovascular, central nervous system (CNS), or respiratory system functional effects observed in monkeys during 25 days of every 3 weeks (Q3W) intravenous (IV) administration of MYTX-011 at 18 mg/kg/dose.

The nonclinical pharmacokinetics (PK) and toxicokinetics of MYTX-011 were characterized in monkeys and support the proposed Q3W dosing regimen in humans. Data from these studies suggest that the nonclinical PK of MYTX-011 is as expected for a vcMMAE-containing ADC and is consistent for an IgG1.

The nonclinical toxicity profile of MYTX-011 has been evaluated through the conduct of a pivotal 25-day repeat-dose IV toxicity study in monkeys. MYTX-011 was administered to monkeys Q3W via IV injection for up to 25 days (2 total doses) at 0, 6, 12, or 18 mg/kg/dose. Primary MYTX-011-related findings in the pivotal repeat-dose toxicity study were limited to minimal to moderate decreases in red blood cell (RBC) mass parameters, reticulocytes, neutrophils, and/or white blood cells at ≥12 mg/kg/dose. The primary microscopic changes included atypical mitotic figures in multiple organs at ≥6 mg/kg and mild to moderate decreased hematopoiesis in the bone marrow at 18 mg/kg/dose. All MYTX-011 changes were fully reversible by the end of the 6-week recovery period. The clinical pathology and microscopic findings were most likely MMAE-payload related toxicities (i.e., neutropenia, decreases in bone morrow hematopoiesis, and atypical mitotic figures in tissues and organs).

## 2.2. RISK/BENEFIT

No prior clinical studies have been conducted with MYTX-011; therefore, the only clinical data to date is from MYTX-011-01 (current ongoing study), and the benefits and safety profile of MYTX-011 have not been established in humans.

The potential risks of MYTX-011 are based on literature review of the clinical toxicity of ADCs with a vcMMAE linker/payload showed that the adverse event (AE) profiles for ADCs are consistent and independent of the antibody target (Masters et al. 2018).The potential risks associated with MYTX-011 administration are based on clinical experience with other vcMMAE ADCs approved by the US Food and Drug Administration (FDA): enfortumab-vedotin-ejfv (PADCEV® [package insert] 2021), polatuzumab-vedotin-piiq (POLIVY® [package insert] 2023), brentuximab vedotin (ADCETRIS® [package insert] 2023), and tisotumab-vedotin-tftv (TIVDAK® [package insert] 2021). The potential risks of MYTX-011 are also informed by published literature on telisotuzumab vedotin, another investigational cMET-targeted ADC, investigational vcMMAE ADCs that are site-specific DAR2 drug conjugates, and the *MET*-targeted therapies emibetuzumab, capmatinib, and tepotinib.

Preliminary safety and efficacy data from in vitro and in vivo nonclinical assessments of MYTX-011 further support development as a treatment for advanced NSCLC in appropriately designed clinical research studies.

Please refer to the MYTX-011 Investigator's Brochure (IB) for additional information.

The benefit to risk assessment is in favor of studying MYTX-011 in subjects with cMET-expressing advanced NSCLC. Doses up to 6.7 mg/kg were shown to be tolerable in Part 1 of this study. Clinical data, exposure-response, exposure-safety analyses, and PK modeling from Part 1 supported the selection of 5 mg/kg every 21 days for 2 cycles, followed by a 3-week dose break,

then repeat as RP2D and 4.0 mg/kg every 21 days, as an alternative regimen, given the benefit-risk considerations.

Based on ongoing review of the data from Parts 1 and 2 of the study, the sponsor may determine that one of the two dose regimens (RP2D or Alternative Dose) being administered in Part 2 appears to show a better benefit:risk ratio than the other. In this case, the Sponsor may decide to assign ongoing patients and all newly enrolled patients to the dose regimen that appears to have the more favorable benefit:risk ratio, and no longer assign doses via randomization**.**

As additional safety and efficacy data are obtained from both Parts 1 and 2 of the study, other doses (not to exceed the MTD or the highest dose tested during Part 1 dose escalation if the MTD is not determined) may be incorporated into one or more Part 2 cohorts to further guide dose selection for pivotal evaluations and the overall benefit:risk profile of MYTX-011.

## 2.3. RATIONALE FOR STARTING DOSE

The selection of the starting dose was based on the established guidelines (DeGeorge et al. 1998; Saber and Leighton 2015), using the Good Laboratory Practices repeat-dose toxicity study conducted in cynomolgus monkeys. In this study, a dose of 18 mg/kg administered Q3W was defined as the highest non-severely toxic dose. This dose was converted to the human equivalent dose (HED), based on normalization of the dose to body surface area, and a safety factor of 6 was applied to the HED. Based on the results of the nonclinical studies, a starting dose of 1 mg/kg administered IV Q3W was selected for the planned study. Furthermore, nonclinical doses of MYTX-011 at 0.5 mg/kg were efficacious in a mouse NSCLC xenograft tumor model with high levels of cMET expression (MYTX-011 IB, Figure 8), supporting the rationale that a starting dose of 1 mg/kg might have clinical activity in patients who have tumors with high cMET expression. Please see the IB for additional details.

## 2.4. RATIONALE FOR STUDY DESIGN

Lung cancer is the leading cause of death worldwide with an estimated 1.8 million deaths (Sung et al. 2021). In the United States (US), lung cancer accounts for 12.3% of all new cancer cases and 21.4% of all cancer deaths (National Cancer Institute 2023). The 5-year relative survival of lung cancer is 22.9%.

The treatment of lung cancer depends on the histology, stage, and presence of driver mutations and the general condition of the patient (Alexander et al. 2020; Mithoowani and Febbraro 2022). The treatment for patients with advanced lung cancer typically consists of cytotoxic chemotherapy and/or immunotherapies. Patients with actionable mutations are treated with targeted therapies (Alexander et al. 2020).

In NSCLC, expression of cMET is upregulated by gene amplification (2% to 5% of patient tumors), exon 14 skipping mutations (2% to 4%), and expression (30% to 60%) (Salgia 2017). In NSCLC, cMET upregulation has been studied as a resistance mechanism for several approved epidermal growth factor receptor (*EGFR*)-targeted kinase inhibitors, and this resistance may limit their effectiveness (Fernandes et al. 2021).

In addition to NSCLC, cMET is also deregulated in many other cancers including gastric, head and neck, pancreatic, and colon cancer (Sierra and Tsao 2011).

Several cMET-targeted therapies are being, or have been, evaluated in clinical trials (such as telisotuzumab vedotin [ADC] and emibetuzumab [naked antibody]). Kinase inhibitors capmatinib (Tabrecta®) and tepotinib (Tepmetko®) have received accelerated approval from the US FDA for select subpopulations of patients with NSCLC whose tumors have a mutation that leads to *MET* exon 14 skipping and other kinase inhibitors targeting MET signaling are in clinical development.

Recently, a cMET-targeted ADC in clinical development, telisotuzumab vedotin, showed a ~35% response rate in patients with cMET highly expressing non-squamous NSCLC without *EGFR* mutations (Camidge et al. 2024), and telisotuzumab adizutecan (ABBV-400), another cMET-targeting ADC with a topoisomerase 1 inhibitor payload, showed a response rate ~48% in second line and later patients with non-squamous, EGFR wild-type NSCLC (De Miguel et al. 2024); suggesting the potential of ADCs to be effective in a much broader population of patients with NSCLC whose tumors express cMET but are not dependent on cMET signaling.

This is a first in human (FIH), Phase 1, multicenter, open-label, dose escalation, and expansion study designed to evaluate the safety, tolerability, and PK of MYTX-011, to determine the recommended Phase 2 dose (RP2D) and/or maximum tolerated dose (MTD), and to evaluate the preliminary anti-tumor activity in subjects with previously treated advanced NSCLC with cMET expression.

The study will be conducted in two parts. Part 1 will assess the safety and tolerability of MYTX-011 and identify the dose to be studied in Part 2. Part 2 will include subjects with advanced NSCLC with cMET expression, a population with a current unmet medical need.

In Part 1, subjects will be enrolled to evaluate the safety of escalating doses of MYTX-011 as monotherapy and to establish the RP2D and/or MTD. The dose escalation scheme is based on a 3-subject cohort minimum Bayesian Optimal Interval (BOIN) design (Yuan et al. 2016), a model-assisted design that employs an escalation/de-escalation procedure, similarly implemented as a classical 3 + 3 design, but optimized to minimize the probability of making an erroneous decision.

The RP2D will be selected as a biologically active dose at or below the MTD (or the highest dose tested if an MTD is not identified during the study) and will be informed by safety and tolerability, PK data, and preliminary anti-tumor activity of MYTX-011 based on Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).

Part 2 of the study will be initiated once the RP2D has been determined and will enroll subjects into different cohorts (A-F) based on cMET positivity cutoff, histological types, and/or EGFR mutation status. All cohorts are defined to explore preliminary anti-tumor activity in populations with different thresholds of cMET positivity that were selected based on data for cMET expression and efficacy observed with MYTX-011 in nonclinical models, published data for responses to cMET-targeting agents, and practical considerations given available data on the

prevalence of subject tumors with different expression levels. Cohorts A, B2, and E2 are also specifically designed to explore 2 dose levels in a randomized fashion to explore the optimal biological activity. Cohorts B2 and E2 may be opened if Cohorts B or E, respectively, pass interim analyses for futility (i.e., futility criteria are not met).

The study will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) E6, Good Clinical Practices (GCP), and applicable regulatory requirements.

## 2.5. POPULATION TO BE STUDIED

During dose escalation (Part 1 of the study), subjects with NSCLC that is locally advanced, recurrent (and not a candidate for curative therapy), or metastatic and that has failed available standard of care therapy will be enrolled irrespective of cMET status. cMET status by immunohistochemistry (IHC) may be assessed at any timepoint (including pre-screening).

Part 2 of the study will enroll subjects with previously treated advanced NSCLC that has failed available standard of care therapy into the following cohorts:

- **Cohort A:** Advanced non-squamous NSCLC without actionable *EGFR* mutations, with high cMET expression by IHC (3+ with tumor cell positivity of ≥50%)
- **Cohort B:** Advanced non-squamous NSCLC without actionable *EGFR* mutations, with intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25% to <50%)
- **Cohort B2:** Advanced non-squamous NSCLC without actionable *EGFR* mutations, with intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25% to <50%). Cohort B2 may open if Cohort B passes interim analysis for futility (i.e., futility criteria are not met). Subjects will be randomized 1:1 to 1 of 2 dose levels
- **Cohort C:** Advanced squamous cell NSCLC without actionable *EGFR* mutations, with cMET expression by IHC (2+ with tumor cell positivity of ≥25%)
- **Cohort D**: Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with low cMET expression by IHC (2+ with tumor cell positivity of ≥25%), that does not meet inclusion criteria for Cohorts A, B, or B2
- **Cohort E:** Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%)
- **Cohort E2:** Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%). Cohort E2 may open if Cohort E passes the interim analysis for futility (i.e., futility criteria are not met). Subjects will be randomized 1:1 to 1 of 2 dose levels
- **Cohort F**: Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with ultra-low cMET expression by IHC (1+ with tumor cell positivity of ≥75%), that does not meet inclusion criteria for Cohorts A, B, B2, or D

  Additional dosing cohorts defined by other dose levels to be evaluated may be added as noted in Section 4.2.

# 3. OBJECTIVES AND ENDPOINTS

## 3.1. OBJECTIVES FOR PART 1: MYTX-011 DOSE ESCALATION

### 3.1.1. Primary Objectives

- To evaluate the safety and tolerability of MYTX-011
- To determine the RP2D and/or MTD of MYTX-011

### 3.1.2. Secondary Objectives

- To characterize the PK profile of MYTX-011, including total ADC, total antibody, and free MMAE
- To determine the optimal biological dose of MYTX-011 for use in Part 2 Cohorts A, B2, and E2 based on safety, PK, and preliminary anti-tumor activity
- To assess the incidence and persistence of anti-drug antibodies (ADA) to MYTX-011
- To determine preliminary anti-tumor activity of MYTX-011

### 3.1.3. Exploratory Objectives

- To measure the level of cMET expression in tumor tissue and presence of alterations in *MET*
- To assess biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein)

## 3.2. OBJECTIVES FOR PART 2: MYTX-011 DOSE EXPANSION

### 3.2.1. Primary Objectives

To evaluate preliminary anti-tumor activity of MYTX-011 in subjects with the following:

- Advanced non-squamous NSCLC without actionable *EGFR* mutations, with high cMET expression
- Advanced non-squamous NSCLC without actionable *EGFR* mutations, with intermediate cMET expression
- Advanced squamous cell NSCLC without actionable *EGFR* mutations, with cMET expression
- Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with low cMET expression,
- Advanced NSCLC harboring actionable *EGFR* mutations, with high or intermediate cMET expression
- Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with ultra-low cMET expression.

### 3.2.2. Secondary Objectives

- To evaluate the safety and tolerability of MYTX-011
- To characterize the PK profile of MYTX-011, including total ADC, total antibody, and free MMAE
- To characterize anti-tumor activity of MYTX-011
- To explore the optimal biological dose of MYTX-011 in various subgroups
- To assess the incidence and persistence of ADA to MYTX-011

### 3.2.3. Exploratory Objectives

- To measure the level of cMET expression in tumor tissue and presence of alterations in *MET*
- To assess biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein)

## 3.3. ENDPOINTS

### 3.3.1. Part 1 Dose Escalation

#### 3.3.1.1. Primary

- Safety and tolerability will be defined as the incidence and severity of treatment-emergent adverse events (TEAEs), treatment-related AEs, and clinically significant changes from baseline in vital signs, ECGs, and laboratory parameters.
- The RP2D will be selected as a biologically active dose at or below the MTD (or the highest dose tested if the MTD is not identified during the study)
- MTD will be determined by dose-limiting toxicities (DLTs) during Cycle 1.
  The observation period for DLTs is Cycle 1 (21 days).

#### 3.3.1.2. Secondary

- PK values for MYTX-011 including, but not limited to, total antibody, conjugated payload, and free payload (maximum concentration [$C_{max}$], time to maximum concentration [$T_{max}$], last measurable concentration [$C_{last}$], time to last measurable concentration [$T_{last}$], area under the concentration-time curve [AUC], half-life, total clearance [CL], volume of distribution at steady state [$V_{ss}$])
- Presence of anti-drug antibodies (ADAs) at multiple timepoints during the study
- Overall response rate (ORR; confirmed complete response [CR] + confirmed partial response [PR]) using RECIST 1.1

  Note: CR and PR must be confirmed by 2 tumor imaging assessments conducted at least 4 weeks apart.
- Duration of response (DOR) for subjects who achieve a confirmed CR or PR

- Time to response
- Best overall response
- Disease control rate (DCR; confirmed CR+PR+stable disease [SD])
- Progression-free survival (PFS)
- Overall survival (OS)

Details of anti-tumor activity endpoints are specified in the Statistical Analysis Plan (SAP).

#### 3.3.1.3. Exploratory

- Level of cMET expression in tumor tissue and presence of alterations in *MET*
- Biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein)

### 3.3.2. Part 2 Dose Expansion

#### 3.3.2.1. Primary

- ORR (confirmed CR+PR) in each expansion cohort according to RECIST 1.1

#### 3.3.2.2. Secondary

- Efficacy assessments according to RECIST 1.1 in each expansion cohort, including:
  - DOR for subjects who achieve confirmed CR or PR
  - Time to response
  - Best overall response
  - DCR (confirmed CR+PR+SD)
  - PFS
  - OS
- Details of anti-tumor activity endpoints are specified in the Statistical Analysis Plan (SAP). Incidence and severity of TEAEs, treatment-related AEs, and clinically significant changes from baseline in vital signs, ECGs, and laboratory parameters
- PK values for MYTX-011 including, but not limited to, total antibody, conjugated payload, and free payload ($C_{max}$, $T_{max}$, $C_{last}$, $T_{last}$, AUC, half-life, CL, $V_{ss}$)
- Presence of ADA at multiple timepoints during the study

#### 3.3.2.3. Exploratory

- Level of cMET expression in tumor tissue based on IHC assay, alterations in *MET,* and correlation to response
- Biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein)

# 4. STUDY DESIGN

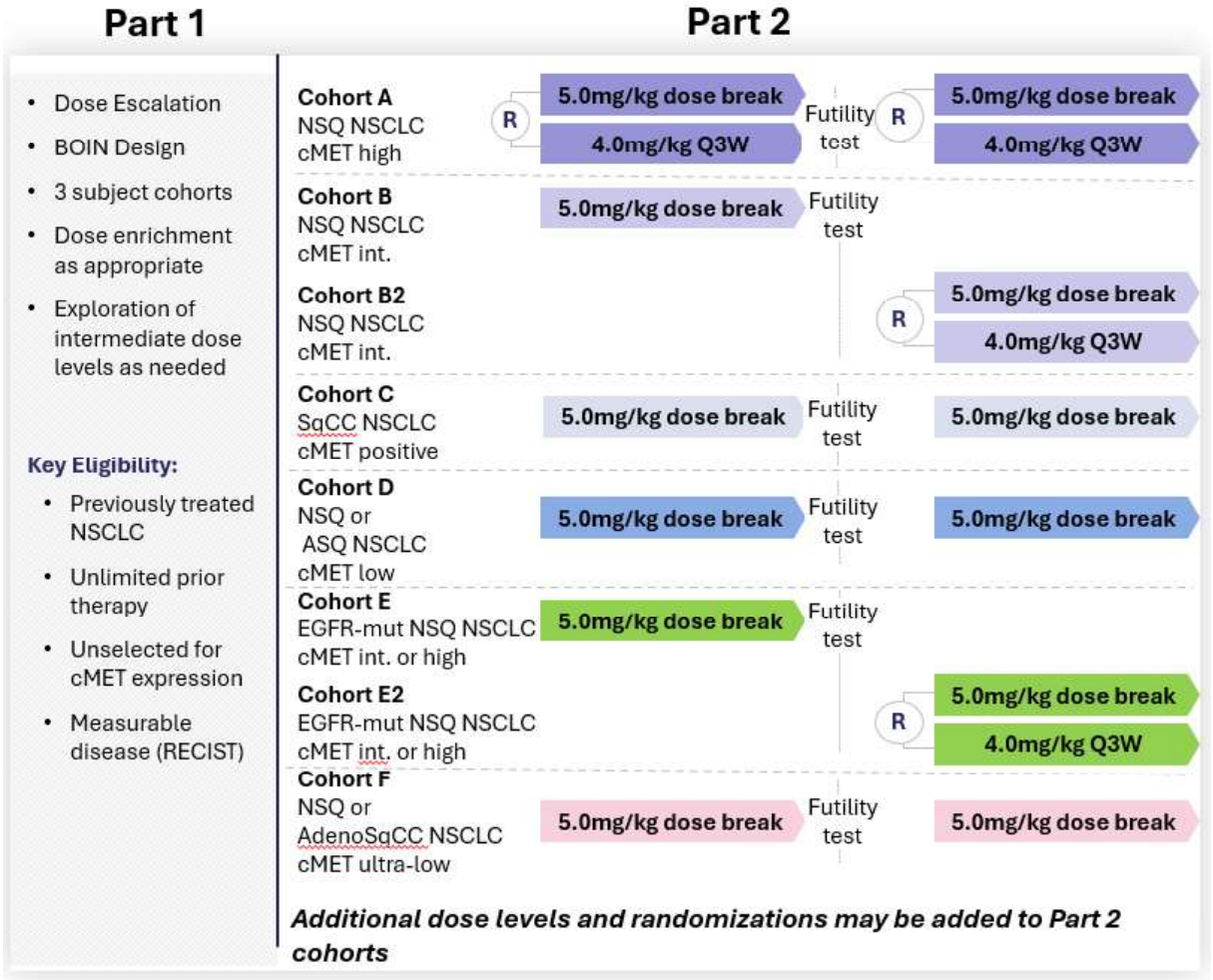
This is an FIH, Phase 1, multicenter, open-label, dose escalation, and expansion study designed to evaluate the safety, tolerability, and PK of MYTX-011, to determine the RP2D and/or MTD, and to evaluate the preliminary anti-tumor activity in subjects with previously treated advanced NSCLC with cMET expression.

The study will be conducted in two parts:

- Part 1 dose escalation
- Part 2 dose expansion

The study design schematic is displayed in Figure 1.

**Figure 1: Study Design Schematic**




AdenoSqCC = adenosquamous; BOIN = Bayesian Optimal Interval; cMET = protein product of the *MET* gene; *EGFR* = epidermal growth factor receptor [gene]; mut = mutated; Non-SqCC = nonsquamous; NSCLC = non-small cell lung cancer; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SqCC = squamous

If Cohort B passes the interim analysis for futility (i.e., futility criteria are not met for Cohort B), a randomization cohort for subjects with intermediate cMET expression (Cohort B2) may be opened. Subjects in Cohort B2 will be randomized 1:1 to 2 dose levels (i.e., RP2D and alternative dose) up to 40 subjects in total.

If Cohort E passes the interim analysis for futility (i.e., futility criteria are not met for Cohort E), the Cohort E2 may be opened for randomization. Cohort E2 has the same eligibility criteria as Cohort E.

Cohort F will be opened on a country-by-country basis, with country-specific timing contingent upon Sponsor's meeting any necessary submission and approval requirements related to the specific IHC assay used to determine cMET expression. Sites will only be permitted to enroll patients in Cohort F after all necessary country and site level diagnostic approvals are in place.

## 4.1. PART 1: MYTX-011 DOSE ESCALATION

In Part 1, subjects will be enrolled to evaluate the safety of escalating doses of MYTX-011 and to establish the RP2D and/or MTD.

The dose escalation scheme is based on a 3-subject cohort minimum BOIN design (Yuan et al. 2016), a model-assisted design that employs an escalation/de-escalation procedure, similarly implemented as a classical 3 + 3 design, but optimized to minimize the probability of making an erroneous decision. DLTs occurring during Cycle 1 will be considered when implementing the dosing algorithm and decisions. A Safety Review Committee (SRC) will review and assess data collected during the study to guide dose escalation and the determination of the RP2D.

A sentinel dosing strategy will be used during Part 1 dose escalation for increasing doses (i.e., the dose level is the highest dose level that has been explored). A minimum of 24 hours must elapse between dosing of the first subject and subsequent subjects at each dose level. If no safety concerns are noted in the first subject at each dose level, subsequent subjects may be enrolled.

If a new dose level is opened at a lower dose after exploring a higher dose level (i.e., de-escalation), sentinel dosing is not needed unless severe acute toxicities, e.g., Grade 3 or higher infusion-related reaction (IRR), occurred within 24 hours after study drug administration in higher dose levels, or the SRC recommends sentinel dosing for the lower dose level.

The first dose of study drug will be administered over 90 minutes or longer. Subjects will be observed closely for at least 2 hours following the initial dose for fever, chills, or other IRRs. Subsequent infusions may be administered over 60 minutes or longer if prior infusions were well tolerated. The average infusion rate must not exceed 1000 mg/hour. For active patients on the study who receive MYTX-011 over 30-60 minutes regularly without experiencing IRR, the infusion duration of prior cycles may be maintained.

The target DLT rate for the MTD is 0.3. Subjects will be enrolled and treated in cohorts of size 3. Definitions of DLTs are provided in Section 4.3, and only those DLTs that occur within Cycle 1 will be considered for dose selection decisions.

The dose escalation will occur as per planned dose level (see Table 8). Intermediate dose levels may be introduced during the dose escalation and will be selected based on safety, PK, and anti-tumor activity at dose levels previously explored. Subjects in the first cohort will receive study drug at dose level 1. Study dose escalation/de-escalation and elimination rules are presented in Table 1 and are summarized as follows:

1. Starting with dose level 1, a minimum of 3 subjects will be treated and followed for 1 cycle for the occurrence of a DLT. A minimum of 3 subjects will be treated at any dose level under evaluation.
2. Given the observed number of DLTs among the evaluable subjects treated at a current dose, an action to either escalate (E), eliminate (DU), de-escalate (D), or stay (S) at the current dose will be applied to the subsequent cohort of 3 subjects. A dose level with an action to escalate is determined to be safe.
3. Starting dose level 1 can be de-escalated to dose "Level -1." Intermediate doses between dose "Level -1" and dose level 1 are permitted if dose "Level -1" was determined to be safe.
4. If the next action is to escalate (E):
    a. The next cohort of 3 subjects will be treated at a dose higher than the current dose, and equal to or less than the next higher dose.
    b. If the next higher dose has been eliminated, the next cohort of 3 subjects may be treated either at the current dose, or at an intermediate dose; if an intermediate dose is used, it will be no greater than halfway between the current dose and the next higher dose that was eliminated.
    c. If the current dose is the highest dose, the next cohort of 3 subjects will be treated at the current dose.
5. If the next action is dose elimination (DU), the current dose and higher doses will be eliminated as unacceptably toxic and will not be used again in the remainder of the study.
6. If the next action is dose elimination (DU) or de-escalation (D):
    a. The next cohort of 3 subjects will be treated at a dose lower than the current dose, which can be either a previously used dose that was determined to be safe or an intermediate dose; if an intermediate dose is used, it will be no greater than halfway between the current dose and the previously used, adjacent lower dose level that was determined to be safe.
    b. If the current dose is dose level 1 and no lower previously used dose was determined to be safe, then the next cohort of 3 subjects will be treated at dose "Level -1".
7. If the next action to be taken is stay (S), the next cohort of 3 subjects will be treated at the current dose.
8. If the current dose is the lowest dose ("Level -1") and the rule indicates dose de-escalation, the next cohort of 3 subjects will be treated at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point the study will be terminated for safety. No MTD will be declared in this case.

The above steps will be repeated following the BOIN design, until the RP2D is identified, at which point the dose escalation Part 1 of the study is complete. Part 1 of the study may also be considered complete if the number of evaluable subjects treated at the current dose is at least 9.

**Table 1: Dose Escalation Rules**

| Number of Subjects with DLTs | Number of Evaluable Subjects | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 0 | E | E | E | E | E | E | E |
| 1 | S | S | E | E | E | E | E |
| 2 | D | D | D | S | S | S | E |
| 3 | DU | DU | D | D | D | D | S |
| 4 | | DU | DU | DU | D | D | D |
| 5 | | | DU | DU | DU | DU | DU |

BOIN = Bayesian Optimal Interval; D = de-escalation; DLT = dose-limiting toxicity; DU = dose elimination; E = escalate; S = treat at current dose
Note: The above table is shown to illustrate how the BOIN design is applied. The protocol does not limit enrollment to 9 subjects per dose level.

The above algorithm employs safety overdose control where a dose and higher dose levels will be eliminated from further consideration if, given the number of observed DLTs at the current dose, there is a greater than 0.95 probability that the true DLT rate is higher than 30% and at least 3 subjects evaluable for DLT have been treated. When the lowest dose is eliminated, the study will be stopped for safety. Under this probability cutoff of 0.95, the dose with 3/3, 4/6, or 5/9 subjects experiencing DLT will be eliminated.

Once all the enrolled subjects complete the DLT observation period and the trial is not stopped early, the BOIN design applies an isotonic regression to select the MTD.

Additional subjects may be enrolled in enrichment cohorts at dose levels that have previously been determined to be safe (including planned dose levels and intermediate dose levels) to better understand the safety, tolerability, PK, and preliminary anti-tumor activity of MYTX-011. No more than 10 subjects will be enrolled per enrichment cohort. For doses and/or dosing schedules where favorable benefit-risk has been demonstrated, up to 20 subjects may be enrolled for further dose optimization after approval by the SRC. Enrollment into enrichment cohorts may continue throughout the conduct of the study until all enrichment cohort slots are filled or it is determined that additional enrollment is not required. DLTs will not be assessed for subjects

enrolled into enrichment cohorts. In addition, the Sponsor may enroll subjects with certain levels of cMET expression (i.e., high, intermediate, low, or ultra-low cMET expression as defined in Part 2) in enrichment cohorts or intermediate dose levels in which preliminary anti-tumor activity is observed.

### 4.1.1. RP2D Selection Criteria

The RP2D will be selected as a biologically active dose at or below the MTD (or the highest dose tested if an MTD is not identified during the study) and will be informed by safety and tolerability, PK data, and preliminary anti-tumor activity of MYTX-011 according to RECIST 1.1 from subjects in Part 1 of the study.

### 4.1.2. Intrapatient Dose Escalation

Subjects assigned to a dose level lower than the RP2D in Part 1 may be considered for intrapatient dose escalation to the RP2D or an alternative (or any additional doses) being evaluated in Part 2, with Sponsor Medical Monitor or designee approval. To be considered for intrapatient dose escalation, individual subjects need to have completed at least 4 cycles of MYTX-011 at their initial dose and be deriving clinical benefit from the treatment in the opinion of the Investigator. In order to be treated with a higher dose, the subject must not have experienced any Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 treatment-related AEs at the initial dose level assigned or have required any dose modification(s). If escalation to the RP2D is ≥100% increase from the initial assigned dose, the subject would need to receive and tolerate a dose between the assigned dose and RP2D for at least 2 cycles before escalating to the RP2D.

## 4.2. PART 2: MYTX-011 DOSE EXPANSION

The dose expansion portion of the study will be initiated once the RP2D has been determined.

- Cohort A: Advanced non-squamous NSCLC without actionable *EGFR* mutations; with high cMET expression by IHC (3+ with tumor cell positivity of ≥50%). Subjects will be randomized 1:1 to 1 of 2 dose levels. An interim analysis for futility will be performed.
- Cohort B: Advanced non-squamous NSCLC without actionable *EGFR* mutations; with intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25% to <50%). An interim analysis for futility will be performed.
- Cohort B2: Advanced non-squamous NSCLC without actionable *EGFR* mutations; with intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25% to <50%). Cohort B2 may open if Cohort B passes the interim analysis for futility (i.e., futility criteria are not met). Subjects will be randomized 1:1 to 1 of 2 dose levels.
- Cohort C: Advanced squamous cell NSCLC without actionable *EGFR* mutations, with cMET expression by IHC (2+ with tumor cell positivity of ≥25%). An interim analysis for futility and efficacy will be performed.

- Cohort D: Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with low cMET expression by IHC (2+ with tumor cell positivity of ≥25%), that does not meet inclusion criteria for Cohorts A, B, or B2.
- Cohort E: Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%).
- Cohort E2: Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%). Cohort E2 may open if Cohort E passes the interim analysis for futility (i.e., futility criteria are not met). Subjects will be randomized 1:1 to 1 of 2 dose levels.
- Cohort F: Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with ultra-low cMET expression by IHC (1+ with tumor cell positivity of ≥75%), that does not meet inclusion criteria for Cohorts A, B, B2, or D

Cohorts A-F may be opened for enrollment simultaneously or in a staggered manner at the discretion of the Sponsor, with the exception of Cohorts B2 and E2, which will open if Cohorts B or E, respectively, pass interim analyses for futility (i.e., if futility criteria are not met). Subjects in Cohorts A, B2, and E2 will be randomized to receive 1 of 2 doses: either the RP2D selected at the end of dose escalation or an alternative dose that is at or below the MTD (or the highest dose tested during dose escalation if the MTD is not determined). Subjects in Cohorts B, C, D, E and F will receive MYTX-011 at the RP2D determined at the end of Part 1. As noted in the paragraphs below, additional doses, based on MYTX-011 data, may be explored in these cohorts as well.

**Additional Doses in Part 2**

While the RP2D and Alternative dose were selected based on the available data, additional data are anticipated from both Parts 1 and 2 of the study that may impact choice of doses in one or more cohorts. In light of this, other doses may be incorporated into one or more Part 2 cohorts after the RP2D and Alternative dose have been declared. The dose(s) to be included will not exceed the MTD (or the highest dose tested during dose escalation (Part 1) if the MTD is not determined) .

Additional dose(s) for evaluation in Part 2 may be added in two ways:

- As a substitute for the RP2D or Alternative dose
- As an additional dose level beyond the RP2D and Alternative doses

When added as a substitute for the RP2D or Alternative dose, the interim and final cohort sizes and rules for futility and efficacy will be applied to this new dose as described for the RP2D or Alternate dose in each cohort as described in Section 8.2.2; enrollment will be re-initiated to account for the additional dose. If added as an additional dose beyond the RP2D and Alternative dose, the rules governing the RP2D for futility, efficacy, and cohort size will be applied. If the RP2D has been evaluated and not found to meet rules for futility, the additional doses may enroll without futility assessment.

Any randomization (in Cohorts A, B2, or E2) already underway may be re-initiated with the additional dose level(s) for evaluation as a substitute for the RP2D or Alternative dose. Randomization may also be added to Cohorts C, D, and F to evaluate additional doses versus RP2D (provided the RP2D has not been found to be futile). Randomization is not required for the evaluation of additional dose(s) and its implementation will be determined by the Sponsor based on the current status of doses evaluated within those cohorts.

Any new doses to be tested in a cohort will be assigned a new identifier.

Screening and Treatment

After providing informed consent, subjects will undergo screening assessments (up to 28 days prior to first dose of study drug).

All subjects enrolled in Part 2 will be required to provide tumor tissue for assessing cMET tumor expression using an IHC-based assay performed at a central laboratory prior to study enrollment. Subjects with actionable mutation, including fusion of *EML4-ALK, ROS1*, *RET*, or *NTRK1-3* or mutation of *EGFR, BRAF*, *KRAS,* or *HER2*, are:

1. Required to provide tumor tissue sampled after progression or discontinuation of the most recent actionable mutation-targeted therapy (e.g., tyrosine kinase inhibitor [TKI], monoclonal/bispecific antibody, ADC) and are
2. Requested but not required, to also provide available archival tumor tissue sampled prior to the first actionable mutation-targeted therapy (e.g., tyrosine kinase inhibitor [TKI], monoclonal/bispecific antibody, ADC.

This specific tumor tissue requirement for actionable mutations does not apply to subjects with *MET* exon 14 skipping mutation or *MET* amplification without other actionable mutations. cMET values must meet the thresholds per the enrollment criteria. If archival tumor tissue is not available, subjects will be required to provide tissue from a new biopsy obtained during screening for cMET biomarker testing during the screening period. Confirmation of cMET status by IHC at the central laboratory must be obtained before the subject can be dosed in Part 2 of the study. Pre-screening may be conducted >28 days before Cycle 1 Day 1, after appropriate informed consent has been obtained. Pre-screening includes provision of an archival tumor sample or fresh tissue biopsy sample, and cMET testing at the central laboratory.

Subjects enrolled in Cohort D must have IHC-based cMET expression that does not meet inclusion criteria for Cohorts A, B, or B2. Subjects enrolled in Cohort F must have IHC-based cMET expression that does not meet criteria for Cohorts A, B, B2 or D.

During dose expansion, anti-tumor activity, safety, and PK of MYTX-011 will be assessed.

MYTX-011 will be administered IV every 21 days (± 2 days) or may be administered a dose break regimen upon enrollment or as per the dose modification guidelines until disease progression, unacceptable toxicity, voluntary withdrawal of consent, or completion of study, whichever occurs first. If the Investigator deems that a subject with disease progression is benefiting from treatment, the Investigator may request that the subject remain on treatment after disease progression (requires Medical Monitor approval). Subjects who achieve a confirmed CR

by 2 tumor imaging assessments conducted at least 4 weeks apart may continue to receive treatment until meeting any of the end of treatment (EOT) criteria (Section 5.3.1).

Computed tomography (CT) scans with contrast (or magnetic resonance imaging [MRI]) will be performed during screening, then every 6 weeks (± 7 days) counting from Cycle 1 Day 1 through Week 24. After Week 24, scans will be performed every 12 weeks (± 2 weeks) thereafter until disease progression or EOT. Per RECIST 1.1, confirmatory CT scans may be done at unscheduled visits. Subjects who discontinue study drug due to reasons other than disease progression or withdrawal of consent will continue to undergo tumor assessments independent of study drug administration schedule, until demonstration of disease progression, withdrawal of consent, the start of another anticancer therapy, or death. Subjects will be assessed every 12 weeks (±2 weeks) after the EOT visit until progression of disease is observed, death, or withdrawal of consent. During the 2-year long-term follow-up, disease status, survival status, and start of anticancer therapy will be collected.

## 4.3. DLT Evaluation Criteria

The DLT observation period is the time from the first dose of study drug to the end of Cycle 1 (cycle = 21 days). DLTs will be assessed during Dose Escalation (Part 1). Subjects will be considered evaluable for DLT if they receive their planned dose of MYTX-011 for Cycle 1 and have either completed Cycle 1 or are withdrawn during Cycle 1 due to a DLT. DLTs will not be assessed for subjects enrolled in the enrichment cohorts.

A DLT is defined as any of the following AEs that occur during the DLT observation period and are not clearly due to the underlying disease or extraneous causes, graded according to the National Cancer Institute (NCI) Version 5.0:

- Grade 4 neutropenia or thrombocytopenia lasting ≥7 days despite supportive care
  - In United Kingdom (UK) only, Grade 4 neutropenia or thrombocytopenia lasting ≥3 days despite supportive care
- Grade 4 neutropenia complicated by fever ≥38.0°C or infection
- Grade 3 or higher thrombocytopenia complicated by significant (Grade ≥2) hemorrhage
- Grade 4 anemia
- Grade 3 or higher aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation
- Any case consistent with Hy's Law
  - AST or ALT >3 × upper limit of normal (ULN) *and*
  - Total bilirubin >2 × ULN *and*
  - Alkaline phosphatase >2 × ULN *and*
  - No other reason for liver injury

- Grade 3 or 4 non-hematologic toxicity, ***excluding***:
  - Fatigue lasting <7 days
  - Grade 3 nausea and/or vomiting, diarrhea or constipation that resolves to Grade ≤1 within 3 days following appropriate supportive care
  - Other Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
  - Grade ≥3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis, or radiological imaging findings of pancreatitis
  - Alopecia
- Grade ≥3 IRR
- Any death not clearly due to the underlying disease or extraneous causes.

### 4.4. STUDY DURATION

Overall, subjects may remain in the study for up to approximately 4 years (or longer), including:

- Screening: up to 28 days prior to Cycle 1 Day 1
- Treatment Period: up to study drug discontinuation (Section 5.3.1)
- Long-Term Follow-up: up to 2 years after EOT

### 4.5. END OF STUDY DEFINITION

**Primary Completion:** Time when the last subject is assessed for purposes of final data collection for the primary analysis. The primary analysis will occur when target enrollment in Parts 1 and 2 is complete and each subject completes at least 6 months on study or withdraws from the study, whichever occurs first. The actual timing of the primary analysis may differ across the cohorts.

**End of Study:** Time of the final analysis after the last subject completes EOT assessment.

## 5. SELECTION AND WITHDRAWAL OF SUBJECTS

### 5.1. INCLUSION CRITERIA

Subjects must meet all the following inclusion criteria to be eligible for participation in this study:

1. Part 1
   a. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic NSCLC and have received available standard of care therapy.

b. There is no limit on the number of prior therapies that can have been received.

2. Part 2 (Cohorts A-D and F)

a. Known to not have an actionable EGFR mutation. Subjects with or without other driver mutations are permitted to enroll.

b. Must have received (or be ineligible for) available standard of care therapy.

c. Must have progressed on at least 1 line of prior systemic therapy in the locally advanced/metastatic setting. Note: multiple TKI for the same actionable mutation count as 1 line of therapy. Maintenance therapy is not considered a separate line of therapy. Rechallenge of the same therapy regimen, or part of the regimen within 6 months of discontinuation date of the therapy is not considered a separate line of therapy. Adjuvant and neoadjuvant therapies count as 1 line of therapy if given within 6 months before study entry. The same rules above apply to all inclusion/exclusion criteria regarding prior lines of therapy.

d. Subjects *without any actionable gene alteration*: must have progressed on (or be considered ineligible for), or be intolerant to, platinum-based chemotherapy and immune checkpoint inhibitor (as monotherapy or in combination with chemotherapy), and have not received more than 2 lines of prior systemic therapy in the locally advanced/metastatic setting.

e. Subjects *with actionable gene alterations (other than* EGFR*) for which immune checkpoint inhibitor therapy is not standard of care* (e.g., anaplastic lymphoma kinase [ALK] translocation): must have progressed on (or be considered ineligible for), or be intolerant to, anticancer therapy targeting driver gene alterations and platinum-based chemotherapy, and have not received more than 3 lines of prior systemic therapy in the locally advanced/metastatic setting.

f. Subjects *with actionable gene alterations (other than* MET exon 14 skipping mutation*) for which immune checkpoint inhibitor is standard of care*: must have progressed on (or be considered ineligible for), or be intolerant to, anticancer therapy targeting driver gene alteration and platinum-based chemotherapy, and also progressed on (or be considered ineligible for) or be intolerant to immune checkpoint inhibitor (as monotherapy or in combination with platinum-based chemotherapy ,and have not received more than 3 lines of prior systemic therapy in the locally advanced/metastatic setting.

g. Subjects with *MET* exon 14 skipping mutation must have progressed on, or be intolerant to, at least one MET TKI if available, and have not received more than 2 lines of prior systemic therapy in the locally advanced/metastatic setting.

3. Part 2

a. Cohort A

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic non-squamous NSCLC.

ii. Tumor sample with high cMET expression by IHC (3+ with tumor cell positivity of ≥50%) confirmed by central laboratory testing.

b. Cohorts B and B2 (Cohort B2 may be opened if Cohort B passes interim analysis for futility)

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic non-squamous NSCLC.

ii. Tumor sample with intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25% to <50%) confirmed by central laboratory testing.

c. Cohort C

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic squamous NSCLC.

ii. Tumor sample with cMET expression by IHC (2+ with tumor cell positivity of ≥25%) confirmed by central laboratory testing.

d. Cohort D

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic non-squamous or adenosquamous NSCLC.

ii. Have low cMET expression on tumor biopsy confirmed centrally by IHC (2+ with tumor cell positivity of ≥25%) that does not meet inclusion criteria for Cohorts A, B, or B2.

e. Cohorts E and E2 (Cohort E2 may be opened if Cohort E passes interim analysis for futility)

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic NSCLC.

ii. Have high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%) confirmed by central laboratory testing.

iii. Harbor actionable *EGFR* mutations, including exon 21 substitution of leucine with arginine at position 858 (L858R), exon 19 deletions, exon 20 variation, and other uncommon sensitizing *EGFR* mutations.

iv. Have previously received and had disease progression following at least 1 EGFR TKI or discontinued treatment due to intolerable toxicity (does not apply to subjects with exon 20 insertion), and have progressed on, intolerable to, or ineligible for platinum-based chemotherapy. Subjects with exon 21 L858R, exon 19 deletions, or substitution of threonine with methionine at position 790 (T790M) should have received osimertinib or other 3$^{rd}$ generation EGFR TKI if available. Subjects with exon 20 insertion should have received amivantamab if available.

v. Must have received an available standard of care therapy and have progressed on at least 1 line of prior therapy and no more than 3 lines of prior systemic therapy in the locally advanced/metastatic setting.

Note: multiple lines of EGFR TKI count as 1 line of therapy. Maintenance therapy is not considered a separate line of therapy. Rechallenge of the same therapy regimen, or part of the regimen within 6 months of discontinuation date of the therapy is not considered a separate line of therapy. Adjuvant and neoadjuvant therapies count as 1 line of therapy if given within 6 months before study entry.

vi. Prior exposure to cMET-targeted antibody (either monoclonal, bi-specific, tri-specific)/bicycle/small peptide therapies is allowed. Prior cMET-targeted ADC or ADC that contains antitubulin payload are not allowed.

f. Cohort F

i. Have histologically or cytologically confirmed locally advanced, recurrent (and not a candidate for curative therapy), or metastatic non-squamous or adenosquamous NSCLC.

ii. Have ultra-low cMET expression on tumor biopsy confirmed centrally by IHC (1+ with tumor cell positivity of ≥75%) that does not meet inclusion criteria for Cohorts A, B, B2, or D.

For all subjects enrolled in Part 1 and Part 2:

4. Subject has at least 1 measurable lesion per RECIST 1.1 (Appendix C)
5. ECOG performance status 0 or 1; see Appendix D
6. Adults aged ≥18 years at time of informed consent
7. Resolution of acute effects of prior therapy or surgical procedures to ≤Grade 1 or baseline (except alopecia, stable immune related toxicity such as hypothyroidism on hormone replacement, adrenal insufficiency on ≤10 mg daily prednisone [or equivalent], or anemia)
8. Cardiac left ventricular ejection fraction (LVEF) ≥50% by either echocardiogram (ECHO) or MUGA scan
9. Adequate organ function as defined as
   a. Absolute neutrophil count (ANC) ≥1500 cells/$mm^3$ (without growth factors within 1 week of first dose of study drug administration)
   b. Platelet count ≥75,000/$mm^3$ (Platelet transfusion not allowed within 1 week prior to first dose of study drug administration)
   c. Hemoglobin ≥9 g/dL (RBC transfusion not allowed within 1 week prior to first dose of study drug administration)
   d. International normalized ratio (INR) aPTT and prothrombin time (PT) ≤1.5 × institution's ULN unless the subject is receiving anticoagulants. Subjects on stable anticoagulant dose are permitted to enroll.

e. Calculated creatinine clearance >30 mL/min as calculated by the Modified Cockcroft-Gault formula. Refer to Appendix E

f. Total bilirubin ≤1.5 × ULN, ≤2.0 × ULN for subjects with Gilbert syndrome

g. AST and ALT ≤2.5 × ULN for subjects without liver metastases. For subjects with liver metastases, AST and ALT ≤5 × ULN.

h. Alkaline phosphatase ≤1.5 × ULN for subjects without liver and/or bone metastases.

i. Serum albumin ≥3.0 g/dL

j. Hemoglobin A1c (HbA1c) <7.5%. Diabetic subjects must be on a stable dose of antidiabetic medications (for ≥4 weeks prior to first dose of study drug)

10. For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly effective method of birth control for the duration of the study treatment and for at least 6 months after the last dose of study drug. See Appendix A.
11. Able to provide informed consent, and willing and able to comply with study protocol requirements.

## 5.2. EXCLUSION CRITERIA

Subjects who meet any of the following exclusion criteria will be excluded from this study:

1. NSCLC with adenosquamous histology (for Cohorts A, B, B2, and C only; subjects with advanced NSCLC with adenosquamous histology are allowed in Cohorts D, E, E2 and F).
2. Radiation to the lung within 6 weeks prior to screening. For all other sites (except lung), therapeutic or palliative radiation within 2 weeks of the first dose of study drug. Must have recovered from all radiation-related toxicity.
3. Major surgery within 28 days before first dose of study drug administration.

   This 28-day washout period includes any surgical intervention that involves the eye or orbital region.
4. Systemic anticancer therapy including investigational drugs, within the lesser of 28 days or 5 half-lives of the prior therapy before starting study drug (14 days or 5 half-lives for small molecule targeted therapy).

   Concurrent use of hormonal therapy for breast cancer or prostate cancer is permitted.
5. Previously received cMET-targeted antibody or ADC, bicycle, or small peptide therapies targeting cMET.

   Note: For Cohort E: Prior exposure to cMET-targeted antibody/bicycle/small peptide therapies is allowed, but subjects who have previously received cMET-targeted ADC will be excluded.
6. Previously received ADC that contains antitubulin (e.g., MMAE, MMAF) payload, regardless of ADC target.
7. Use of any concomitant or prohibited therapies outlined in Section 7.6.

8. Untreated, uncontrolled CNS metastases and/or leptomeningeal disease. Subjects with CNS metastases (not applicable for leptomeningeal disease) who have had surgical resection at least 4 weeks prior to first dose of study drug or who have received radiation therapy to all known sites of CNS disease ending at least 2 weeks prior to first dose of study drug are eligible if:
    a. There is no evidence of disease progression after at least 2 weeks after the end of definitive therapy; **and**
    b. The subject is neurologically stable and either off or on a non-increasing dose (in the past 2 weeks) of systemic steroids.
9. Untreated or uncontrolled human immunodeficiency virus (HIV) infection. For HIV treatments, anti-viral therapies must not be strong CYP3A4 inhibitors or inducers while receiving MYTX-011. The subject must receive/switch to anti-viral therapy that does not interfere with CYP3A4 at least 4 weeks prior to first dose of study drug. For a subject with HIV to be considered controlled, they must:
    a. Have a consistent CD4 count of at least 350/$mm^3$ and undetectable viral load within 3 months prior to first dose of study drug. If the patient switched to a different anti-viral regimen prior to first dose of study drug, one serology test that meets the above qualification must be performed at least 3 weeks after starting new anti-HIV regimen.
    b. Have no history of opportunistic infection within 3 months prior to first dose of study drug.
10. Untreated hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
    a. HBV: Subjects with serological evidence of chronic HBV infection should have an HBV viral load below the limit of quantification to be eligible. In addition, subjects with positive HBsAg should be on anti-HBV therapy at enrollment and while receiving MYTX-011.
    b. HCV: Subjects with history of HCV infection should have completed curative antiviral treatment and have HCV viral load below the limit of quantification.
11. Myocardial infarction, unstable angina, PTCA or CABG or cerebrovascular event (stroke or transient ischemic attack [TIA]) within 6 months before first dose of study drug, symptomatic congestive heart failure (New York Heart Association [NYHA] >Class II; see Appendix B), or ventricular arrhythmias requiring treatment.
12. Elevated corrected QT interval (QTc) >480 ms based on Fridericia's correction formula.
13. History of interstitial lung disease or pneumonitis that required treatment with systemic steroids or evidence of active interstitial lung disease or pneumonitis. A history of prior radiation pneumonitis in the radiation field (fibrosis) is permitted, but the radiation pneumonitis must have resolved to Grade 1 no less than 6 months prior to study entry.
14. Subject requires systemic steroid therapy: prednisone 10 mg daily or equivalent. Inhaled steroids or topical steroid use is permitted.

15. Clinically significant systemic illness that could pose undue risk to the subject or confound the ability to interpret study results.
16. Active infection requiring IV antibiotics, antivirals, or antifungal medication within 14 days of Cycle 1 Day 1.
17. Neuropathy > Grade 1 for any reason.
18. History of cirrhosis, hepatic fibrosis, esophageal or gastric varices, or other clinically significant liver disease.
19. Active or chronic eye disorders specified below:
    a. Severe ocular surface/corneal disorder, such as primary or secondary Sjögren's syndrome, severe dry eye disease (any cause), history of corneal transplantation, ocular chronic graft-versus-host disease, active corneal infection (including herpetic keratitis), neurotrophic keratopathy, or other forms of severe ocular surface disease.
    b. Conditions that may interfere with assessment of vision, such as
        - Monocular status (functional vision in only one eye)
        - Severe visual impairment in one or both eyes (from any cause)
        - Active ocular conditions requiring ongoing procedural intervention (e.g., intravitreal injections for wet age-related macular degeneration).
    c. Uncontrolled glaucoma
    d. Patients with best corrected visual acuity (BCVA) worse than 20/50 (Snellen) or logMAR >0.4 in either eye at baseline are excluded.

       This means:

       **Eligible**: 20/50 or better (≤ 0.4 logMAR)

       **Not eligible**: Worse than 20/50 (> 0.4 logMAR, e.g., 20/60, 20/70, etc.)
20. History of another malignancy within the past 3 years prior to screening except adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the breast or cervix, or organ-confined prostate cancer. Subjects with another malignancy must have completed definitive treatment (e.g., surgery, radiation, chemoradiation, or chemotherapy depending on standard of care of the specific malignancy) more than 3 years prior to screening; subjects may receive adjuvant therapy within 3 years of screening. **For all regions except the UK:** Patients with other adequately-treated, indolent in situ cancers may be permitted to enroll contingent upon approval by the Sponsor Medical Monitor.
21. Known active coronavirus disease 2019 (COVID-19) infection determined by positive COVID-19 antigen test or PCR test, or has signs and symptoms associated with COVID-19 within 14 days prior to first dose of study drug. Subjects must have a negative test and/or no further signs and symptoms associated with COVID-19 within 14 days of administration of first dose of study drug. Subjects who screen fail due to COVID-19 may be rescreened after they have recovered from COVID-19 after discussion with the Sponsor Medical Monitor.

22. Known hypersensitivity to monoclonal antibodies.
23. Pregnant (positive pregnancy test at screening) or lactating female.
24. Known hypersensitivity to MYTX-011 or any of its excipients.

## 5.3. DISCONTINUATION FROM STUDY

### 5.3.1. End of Treatment

For patients who discontinue treatment, end of treatment (EOT) is defined as the documented date of the decision to discontinue treatment, or death, whichever is earlier; if neither date is available, EOT will be defined as D42 from the last dose received. EOT visit must be performed within 30 days of the documented date of EOT. End of participation is defined as the last data collection timepoint, including follow-up visits and data collected for overall survival unless ocular adverse events have not resolved, follow up until resolution to baseline or within 1-2 lines of baseline. Discontinuation from study drug and discontinuation from study might be linked or might be separate events, depending on the triggering action, decision, or outcome. Subjects will be discontinued from study drug for any of the following reasons:

- Disease progression, unless Medical Monitor approves continued treatment
  - If the Investigator deems that a subject is benefiting from treatment, the Investigator may request that the subject remain on treatment after disease progression (requires Medical Monitor approval)
- Intolerable toxicity
- Subject requests to withdraw consent from study
- Subject requests to withdraw consent from treatment
- Pregnancy
- Initiation of therapeutic intervention not permitted by the protocol
- Investigator discretion
- Noncompliance with study procedures
- Discontinuation of the study by the Sponsor

### 5.3.2. Subject Discontinuation/Withdrawal from the Study

Subjects who discontinue from study drug will complete an EOT visit and continue to be followed for AEs and other protocol-required procedures according to Table 2 and Table 3 (unless subject withdraws consent from study).

Subjects may voluntarily withdraw consent from the study at the subject's own request any time and for any reason, and no further study data will be collected. The Investigator must make an effort to determine the primary reason for withdrawal. The Sponsor will continue to retain and use all research results that have already been collected for study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date unless

Sponsor receives a written notification that the subject has withdrawn permission to analyze the samples.

### 5.3.3. Lost to Follow-Up

If the subject is lost to follow-up, the study personnel must make reasonable efforts to contact the subject and determine the reason for discontinuation, including at least 3 documented attempts to contact the subject. In accordance with local regulations, information from public records may be used to collect missing survival data.

### 5.3.4. Replacement of Subjects

During Part 1 dose escalation, subjects who discontinue or withdraw from the study prior to completion of the DLT observation period not due to a DLT may be replaced. In addition, subjects who are enrolled in Part 1 dose escalation cohorts but do not receive study drug will be replaced.

### 5.3.5. Screen Failures

#### 5.3.5.1. Screening and Rescreening Procedures

After written informed consent has been obtained, subjects will be screened to assess eligibility for study participation. If a laboratory assessment listed in the inclusion/exclusion criteria is outside the protocol-specified range, then the assessment may be repeated/subject rescreened once during the screening period. If the repeat value is outside the protocol-specified inclusion/ exclusion criteria, then the subject will not be enrolled in the study.

If the subject has not met all eligibility criteria at the end of the screening period, the subject will be considered a screen failure.

**Rescreening:** Subjects may be rescreened at the discretion of the Investigator and in consultation with the Sponsor Medical Monitor. The subject must be reconsented if the rescreening occurs more than 30 days after the original informed consent form (ICF) was signed. The following assessments do not need to be repeated during rescreening if they were performed during the initial screening within the timeframes noted below:

- ECHO or MUGA scan does not need to be repeated if initial test was medically acceptable and if performed within 60 days prior to Cycle 1 Day 1
- Hepatitis serologies do not need to be repeated if performed within 12 weeks prior to first dose of study drug
- Baseline ophthalmology examination does not need to be repeated if performed within 8 weeks prior to first dose of study drug

#### 5.3.5.2. Information to Be Collected for Subjects Who Are Screen Failures

The following information will be collected for subjects who are screen failures:

- Demographics

- Inclusion/exclusion criteria
- Date informed consent signed
- Screen failure date and reason
- Withdrawal of consent (if applicable)
- AE or serious adverse event (SAE) related to study procedures during the screening period (if applicable)

### 5.3.6. Study Discontinuation/Termination

The Sponsor has the right to terminate the study at an individual site or specific cohorts or the study in its entirety. Reasons for terminating the study or specific cohorts may include, but are not limited to:

- The emergence of an unacceptable risk to subjects
- The criteria for futility are met
- General lack of enrollment or inadequate recruitment of subjects by an Investigator at a specific study site
- Failure of an Investigator or site to adhere to the protocol or regulatory requirements
- The Sponsor's decision to suspend or discontinue development of the study drug
- The Sponsor's decision to suspend or discontinue further development of the study drug in specific cohorts

If the Sponsor decides to terminate the study or study site, the Sponsor will promptly notify the Investigator(s) and relevant regulatory agencies. The Investigator will be responsible for notifying the Institutional Review Board/Ethics Committee of the early termination. Should the study be terminated early, the subject should be seen as soon as possible, and the same assessments performed as for discontinued or withdrawn subjects.

# 6. STUDY ASSESSMENT AND TREATMENT SCHEDULE

After providing informed consent, subjects will undergo screening assessments (up to 28 days prior to first dose of study drug) as indicated in Table 2 and Table 3. Tumor samples will be analyzed for cMET expression, at any time for Part 1. Tumor samples must be provided prospectively to assign subjects to Part 2. Confirmation of cMET status by IHC at a central laboratory is required for Part 2 before the subject can be enrolled in the study. Pre-screening may be conducted >28 days before Cycle 1 Day 1, after appropriate informed consent has been obtained. Pre-screening includes provision of an archival tumor sample or fresh tissue biopsy sample and cMET testing at the central laboratory. Subjects with actionable mutation, including fusion of *EML4-ALK, ROS1, RET,* or *NTRK1-3* or mutation of *EGFR, BRAF, KRAS,* or *HER2,* are required to provide tumor tissue sampled after progression or discontinuation of the most recent actionable mutation-targeted therapy (e.g., TKI, monoclonal/bispecific antibody, ADC). This specific tumor tissue requirement for actionable mutations does not apply to subjects with *MET* exon 14 skipping mutation or *MET* amplification without other actionable mutations. Blood samples collected on study may be tested retrospectively for *MET* alterations (e.g., amplification/ exon 14 skipping).

Once enrolled in the study, MYTX-011 will be administered IV every 21 days (±2 days) or to a dose break regimen i.e. every 21 days (±2 days) for 2 cycles, followed by a 3-week dose break (±7 days) regimen, until disease progression, unacceptable toxicity, voluntary withdrawal of consent, or completion of study, whichever occurs first. Refer to Figure 2 and Figure 3.
For subjects on a dose break regimen, if an unplanned delay (e.g., due to an adverse event) longer than 14 days takes place between the two consecutive 21-day cycles, it is recommended to reset the dose break schedule after the subject has received two consecutive 21-day cycles to maintain dose intensity. Please reach out to the Sponsor Medical Monitor for questions related to the dose break regimen.

**Figure 2: Q3W Dosing Regimen**

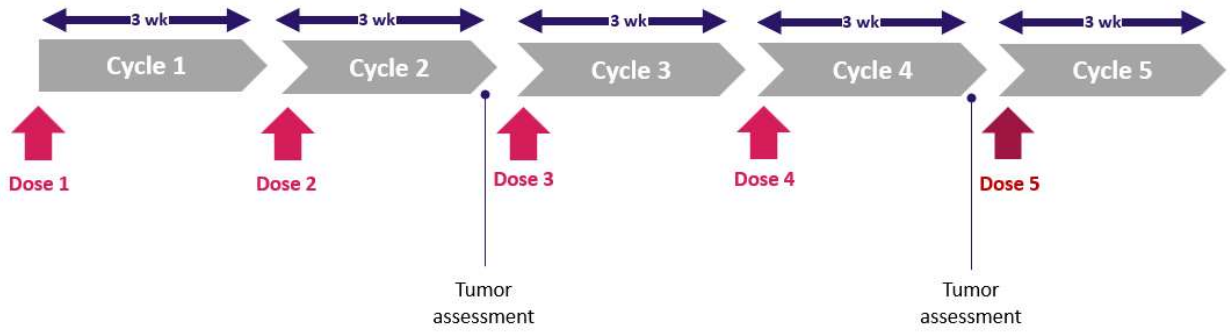
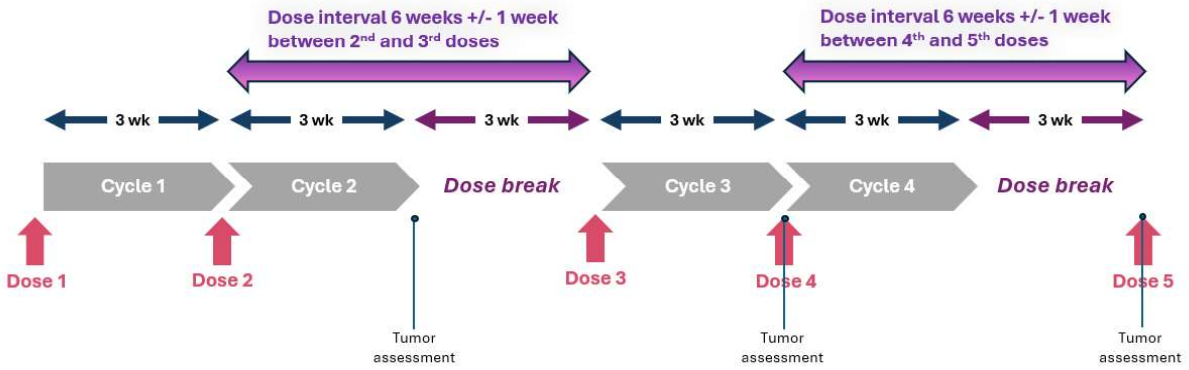


**Figure 3: Dose Break Regimen**




If the Investigator deems that a subject with disease progression is benefiting from treatment, the Investigator may request that the subject remain on treatment after disease progression (requires Medical Monitor approval). Subjects who achieve a confirmed CR by 2 tumor imaging assessments conducted at least 4 weeks apart may continue to receive treatment until meeting any of the EOT criteria (Section 5.3.1).

CT scans (or MRI) with contrast will be performed at the timepoints in Table 2 and Table 3 independent of study drug administration schedule until EOT, death, or withdrawal of consent. Subjects who discontinue study drug due to reasons other than disease progression or withdrawal of consent will continue to undergo tumor assessments until demonstration of disease progression, withdrawal of consent, or death. Subjects will be assessed (this can be done via telephone) every 3 months after the EOT visit until progression of disease is observed, withdrawal of consent, or death. During the 2-year long-term follow-up, disease status, survival status, and start of anticancer therapy will be collected.

This study includes a screening period (up to 28 days), treatment period, EOT visit, and long-term survival follow-up (up to 2 years).

**Table 2: Part 1 Study Assessment and Treatment Schedule**

| Cycle = 21 Days | Pre-screening[1] | Screening | C1 | | | | | C2 | | | 3-week (±7 days) for dose break regimen[3] | C3 | | | | | C4 | | | 3-week (±7 days) for dose break regimen[2, 3] | C5 Onward | EOT[4] | Long-Term Survival F/U[5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Up to Screening** | **D-28 to D-1** | **D1** | **D2** | **D4** | **D8** | **D15[3]** | **D1** | **D8** | **D15** | **D1 of dose break (D22 of second consecutive dosing cycle)** | **D1** | **D2** | **D4** | **D8** | **D15** | **D1** | **D8** | **D15** | **D1 of dose break (D22 second consecu-tive dosing cycle)** | **D1** | **Within 30 days of documented EOT date** | **Q3M** |
| **Visit Window** | | | **See Footnote[6]** | | | | **±1 day** | **±2 days[6]** | **±2 days** | **±2 days** | **±7 days** | **±2 days[6, 7]** | | | | **±1 day** | **±2 days[6]** | **±2 days** | **±2 days** | **±7 days** | **±2 days[6]** | **+7 days** | **±2 weeks** |
| Informed consent | X | X | | | | | | | | | | | | | | | | | | | | | |
| Medical history/ demographics/disease history | | X | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | | X | | | | | | | | | | | | | | | | | | | | | |
| ECOG performance status | | X | ✗ | | | | | ✗ | | | X | ✗ | | | | | ✗ | | | X | ✗ | X | |
| Vital signs[8] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| ECG (12-lead)[9] | | X | X | | | | | X | | | | X | | | | | X | | | | X[9, 10] | X[9, 10] | |
| Echocardiogram or MUGA scan | | X | | | | | | | | | | | | | | | | | | | | | |
| Physical examination[11] | | X | ✗ | X | X | X | X | ✗ | X | X | X | ✗ | X | X | X | X | ✗ | X | X | X | ✗ | X | |
| Full ophthalmic examination[12] | | X | | | | | | | | | | | | | | | | | | | X | X | |
| Partial ophthalmic examination – slit lamp and BCVA[13] | | | | | | | | X | | | X | | | | | | X | | | X | X | | |
| Hepatitis B and C serology | | X | | | | | | | | | | | | | | | | | | | | | |
| HIV viral load and CD4 count[14] | | X | X | | | | | | | | | | | | | | | | | | | | |
| Serum pregnancy test[15] | | X | | | | | | | | | | | | | | | | | | | | | |
| Serum or urine pregnancy test[16] | | | X | | | | | X | | | | X | | | | | X | | | | X | X | X |
| Urinalysis[17] | | X | X | | | | X | ✗ | | | X | X | | | | X | ✗ | | | X | X | X | |
| Blood chemistry[17] | | X | ✗ | X | | X | X | ✗ | X | X | X | ✗ | X | | X | X | ✗ | X | X | X | X | X | |
| Hematology[17] | | X | ✗ | X | | X | X | ✗ | X | X | X | ✗ | X | | X | X | ✗ | X | X | X | X | X | |
| Coagulation[17] | | X | X | X | | X | X | ✗ | | | | X | X | | X | X | ✗ | | | | X | X | |

**Table 2: Part 1 Study Assessment and Treatment Schedule (Continued)**

| Cycle = 21 Days | Pre-screening[1] | Screening | C1 | | | | | C2 | | | 3-week (±7 days) for dose break regimen[3] | C3 | | | | | C4 | | | 3-week (±7 days) for dose break regimen[2, 3] | C5 Onward | EOT[4] | Long-Term Survival F/U[5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Up to Screening** | **D-28 to D-1** | **D1** | **D2** | **D4** | **D8** | **D15[3]** | **D1** | **D8** | **D15** | **D1 of dose break (D22 of second consecutive dosing cycle)** | **D1** | **D2** | **D4** | **D8** | **D15** | **D1** | **D8** | **D15** | **D1 of dose break (D22 second consecu-tive dosing cycle)** | **D1** | **Within 30 days of documented EOT date** | **Q3M** |
| **Visit Window** | | | **See Footnote[6]** | | | | **±1 day** | **±2 days[6]** | **±2 days** | **±2 days** | **±7 days** | **±2 days[6, 7]** | | | | **±1 day** | **±2 days[6]** | **±2 days** | **±2 days** | **±7 days** | **±2 days[6]** | **+7 days** | **±2 weeks** |
| HbA1c | | X | | | | | | | | | | | | | | | | | | | | | |
| PK blood plasma sampling[18] | | | X | X | X | X | X | X | | | | X | X | X | X | X | X | | | | X | X | |
| Immunogenicity sampling[19] | | | X | | | | | X | | | | X | | | | | X | | | | X | X | |
| Pharmacodynamic/biomarker sampling[20] | | | X | | | | | X | | | | X | | | | | | | | | X | X | |
| MYTX-011 administration[21] | | | X | | | | | X | | | | X | | | | | X | | | | X | | |
| Radiological imaging (CT/MRI)/tumor evaluation per RECIST 1.1 | | X[22] | | | | | | | | | | | | | | | | | | | | | |
| MRI brain | | X[23] | | | | | | | | | | | | | | | | | | | | | |
| Tumor tissue sample collection[24] | X | | | | | | | | | | | | | | | | | | | | | | |
| Optional fresh tumor sample[25] | | | | | | | | X | | | | | | | | | | | | | | X | |
| AEs[26] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Concomitant medications | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Survival status and anticancer therapy F/U[5] | | | | | | | | | | | | | | | | | | | | | | | X |

ADA = anti-drug antibodies; AE = adverse event; C = cycle; BCVA = best corrected distance visual acuity; cMET = protein product of the *MET* gene; CNS = central nervous system; CR = complete response; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; F/U = follow-up; HbA1c = hemoglobin A1c; IHC = immunohistochemistry; M = month; *MET* = *MET* proto-oncogene, receptor tyrosine kinase; min = minute; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PK = pharmacokinetics; PR = partial response; Q3M = every 3 months; RECIST = Response Evaluation Criteria in Solid Tumors

[1] Pre-screening may be conducted >28 days before C1D1, after appropriate informed consent has been obtained. Pre-screening includes provision of an archival tumor sample or fresh tissue biopsy sample and cMET testing at the central laboratory.

[2] Dose break visits will continue to be performed after every two consecutive dosing cycles for the duration of treatment.

[3] Only applies to subjects assigned to the dose break cohort and/or subjects reduced to lower dose levels that entail dose break in Table 10. The 3-week dose break can flex between 14 to 28 days (2-4 weeks) per the investigator's discretion. Shortening of dose break to <14 days requires approval from the Sponsor Medical Monitor.

[4] The EOT visit will be conducted for all subjects who discontinue study drug for any reason. EOT is defined as the documented date of the decision to discontinue or death, whichever is earlier; if neither date is available, EOT will be defined as D42 from the last dose received. EOT visit must be performed within 30 days of the documented date of EOT. AEs that are ongoing at the time of EOT should be followed as described in Section 9.2.6.

[5] Survival status and anti-cancer therapy follow-up will be conducted via a telephone call (information may also be accessed from the medical records) every 3 months for up to 2 years after the EOT visit or documented date of discontinuation, whichever is later. Radiological imaging, tumor evaluation as per Investigator decision/standard of care. For subjects who discontinued treatment due to clinical progression, an image assessment after date of clinical progression should be performed for documentation of radiographic progression whenever possible. The documentation of further image assessment is not required after radiographic progression with the exception of treatment beyond progression.

[6] ***Boldface italic*** assessments can be performed up to 72 hours prior to study drug infusion.

[7] Visit window for C3 only. If C3D1 is delayed, all other days are in reference to the day the visit was actually performed.

[8] Vital signs include temperature, heart rate, blood pressure, respiratory rate, oxygen saturation; height (taken at screening only), and weight (taken at screening and on D1 of every cycle). If, over the course of treatment, the subject's weight changes by ≥ 10% of the initial weight, then the dose will be recalculated based on the updated weight. First dose: Measured prior to administration of MYTX-011, every 15 min (± 3 min), at end of infusion (± 5 min), and 30 min (± 5 min), 60 min (± 5 min), and 2 hours (± 10 min) after infusion. Subsequent infusions: prior to administration of MYTX-011, every 15 min during the infusion (± 3 min), at end of each infusion (± 5 min), and 30 min (± 5 min) after the infusion.

[9] Triplicate 12-lead ECGs will be read locally and may be collected for central retrospective analysis. Refer to Table 4 for details on timepoints.

[10] From C5 onward, ECGs will be collected only at C6D1 and C12D1 and EOT.

[11] Full physical examinations will be performed at screening, pre-treatment C1D1, and EOT visit. For C1D2, C1D4, C3D2, and C3D4, physical examinations are to be performed if clinically indicated. All other visits: symptom-directed physical examination.

[12] Full ophthalmic examination with dilation should be conducted at screening, at 1 year post C1D1, at EOT visit, and as clinically indicated. Subjects who develop ocular symptoms/AEs should have ophthalmologic evaluations every other cycle until resolution of the AE. Ocular surface assessment using vital dye such as fluorescein and optional Schirmer's test with or without anesthetic, if available, should be performed at the timepoints when full ophthalmic examinations are conducted. See Section 6.1.3.6.

[13] Partial ophthalmic examination: All patients should be assessed for ocular AEs via slit lamp examination and BCVA prior to every other consecutive dosing cycle (e.g. between C1 and C2, between C3 and C4) and during the dose break period, when applicable. Ophthalmic examinations may occur at least 1 week after the previous dose and within 2 weeks before the next dose (and ideally as close to the next dose as possible). Subjects with ongoing ocular AE at EOT visit should continue to undergo partial ophthalmic exams (full ophthalmic exams may replace partial exams per the eye care provider's discretion) every 3-4 weeks (or shorter interval as clinically indicated) until resolution or return to baseline. Additional examinations may also be conducted if new or worsening ocular symptoms occur or as clinically indicated. See Section 6.1.3.6. A full ophthalmic examination, as directed in Footnote 12 above, may be performed instead of the partial examination.

[14] For patients with HIV, HIV viral load and CD4 count must be measured at screening and every 3 months while the patient is receiving study treatment, or as clinically indicated or based on local standard of care.

[15] For women of childbearing potential only. Serum pregnancy test must be done within 3 days prior to C1D1.

[16] Urine or serum pregnancy test (for women of childbearing potential) prior to each administration of MYTX-011 and at the EOT visit and monthly for 6 months after EOT as per local requirements.

[17] Urinalysis, hematology, blood chemistry, and coagulation are assessed as follows (all 4 tests except where noted otherwise): at Screening; pre-dose C1D1, C1D2 (blood chemistry, hematology, and coagulation), C1D8 (blood chemistry, hematology, and coagulation), C1D15, C2D1, C2D8 (blood chemistry and hematology), C2D15 (blood chemistry and hematology), C3D1, C3D2 (blood chemistry, hematology, and coagulation), C3D8 (blood chemistry, hematology, and coagulation), C3D15, C4D1, C4D8 (blood chemistry and hematology), C4D15 (blood chemistry and hematology), C5D1, and D1 of all subsequent treatment cycles; and at EOT. If total bilirubin is elevated, assess direct bilirubin. Additional safety laboratory assessments may be performed at any time during the trial per Investigator's discretion.

[18] Refer to exact PK sampling schedule outlined in Table 6.

[19] Refer to exact ADA sampling schedule outlined in Table 6.

[20] Pharmacodynamic samples will be collected at pre-dose timepoint for C1D1 (baseline), C2D1, C3D1, C6D1, and EOT. Includes blood samples for ctDNA analysis and sMET (soluble cMET); samples may be used for exploratory biomarker analyses during or at the end of the study.

[21] MYTX-011 infusion will be on D1 every 21 days (± 2 days) or follow a dose break regimen, for the duration of treatment. A cycle is 21 days. While on study treatment, all subjects should apply prophylactic eye medications as outlined in Section 7.5.2.

[22] CT scan (with contrast) or MRI (with contrast) of chest, abdomen, and pelvis to be done at screening. CT scans (with contrast) of chest, abdomen, and pelvis, and other known sites of disease will be done every 6 weeks (±7 days) counting from C1D1, through Week 24. After Week 24, CT scans will be done every 12 weeks (± 7 days). The image assessment is independent of study drug administration schedule. Per RECIST 1.1, confirmatory CT scans may be done at unscheduled visits. Radiographic response (CR or PR) requires confirmation by a repeat assessment at least 4 weeks after the first detection of response. If CT scan cannot be done with contrast, obtain CT scan of chest without contrast and contrast-enhanced MRI of abdomen and pelvis. The imaging modality used at screening must be used throughout the study for all subsequent scans. See Section 6.1.2.1.

[23] Gadolinium-enhanced MRI of the brain will be conducted during screening to assess for brain metastases and every 6 weeks counting from C1D1, if brain metastases are present. If MRI contrast is contraindicated, MRI without contrast is acceptable. If an MRI is contraindicated, then a CT scan with contrast may be performed. See Section 6.1.2.1.

[24] Tumor samples are requested at screening for subjects in Part 1. These samples are collected for analysis of cMET by IHC at the central laboratory. Archival tissue can be submitted or tumor biopsies performed during pre-screening or screening after the appropriate informed consent has been obtained. For Part 1, confirmation of cMET status is strongly preferred but is not an eligibility requirement. If a tumor tissue sample was collected at pre-screening, tumor tissue should not be collected again at screening. See Sections 6.1.1.3 and 6.1.2.2 and Laboratory Manual.

[25] Optional fresh tumor biopsy obtained at C2D1 (-7 to +14 day window) is encouraged. EOT optional biopsy should be performed within 42 days after the last dose of study drug (prior to EOT visit). See Section 6.1.2.3.

[26] All AEs regardless of severity or relationship to the study drug are to be recorded on the eCRF until 30 days after documented date of discontinuation or completion of protocol-specific treatment. See Section 9.2.6.

**Table 3: Part 2 Study Assessment and Treatment Schedule**

| **Cycle = 21 Days** | **Pre-screening[1]** | **Screening** | **C1** | | | | | **C2** | | | **3-week (±7 days) for dose break regimen[2]** | **C3** | | | | | **C4** | | | **3-week (±7 days) for dose break regimen[2, 3]** | **C5 Onward** | **EOT[4]** | **Long-Term Survival F/U[5]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Up to Screening** | **D-28 to D-1** | **D1** | **D2** | **D4** | **D8** | **D15** | **D1** | **D8** | **D15** | **D1 of dose break (D22 of second consecutive dosing cycle)** | **D1** | **D2** | **D4** | **D8** | **D15** | **D1** | **D8** | **D15** | **D1 of dose break (D22 second consecutive dosing cycle)** | **D1** | **Within 30 days of documented EOT date** | **Q3M** |
| **Visit Window** | | | **See Footnote[6]** | | | | **±1 day** | **±2 days[6]** | **±2 days** | **±2 days** | **±7 days** | **±2 days[6, 7]** | | | | **±1 day** | **±2 days[6]** | **±2 days** | **±2 days** | **±7 days** | **±2 days[6]** | **+7 days** | **±2 weeks** |
| Informed consent | X | X | | | | | | | | | | | | | | | | | | | | | |
| Medical history/ demographics/disease history | | X | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | | X | | | | | | | | | | | | | | | | | | | | | |
| ECOG performance status | | X | ✗ | | | | | ✗ | | | X | ✗ | | | | | ✗ | | | X | ✗ | X | |
| Vital signs[8] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| ECG (12-lead)[9] | | X | X | | | | | X | | | | X | | | | | X | | | | X[9, 10] | X[9, 10] | |
| Echocardiogram or MUGA scan | | X | | | | | | | | | | | | | | | | | | | | | |
| Physical examination[11] | | X | ✗ | X | X | X | X | ✗ | X | X | X | ✗ | X | X | X | X | ✗ | X | X | X | ✗ | X | |
| Full ophthalmic examination[12] | | X | | | | | | | | | | | | | | | | | | | X | X | |
| Partial ophthalmic examination – slit lamp and BCVA[13] | | | | | | | | X | | | X | | | | | | X | | | X | X | | |
| Hepatitis B and C serology | | X | | | | | | | | | | | | | | | | | | | | | |
| HIV viral load and CD4 counts[14] | | X | X | | | | | | | | | | | | | | | | | | | | |
| Serum pregnancy test[15] | | X | | | | | | | | | | | | | | | | | | | | | |
| Serum or urine pregnancy test[16] | | | X | | | | | X | | | | X | | | | | X | | | | X | X | X |
| Urinalysis[17] | | X | ✗ | | | | X | ✗ | | | X | ✗ | | | | X | ✗ | | | X | ✗ | X | |
| Blood chemistry[17] | | X | ✗ | | | | X | ✗ | | | X | ✗ | | | | X | ✗ | | | X | ✗ | X | |
| Hematology[17] | | X | ✗ | | | | X | ✗ | | | X | ✗ | | | | X | ✗ | | | X | ✗ | X | |
| Coagulation[17] | | X | ✗ | | | | X | ✗ | | | | ✗ | | | | X | ✗ | | | | ✗ | X | |
| HbA1c | | X | | | | | | | | | | | | | | | | | | | | | |

**Table 3: Part 2 Study Assessment and Treatment Schedule (Continued)**

| Cycle = 21 Days | Pre-screening[1] | Screening | C1 | | | | | C2 | | | 3-week (±7 days) for dose break regimen[2] | C3 | | | | | C4 | | | 3-week (±7 days) for dose break regimen[2, 3] | C5 Onward | EOT[4] | Long-Term Survival F/U[5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Up to Screening** | **D-28 to D-1** | **D1** | **D2** | **D4** | **D8** | **D15** | **D1** | **D8** | **D15** | **D1 of dose break (D22 of second consecutive dosing cycle)** | **D1** | **D2** | **D4** | **D8** | **D15** | **D1** | **D8** | **D15** | **D1 of dose break (D22 second consecutive dosing cycle)** | **D1** | **Within 30 days of documented EOT date** | **Q3M** |
| **Visit Window** | | | **See Footnote[6]** | | | | **±1 day** | **±2 days[6]** | **±2 days** | **±2 days** | **±7 days** | **±2 days[6, 7]** | | | | **±1 day** | **±2 days[6]** | **±2 days** | **±2 days** | **±7 days** | **±2 days[6]** | **+7 days** | **±2 weeks** |
| PK blood plasma sampling[18] | | | X | X | | X | | X | | | | X | X | | X | | X | | | | X | X | |
| Immunogenicity sampling[19] | | | X | | | | | X | | | | X | | | | | X | | | | X | X | |
| Pharmacodynamic/biomarker sampling[20] | | | X | | | | | X | | | | X | | | | | X | | | | X | X | |
| MYTX-011 administration[21] | | | X | | | | | X | | | | X | | | | | X | | | | X | | |
| Radiological imaging (CT/MRI)/tumor evaluation per RECIST 1.1 | | X[22] | | | | | | | | | | | | | | | | | | | | | |
| MRI brain | | X[23] | | | | | | | | | | | | | | | | | | | | | |
| Tumor tissue sample collection[24] | X | X | | | | | | | | | | | | | | | | | | | | | |
| Optional fresh tumor sample[25] | | | | | | | | X | | | | | | | | | | | | | | X | |
| AEs[26] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Concomitant medications | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Survival status and anticancer therapy F/U[5] | | | | | | | | | | | | | | | | | | | | | | | X |

[1] Pre-screening may be conducted >28 days before C1D1, after appropriate informed consent has been obtained. Pre-screening includes provision of an archival tumor sample or fresh tissue biopsy sample and cMET testing at the central laboratory.

[2] Only applies to subjects assigned to the dose break cohort and/or subjects reduced to lower dose levels that entail dose break in Table 10. The 3-week dose break can flex between 14 to 28 days (2-4 weeks) per the investigator's discretion. Shortening of dose break to <14 days requires approval from the Sponsor Medical Monitor.

[3] Dose break visits will continue to be performed after every two consecutive dosing cycles for the duration of treatment.

[4] The EOT visit will be conducted for all subjects who discontinue study drug for any reason. EOT is defined as the documented date of the decision to discontinue treatment or death, whichever is earlier; if neither date is available, EOT will be defined as D42 from the last dose received. EOT visit must be performed within 30 days of the documented date of EOT. AEs that are ongoing at the time of EOT should be followed as described in Section 9.2.6.

[5] Survival status and anti-cancer therapy follow-up will be conducted via a telephone call (information may also be accessed from the medical records) every 3 months for up to 2 years after the EOT visit or documented date of discontinuation, whichever is later. For subjects who discontinued treatment due to clinical progression, an image assessment after date of clinical progression should be performed for

documentation of radiographic progression whenever possible. Radiological imaging, tumor evaluation as per Investigator decision/standard of care. The documentation of further image assessment is not required after radiographic progression with the exception of treatment beyond progression.

[6] ***Boldface italic*** assessments assessment can be performed up to 72 hours prior to study drug infusion.

[7] Visit window for C3 only. If C3D1 is delayed, all other days are in reference to the day the visit was actually performed.

[8] Vital signs include temperature, heart rate, blood pressure, respiratory rate, oxygen saturation; height (taken at screening only), and weight (taken at screening and on D1 of every cycle). If, over the course of treatment, the subject's weight changes by ≥ 10% of the initial weight, then the dose will be recalculated based on the updated weight. First dose: Measured prior to administration of MYTX-011, every 15 min (± 3 min), at end of infusion (± 5 min), and 30 min (± 5 min), 60 min (± 5 min), and 2 hours (± 10 min) after infusion. Subsequent infusions: prior to administration of MYTX-011, every 15 min during the infusion (± 3 min), at end of each infusion (± 5 min), and 30 min (± 5 min) after the infusion.

[9] Triplicate 12-lead ECGs will be read locally and may be collected for central retrospective analysis. Refer to Table 4 for details on timepoints.

[10] From C5 onward, ECGs will be collected only at C6D1 and C12D1 and EOT.

[11] Full physical examinations will be performed at screening, pre-treatment C1D1, and EOT visit. For C1D2, C1D4, C3D2, and C3D4, physical examinations are to be performed if clinically indicated. All other visits: symptom-directed physical examination.

[12] Full ophthalmic examination with dilation should be conducted at screening, at 1 year post C1D1, at EOT visit, and as clinically indicated. Subjects who develop ocular symptoms/AEs should have ophthalmologic evaluations every other cycle until resolution of the AE. Ocular surface assessment using vital dye such as fluorescein and optional Schirmer's test with or without anesthetic, if available, should be performed at the timepoints when full ophthalmic examinations are conducted. See Section 6.1.3.6.

[13] Partial ophthalmic examination: All patients should be assessed for ocular AEs via slit lamp examination and BCVA prior to every other consecutive dosing cycle (e.g. between C1 and C2, between C3 and C4) and during the dose break period, when applicable. Ophthalmic examinations may occur at least 1 week after the previous dose and within 2 weeks before the next dose (and ideally as close to the next dose as possible). Subjects with ongoing ocular AE at EOT visit should continue to undergo partial ophthalmic exams (full ophthalmic exams may replace partial exams per the eye care provider's discretion) every 3-4 weeks (or shorter interval as clinically indicated) until resolution or return to baseline. Additional examinations may also be conducted if new or worsening ocular symptoms occur or as clinically indicated. See Section 6.1.3.6. A full ophthalmic examination, as directed in Footnote 12 above, may be performed instead of the partial examination.

[14] For patients with HIV, HIV viral load and CD4 count must be measured at screening and every 3 months while the patient is receiving study treatment, or as clinically indicated or based on local standard of care.

[15] For women of childbearing potential only. Serum pregnancy test must be done within 3 days prior to C1D1.

[16] Urine or serum pregnancy test (for women of childbearing potential) prior to each administration of MYTX-011 and at the EOT visit and monthly for 6 months after EOT as per local requirements.

[17] Urinalysis, hematology, blood chemistry, and coagulation are assessed at Screening; pre-dose C1D1, C1D15, C2D1, C3D1, C3D15, C4D1, C5D1, and D1 of all subsequent treatment cycles; and at EOT. If total bilirubin is elevated, assess direct bilirubin. Additional safety laboratory assessments may be performed at any time during the trial per Investigator's discretion.

[18] Refer to exact PK sampling schedule outlined in Table 7.

[19] Refer to exact ADA sampling schedule outlined in Table 7.

[20] Pharmacodynamic samples will be collected at pre-dose timepoint for C1D1 (baseline), C2D1, C3D1, C6D1, and EOT. Includes blood samples for ctDNA analysis and sMET (soluble cMET); samples may be used for exploratory biomarker analyses during or at the end of the study.

[21] MYTX-011 infusion will be on D1 every 21 days (± 2 days) or follow a dose break regimen, for the duration of treatment. A cycle is 21 days. While on study treatment, all subjects should apply prophylactic eye medications as outlined in Section 7.5.2.

[22] CT scan (with contrast) or MRI (with contrast) of chest, abdomen, and pelvis to be done at screening. CT scans (with contrast) of chest, abdomen, and pelvis, and other known sites of disease will be done every 6 weeks (±7 days) counting from C1D1, through Week 24. After Week 24, CT scans will be done every 12 weeks (± 7 days). The image assessment is independent of study drug administration schedule. Per RECIST 1.1, confirmatory CT scans may be done at unscheduled visits. Radiographic response (CR or PR) requires confirmation by a repeat assessment at least 4 weeks after the first detection of response. If CT scan cannot be done with contrast, obtain CT scan of chest without contrast and contrast-enhanced MRI of abdomen and pelvis. The imaging modality used at screening must be used throughout the study for all subsequent scans. See Section 6.1.2.1.

[23] Gadolinium-enhanced MRI of the brain will be conducted during screening to assess for brain metastases and every 6 weeks counting from C1D1, if brain metastases are present. If MRI contrast is contraindicated, MRI without contrast is acceptable. If an MRI is contraindicated, then a CT scan with contrast may be performed. See Section 6.1.2.1.

[24] Tumor samples are required before enrollment into Part 2. Confirmation of cMET status by IHC at the central laboratory is required for subjects to be enrolled in Part 2. Subjects with actionable mutation, including fusion of EML4-ALK, ROS1, RET, or NTRK1-3 or mutation of EGFR, BRAF, KRAS, or HER2, are required to provide tumor tissue sampled after progression or discontinuation of the most recent actionable mutation-targeted therapy (e.g., tyrosine kinase inhibitor, monoclonal/bispecific antibody, ADC). Subjects with these actionable mutations are requested, but not required to also provide available archival tumor tissue sampled prior to the first actionable mutation-targeted therapy e.g. tyrosine kinase inhibitor (TKI), monoclonal/bispecific antibody, ADC. This specific tumor tissue requirement for actionable mutations does not apply to subjects with MET exon 14 skipping mutation or MET amplification without other actionable mutations. Archival tissue can be submitted or tumor biopsies performed during pre-screening or screening after the appropriate informed consent has been obtained. If a tumor tissue sample was collected at pre-screening, tumor tissue should not be collected again at screening.. See Sections 6.1.1.3 and 6.1.2.2 and Laboratory Manual.

[25] Optional fresh tumor biopsy obtained at C2D1 (-7 to +14 day window) is encouraged. EOT optional biopsy should be performed within 42 days after the last dose of study drug (prior to EOT visit). See Section 6.1.2.3.

[26] All AEs regardless of severity or relationship to the study drug are to be recorded on the eCRF until 30 days after documented date of discontinuation or completion of protocol-specific treatment. See Section 9.2.6.

# 6.1. TRIAL ASSESSMENTS

## 6.1.1. Baseline Assessments

### 6.1.1.1. Informed Consent

Subjects potentially eligible for study enrollment must sign an ICF prior to initiation of any study-specific assessments or procedures.

### 6.1.1.2. Medical History, Demographics, and Disease History

Medical (including smoking) and surgical history, current medical conditions, and demographics will be captured at screening.

Details of NSCLC will be recorded at screening including date of initial diagnosis, histological classification, date metastatic disease was identified, stage at study entry, and current sites of active disease/metastases. Prior therapies (surgeries, radiation, systemic anticancer therapies) along with dates, number of cycles, best observed response (BoR) to each treatment, DOR to each treatment (if subject had a response), and date of most recent disease progression will be recorded. Programmed death ligand 1 status (if positive and % positivity) and presence of other actionable mutations (including *MET*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *RET*) if known should be recorded. *EGFR* mutational status should be recorded. Other known mutations should also be captured.

### 6.1.1.3. Tumor Tissue for cMET IHC Prior to Study Entry

**Part 1:** Tumor samples are requested at screening for subjects in Part 1. These samples are collected for analysis of cMET by IHC at the central laboratory. Archival tissue can be submitted or tumor biopsies performed during pre-screening or screening after the appropriate informed consent has been obtained. For Part 1, confirmation of cMET status is strongly preferred but is not an eligibility requirement.

**Part 2:** Tumor samples are **required** before enrollment into Part 2. Confirmation of cMET status by IHC at the central laboratory is required for subjects to be enrolled in Part 2. Subjects with actionable mutation, including fusion of *EML4-ALK, ROS1, RET,* or *NTRK1-3* or mutation of *EGFR, BRAF, KRAS,* or *HER2,* are required to provide tumor tissue sampled after progression or discontinuation of the most recent actionable mutation-targeted therapy (e.g., TKI, monoclonal/bispecific antibody, ADC). This specific tumor tissue requirement for actionable mutations does not apply to subjects with *MET* exon 14 skipping mutation or *MET* amplification without other actionable mutations. If more than 1 cMET IHC result from different tumor samples is available, eligibility for enrollment and cohort assignment will be based on the results from the tumor sample taken most recently. If more than 1 cMET IHC result is available from the tissue taken from the same date, eligibility for enrollment and cohort assignment will be based on the result with the lowest cMET expression.

**Part 1 and Part 2:** Archival tissue can be submitted or tumor biopsies performed during pre-screening or screening after the appropriate informed consent has been obtained.

Pre-screening may be conducted >28 days before Cycle 1 Day 1, after appropriate informed consent has been obtained. Pre-screening includes provision of an archival tumor sample or fresh tissue biopsy sample and cMET testing at the central laboratory.

Core needle biopsy, excisional biopsy, or incisional biopsy is preferred for obtaining tumor tissue. Acceptable cytology samples include those acquired via fine needle aspiration, bronchoalveolar lavage (BAL), and bronchial brush, as well as pleural/pericardial fluids that can be spun down and made into paraffin-embedded cell blocks. Cytology samples must NOT be placed into alcohol or alcohol-based fixative/preservative prior to fixation in 10% neutral buffered formalin. Cytology smears from any other source are not acceptable for cMET testing via IHC.

See Laboratory Manual for more information about submitting samples.

#### 6.1.1.4. Blood Specimens for Circulating Nucleic Acid Profiling

Whole blood samples will be collected for biomarker research from all subjects as specified in Table 2 and Table 3. Samples will be tested for circulating nucleic acids (e.g., circulating free DNA) to evaluate their association with the observed clinical responses to MYTX-011.

### 6.1.2. Efficacy Assessments

#### 6.1.2.1. Assessment of Anti-tumor Activity/Response Assessment

The extent of disease and response assessment will be evaluated by contrast-enhanced CT scan/MRI based on RECIST 1.1 criteria (Appendix C). Assessments should include the chest, abdomen, pelvis, brain, and other known sites of disease. Imaging will be assessed locally by the Investigator. Sites should retain digital copies of radiological images. Radiology images may be requested for potential retrospective independent review.

Confirmation of Investigator-assessed ORR and DOR will be performed in study Parts 1 and 2, through an Independent Review Committee. See Study Manual for details.

Screening assessments will be done within the screening period (within 28 days prior to first dose of MYTX-011) and will be used as the baseline scan. A scan obtained for standard of care before informed consent is obtained but within 28 days of first dose is allowed to be used as the baseline scan. The same method of assessment/imaging modality should be used at subsequent visits for a given subject.

CT scans with contrast (preferred) will be performed during screening, then every 6 weeks (±7 days) counting from Cycle 1 Day 1 through Week 24. After Week 24, CT scans will be done every 12 weeks until disease progression or withdrawal of consent. Per RECIST 1.1, confirmatory CT scans may be done at unscheduled visits. If contrast cannot be used, a non-contrast CT scan of the chest and a contrast-enhanced MRI of the abdomen and pelvis may be performed. If both contrast-enhanced CT and MRI are contraindicated, non-contrast imaging may be performed after the local radiologist determines that the lesions are clearly traceable and assessable on non-contrast imaging. The same technique must be used throughout the course of

the study. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to non-contrast CT or MRI (enhanced or non-enhanced) should be performed at the discretion of the Investigator in consultation with the radiologist and to optimize comparison to prior scans if possible. A radiographic response (CR or PR) should be confirmed by a repeat scan at least 4 weeks after the first documentation of response.

Gadolinium-enhanced MRI of the brain will be conducted during screening to assess for brain metastases and every 6 weeks counting from Cycle 1 Day 1, if brain metastases are present. If MRI contrast is contraindicated, MRI without contrast is acceptable. If an MRI is contraindicated, then a CT scan with contrast may be performed.

A bone scan and/or positron emission tomography (PET) scan is allowed for subjects at baseline and during the study if bone metastases are considered and at the discretion of the Investigator as per standard of care; however, the CT/MRI scans should be used for tumor assessments as described above.

Subjects who discontinue study drug due to reasons other than disease progression or withdrawal of consent will continue to undergo tumor assessments until demonstration of disease progression, withdrawal of consent, or death. Subjects will be assessed every 12 weeks (±2 weeks) after the EOT visit until progression of disease is observed. For subjects who discontinued treatment due to clinical progression, an image assessment after date of clinical progression should be performed for documentation of radiographic progression whenever possible. Documentation of further image assessment is not required after radiographic progression with the exception of treatment beyond progression.

#### 6.1.2.2. Tumor Tissue for Exploratory Analyses

Tumor biopsy samples (archival or fresh tissue) collected for screening, if available in sufficient quantity, may also be used to assess tumor genes or proteins of interest that are associated with the drug response. These tumor specimens for assessment of candidate protein or nucleic acid (e.g., DNA, ribonucleic acid [RNA]) biomarkers can predict or identify those subjects who are most likely to benefit from treatment with the study drug. Biomarkers that may be analyzed include, but may not be limited to, cMET expression and alterations in the *MET* gene.

#### 6.1.2.3. Fresh Tumor Biopsy for Exploratory Analyses

Optional, fresh on-treatment tumor biopsies will be collected only at the timepoints outlined in Table 2 and Table 3 if consented to by the subject and if the procedure is deemed safe by the Investigator. A fresh tumor biopsy consists of an incisional or excisional biopsy, or a core needle biopsy, of a primary or metastatic lesion. Fine needle aspiration is an acceptable approach if the aforementioned procedures cannot be performed, and samples should be fixated in 10% neutral buffered formalin (alcohol-containing buffers are prohibited). These samples will be used to evaluate DNA, RNA, or protein biomarkers as pharmacodynamic readouts to measure activity of MYTX-011 in the disease tissue. The tumor tissue will be processed as specified in the Laboratory Manual.

### 6.1.3. Safety Assessments

#### 6.1.3.1. ECOG Performance Status

ECOG performance status will be performed at screening and at timepoints indicated in Table 2 and Table 3.

#### 6.1.3.2. Vital Signs and Physical Examination

Vital signs (temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation) should be measured prior to study drug administration and at timepoints noted in Table 2 and Table 3. Vital signs should be assessed prior to any scheduled blood draws and after the subject has been resting for 5 minutes. Height and weight will be recorded at timepoints noted in Table 2 and Table 3. If, over the course of treatment, the subject's weight changes by ≥10% of the initial weight, then the dose will be recalculated based on the updated weight.

#### 6.1.3.3. Electrocardiogram

Triplicate 12-lead electrocardiograms (ECGs) will be read locally at screening and at timepoints noted in Table 4 and will include measurement of heart rate and intervals for PR, QT, QRS, R-R, and QTc. The QTc will be calculated using Fridericia's correction formula. The Investigator should assess abnormalities in the ECG for clinical significance. Pre-dose ECG should be performed on Day 1 of each designated cycle.

**Table 4: Schedule of Triplicate Electrocardiogram Collections with Pharmacokinetic Sampling (Subjects Enrolled in Part 1 and Part 2)**

| Cycle | Day -28 to -1 | Scheduled Timepoint |
|---|---|---|
| Screening | | Any time |
| 1 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion |
| 2 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion |
| 3 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion |
| 4 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion |
| 6 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion |
| 12 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion |
| EOT Visit | | Any time |

EOT = end of treatment
Note: Pre-dose ECG should be performed on Day 1 of each designated cycle.

All ECG recordings must be performed using an institutionally approved ECG. Lead placement should be as consistent as possible. ECG recordings should be performed after the subject has

been resting in a supine position for approximately 10 minutes. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

All ECGs should be collected and available if requested by the Sponsor for independent review by a central laboratory. Instructions for the collection and transmission of ECGs to the central ECG laboratory will be provided in the event this is requested.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings. Copies of ECG tracings will be kept as part of the subject's permanent study file at the site. The following should be recorded on the appropriate eCRF page: heart rate, R-R interval, QRS interval, PR duration, uncorrected QT interval, and QTcF, based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF page. All eligibility and subject management decisions should be made based on the local reading of the ECG.

#### 6.1.3.4. ECHO/MUGA Scan

An ECHO or MUGA scan will be performed at screening to assess LVEF.

#### 6.1.3.5. Physical Examination

Physical examinations (complete or symptom directed) will be conducted at timepoints noted in Table 2 and Table 3.

#### 6.1.3.6. Ophthalmic Assessments

Refer to Table 2 and Table 3 for the assessment schedule.

All ophthalmic assessment visits (including screening) must document the best corrected visual acuity (BCVA) (distance) using either manifest refraction or subject's glasses (with pinhole). If vision is affected by conditions unrelated to study drug (e.g., cataracts, age-related macular degeneration), establish a new baseline visual acuity.

Full or comprehensive ophthalmic examination should be conducted by an eye care professional at screening (prior to first administration of study drug), at 1 year post Cycle 1 Day 1, EOT visit, and as clinically indicated. This should include BCVA, slit lamp examination with ocular surface staining, dilated fundus exam, and an optional Schirmer's test score (with or without anesthesia).

Partial ophthalmic examinations, including BCVA and slit lamp examination with ocular surface staining, are required prior to every other cycle (within 2 weeks before upcoming dose) and during the dose break period (if applicable). If an unscheduled visit falls within the required exam window for an ophthalmic exam, it may replace the scheduled assessment. Partial exams may be replaced by full exams if clinically necessary, as determined by the managing eye care professional.

Perform a full ophthalmic exam at the EOT visit. If the subject's reported ocular AE persists, continue follow-up until recovery or until deemed clinically insignificant (e.g., AE returns to Gr. 1 or within 1-2 lines of baseline vision) by the eye care professional. Subjects with ongoing ocular AE at EOT visit should continue to undergo partial ophthalmic exams (full ophthalmic

exams may replace partial exams per the eye care provider's discretion) every 3-4 weeks (or shorter interval as clinically indicated) until resolution or return to baseline.

Ocular symptom assessments (e.g., blurred vision, redness, dryness or excessive watering, itching, burning sensation, light sensitivity, eye pain) should be evaluated prior to each MYTX-011 dose. Grade symptoms on a 0-10 scale (0 = none, 10 = worst).

Any subjects who develop new or worsening ocular AEs should be referred to an eye care professional for evaluation. Refer to dose modification guidelines for management of ocular AEs (Section 7.5.2).

#### 6.1.3.7. Laboratory Assessments

Laboratory assessments will be collected as specified in Table 2 and Table 3. Additional laboratory testing may be done to ensure subject safety at the discretion of the treating Investigator.

Laboratory assessments on days of MYTX-011 administration should be obtained at timepoints noted in Table 2 and Table 3 prior to MYTX-011 administration, and the results should be reviewed prior to administration of MYTX-011.

The Investigator should assess out-of-range clinical laboratory values for clinical significance. Clinically significant abnormalities should be reported as an AE.

##### 6.1.3.7.1. Local Laboratory Assessments

1. Hematology and chemistry, including the tests shown in Table 5.

**Table 5: Hematology and Chemistry Laboratory Tests**

| **Hematology** | | |
|---|---|---|
| Hematocrit | Neutrophils | Platelet count |
| Hemoglobin | Lymphocytes | |
| Erythrocyte count | Monocytes | |
| Leukocyte count | Eosinophils | |
| Absolute neutrophil count | Basophils | |
| **Chemistry** | | |
| Albumin | Creatinine | Aspartate aminotransferase |
| Alkaline phosphatase | Glucose | Alanine aminotransferase |
| Bicarbonate/carbon dioxide | Lactate dehydrogenase | Sodium |
| Blood urea nitrogen | Magnesium | Total bilirubin (direct bilirubin if total bilirubin is elevated) |
| Calcium | Phosphorus | Total protein |
| Chloride | Potassium | Uric acid |
| Amylase | Lipase | |

2. HbA1c at screening

3. Serum pregnancy test (for women of childbearing potential) at screening (within 3 days before first dose)
4. Urine or serum pregnancy test (for women of childbearing potential) prior to each administration of MYTX-011 and at the EOT visit and monthly for 6 months after EOT as per local requirements
5. Coagulation laboratory tests include PT, aPTT, and INR
6. Serum virology includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis C virus antibody (HCVAb) at screening. If HBsAg, HBcAb, and/or HCVAb results are positive, subjects must be evaluated for the presence of active HBV or HCV by a polymerase chain reaction (PCR) test
7. Urinalysis by dipstick to include pH, specific gravity, protein, glucose, ketones, blood, nitrite, leukocytes, and microscopy assessment (if indicated)
8. For patients with HIV, HIV viral load and CD4 count must be measured at screening and every 3 months while the patient is receiving study treatment, or as clinically indicated or based on local standard of care

#### 6.1.3.7.2. Central Laboratory Assessments

Samples collected at the timepoints shown in Table 6 and Table 7 will be shipped to and analyzed at a central laboratory. Pre-dose PK samples need to be collected on the same day as study drug infusion (Day 1 of each designated cycle). In the event of missed PK sample collection, for example due to dose delays or adverse events, PK samples may be collected at alternative timepoints using the unscheduled visit laboratory kit. Refer to the Laboratory Manual for processing, handling, and shipping instructions.

**Table 6: Schedule of PK and ADA Sampling (Subjects Enrolled in Part 1 Dose Escalation)**

| Cycle | Day | Scheduled Timepoint (PK) MYTX-011 (Total Antibody, Total ADC, and MMAE)* | Scheduled Timepoint (ADA) |
|---|---|---|---|
| 1 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion, 2, 4, 6 hours post-infusion (±30 minutes) | Pre-dose |
| | 2 | 24 hours (±1 hour) post-infusion | |
| | 4 | 3 days (72 hours ±4 hours) post-infusion | |
| | 8 | 7 days (168 hours ±8 hours) post-infusion | |
| | 15 | 14 days (336 hours ±24 hours) post-infusion | |
| 2 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 3 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion, 2, 4, 6 hours post-infusion (±30 minutes) | Pre-dose |
| | 2 | 24 hours (±1 hour) post-infusion | |
| | 4 | 3 days (72 hours ±4 hours) post-infusion | |
| | 8 | 7 days (168 hours ±8 hours) post-infusion | |
| | 15 | 14 days (336 hours ±24 hours) post-infusion | |
| 4 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 6 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 8 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 10 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 12 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 15 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| EOT Visit | | Any time | Any time |

ADA = anti-drug antibodies; ADC = antibody-drug conjugate; EOT = end of treatment; MMAE = monomethyl auristatin E; PK = pharmacokinetic.
Note: Pre-dose PK samples need to be collected on the same day as study drug infusion (Day 1 of each designated cycle).
Note: In the event of missed PK sample collection, for example due to dose delays or adverse events, PK samples may be collected at alternative timepoints using the unscheduled visit laboratory kit.
* All post-infusion times refer to time after the end of infusion.

**Table 7: Schedule of PK and ADA Sampling (Subjects Enrolled in Part 2 Dose Expansion)**

| Cycle | Day | Scheduled Timepoint (PK) MYTX-011 (Total Antibody, Total ADC, and MMAE)* | Scheduled Timepoint (ADA) |
|---|---|---|---|
| 1 | 1 | Pre-dose and 30 minutes (±5 minutes) and 2 hours (±15 minutes) post-infusion | Pre-dose |
| | 2 | 24 hours (±1 hour) post-infusion | |
| | 8 | 7 days (168 hours ±8 hours) post-infusion | |
| 2 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 3 | 1 | Pre-dose and 30 minutes (±5 minutes) and 2 hours (±15 minutes) post-infusion | Pre-dose |
| | 2 | 24 hours (±1 hour) post-infusion | |
| | 8 | 7 days (168 hours ±8 hours) post-infusion | |
| 4 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 6 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 8 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 10 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 12 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| 15 | 1 | Pre-dose and 30 minutes (±5 minutes) post-infusion | Pre-dose |
| EOT Visit | | Any time | Any time |

ADA = anti-drug antibodies; ADC = antibody-drug conjugate; EOT = end of treatment; MMAE = monomethyl auristatin E; PK = pharmacokinetic.
Note: Pre-dose PK samples need to be collected on the same day as study drug infusion (Day 1 of each designated cycle).
Note: In the event of missed PK sample collection, for example due to dose delays or adverse events, PK samples may be collected at alternative timepoints using the unscheduled visit laboratory kit.
* All post-infusion times refer to time after the end of infusion.

#### 6.1.3.8. Adverse Events

AEs will be collected from the time of informed consent and then continuously throughout the study until 30 days after last administration of MYTX-011. Adverse events of special interest (AESIs) and SAEs considered related to MYTX-011 should be reported to the Sponsor even after the 30-day period has been completed. Investigators will assign a severity grade based on the NCI CTCAE Version 5.0. See Section 9.2.6 for more details.

#### 6.1.3.9. Concomitant Medications

All medications (including over-the-counter medications) taken within 30 days prior to first dose of study drug, during the treatment period, and for 30 days after the last dose of study drug, will be recorded at each visit from Screening through EOT. During the course of the study, any changes in concomitant medications should be recorded. Concomitant medications should

include the name of the medication, indication for use, dose and frequency, route of administration and start and stop dates/ongoing (as applicable).

## 6.1.4. Other Assessments

### 6.1.4.1. Pharmacogenomics

A blood sample will be collected and may be used to assess genetic variants (unless prohibited by local regulations).

The results of pharmacogenetic analyses and other exploratory studies will not be placed in the subject's medical records, and the results will not be available to the subject, sites, or other third parties, except as specified in the ICF. The subject retains the right to request that stored sample material for exploratory biomarker and pharmacogenetic analyses be destroyed by contacting the Investigator. The Investigator will notify the Sponsor if the subject requests the samples be destroyed. Information collected from samples prior to the request for destruction will be retained by the Sponsor.

### 6.1.4.2. Disease Status and Survival during Long-Term Follow-up

During long-term follow-up survival, information, disease status, and start of anticancer therapies will be captured. Follow-up can be done via telephone. Information may also be accessed from the medical records.

# 7. STUDY DRUG(S) AND CONCOMITANT THERAPY

## 7.1. MYTX-011

**Classification:** cMET-targeted ADC

**Chemical Name:** Q397, an IgG1, anti-(human antigen cMET) with a humanized heavy chain and light chain kappa with engineered site-specific cysteine (V205C), conjugated DAR 2.0 maleimidocaproyl-valinecitrulline-p-aminobenzyloxycarbonyl monomethylauristatin E.

**How Supplied:** 10 mL in a 50 mL single-use vial, 100 mg/vial (10 mg/mL concentration), as a frozen liquid

**Route of Administration:** Intravenous

**Packaging:** MYTX-011 will be provided as a vial in a kit.

**Availability:** MYTX-011 is available from Mythic Therapeutics, Inc.

The MYTX-011 IB is the primary source for safety information. The IB includes a discussion on potential risks and AESIs that may be predicted to occur. Refer to the most recent IB, which is updated periodically, for current information.

## 7.2. STUDY DRUG(S) ADMINISTRATION

MYTX-011 will be administered via IV infusion in 21-day cycles or on a dose break regimen. The Planned Dose levels are summarized in Table 8 below.

**Table 8: Planned Dose Levels**

| Dose Level | Dose (mg/kg)[1,2] |
|---|---|
| -1[3] | 0.3 |
| 1 | 1.0 |
| 2 | 2.0 |
| 3 | 3.3 |
| 4 | 5.0 |
| 5 | 6.7 |
| 6 | 8.3 |
| 7 | 10.0 |

BOIN = Bayesian Optimal Interval; PK = pharmacokinetics; SRC = Safety Review Committee

[1] mg/kg dose for subjects weighing up to 100 kg. Subjects weighing >100 kg will receive a fixed dose. Fixed dose for these subjects will be the same dose as subjects who weigh 100 kg. Based on emerging PK, safety, and preliminary anti-tumor activity data during the study, the SRC may recommend changing the fixed dose to a mg/kg dose for subjects who weigh >100 kg.
[2] Intermediate dose level(s) and/or a different dosing schedule may be implemented by the Sponsor or recommended by the SRC to assess the safety PK, and preliminary anti-tumor activity data.
[3] If a dose de-escalation is needed at dose level 1 based on the BOIN design, the SRC will review the emerging data and determine if the study should be amended, terminated, or a lower dose explored. The lower dose to be explored may be 0.3 mg/kg, but the SRC may recommend a different dose based on emerging data.

### 7.2.1. Guidelines for Administration of MYTX-011

MYTX-011 will be administered as an IV infusion over 60-90 minutes (or longer) Q3W or on a dose break schedule. The initial dose (Cycle 1 Day 1) will be administered over 90 minutes or longer. If there are no infusion-associated reactions with the first dose, subsequent doses may be administered over 60 minutes or longer. Flexibility is allowed to extend the infusion time beyond 90 minutes, while remaining compliant with the Pharmacy Manual requirements for preparation and administration of MYTX-011. The average infusion rate must not exceed 1000 mg/hour. For active patients on the study who receive MYTX-011 over 30-60 minutes regularly without experiencing IRR, the infusion duration of prior cycles may be maintained. See Section 7.5.1 for management of IRRs.

Dosing of MYTX-011 will be on a mg/kg basis for subjects weighing up to 100 kg. Subjects weighing >100 kg will receive a fixed dose. The fixed dose for these subjects will be the same dose as subjects who weigh 100 kg. Based on emerging PK, safety, and preliminary anti-tumor activity data during the study, the SRC may recommend changing the fixed dose to a mg/kg dose for subjects who weigh >100 kg. The subject's weight at screening will be used to calculate the subject's dose for the duration of treatment. If, over the course of treatment, the subject's weight changes by ≥10% of the initial weight, then the dose will be recalculated based on the updated weight.

Subjects will be observed closely for IRRs during the infusion and for at least 2 hours following the initial dose. Subjects will be monitored closely during the infusion and for at least 30 minutes after for subsequent infusions.

MYTX-011 should not be administered as an IV push or IV bolus. MYTX-011 should be administered through a dedicated IV line and not mixed with other medications. MYTX-011 infusion should be completed within the time period specified in the Pharmacy Manual.

## 7.3. PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

### 7.3.1. Preparation, Handling, and Storage

Please refer to the Pharmacy Manual for detailed instructions on storage, preparation, and administration of MYTX-011. Procedures for proper handling, storage, and disposal of anticancer drugs should be followed in accordance with institutional guidelines.

MYTX-011 is provided as a single-use vial containing 100 mg of MYTX-011 as a frozen liquid.

### 7.3.2. Preparation and Dilution

- Appropriate aseptic technique should be used for preparation of MYTX-011. Any partially used vials should be discarded according to standard institutional guidelines.
- Determine the number of vials needed based on the subject's weight and assigned dose.
- MYTX-011 will be thawed then diluted in normal saline (0.9% sodium chloride). After dilution with normal saline, the infusion should be initiated as soon as possible. If not used immediately, the infusion bag containing MYTX-011 can be stored refrigerated at 2°C to 8°C or room temperature for up to 4 hours (including the infusion time). MYTX-011 should not be refrozen.
- MYTX-011 should be administered IV with an integrated or externally connected 0.2 or 0.22 μm filter.
- MYTX-011 should not be mixed with or administered with other medicinal products.

### 7.3.3. Study Drug Accountability

The Sponsor will provide MYTX-011 for administration in the study. Accountability for investigational medicinal product at the site is the responsibility of the Investigator.

Study drug must be stored at the site in a secure, limited access environment in accordance with the required storage conditions (refer to Pharmacy Manual). Accurate records of all study drug received and dispensed must be maintained. Only subjects enrolled in the study may receive the study drug. The Sponsor or its designee will review drug accountability at the site on an ongoing basis.

At the completion of the study, unused study drug must be held for final study drug accountability prior to being returned to the Sponsor or destroyed at the site per the Sponsor instructions.

For detailed information on study drug receipt, storage, dispensation, accountability, returns/destruction please refer to the Pharmacy Manual.

## 7.4. ASSIGNMENT TO STUDY INTERVENTION

Study subjects who have signed an informed consent will be registered to the study and receive a unique study identifier. See Study Manual for further details and step-by-step instructions for registration and enrollment of subjects in the Interactive Response Technology (IRT) system. Each subject will have a unique subject ID. Subjects must be registered into the Suvoda system prior to any drug being dispensed to the site or to the subject.

In Part 2, Cohorts A, B2, and E2 may randomize subjects to 1 of 2 dose levels (the RP2D and 1 other dose); the optimal biological dose will further be evaluated based on anti-tumor activity, safety, and PK. Additional dose levels and randomizations may be added to any Part 2 cohort, as discussed in Section 4.2.

## 7.5. MANAGEMENT OF POTENTIAL TOXICITIES

Dose modification levels for each planned dose level and known intermediate dose levels in Part 1 are provided in Table 9. Dose modification levels for the RP2D and alternative dose in Part 2 are provided in Table 10. Ongoing Part 1 subjects have the option (based on investigator discretion) to follow Part 2 dose modification guidance outlined in Table 10. Dose modification schemes that deviate from Table 9 (e.g., larger magnitude of dose reduction) can be considered as an option only with the approval of the Sponsor Medical Monitor or designee. There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified in Table 11, Table 13, or Table 14.

**Table 9: Part 1 Dose Modification Levels for MYTX-011**

| Dose Modification | Dose (mg/kg) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **1.0** | ***1.5*** | **2.0** | ***2.6*** | **3.3** | ***4.0*** | **5.0** | ***5.8*** | ***6.2*** | **6.7** | ***7.2*** | ***7.5*** | **8.3** | **10.0*** |
| 1st dose modification | 0.3 | 1.0 | *1.5* | 2.0 | *2.6* | 3.3 | *4.0* | *4.0* | *5.0* | 5.0 | 5.0 | 5.0 | 6.7 | 8.3 |
| 2nd dose modification | | 0.3 | 1.0 | *1.5* | 2.0 | *2.6* | 3.3 | 3.3 | 4.0 | *4.0* | *4.0* | *4.0* | 5.0 | 6.7 |
| 3rd dose modification | | | | | | 2.0 | *2.6* | *2.6* | *3.3* | 3.3 | 3.3 | 3.3 | *4.0* | 5.0 |

* For dose levels not tested in the study by the time of Protocol version 7.0, the dose modification scheme may change depending on emerging clinical and pharmacokinetic data.

*Italics* = Intermediate dose levels

Note: For subjects enrolled in Part 1 receiving a dose break regimen, it is recommended to follow Part 2 dose modification levels in Table 10.

**Table 10: Part 2 Dose Modification Levels for MYTX-011**

| Dose Modification | Dosing Schedule (mg/kg) | | | |
|---|---|---|---|---|
| | **6.7 dose break** | **6.2 dose break** | **5.0 dose break** | **4.0 Q3W** |
| 1st dose modification | 5.0 dose break | 5.0 dose break | 4.0 dose break | 4.0 dose break |
| 2nd dose modification | 4.0 dose break | 4.0 dose break | 3.3 dose break | 3.3 dose break |
| 3rd dose modification | 3.3 dose break | 3.3 dose break | 2.6 dose break | 2.6 dose break |

Notes: Recommend the same dose level if ≤Gr. 2 ocular AE (e.g. blurred vision and/or corneal surface changes) occurs. Dose reduction should be considered after ocular AE returns to baseline for ≥Gr.3 Ocular AE. Reduction of more than 3 dose levels requires approval from the Sponsor Medical Monitor.

For subjects on dose break regimen, if an unplanned delay (e.g., due to an adverse event) longer than 14 days takes place between the two consecutive 21-day cycles, it is recommended to reset the dose break schedule after the

subject has received two consecutive 21-day cycles after resuming treatment to maintain dose intensity. Please contact the Sponsor Medical Monitor for questions related to dose break regimen.

Once the dose of study treatment has been modified because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose modification is required. Subjects may not resume original dose or dose increase if a reduction due to toxicity was required. For subjects treated at a dose of 1 mg/kg, only 1 dose modification will be allowed. For subjects treated at doses ≥4.0 mg/kg, 3 dose modifications will be allowed. For all other dose levels, if toxicity continues after 2 dose modifications, then the subject will be withdrawn from study treatment, unless the subject is deriving clinical benefit from the treatment in the opinion of the Investigator and further dose modification is approved by the Sponsor Medical Monitor.

Subjects enrolled in Part 2 should follow the dose modification defined in Table 10. Ongoing subjects in Part 1 may choose to follow the dose modification in Table 10 per the investigator's discretion.

Cycles will continue in consecutive order regardless of dose delays. In the event of a dose delay, the subsequent cycle will begin once the subject meets the criteria to resume treatment. The cycle number will not be reset or skipped due to the delay.

Investigators should contact the Sponsor Medical Monitor or designee to discuss questions regarding dose modification or discontinuation of study treatment.

Guidelines for management of toxicities and dose modifications in subjects with treatment-related toxicities are specified in Table 11, Table 13, or Table 14 but do not replace Investigator judgment, and dose modification can be discussed with the Sponsor Medical Monitor on a case-by-case basis per Investigator discretion.

## Table 11: Management of Toxicities Defined as Study Treatment-Related Only

| Worst Toxicity CTCAE Grade Unless Otherwise Specified (Value) | Dose Modification Guidelines |
|---|---|
| **IRR** | |
| **Infusion Reaction Grade 1**<br>Transient flushing or rash, fever <38°C (<100.4°F); intervention not indicated | **Management**<br>Stop infusion immediately and keep line open.<br>Monitor vital signs (blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.<br>Resume infusion once infusion reaction resolves (complete infusion within 4 hours of dilution):<br>• After Investigator considers subject clinically stable, restart infusion at 50% of previous rate (i.e., from 2 mL/min to 1 mL/min) under continuous observation.<br>• Maintain dose level.<br>• Administer oral pre-medication (e.g., 1000 mg of acetaminophen/paracetamol, 50-100 mg diphenhydramine hydrochloride or alternative antihistamine), within 60 minutes of restarting the infusion.<br>• If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then the dose should be skipped, and the subject should receive pre-medication for any subsequent administration. |
| **Infusion Reaction Grade 2**<br>Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hours | **Management**<br>• Stop infusion immediately and keep line open.<br>• Provide supplemental oxygen and fluids, as needed.<br>• Monitor vital signs (e.g., blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.<br>• Administer medications for symptomatic relief as needed:<br>o Urticaria: Diphenhydramine or alternative (25-100 mg IV) as needed every 4 to 6 hours.<br>o Fever: Acetaminophen/paracetamol (650-1000 mg by mouth) as needed every 4 to 6 hours.<br>o Rigors: Meperidine 25 mg IV as needed every 6 hours.<br>o Corticosteroids can be administered.<br>• Resume infusion once infusion reaction resolves (complete infusion within 4 hours of dilution):<br>o After Investigator considers subject clinically stable, restart infusion at 50% of previous rate (i.e., from 2 mL/min to 1 mL/min) under continuous observation.<br>o Maintain dose level.<br>o Administer oral pre-medication (e.g.,1000 mg of acetaminophen/paracetamol, 50-100 mg diphenhydramine hydrochloride or alternative antihistamine), within 60 minutes of restarting the infusion.<br>o If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then the dose should be skipped, and the subject should receive pre-medication for any subsequent administration. |

**Table 11: Management of Toxicities Defined as Study Treatment-Related Only (Continued)**

| Worst Toxicity CTCAE Grade Unless Otherwise Specified (Value) | Dose Modification Guidelines |
|---|---|
| **IRR (continued)** | |
| **Infusion Reaction Grade 3**<br>Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates) | **Management**<br>• Discontinue infusion immediately and discontinue subject from study treatment.<br>• Provide supplemental oxygen and fluids, as needed.<br>• Monitor vital signs (e.g., blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.<br>• Medication such as antihistamines or corticosteroids should be given for symptomatic relief. |
| **Infusion Reaction Grade 4**<br>Life-threatening | Urgent intervention indicated |
| **HEMATOLOGICAL TOXICITIES** | |
| **Thrombocytopenia** | |
| Grade 1 (PLT <LLN - 75 × $10^9$/L) | Maintain dose level |
| Grade 2 (PLT <75 - 50 × $10^9$/L) | Maintain dose level |
| Grade 3 (PLT <50 - 25 × $10^9$/L) | Omit dose until resolved to ≤Grade 1, then:<br>• If resolved in ≤7 days (≤3 days in UK only), then maintain dose level.<br>• If resolved in >7 days (>3 days in UK only), then reduce 1 dose level. |
| Grade 4 (PLT <25 × $10^9$/L) | Omit dose until resolved to ≤ Grade 1, then reduce 1 dose level. |
| **Neutropenia (ANC)** | |
| Grade 1 (ANC <LLN - 1.5 × $10^9$/L) | Maintain dose level. |
| Grade 2 (ANC <1.5 - 1.0 × $10^9$/L) | Maintain dose level. |
| Grade 3 (ANC <1.0 - 0.5 × $10^9$/L) | Omit dose until resolved to ≤Grade 1, then:<br>• If resolved in ≤7 days (≤3 days in UK only), then maintain dose level.<br>• If resolved in >7 days (>3 days in UK only), then reduce 1 dose level. |
| Grade 4 (ANC <0.5 × $10^9$/L) | Omit dose until resolved to ≤Grade 1, then reduce 1 dose level and resume. |
| Febrile neutropenia (decrease in neutrophils associated with fever, ANC <1.0 × $10^9$/L, fever ≥38.5°C [not CTCAE grade]) | Omit dose until resolved, then reduce 1 dose level. |
| Anemia<br>Grade 4 (Hgb <6.5 g/dL, life-threatening consequences, urgent intervention indicated) | Omit dose until resolved to ≤Grade 1, then reduce 1 dose level for all subsequent treatment cycles. |

**Table 11: Management of Toxicities Defined as Study Treatment-Related Only (Continued)**

| Worst Toxicity CTCAE Grade Unless Otherwise Specified (Value) | Dose Modification Guidelines |
|---|---|
| **NON-HEMATOLOGICAL TOXICITIES** | |
| **Renal** | |
| Serum creatinine | |
| <2 × ULN | Maintain dose level. |
| 2-3 × ULN | Omit dose until resolved to ≤Grade 1, then:<br>• If resolved in ≤7 days, then maintain dose level.<br>• If resolved in >7 days, then reduce 1 dose level for all subsequent treatment cycles. |
| Grade ≥3 (>3.0 baseline; >3.0 × ULN) | Omit dose and discontinue subject from study treatment. |
| **Hepatic** | |
| Total bilirubin | In cases where total bilirubin is elevated (>ULN), direct and indirect bilirubin should also be assessed. |
| <2 × ULN | Maintain dose level. |
| 2-3 × ULN | Omit dose until resolved to ≤Grade 1, then:<br>• If resolved in ≤7 days, then maintain dose level.<br>• If resolved in >7 days, then reduce 1 dose level. |
| Grade 3 (>3.0-10.0 × ULN) | Omit dose until resolved to ≤Grade 1, then:<br>• If resolved in ≤7 days, reduce 1 dose level for all subsequent treatment cycles.<br>• If resolved in >7 days discontinue subject from study treatment. |
| Grade 4 (>10.0 × ULN) | Omit dose and discontinue subject from study treatment.<br>Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduce 1 dose level and continue treatment at the discretion of the Investigator.<br>For subjects with total bilirubin ≥Grade 3, a CT scan or equivalent imaging procedure to exclude disease progression or potential other liver disease should be performed. |
| AST or ALT | |
| Grade 1 (>ULN - 3.0 × ULN) | Maintain dose level. |
| Grade 2 (>3.0 - 5.0 × ULN) | Maintain dose level. |

**Table 11: Management of Toxicities Defined as Study Treatment-Related Only (Continued)**

| Worst Toxicity CTCAE Grade Unless Otherwise Specified (Value) | Dose Modification Guidelines |
|---|---|
| **Hepatic (continued)** | |
| Grade 3 (>5.0 - 20.0 × ULN) | Omit dose until resolved to ≤Grade 1 (or ≤Grade 2 in case of liver metastasis), then:<br>• If resolved in ≤7 days, then maintain dose level.<br>• If resolved in >7 days, then reduce 1 dose level for all subsequent treatment cycles. |
| Grade 4 (>20.0 × ULN) | Omit dose until resolved to ≤Grade 1, then reduce 1 dose level. |
| Drug-induced liver injury by Hy's Law<br>(AST or ALT >3 × ULN and total bilirubin >2 × ULN without other reason for liver injury than related to the study drug) | Discontinue subject from study treatment. |
| **CARDIAC TOXICITIES** | |
| **Troponin I or T*** | |
| Elevated cardiac troponin I or T level, ECG evaluations and LVEF measurements are within normal range | Maintain dose level, and repeat LVEF measurement at 4-week intervals until troponin I or T level returns to baseline or until stabilization. |
| Elevated cardiac troponin I or T level, LVEF measurement is abnormal | Follow instructions below as appropriate. |
| LVEF | |
| ≥16% absolute decrease in LVEF from pre-treatment values<br>OR<br>LVEF below institutional limits of normal and ≥10% absolute decrease in LVEF from pre-treatment values | Omit dose for 4 weeks, then:<br>• If resolved (returns to normal limits and the absolute decrease from baseline is ≤15%), then maintain dose level.<br>• If not resolved, discontinue subject from study treatment. |
| Left ventricular systolic dysfunction<br>Grade 3 or 4 | Omit dose and discontinue subject from study treatment. |
| Heart failure<br>Grade 2 through Grade 4 | Omit dose and discontinue subject from study treatment. |
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (excluding interstitial lung disease/pneumonitis; refer to Section 7.5.3)** | |
| Grade 2 | Omit dose until resolved to ≤Grade 1, then:<br>• If resolved in ≤7 days, then maintain dose level.<br>• If resolved in >7 days, then reduce 1 dose level. |
| Grade 3 | Omit dose until resolved to ≤Grade 1, then reduce 1 dose level for all subsequent treatment cycles after discussion with the Sponsor. |

**Table 11: Management of Toxicities Defined as Study Treatment-Related Only (Continued)**

| Worst Toxicity CTCAE Grade Unless Otherwise Specified (Value) | Dose Modification Guidelines |
|---|---|
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (excluding interstitial lung disease/pneumonitis; refer to Section 7.5.3) (continued)** | |
| Grade 4 | Omit dose and discontinue subject from study treatment. |
| Peripheral neuropathy | Peripheral neuropathy should be managed using a combination of dose delay and modification. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at next lower dose level. For Grade 4 peripheral neuropathy, MYTX-011 should be discontinued. |
| **Other Laboratory AEs** | |
| Grade 3 | Delay dose until resolved to ≤Grade 1 or baseline level, then:<br>• If resolved in ≤7 days from day of onset, maintain dose.<br>• If resolved in >7 days from day of onset, reduce 1 dose level for all subsequent treatment cycles. |
| Grade 4 | Discontinue subject from study treatment |
| **Other Non-laboratory AEs** | |
| Grade 3 | Delay dose until resolved to ≤Grade 1 or baseline, then:<br>• If resolved in ≤7 days from day of onset, maintain dose<br>• If resolved in >7 days from day of onset, reduce 1 dose level for all subsequent treatment cycles |
| Grade 4 | Discontinue subject from study treatment |

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CT = computed tomography; CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0; ECG = electrocardiogram; Hgb = hemoglobin; IRR = infusion-related reaction; IV = intravenous; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; PLT = platelet count; UK = United Kingdom; ULN = upper limit of normal.
* Troponin I or T levels are to be based on institutional guidelines.
Note: Dose modification decisions due to hematopoietic toxicities should be discussed with the Mythic clinical team prior to the next dose administration.
Note: All dose modifications should be based on the worst preceding toxicity (see Section 7.5).

### 7.5.1. Management of Infusion-Related Reactions

IRRs and hypersensitivity reactions/anaphylaxis may occur during the administration of MYTX-011. The infusion site should be properly equipped and staffed to manage IRRs and anaphylaxis should it occur. Medications for IRRs such as epinephrine and antihistamines should be available for immediate use and the subject should be managed appropriately according to institutional guidelines (please refer to Table 11).

Pre-medication may be used for subjects for subsequent infusions if they develop IRR (e.g., acetaminophen [650 mg orally] or equivalent, diphenhydramine [25-50 mg orally or 10-25 mg IV] or equivalent) and is to be administered 30-60 minutes prior to the infusion.

### 7.5.2. Management of Ocular AEs

Subjects should be advised to avoid using contact lenses while on MYTX-011 until EOT, unless otherwise directed by an eye care professional. Surgical interventions that involve the eye (e.g., cataract surgery) or orbital region must be performed at least 28-days before C1D1 and are prohibited while the patient is on study drug unless approved by the Sponsor Medical Monitor.

If a subject has mild ocular surface disease (e.g., dry eye, punctate staining, decreased tear production), it is recommended the subjects' ocular surface is treated/optimized prior to dosing by the eye care professional.

All subjects should instill artificial tears to both eyes at least 4 times a day (sample schedule: breakfast, lunch, dinner, and bedtime), starting from C1D1 and continuing while the subject is on study treatment, including during dose break (if applicable). The use of temporary lower punctal plugs to increase lubrication of the eyes is optional if lubricating artificial tears are not sufficient.

All subjects will receive prophylactic low-potency steroid eye drops (once daily on Days 1-3 of each treatment cycle) and alpha-adrenergic agonist eye drops (twice daily from Days 1-8 of each treatment cycle) to potentially reduce the incidence or severity of ocular adverse events, unless contraindicated.

Study staff should instill one drop in each eye prior to infusion, then subject will administer prophylactic eyedrops as indicated. The recommended administration is to instill one drop of low-potency steroid eye drops 30 minutes prior to infusion, followed by one drop of alpha-adrenergic eye drop to each eye 10-15 minutes later. Avoid use of artificial tear drops 30 minutes prior to infusion of steroid and alpha-adrenergic eye drops to prevent a wash out effect of the prophylaxis.

The subject is responsible for following the remaining schedule of eyedrops after infusion and separate the use of eye drops by 10-15 minutes. Application of cold packs which cover both eyes during the entire infusion is also recommended.

The choice of steroid, alpha-adrenergic agonist, and artificial tear eye drops are per the investigator or eye care professionals' discretion. Preservative free eye drops are recommended. These prophylactic measures are summarized in Table 12. A version of the prophylactic measures mentioned above has been implemented for similar on-market ADC products (ELAHERE® [package insert] 2022; Kim et al. 2022; Matulonis et al. 2019; TIVDAK® [package insert] 2021).

**Table 12: Schedule of Prophylactic Measures for Ocular Adverse Events**

| Prophylaxis | Day of Each Treatment Cycle | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9-21 | Dose-Break |
| Artificial tears (QID + PRN) | X | X | X | X | X | X | X | X | X | X |
| Low potency steroid eyedrops (QD) | X[1] | X | X | | | | | | | |
| Alpha-adrenergic agonist eye drop (BID) | X[2] | X | X | X | X | X | X | X | | |
| Cold packs to eyes | X[3] | | | | | | | | | |

BID = twice daily; PRN = as needed; QID = 4 times a day; QD = once daily
[1] Recommend instilling one drop in each eye 30 minutes prior to infusion.
[2] Recommend instilling one drop in each eye 15 minutes prior to infusion.
[3] Applied during the entire infusion; ensure eye packs are cold throughout the duration of infusion.

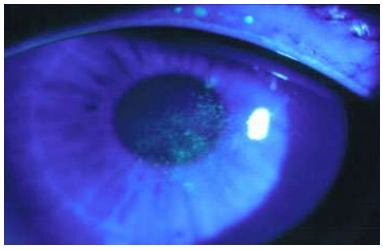
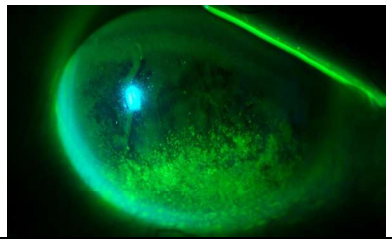
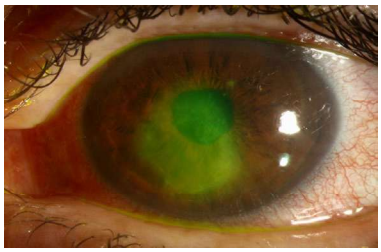
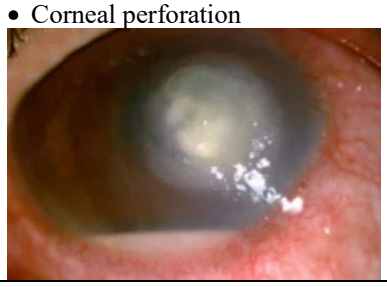
If new or worsening ocular symptoms occur (e.g., blurred vision, dry eyes, eye pain), an ophthalmic evaluation should be performed. A slit-lamp examination with fluorescein staining is recommended to assess corneal changes (e.g., distinguishing between staining and non-staining lesions such as pseudo-microcysts). For subjects with Grade 3 or higher ocular AEs (≥4 lines of vision change from baseline), more frequent ophthalmic monitoring is advised, with management and treatment guided by the eye care provider. Subjects with ongoing ocular AE at EOT visit should continue to undergo partial ophthalmic exams (full ophthalmic exams may replace partial exams per the eye care provider's discretion) every 3-4 weeks (or shorter interval as clinically indicated) until resolution or return to baseline. Please refer to Table 13 for the management of ocular AEs. If autologous serum eye drops are planned for ocular AE management, subject serum should ideally be collected prior to Cycle 1 Day 1 (C1D1) or within 3 days before study drug administration (for subjects who have already started treatment) to minimize potential MYTX-011 concentration in the serum eye drops.

Subjects experiencing ocular adverse events that may affect their ability to perform tasks requiring full visual capacity (e.g., driving, operating machinery) should be advised to use caution or avoid such activities if clinically indicated.

The benefit-risk profile for each subject should be carefully evaluated when considering MYTX-011 dose modifications. Any proposed deviations from the ocular AE management guidelines require discussion with the Sponsor Medical Monitor.

Corneal AEs must be documented in the eCRF using preferred terms (e.g., keratitis, corneal erosion, keratopathy, or other relevant eye disorders) and graded per CTCAE v5.0 for consistent safety reporting. However, CTCAE grading alone should not guide clinical management decisions (e.g., dose modifications), as this scale was not designed to assess MYTX-011-specific ocular toxicities. Instead, management should follow the protocol-defined criteria in Table 13, which are tailored to capture clinically relevant corneal changes.

**Table 13: Dose Modification Recommendation for Ocular Adverse Events[1]**

| Ocular Symptoms and Signs | | | MYTX-011 Recommended Modification |
|---|---|---|---|
| **Blurred Vision or Reduced Visual Acuity (Measured by Best Corrected Visual Acuity (BCVA)[2]** | **Eye Symptoms[3] (e.g., discomfort, pain, photophobia)** | **Cornea[4] (Eye Signs)** | |
| • 1 line decrease from baseline BCVA related to study drug, or<br>• 20/25 Snellen equivalent BCVA | • Mild eye symptoms (1-3/10) | • Non-confluent epitheliopathy<br>• Scattered staining/SPK<br>  | • Continue at same dose and per protocol scheduled ophthalmic exams |
| • 2-3 line decrease in baseline BCVA related to study drug, or<br>• 20/30-20/40 Snellen equivalent BCVA | • Moderate eye symptoms (4-6/10) | • Confluent epitheliopathy<br>• Diffuse staining/SPK<br>  | • Continue at same dose or reduce by 1 dose level per Investigators discretion<br>• Recommend close ocular follow ups, if needed |
| • 4-8 line decrease in baseline BCVA, or<br>• 20/50-20/150 Snellen equivalent BCVA | • Severe eye symptoms (7-9/10) | • Epithelial defect<br>• Corneal Ulcer<br>  | • Delay dose until return to baseline or within 1-2 lines from baseline BCVA<br>• If eye symptoms are present, delay dose until symptoms improve to mild or baseline , then consider dose reduction |
| • >8 line decrease in baseline BCVA or<br>• ≥20/200 Snellen equivalent BCVA | • Extreme eye symptoms (10/10) | • Corneal perforation<br>  | • Consider discontinuation |

[1] Modify dose using the worst assessment from blurred vision, eye symptoms, and corneal changes

[2] Best Corrected Visual Acuity (BCVA) should be measured with manifest refraction or pinhole with correction (current glasses) at distance
[3] Eye symptoms: Can be assessed using a 0-10 scale (0 meaning no ocular symptoms and 10 the worst symptoms)
[4] Corneal changes: For management of corneal AEs, eye care professionals are encouraged to treat using best judgement and may initiate adjunctive therapy per standard of care, when ≥Gr. 2 eye signs or symptoms are present

ADL = activities of daily living; AE = adverse event
All dose modifications should be based on the worst preceding toxicity.
For further guidance on dose modifications, see Section 7.5.

### 7.5.3. Monitoring and Management of Suspected Interstitial Lung Disease/Pneumonitis

If a subject develops an acute onset of new or worsening pulmonary or other related signs/ symptoms such as dyspnea, cough, or fever, rule out interstitial lung disease (ILD)/pneumonitis. Subjects with prior radiation therapy to the thorax (e.g., lung, mediastinum, chest wall) within 6 months of study entry should be monitored closely, as they may have increased risk of developing ILD/pneumonitis during treatment. Subjects with newly developed shortness of breath, suspicious findings on CXR, or a decrease in SpO2 at rest of 2-4% for 1-3 days as measured as a continuous variable at home, or a decrease in SpO2 after exertion of 2-5% for 1-7 days, should be evaluated for ILD/pneumonitis immediately.

If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in Table 11.

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be paused pending further evaluations.

Further evaluations should include:

- High-resolution CT
- Pulmonologist consultation
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible

Other evaluations could include:

- Pulmonary function tests including diffusing capacity of the lungs for carbon monoxide, peripheral oxygen saturation, and arterial blood gases
- Serum marker testing (e.g., KL-6, surfactant protein D)
- Other tests as needed (e.g., infectious work-up, etc.)

As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines. Refer to drug-induced lung disease guidelines (Swain et al. 2022; Tarantino et al. 2011). It is recommended that subjects with prior radiation therapy to the thorax within 6 months of study entry to be treated more aggressively, and high-dose IV corticosteroid should be initiated in such subjects with suspected ≥Grade 2 (symptomatic)

ILD/pneumonitis. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined in Table 14.

**Table 14: Management of Confirmed Interstitial Lung Disease/Pneumonitis**

| | |
|---|---|
| **Grade 1** | Delay dose until resolved to Grade 0, then:<br>• If resolved in ≤28 days from day of onset, maintain dose<br>• If resolved in >28 days from day of onset, reduce 1 dose level for all subsequent cycles<br>However, if the Grade 1 interstitial lung disease /pneumonitis occurs beyond Cycle Day 22 and has not resolved within 49 days from the last infusion, the study treatment should be discontinued.<br>For further management, see guidance from Swain et al. 2022. |
| **Grade 2, 3, or 4** | Discontinue subject from study treatment.<br>For further management, see guidance by Swain et al. 2022. |

Source: Swain et al. 2022

### 7.5.4. Management of Dermatological AEs

Consider topical steroids and antihistamines as clinically indicated to manage dermatologic AEs. In case of suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) hold MYTX-011 and obtain dermatology consult and contact the medical monitor. MYTX-011 must be discontinued if SJS/TEN confirmed.

### 7.5.5. Infusion Site Extravasation

The infusion site should be monitored during MYTX-011 administration and the infusion interrupted if there is extravasation.

## 7.6. Concomitant Therapy and Prohibited Medications

Any medication or vaccine (including over-the-counter or prescription medications, recreational drugs, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information including the dose and frequency

The following medications are prohibited during the study:

- Systemic anticancer therapy including cytotoxic agents, targeted agents, immunotherapy, and other investigational therapeutic agents

- Radiation (except for palliative radiation to known metastatic sites). Palliative radiation to the thorax, including the lungs and chest wall, during the study is not allowed unless approved by the Sponsor Medical Monitor
- Systemic chronic steroid therapy: prednisone 10 mg daily or equivalent. Short-term use of systemic steroid therapy as pre-medication, to manage IRRs or AEs, is permitted. Inhaled steroids or topical steroid use is permitted
- IV antibiotics, antivirals, or antifungal medication within 1 week prior to first dose of study drug administration
- Live/attenuated vaccine within 30 days before the first dose of study drug, during treatment with MYTX-011, and up to 30 days after EOT

The following medications should be used with caution and avoided, if possible:

- Use of strong CYP3A4/5 inhibitors should be avoided since MMAE is a CYP3A4/5 substrate. If CYP3A4/5 inhibitor use is medically necessary, the subject should be closely monitored for adverse reactions
- Use of strong CYP3A4/5 inducers or substrates may decrease unconjugated MMAE AUC and should be avoided if possible
- MMAE is a substrate of P-glycoprotein (P-gp). Concomitant use of P-gp inhibitors may increase exposure to MMAE. If P-gp inhibitor use is medically necessary, the subject should be closely monitored for adverse reactions
- A list of strong CYP3A4/5 inhibitors, inducers, and substrates and P-gp inhibitors (FDA 2022)

Palliative Radiation therapy cannot be administered on the same day IP is given throughout the course of the study.

In addition, subjects will be advised that the consumption of grapefruit and grapefruit juice should be avoided due to its known inhibitory effect on CYP3A4/5.

The Sponsor Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### 7.6.1. Supportive Care Guidelines

Prophylactic hematopoietic growth factors should not be administered during Cycle 1 of the study in Part 1; subjects may receive growth factors if clinically indicated (e.g., development of neutropenia after administration of the first dose of MYTX-011). Prophylactic growth factors are allowed thereafter in subsequent cycles as clinically indicated. Subjects enrolled in Part 2 of the study may receive prophylactic growth factors in all cycles at the Investigator's discretion; and for treatment of neutropenia as clinically indicated.

See Section 7.5.2 (Table 13) for required steps for prevention and management of ocular AEs for all subjects enrolled.

Prophylactic anti-emetics may not be administered during Cycle 1 of the study in Part 1 dose escalation cohorts, but may be used in subsequent cycles for Part 1 dose escalation cohorts, and in all cycles for all other subjects.

Febrile neutropenia should be managed according to institutional guidelines.

Blood products may be used according to institutional guidelines during the study (excluding eligibility requirements; see Section 5.1).

# 8. STATISTICAL CONSIDERATIONS

Details of the statistical analyses and data reporting will be provided in the Statistical Analysis Plan to be finalized prior to the database lock. Results will be presented by study part (Part 1: Dose Escalation and Part 2: Dose Expansion).

Primary efficacy analysis will be completed per each expansion cohort when all subjects treated in a cohort are evaluable for the evaluation of response. A final analysis is planned after all dose escalation and dose expansion cohorts have completed the study.

## 8.1. ANALYSIS POPULATIONS

**Safety Analysis Population:** All subjects who receive at least 1 dose of MYTX-011. All safety analyses will be performed using this analysis population.

**DLT Evaluable Population:** All subjects enrolled in Part 1 (dose escalation; not including the enrichment cohorts) who receive at least 1 dose of MYTX-011 and have either completed Cycle 1 or withdrawn during Cycle 1 due to a DLT. Analyses to determine the MTD will be performed using this analysis population.

**Efficacy Evaluable Population:** All subjects who receive at least 1 dose of MYTX-011 have a measurable disease on the baseline tumor assessment, and either have at least 1 post-infusion disease assessment or have discontinued treatment for any reason prior to the first response assessment.

**Response Evaluable Population**: All subjects who receive at least 1 dose of MYTX-011 have a measurable disease on the baseline tumor assessment and have at least one post-infusion tumor assessment.

**PK Analysis Population:** All subjects who receive at least 1 dose of MYTX-011 and have evaluable PK data. This population will be used for summaries of PK parameters.

**Immunogenicity Analysis Population:** All subjects who receive at least 1 dose of MYTX-011 and have at least 1 post-infusion immunogenicity sample. This population will be used for summaries of ADAs.

## 8.2. SAMPLE SIZE

The sample size in Part 1, dose escalation depends on the observed safety profile, which will determine the total number of cohorts. The dose escalation scheme in Part 1 is based on a 3 -subject cohort minimum BOIN design (Yuan et al. 2016) and will initially consider a series of 7 escalating dose levels (plus dose “level -1” if needed), with no skipping of dose levels permitted. However, additional intermediate dose levels may be introduced based on a review of the cumulative safety data and upon recommendation by the SRC, provided that the intermediate dose is not higher than the next scheduled dose to be tested or that it does not exceed MTD if the MTD has already been determined. The intermediate dose can also be lower than the currently considered dose level. A minimum of 3 subjects will be treated in each cohort.

### 8.2.1. Enrichment Cohorts

Additional subjects may be enrolled in enrichment cohorts, at dose levels that have previously been determined to be safe (including planned dose levels and intermediate dose levels), to better understand the safety, tolerability, PK, and preliminary anti-tumor activity of MYTX-011. No more than 10 subjects will be enrolled per enrichment cohort. For doses and/or dosing schedules where favorable benefit-risk has been demonstrated, up to 20 subjects may be enrolled for further dose optimization after approval by the SRC. Enrollment into enrichment cohorts may continue throughout the conduct of the study until all enrichment cohort slots are filled or it is determined that additional enrollment is not required. DLTs will not be assessed for subjects enrolled into enrichment cohorts. In addition, the Sponsor may enroll subjects with certain levels of cMET expression (i.e., high, intermediate, low, or ultra-low cMET expression as defined in Part 2) in enrichment cohorts or intermediate dose levels in which preliminary anti-tumor activity is observed.

### 8.2.2. Sample Size for Part 2

Eight disease cohorts (A, B, B2, C, D, E, E2 and F) will be initially considered in Part 2 of the study. Additional dosing cohorts may be added, as described in Section 4.2.

Expansion Cohort A will be monitored for efficacy using the Bayesian Optimal Phase 2 (BOP2) design (Zhou et al. 2017). The BOP2 design is optimized to maximize power under the alternative hypothesis while controlling the Type I error rate at 0.10. The optimization is performed assuming the uninformative prior Beta (0.5, 0.5) distribution. In Cohort A, the reference (uninteresting) rate is 15% and the efficacy response rate is assumed to be 55%. Initially, 20 subjects will be randomized to 2 dose levels (10 subjects each). An interim analysis for futility will be performed after 10 subjects per dose level are available in the Response Evaluable Population; enrollment will be paused to assess futility. This number may be adjusted during the course of enrollment based on Sponsor discretion. Subjects will be randomized to 2 dose levels. At the interim analysis, a dose will be deemed unacceptable if fewer than 2 responses are observed, and the dose will be terminated. Following the interim analysis, an additional 10 subjects will be enrolled in each dose that is not terminated, for a total of up to 40 enrolled in Cohort A. At the primary analysis, efficacy of a dose level will be declared if 6 or more responses are observed in 20 subjects. If the true response rate is greater than 40%, the study will have at least 80% power to reject the reference rate of 15%.

Cohort B will be monitored for efficacy using the BOP2 design (Zhou et al. 2017). The BOP2 design is optimized to maximize power under the alternative hypothesis while controlling the probability of Type I error, set at 0.10. The optimization is performed assuming a prior Beta (0.5, 0.5) distribution. For Cohort B, the reference rate is 15% and the assumed efficacy rate is 35%. Initially, 15 subjects will be given MYTX-011 at the RP2D. The interim analysis for futility will be performed after 15 subjects are available in the Response Evaluable Population. At the interim analysis, futility criteria are met if there are 2 or fewer responders in 15 subjects.

If Cohort B passes the interim analysis for futility (i.e., if 3 or more responders are observed in the first 15 subjects [which may occur before all 15 subjects are enrolled]), a randomization cohort for subjects with intermediate cMET expression (Cohort B2) may be opened. In Cohort B2, up to 40 subjects will be randomized 1:1 into 2 dose levels (i.e., RP2D [which was used in Cohort B] and an alternative dose). Subjects will be randomized to 1 of 2 dose levels.

At the primary analysis of RP2D in the subject population fulfilling inclusion into Cohort B and Cohort B2, efficacy of RP2D will be evaluated using all subjects receiving RP2D in Cohort B and Cohort B2. If 35 subjects received RP2D, efficacy will be declared if 9 or more ORRs are observed in the 35 subjects. If the true ORR is ≥35%, Cohort B + Cohort B2 with a total of 35 subjects will have approximately 88% power to reject the reference rate of 15% for RP2D and the estimated Type I error rate is 6.2% (based on 10,000 clinical trial simulations).

Efficacy of the alternative dose will be declared if 6 or more ORRs are observed out of 20 subjects enrolled in Cohort B2 receiving the alternative dose. The study will have approximately 75% power to reject the reference rate of 15% if the true rate is assumed to be 35%, with the probability of Type I error of 6.7% based on the binomial distribution.

Cohort C will be evaluated using the Bayesian efficacy monitoring with predictive probability approach (Lee and Liu 2008) and assumes a 91% threshold for declaring efficacy at the final analysis, with a 99% threshold for stopping for efficacy and a 10% threshold for early stopping for futility based on the evaluation of posterior probability at interim. A distribution of Beta (0.5, 0.5) is used as prior distribution for the efficacy response rate. For Cohort C, the reference response rate is 15%, while the efficacy rate is assumed to be 35%. When the Response Evaluable Population contains 15 subjects interim analysis will be performed to evaluate for evidence of early efficacy or futility; enrollment will be paused to assess futility. Cohort C will be terminated for futility if 1 or fewer responses are observed among 15 evaluable subjects. Early efficacy will be declared if 7 or more responses are observed in 15 subjects. Enrollment may be continued after early efficacy is declared. A primary analysis will be performed when a total of 40 subjects are included in the Response Evaluable Population, and efficacy will be declared if there are 10 or more subjects among the 40 subjects with a response observed.

Cohort D will be evaluated using the Bayesian efficacy monitoring with predictive probability approach (Lee and Liu 2008) in the same way as Cohort C. The approach assumes a 90% threshold for declaring efficacy at the final analysis, with a 95% threshold for early stopping for efficacy and a 10% threshold for early stopping for futility based on the evaluation of posterior probability at interim. A distribution of Beta (0.5, 0.5) is used as prior distribution for the efficacy response rate. For Cohort D, the reference response rate is 15%, while the efficacy rate is assumed to be 35%. When the Response Evaluable Population contains 15 subjects interim analysis will be performed to evaluate for evidence of early efficacy or futility; enrollment will be paused to assess futility. Cohort D will be terminated for futility if 1 or fewer responses are observed among 15 evaluable subjects. Early efficacy will be declared if 6 or more responses are observed in 15 subjects. Enrollment may be continued after early efficacy is declared. A primary analysis will be performed when a total of 65 subjects are included in the Response Evaluable Population, at which time the efficacy will be declared if there are 14 or more responses

observed. Cohort D will have approximately 97% power to reject the reference rate of 15% if the true rate is assumed to be 35%, with the probability of Type I error of <10% (approximately 9.99%) based on 10,000 clinical trial simulations.

Cohort E will be monitored for efficacy using the BOP2 design (Zhou et al. 2017) in the same way as Cohort B. For Cohort E, the reference rate is 15% and the assumed efficacy rate is 35%. Initially, 15 subjects will be given MYTX-011 at the RP2D. The interim analysis for futility will be performed when the Response Evaluable Population contains 15 subjects. At the interim analysis, futility criteria are met if there are 2 or fewer responders in 15 subjects.

If Cohort E passes the interim analysis for futility (i.e., if 3 or more responders are observed in the first 15 subjects, which may occur before all 15 subjects are enrolled), a randomization part, E2, may be opened, where up to 40 subjects will be randomized 1:1 into 2 dose levels (i.e., either RP2D [which was used in the first 15 subjects] or an alternative dose).

At the primary analysis of RP2D in the subject population fulfilling inclusion into Cohorts E and E2, efficacy of RP2D will be evaluated using all subjects receiving RP2D (i.e. up to 35 subjects (initial 15 subjects [Cohort E] + 20 subjects in the randomized part [Cohort E2]). If 35 subjects received RP2D, efficacy will be declared if 9 or more ORRs are observed in the 35 subjects. If the true ORR is ≥35%, Cohorts E + E2 with a total of 35 subjects will have approximately 88% power to reject the reference rate of 15% for RP2D and the estimated Type I error rate would be 6.2% (based on 10,000 clinical trial simulations).

Efficacy of the alternative dose will be declared if 6 or more ORRs are observed out of 20 subjects enrolled in Cohort E2 receiving the alternative dose. The study will have approximately 75% power to reject the reference rate of 15% if the true rate is assumed to be 35%, with the probability of Type I error of 6.7% based on the binomial distribution.

Cohort F will be evaluated using the Bayesian efficacy monitoring with predictive probability approach (Lee and Liu 2008) in the same way as Cohort C using the same design, same response assumptions and the same decision rules. This assumes a 91% threshold for declaring efficacy at the final analysis, a 99% threshold for stopping for efficacy and a 10% threshold for early stopping for futility based on the evaluation of posterior probability at interim. A distribution of Beta (0.5, 0.5) is used as prior distribution for the efficacy response rate. For Cohort F, the reference response rate is 15%, while the efficacy rate is assumed to be 35%. When the Response Evaluable Population contains 15 subjects, an interim analysis will be performed to evaluate for evidence of early efficacy or futility; enrollment will be paused to assess futility. Cohort F will be terminated for futility if one or no response is observed among the 15 subjects. Early efficacy will be declared if 7 or more responses are observed in 15 subjects. Enrollment may be continued after early efficacy is declared. A primary analysis will be performed when a total of 40 subjects are included in the Response Evaluable Population, and efficacy will be declared if there are 10 or more subjects among the 40 subjects with a response observed.

When clinical safety and efficacy data are available for the subjects in expansion Cohorts A, B, B2, C, D, E, E2 and F, the DSMB will review and determine clinical merit and recommend continuing or discontinuing a cohort.

Based on ongoing review of the data from Parts 1 and 2 of the study, the sponsor may determine that one of the two dose regimens (RP2D or Alternative Dose) being administered in Part 2 appears to show a better benefit:risk ratio than the other. In this case, the sponsor may decide to assign ongoing patients and all newly enrolled patients to the dose regimen that appears to have the more favorable benefit:risk ratio, and no longer assign doses via randomization.

Additionally, the Sponsor may determine that one or more other doses (not the originally selected RP2D or Alternative dose) be evaluated in Part 2 (see Section 4.2). If other dose(s) are added as a substitute for the RP2D or Alternative dose, the interim and final cohort sizes and rules for futility and efficacy will be used as described above for the RP2D or Alternate dose in each cohort; enrollment will be re-initiated to account for full enrollment of the other dose.

If the additional dose to be evaluated is not a substitute for the RP2D or Alternative dose, the rules above governing futility, interim and final cohort sizes, and declaration of efficacy will be based on those used for the RP2D above.

Efficacy will be summarized by the point and interval estimate of ORR, accompanied by the posterior probability statements to further characterize the effect of treatment in this cohort.

### 8.2.3. Additional Enrollment

If futility criteria are not met within a cohort for a dose level based on the rules outlined above, additional patients may be enrolled at that dose level for a total of up to approximately 80 evaluable patients. This is in order to provide a more precise estimation of clinical benefit based on the ORR and associated 95% confidence interval (see Table 15) and to guide future development and potential regulatory interactions.

**Table 15: ORR and Associated 95% Confidence Interval for N=80 Subjects**

| Responders | ORR | 95% Confidence Interval |
|---|---|---|
| 20 | 25% | 15.9, 35.9 |
| 22 | 28% | 18.1, 38.6 |
| 24 | 30% | 20.3, 41.3 |
| 26 | 33% | 22.5, 43.9 |
| 28 | 35% | 24.7, 46.5 |
| 30 | 38% | 26.9, 49.0 |
| 32 | 40% | 29.2, 51.6 |
| 34 | 43% | 31.5, 54.0 |

## 8.3. SUBJECT DISPOSITION

A tabulation of subject disposition will be provided by dose level (Part 1) and by study cohort (Part 2), including the number screened, the number enrolled, the number included in each analysis population, the number that discontinued treatment and reasons for treatment discontinuation, and the number that withdrew from the study and reasons for withdrawal.

## 8.4. SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline demographic and other baseline data including height, weight, baseline ECOG status, LVEF, and medical history will be summarized. Disease characteristics including histological diagnosis, stage, prior therapies, cMET status, MET amplifications/exon 14 skipping mutations, presence of actionable mutations, etc., will be listed individually and by group using descriptive statistics.

Extent of Exposure: The dose (mg) of study drug administered, the cumulative dose (mg) of study drug administered, and the duration of treatment (number of study cycles) will be summarized with descriptive statistics. The number and percentage of subjects whose dose is modified at any time will be summarized by each type of modification by cycle and overall.

Discontinuations and reasons for discontinuation will be presented.

## 8.5. STATISTICAL METHODOLOGY

### 8.5.1. General Considerations

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant PK and immunogenicity parameters. When estimating proportions, the denominator to be used in the calculation will be the total number of subjects in the indicated analysis population for a specific dose level or cohort. Unless otherwise noted, estimation will be based on exact methods. Interval estimates will be based on the 90% confidence level. When summarizing time-to-event endpoints, censoring will be defined for each endpoint separately. Time-to-event endpoints will be analyzed using the Kaplan-Meier method to include point and interval estimates around the median and other percentiles as well as plots of survival curves by dose levels or cohorts.

Tabular summaries will also be accompanied with by-subject listings. Subject data collected up to the time of study completion/withdrawal from study will be included in the analysis, regardless of the actual duration of treatment. Individual subject duration of follow-up will vary across subjects, depending on individual safety, efficacy, and tolerability.

### 8.5.2. Dose Escalation for MTD: BOIN Design

Part 1 dose escalation algorithm is based on a 3-subject cohort minimum BOIN design (Yuan et al. 2016), a model-assisted design that employs an escalation/de-escalation procedure, similarly implemented as a classical 3 + 3 design, but optimized to minimize the probability of making an

erroneous decision. DLTs occurring during Cycle 1 will be considered when implementing the dosing algorithm and decisions. The dose escalation/de-escalation scheme and its parameters are provided in Section 4.1. The design employs safety overdose control where a dose and higher dose levels will be eliminated from further consideration, if, given the number of observed DLTs at the current dose, there is a greater than 0.95 probability that the true DLT rate is higher than 30%, and at least 3 subjects evaluable for DLT have been treated. This posterior probability is evaluated assuming Beta (1,1) prior probability of true DLT rate. When the lowest dose is eliminated, the study will be stopped for safety. Once all the enrolled subjects in Part 1 complete the DLT observation period and the study is not stopped early, the BOIN design applies an isotonic regression to select the MTD.

### 8.5.3. Cohort Expansion Monitoring for Efficacy

The decision rules in Section 8.2.2 are based on different methods and assumptions as described, together with their statistical properties (power to declare efficacy and Type I error rate).

Additional analyses, for the purposes of internal decision making, planning of future studies, or responding to requests by the regulatory authorities, may be performed at the discretion of the Sponsor.

## 8.6. EFFICACY ANALYSES

Efficacy endpoints will be based on RECIST 1.1 (Appendix C) by Investigator assessment for the primary analysis. Confirmation of Investigator-assessed ORR and DOR may be performed retrospectively through an Independent Review Committee. The following efficacy endpoints will be assessed in both Part 1 and Part 2 of the study:

- **Overall Response Rate**

  ORR is defined as the proportion of subjects with the BoR of CR or PR. All response data will also be summarized over time for all subjects using all available scans.

  Note that CR and PR must be confirmed by 2 tumor imaging assessments conducted at least 4 weeks apart.

- **Duration of Response (for subjects who achieve CR or PR)**

  DOR is defined as time from the date of first documented evidence of CR or PR until first documented disease progression or death, whichever comes first. For subjects without PD or death prior to analysis cutoff date, DOR will be censored at the date of last available tumor assessment.

- **Overall Survival**

  OS is defined as the time from the date of first administration of MYTX-011 to the date of death due to any cause. OS will be censored at the last reported date of contact.

- **Progression-Free Survival**

  PFS is defined as the time from the date of first administration of MYTX-011 to the date of documented disease progression per RECIST 1.1, date of clinical progression if no imaging documenting progression is performed, date of starting subsequent anti-cancer therapy, or date of death (in the absence of progression), whichever comes first. For subjects who have not progressed, started subsequent anti-cancer therapy, or died before the analysis cutoff date, PFS will be censored at the date of the last available tumor assessment.

- **Disease Control Rate**

  DCR is defined as the proportion of subjects who achieve a BoR of CR or PR or SD.

- **Best Observed Response**

  A single BoR is defined per each subject as the best result obtained among all tumor assessment visits from baseline until determination of PD.

- **Time to Response**

  Time to response (TTR) is defined as the time from the first administration of MYTX-011 to the first documentation of CR or PR. TTR will only be calculated for subjects with BoR of CR or PR.

  Note:Details of anti-tumor activity endpoints are specified in the Statistical Analysis Plan (SAP).

## 8.6.1. Pharmacokinetic and Immunogenicity Analyses

PK data will be presented overall and by dose level and will include subjects who have received at least 1 dose of MYTX-011 and have evaluable PK data. Analyses to describe the relationship between MYTX-011 exposure (total antibody, total ADC, and MMAE) and clinical outcomes (e.g., safety and anti-tumor activity) may be performed.

Immunogenicity analyses: ADAs will be reported at multiple timepoints during the study. Titers, relationship of antibodies to MYTX-011 dose level, PK, anti-tumor activity, and safety may be reported.

### 8.6.1.1. Pharmacokinetics

MYTX-011 (total antibody, total ADC, and MMAE) levels will be determined using blood samples collected before and after dosing through the EOT visit. These determinations will be used to calculate the single- and repeat-dose PK profiles for each evaluable subject at each dose level administered. Single-dose and multiple-dose MYTX-011 (total antibody, total ADC, and MMAE) PK parameters will be estimated using non-compartmental analysis in dose escalation and dose expansion if possible. PK parameters for dose escalation and dose expansion will include, but are not limited to, accumulation ratio, $C_{max}$, $T_{max}$, $C_{last}$, $T_{last}$, $AUC_{0\text{-}last}$ (e.g., $AUC_{504h}$), volume of distribution (Vd), CL, and $t_{½}$. A compartmental method will also be used to explore the MYTX-011 PK profile if possible.

The MYTX-011 concentration will be listed and summarized in tabular formats using descriptive statistics. MYTX-011 (total antibody, total ADC, and MMAE) concentrations will be plotted against timepoints by cohort. Individual and summary PK parameters will be listed and summarized in tabular format using descriptive statistics.

Timepoints for the collection of PK and ADA assessments are provided in Table 6 and Table 7 for dose escalation and dose expansion, respectively. The presence of MYTX-011 (total antibody, total ADC, and MMAE) will be quantified by a validated assay.

#### 8.6.1.2. Immunogenicity

Immunogenicity incidence and persistence to MYTX-011 will be assessed and summarized descriptively.

### 8.6.2. Exploratory Analyses

Correlation between anti-tumor activity and baseline subject and disease characteristics (e.g., oncogenic drivers) will be explored. The relationship between potential biomarkers and predictors of response and resistance of MYTX-011 in the tumor and blood and subject outcomes (e.g., anti-tumor activity) may be explored as well as any changes in biomarkers and predictors of response and resistance to MYTX-011 from baseline such as:

- Biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein)

Details of other secondary and exploratory endpoint analyses will be provided in the Statistical Analysis Plan (SAP).

#### 8.6.2.1. Exploratory Pharmacokinetic Exposure Response Analysis

**Exposure-Dose-Efficacy**

The concentration/dose−efficacy relationship will be explored graphically and, if appropriate, evaluated by a mixed effects model to characterize the relationship between changes from baseline to maximal tumor shrinkage and the plasma concentration of MYTX-011. If appropriate, effects of covariates (e.g., age, sex assigned at birth, race, and concomitant medications) will be evaluated as well. This will be done in 2 steps. First, a descriptive analysis will be performed graphically between PK exposure values and major safety, efficacy, and biomarker parameters (either as categories or continuous variables). If any potential correlation is identified, further investigation will be performed using a mechanism-based modeling approach, as appropriate.

**Exposure-QT Prolongation**

The concentration−QT relationship will be explored graphically, and if appropriate, evaluated by a mixed effects model to characterize the relationship between changes from baseline in QTcF and the plasma concentration of MYTX-011. If appropriate, effects of covariates (e.g., age, sex

assigned at birth, race, presence of medications known to cause QT prolongation, and other concomitant medications) will be evaluated as well.

In addition, the potential correlation between MYTX-011 exposure and other endpoints (major safety, efficacy, and biomarker parameters) will be evaluated. This will be done in 2 steps. First, a descriptive analysis will be performed graphically between PK exposure values and major safety, efficacy, and biomarker parameters (either as categories or as continuous variables). If any potential correlation is identified, further investigation will be performed using a mechanism-based modeling approach, as appropriate.

**Immunogenicity-Exposure and/or Adverse Event Relationship**

The concentration/AE-immunogenicity relationship will also be explored graphically and tabulated to characterize a relationship between the changes from screening immunogenicity presence and plasma concentration of MYTX-011. In addition, the potential correlation between immunogenicity and other endpoints (major safety, efficacy, and biomarker parameters) may be evaluated. This will be done in 2 steps. First, a descriptive analysis will be performed graphically between immunogenicity change from screening values and major safety, efficacy, and biomarker parameters (either as categories or continuous variables). If any potential correlation is identified, further investigation will be performed using a mechanism-based modeling approach, as appropriate.

## 8.7. SAFETY ANALYSES

All subjects who receive at least 1 dose of MYTX-011 will be included in the Safety Analysis Population to be used in safety analyses. Safety analyses will be presented overall and by dose level (Part 1) and cohort (Part 2). Safety analyses will also include summaries of TEAEs, treatment-related AEs, SAEs, and DLTs during Cycle 1 in Part 1. The number and percentage of subjects reporting any TEAE will be summarized and reported by Preferred Term and System Organ Class according to the Medical Dictionary for Regulatory Activities and by relationship to MYTX-011.

Safety endpoints will include:

- Incidence and severity of TEAEs, Grade 3 or higher TEAEs, SAEs, and TEAEs leading to dose modification, dose hold, or dose discontinuation
- Incidence and severity of Grade 3 or higher treatment-related AEs
- Incidence of Grade 3 and 4 clinical laboratory abnormalities and changes from baseline
- Changes in vital signs, clinical laboratory parameters, and ECG from baseline

Safety analyses will be based primarily on the incidence, severity, and type of AEs, as well as on clinically meaningful laboratory results, physical examination, and vital signs as available. Safety variables will be tabulated and presented by the dose of study drug received. Exposure to study drug and reasons for discontinuation of study drug will also be tabulated.

Detailed information collected for each AE will be included in a listing: AE term, start/stop dates of the AE, seriousness, severity, relationship to study drug(s), action taken, and outcome. In addition, the number and percentage of subjects experiencing at least 1 TEAE will be tabulated by body system, Preferred Term, and CTCAE grade. TEAEs, treatment-related AEs, AESIs, SAEs, AEs with a fatal outcome, and AEs leading to discontinuation/dose modification will be further summarized. Summary statistics for actual values and for changes from baseline will be tabulated for clinical laboratory results by scheduled visit. Subjects with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized and graded per NCI CTCAE Version 5.0 as applicable. Subject incidence of abnormal laboratory results will be summarized by treatment group and maximum grade for each abnormal laboratory finding.

## 8.8. MISSING VALUE HANDLING PROCEDURES

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. Any exceptions will be provided in the SAP.

# 9. ADVERSE EVENT REPORTING AND CRITERIA

## 9.1. DEFINITION OF ADVERSE EVENT

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product. Any AE starting or worsening after first treatment of study drug and noted within 30 days of the last treatment of study drug will be considered a TEAE. An AE does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition. It is the responsibility of the Investigator, based on their knowledge and experience, to determine which untoward medical occurrences should be considered AEs.

## 9.2. CRITERIA FOR SERIOUS ADVERSE EVENTS

The definitions of SAEs are described below. The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that meets at least 1 of the following criteria:

- **Results in death**

  In the case of deaths, the event(s) leading to the death should be recorded and reported as SAE(s) with the outcome "Fatal." The death itself will not be reported as an SAE, unless the cause of the death is unknown (e.g., in case of unexplained or sudden death).

- **Is life-threatening**

  The term "life-threatening" refers to an event in which the subject is at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**

- **Results in persistent or significant disability/incapacity**

  A disability is defined as any substantial disruption of a subject's ability to conduct normal life functions.

- **Is a congenital anomaly/birth defect**

- **Is medically important**

  Medical and scientific judgment must be exercised in deciding whether an AE is considered "medically important." Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in this definition.

Progression of disease (including fatal outcomes) should not be reported as an SAE.

### 9.2.1. Situations Not Considered SAEs

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported; i.e., could meet the definition of important medical event):

- Emergency department or emergency room
- Hospitalization for drug administration, diagnostic procedure, or social circumstances
- Outpatient or same-day surgery unit
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing home, custodial care, or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (1 planned prior to entry in the study), does not require reporting as an SAE to the Sponsor, but if hospitalization is prolonged due to an event, then this would be reportable to Sponsor or designee.

### 9.2.2. Serious versus Severe AEs

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

### 9.2.3. Adverse Event/Serious Adverse Event Grading

The NCI CTCAE Version 5.0 is to be used for the grading of severity of AEs.

For AEs not covered by the NCI CTCAE grading system, the following definitions should be used:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

### 9.2.4. Adverse Events of Special Interest

The following AESIs will be closely monitored during the study including:

- IRRs
- Ocular AEs
- Clinically significant pulmonary AEs (e.g., suspected pneumonitis/ILD)
- Peripheral neuropathy
- Hyperglycemia (based on laboratory results)
- Clinically significant neurological disorder

In addition, the occurrence of Grade 3 and 4 neutropenia and thrombocytopenia (based on laboratory results) will be monitored during the study.

### 9.2.5. Adverse Events/Serious Adverse Event Causality Assessment

The Investigator must also assess the causal relationship of any AE to the study drug, based on available information, using the following guidelines:

| | |
|---|---|
| **Not related/unrelated** | Exposure to study drug did not occur or the occurrence of the AE is not reasonably related in time to study drug administration. |
| **Unlikely related** | AE with time to study drug administration that makes relationship improbable (but not impossible). Disease or other drugs provide plausible explanations. |
| **Possibly related*** | AE with reasonable time relationship to study drug administration. Could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear. |
| **Probably related*** | AE with reasonable time relationship to study drug administration. Unlikely attributed to disease or other drugs. |
| **Definitely related*** | AE with plausible time relationship to study drug administration. Cannot be explained by disease or other drugs. Response to withdrawal plausible. |

* If other necessary ICH E2A criteria are met, these causalities would qualify for expedited reporting.

### 9.2.6. Adverse Event/Serious Adverse Event Recording

All non-serious AEs regardless of severity or relationship to the study drugs are to be recorded in the electronic data capture (EDC) system on the appropriate eCRF from signing of informed consent until 30 days after documented date of discontinuation or completion of protocol-

specific treatment. All AEs must include the Investigator's assessment of the event's seriousness, severity, and causality to study drug.

All SAEs, regardless of severity or relationship to the study drug(s), are to be recorded in the EDC system on the appropriate eCRF from signing of informed consent until 30 days after documented date of discontinuation or completion of protocol-specific treatment. All SAEs must include the Investigator's assessment of the event's seriousness, severity, and causal relationship to study drug. AESIs and SAEs considered related to MYTX-011 must be reported to the Sponsor even after the 30-day period has been completed.

If an AE is deemed by the Investigator as serious, as per the SAE criteria, it should be reported **as soon as possible and no later than 24 hours** of awareness to the Sponsor or designee using the appropriate eCRF in the EDC system. If a non-serious AE is deemed by the Investigator as a potential or suspected pneumonitis or ILD, it should also be reported as soon as possible and no later than 24 hours of awareness to the Sponsor or designee using the appropriate eCRF in the EDC system. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported **as soon as possible but no later than 24 hours** to the Sponsor or designee using the appropriate eCRF in the EDC system. SAEs should be followed until resolution (including results of an autopsy report, if applicable). An electronic SAE form is available for use if the EDC is unavailable. If an electronic SAE form is needed, the data must be reviewed and the electronic SAE form signed by the Investigator or designee.

If the EDC system is unavailable, electronic SAEs must be reported to:

**Pharmacovigilance Department**
**Catalyst Clinical Research**
safety@catalystcr.com

New information relating to a previously reported SAE must be reported to the Sponsor within 24 hours following knowledge of the new information. The Investigator may be requested to provide additional follow-up information such as discharge summaries and extracts from medical records.

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date when the SAE no longer meets serious criteria.

Symptoms of the disease under study should not be classed as AEs if they are within the normal day-to-day fluctuation or expected progression of the disease. However, unexpected and significant worsening of the symptoms should be recorded as an AE.

Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE.

Other untoward events occurring in the framework of the study are also to be recorded as AEs (i.e., AEs that occur prior to assignment of study drug that are related to a protocol mandated intervention, including invasive procedures such as biopsies).

Subjects who discontinue from the study for a study-related AE or an abnormal laboratory value must be followed until resolution to baseline (or to Grade ≤1), or stabilization, or the event is considered to be chronic and/or irreversible, whichever comes first.

All new AEs (non-serious and serious) occurring during the follow-up period must be reported and followed until resolution unless, in the Investigator's judgment, these are not likely to improve due to the underlying disease.

Investigators must report SAEs and follow-up information to their responsible Institutional IRB)/IEC according to the policies of the responsible IRB/IEC.

Investigators should use correct medical terminology/concepts and avoid colloquialisms and abbreviations when recording AEs or SAEs on the eCRF and/or SAE Report Form.

The outcome of the AE must be recorded on the eCRF:

- Fatal
- Not recovered/not resolved
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering
- Unknown

#### 9.2.6.1. Abnormal Laboratory Values and Other Safety Evaluations

Some laboratory values may be outside the normal range due to the underlying disease. Abnormalities or changes in laboratory values, vital signs, or ECG assessments may represent an AE if the change is clinically significant. Clinically significant values/changes are those that result in an intervention or alteration in medical care, meet the criteria for an SAE or DLT, those causing dose delays/modifications and those that indicate a reason for subject discontinuation from study drug. Clinical syndromes associated with laboratory values should be recorded as appropriate on the AE eCRF page.

### 9.2.7. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the AE Report Form and/or the eCRF. If a persistent AE becomes more severe (changes from a Grade 1 or 2 AE to a Grade 3 or 4 AE) or lessens in severity (changes from a Grade 3 or 4 AE to a Grade 1 or 2 AE), it should be recorded on a separate AE Report Form and/or eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation timepoints, and subsequently recurs. All recurrent AEs should be recorded on an AE Report Form and/or eCRF for each recurrence.

### 9.2.8. Deaths

Deaths that occur during the protocol-specified AE reporting period and are attributed by the Investigator solely to progression of the subject's disease for up to 30 days after the last dose of study drug will be recorded on the appropriate study eCRF page and will be exempt from SAE reporting. The term "disease progression" should not be used. Death due to disease progression in the absence of signs and symptoms should be recorded as the primary malignancy (e.g., metastatic NSCLC) on the eCRF Death page.

All other on-study deaths (i.e., not solely attributed to disease progression) will be reported to the Sponsor or designee on an SAE Report Form and recorded on the AE page of the eCRF.

When recording the death as an SAE, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE page of the eCRF: only one SAE representing the primary cause of death should be reported with serious criteria "Death", severity "Grade 5" and outcome "Fatal." If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF AE page.

## 9.3. HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

Any AE that results in hospital admission or prolongs hospitalization should be documented and reported as an SAE. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE.

## 9.4. STOPPING RULES

Enrollment may be stopped if an interim risk-benefit assessment by the DSMB and/or SRC of all available data determines that potential risk outweighs demonstrated/anticipated benefits of the investigational agent. In this situation, review of alternative dosing, administration, prophylaxes, or other maneuvers to reduce risk will be performed, and will be endorsed by SRC or DSMB prior to any final decisions on re-initiation of enrollment.

An ad-hoc DSMB meeting will be held to discuss the benefit:risk profile of MYTX-011 if either of the below criteria are met:

- ≥2% treatment-related deaths (other than PD or confounded by PD) at any time or
- ≥2 subjects with treatment-related deaths (other than PD or confounded by PD) with ≤20 subjects dosed with MYTX-011 in the same dose cohort

## 9.5. PRE-EXISTING MEDICAL CONDITIONS

A pre-existing relevant medical condition is one that is present at the start of the study. Such conditions should be recorded on the study's appropriate medical history eCRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the appropriate SAE Report Form and/or eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

## 9.6. PREGNANCY

During the study, all female subjects of childbearing potential (the definition of females of childbearing potential is given in Appendix A) must contact the treating Investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating Investigator).

If an Investigator suspects that a subject may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the subject must not receive any study drug(s) and must be discontinued from the study.

If an Investigator suspects that a subject may be pregnant after the subject has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the subject must be discontinued from the study, and the Investigator must notify the Sponsor Medical Monitor within 24 hours of awareness.

If a female partner of a male subject becomes pregnant during the male subject's participation in the study, the pregnancy must be reported immediately.

Pregnancy should be recorded on a Pregnancy Report Form and reported by the Investigator to the Sponsor or designee in the same timeframe (within 24 hours of awareness) as reporting an SAE.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. The pregnancy should be followed up to 6 months after the end of the pregnancy, which can include birth, spontaneous abortion, or voluntary termination, to collect the outcome with details of the birth and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, as applicable. Follow-up to a pregnancy should be recorded on a Pregnancy Report Form and should include an assessment of the causal relationship to the study drug and reported by the Investigator to the Sponsor or designee. Pregnancy outcomes must be reported for the female partners of any males who took study drug on the Pregnancy Report Form. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Any SAE experienced during pregnancy must be reported on the SAE Report Form. Pregnancy complications such as spontaneous abortion/miscarriage are considered an SAE. An elective abortion/termination of pregnancy is not considered an SAE. Congenital anomalies/birth defects **always** meet SAE criteria and should therefore be reported as an SAE using the previously described process for SAE reporting.

## 9.7. MEDICATION ERRORS AND STUDY DRUG OVERDOSE

Symptomatic and asymptomatic overdose must be reported in the appropriate eCRF. Any accidental or intentional overdose with any of the study drug(s), even if not fulfilling a

seriousness criterion, is to be reported to the Sponsor or designee immediately (within 24 hours of awareness) using the SAE Report Form and following the same process described for SAEs.

A medication error is an error made in the prescribing, dispensing, administration, and/or use of the study drug. Medication errors including use of unassigned treatment, incorrect dosage, or expired product should be reported within 24 hours to the Sponsor.

## 9.8. REFERENCE SAFETY INFORMATION

The reference for safety information for this study is the MYTX-011 IB, which will be provided to the Investigators by the Sponsor or designee.

## 9.9. SAFETY REPORTING TO REGULATORY AGENCIES, ETHICS COMMITTEES, AND INVESTIGATORS

The Sponsor or designee will notify the appropriate regulatory agencies and all participating Investigators on an expedited basis and in accordance with local regulations if there are suspected unexpected serious adverse drug reactions (SUSARs) associated with MYTX-011 administration. The Investigator (or Sponsor where required) will report the SUSARs to the appropriate IRB/IEC.

# 10. CLINICAL DATA COLLECTION AND MONITORING

## 10.1. SAFETY OVERSIGHT COMMITTEES

### 10.1.1. Safety Review Committee

Safety will be monitored throughout the study by an SRC established by the Sponsor and will consist of participating Investigators and the Sponsor Medical Monitor. The Sponsor's biostatistician and clinical pharmacologist will be consulted and may attend the meetings. Representatives of the Sponsor Clinical Development Team may also attend the SRC meetings. At a minimum, the SRC will meet when subjects in each cohort have completed the DLT observation period in Part 1, at the end of dose escalation for all cohorts/determination of the RP2D, and at the time of any planned futility analysis. Ad hoc meetings will be scheduled if there are unexpected safety findings.

All available data will be reviewed by the SRC. The data to be reviewed may be unqueried. During Part 1, the SRC will make recommendations on dose escalation/de-escalation/cohort expansion, exploring intermediate dose cohorts or alternate dosing regimens, and recommend the RP2D. The SRC will also recommend the alternative dose to be selected for cohorts that involve dose randomization.

After reviewing cumulative safety data, the SRC may make recommendations on the conduct of the study including dosing regimens, supportive care measures, and protocol amendments if needed. During dose expansion, in addition to the Data Safety Monitoring board, the SRC may be consulted to make recommendations on opening cohorts, cohort modifications including enrollment pause or resumption, expansion, or termination as appropriate.

### 10.1.2. Independent Data Safety Monitoring Board

To ensure subjects' safety during Part 2 of the study (Dose Expansion), safety data will be reviewed by an independent Data Safety Monitoring Board (DSMB) on an ongoing basis. Based on the available safety data from the entire study, the DSMB will make recommendations on continuation, modification, or suspension of the study or of a particular expansion cohort in Part 2 of the study (Dose Expansion). The DSMB will meet at the following timepoints: 6 months after the first patient is dosed in Part 2, and then every 6 months thereafter until the primary analysis for Part 2 has been conducted. The DSMB may increase the frequency of meetings if deemed appropriate during the course of the trial. The specific working procedures will be described in a DSMB charter, which will be established prior to the first data review meeting held by the DSMB.

Recommendations made by the SRC and DSMB will be documented and maintained in the Sponsor's Trial Master File.

## 10.2. SITE MONITORING PLAN

A study initiation site visit, a teleconference, and/or a planned Investigator meeting will be performed to review Investigator responsibilities and protocol requirements. During the study, the Sponsor or Sponsor delegate will make visits to the sites or perform remote monitoring as defined in the monitoring plan to review protocol compliance, examine eCRFs, laboratory data, safety data, and individual subject medical records and to ensure that the study is being conducted according to the protocol and pertinent regulatory requirements.

Site monitoring shall be conducted to ensure that the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the Sponsor, GCP/ICH, and, when appropriate, regulatory guidelines. The Site Monitoring Plan shall define aspects of the monitoring process.

## 10.3. CURRICULA VITAE AND FINANCIAL DISCLOSURES

All Principal Investigators will be required to submit to the Sponsor or its designee a current signed curriculum vitae (CV), a completed FDA Form 1572 (or equivalent form), and financial disclosure statement. In addition, all sub-Investigators will be required to submit to the Sponsor or its designee a current signed CV and a completed financial disclosure statement.

## 10.4. DATA OWNERSHIP AND PUBLICATION

The results of and all data generated during the conduct of this study belong to the Sponsor, are considered Sponsor's proprietary and confidential information, and are subject to the confidentiality provisions in the Clinical Trial Agreement (CTA) governing the participation of the Investigator in the study. Sponsor retains the sole and exclusive right to the first publication of the results of this study. Such publication is intended to be a multicenter publication, collected from all Investigators and institutions participating in the study rather than publication based on individual site data. Any manuscripts, abstracts, or other presentation materials generated by Investigator must be reviewed and approved by the Sponsor prior to submission as set forth in the CTA and must meet all other applicable conditions set forth in the CTA.

# 11. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Applicable ICH GCP Guidelines.
- Applicable laws and regulatory requirements.
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

## 11.1. IRB/IEC APPROVAL

The study protocol and amendments, ICFs, subject-facing documents (e.g., study diary), advertisements), information about payments (i.e., Investigator payments) and compensation available to the subjects and documentation evidencing the Principal Investigator's qualifications must be submitted to the IRB/IEC per their guidelines for ethical review and approval prior to the study start. The IRB/IEC will also be provided with a copy of the IB.

The Investigator will not start the study, nor will study drug be shipped to the investigational site before the Sponsor has been provided evidence of the IRB/IEC approval.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure initial and ongoing IRB/IEC study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICFs unless there is an emergent subject safety issue.

If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects.

If applicable, the Investigator will notify the IRB/IEC at the end of the study, or if the study terminates early, the Investigator must notify the IRB/IEC of the termination. A reason for the early termination must be provided (as defined in Directive 2001/20/EC).

## 11.2. REGULATORY APPROVAL

As required by local regulations, the Sponsor will ensure approval of the appropriate regulatory bodies is obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of any substantial amendment to the protocol and other relevant study documents happens only after approval by the relevant regulatory authorities.

Safety updates for MYTX-011 will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority.

## 11.3. FINANCIAL DISCLOSURE

The Investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR Part 54.

In addition, the Investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

## 11.4. INSURANCE AND INDEMNITY

Details of insurance and/or indemnity will be contained within the written agreement between the Investigator or site and the Sponsor.

## 11.5. INFORMED CONSENT

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF. It is the responsibility of the Investigator to obtain written informed consent.

The ICF will be submitted for approval to the IRB/IEC that is responsible for review and approval of the study. Each consent form must include all the relevant elements currently required by the responsible regulatory authority, as well as local county authority or state regulations and national requirements. The copy of the IRB/IEC-approved ICF to be utilized in the study must be submitted to the Sponsor prior to study initiation. Before recruitment and enrollment into the study, each prospective subject will be given a full explanation of the study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual subject understands the implications of participating in this study, the subject will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the subject’s medical

record. A copy of the ICF, to include the subject's signature, will be provided by the Investigator to the subject. Written informed consent for participation in the study must be obtained from the subject or legally authorized representative before performing any study-specific screening tests or evaluations.

If an amendment to the protocol substantially alters the study design or the potential risks to the subjects, the subject's consent to continue participation in the study must be obtained.

## 11.6. SUBJECT CONFIDENTIALITY

Confidentiality of subject's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws. To protect the personal data of subjects, the Sponsor will assign a unique study number to each subject, which will be used on the eCRF or other documents submitted to the Sponsor. This information, together with the subject's date of birth, will be used in the database for subject identification. Participant names or other information that would make the participant identifiable will not be entered in the eCRF or database or transferred in other documents submitted to Sponsor. No material bearing a subject's name will be kept on file by the Sponsor.

Subjects will be informed of their rights within the ICF. HIPAA regulations require that, to participate in the study, the subject should be informed of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization

If a subject revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR, it is a requirement that the Investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities, and the IRB/IEC direct access to review the subject's original medical records at the

site for verification of study-related procedures and data. The subject must be informed about the potential for this type of monitoring and auditing access.

**CTR Compliant Data Protection in the European Economic Area**

Mythic Therapeutics, Inc., as Data Controller, ensures that all processing activities involving personal data performed in the scope of this Study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, Mythic Therapeutics, Inc. has implemented and maintains the following measures:

- Restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel and approved visitors
- Ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial
- Implementing the pseudonymization and encryption of personal data, as appropriate
- Implementing the ability to ensure the ongoing confidentiality, integrity, availability, and resilience of processing systems and services
- Implementing network, application, and database security by means of firewalls and antivirus/anti-malware software; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, and disabling of security measures and response to such attacks
- Means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident
- Logging of security events/incidents in information systems
- Implementing procedures that cover reporting, analysis, monitoring, and resolution of security incidents
- Ensuring that information systems, computers, and software involved in the performance of the services provided in the Study are backed up
- A process for regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing

Mythic Therapeutics, Inc. is currently implementing and will maintain the following measures:

- Procedures to capture within reasonable time any personal data breach occurred
- Procedures and practices for securing destruction of paper documents containing personal data

- Business continuity procedures ensuring that Mythic Therapeutics, Inc. can continue to provide services through operational interruption

All locations, personnel, and information systems that are used to perform services for the Study will be covered.

Mythic Therapeutics, Inc. will ensure that the technical and organizational security measures described above are regularly reviewed and updated to take into account any evolution of technological developments.

Mythic Therapeutics, Inc. may apply additional specific statutory requirements, where applicable in the national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the foregoing technical and organizational measures, Mythic Therapeutics, Inc., by means of internal measures and imposed contractual clauses to the selected sub-contractors, ensures the confidentiality of records and personal data of subjects.

With exception of the activities in the scope of the on-site monitoring, the name of the subject will neither be asked for nor recorded by the Mythic Therapeutics, Inc. An identification number will be allocated to each subject registered in the Study. This number will identify the subject and will be included on all case report forms and corresponding material and data associated with the subject.

Monitors and auditors acting on behalf of the Mythic Therapeutics, Inc. will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under clinical trial framework, including the ICH-GCP obligations applicable to the conduct of the Study. Staff involved in the performance of this task are bound by any additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

Mythic Therapeutics, Inc. is establishing a functional process of reporting of any data breach occurring at Mythic Therapeutics, Inc.’s or its sub-contractor’s facilities and premises. In case of the occurrence of any data breach, Mythic Therapeutics, Inc. will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, including taking into account its source, underlying intentions, and possibilities of recovery. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of Mythic Therapeutics, Inc.’s becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, data subjects will be informed by the Mythic Therapeutics (via clinical Study site).

## 11.7. INVESTIGATOR AND STAFF INFORMATION

Personal data of the Investigators and sub-Investigators may be included in the Sponsor database and shall be treated in compliance with all applicable laws and regulations. When archiving or

processing personal data pertaining to the Investigator or sub-Investigator, the Sponsor shall take all appropriate measures to safeguard and prevent access to these data by any unauthorized party.

## 11.8. FINANCIAL INFORMATION

The finances for this study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures applicable to 21 CFR Part 54 shall be appropriately provided.

# 12. RECORD RETENTION AND DOCUMENTATION OF THE STUDY

## 12.1. DOCUMENTATION REQUIRED TO INITIATE STUDY

The Sponsor/Sponsor designee will ensure that documentation is required to be in place before the study may start, in accordance with FDA regulations and/or local regulatory authorities, ICH E6, and Sponsor Standard Operating Procedures will be available before any study sites are initiated.

Documents at a minimum required to begin the study include, but are not limited to, the following:

- A signature authorized protocol and contract
- A copy of the official IRB/IEC approval of the study and the IRB/IEC members list or assurance verification
- Current CVs for the principal Investigator and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- FDA Form 1572 (Statement of Investigator), or equivalent, appropriately completed and signed
- A copy of the IRB/IEC-approved consent form
- Financial disclosure forms for all Investigators listed on FDA Form 1572
- GCP certificates for study training
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

## 12.2. STUDY DOCUMENTATION AND STORAGE

The Investigator must maintain a list of appropriately qualified persons to whom he or she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the subject's eCRF are to be supported by source documentation.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the subject's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, scans, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Investigator Study File [ISF]/Site Study File [SSF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP and 8 CFR Part 312.57, including key documents such as the IB and any amendments, protocol, and any amendments, signed ICFs, IRB/IEC approval documents, Financial Disclosure forms, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drugs. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21 CFR Part 54.6 and Part 312.57 for:

- No less than 2 years after the last marketing application has been approved in an ICH region; or
- No less than 2 years in the event that the marketing application has not been approved in an ICH region; or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No study records should be destroyed without prior authorization from the Sponsor.

The IRB/IEC shall maintain adequate documentation/records of IRB/IEC activities as per 21 CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., medical records), all original, signed ICFs, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor or its representative will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, either the Sponsor or its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or another Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study and will be transferred to the Sponsor at the conclusion of the study.

## 12.3. AMENDMENTS TO THE PROTOCOL

If an amendment to the protocol is required, the amendment will be originated by the Sponsor and approved by the Sponsor. The written amendment must be submitted to the IRB/IEC at the Investigator's facility for approval as per IRB/IEC requirements.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable.

If an amendment to the protocol substantially alters the study design or the potential risks to the subjects, their consent to continue participation in the study should be obtained.

## 12.4. DATA COLLECTION

The study eCRF is the primary data collection instrument for the study. An eCRF will be utilized for the collection of all data and all data will be entered using the English language and should be kept current to enable the monitor to review the subjects' status throughout the course of the study.

To maintain confidentiality, only study number, subject number, and partial date of birth will identify the subject in the eCRF. The Investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to enable records to be identified and verified as authentic. Subject data/information will be kept confidential and will be managed according to applicable local, state, and federal regulations.

## 12.5. STUDY MONITORING, AUDITING, AND INSPECTING

The Investigator will permit study-related monitoring, quality audits, and inspections by government regulatory authorities, the Sponsor, or its representative(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, eCRFs). The Investigator will ensure the capability for inspections of applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or quality assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

## 12.6. QUALITY ASSURANCE AND QUALITY CONTROL

Independent auditing may be conducted during the conduct of the study to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance with the protocol, accuracy in relation to source documents, and compliance with GCP and applicable regulations.

Each study site shall be required to have processes that enable compliant study conduct and Investigator oversight of data generation and collection, as well as recording and reporting of data/documentation according to the protocol, GCP, and any applicable local, national, or international regulations.

Accurate and reliable data collection will be ensured by SDV, and cross-checking of the eCRFs against the Investigator's records will be performed by the study monitor. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

## 12.7. DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. By conducting this study, the Investigator affirms to the Sponsor that he or she will maintain, in strict confidence, information furnished by the Sponsor including the results of and data generated from this study, except as exempted for regulatory purposes.

A clinical study report will be prepared upon completion of the study. The format of the clinical study report will comply with ICH E3 guidelines for structure and content of a clinical study report. The Sponsor will comply with any applicable local laws/regulations regarding the posting of study results.

The financial disclosure information will be provided to the Sponsor prior to study participation from all Principal Investigators and sub-Investigators who are involved in the study and named on FDA Form 1572.

All data generated during the conduct of this study are owned by the Sponsor and may not be used by the Investigator or affiliates without the expressed written consent of the Sponsor.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. The Sponsor will comply with applicable requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement, and authorship will comply with International Committee of Medical Journal Editors standards. Furthermore, the Investigator agrees that any publication by the Investigator of the results of the study conducted at the study site shall not be made before the first multicenter publication.

All manuscripts, abstracts, or other presentation materials generated by site Investigators must be reviewed and approved by the Sponsor prior to submission as set forth in the CTA governing the Investigator or his or her institution's participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor at the earliest practicable time prior to submission or presentation and otherwise within the time set forth in the CTA.

# 13. REFERENCES

ADCETRIS® [package insert]. 2023. Seagen Inc. https://docs.seagen.com/Adcetris_Full_Ltr_Master.pdf.

Alexander, M., S. Y. Kim, and H. Cheng. 2020. 'Update 2020: Management of Non-Small Cell Lung Cancer', *Lung*, 198: 897-907.

Camidge DR, Bar J, Horinouchi H, Goldman J, Moiseenko F, Filippova E, Cicin I, Ciuleanu T, Daaboul N, Liu C, Bradbury P, Moskovitz M, Katgi N, Tomasini P, Zer A, Girard N, Cuppens K, Han JY, Wu SY, Baijal S, Mansfield AS, Kuo CH, Nishino K, Lee SH, Planchard D, Baik C, Li M, Ansell P, Xia S, Bolotin E, Looman J, Ratajczak C, Lu S. Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein-Overexpressing Advanced Nonsquamous *EGFR*-Wildtype Non-Small Cell Lung Cancer in the Phase II LUMINOSITY Trial. J Clin Oncol. 2024 Sep 1;42(25):3000-3011.

DeGeorge, J. J., C. H. Ahn, P. A. Andrews, M. E. Brower, D. W. Giorgio, M. A. Goheer, D. Y. Lee-Ham, W. D. McGuinn, W. Schmidt, C. J. Sun, and S. C. Tripathi. 1998. 'Regulatory Considerations for Preclinical Development of Anticancer Drugs', *Cancer Chemother Pharmacol*, 41: 173-85.

De Miguel M, Yamamoto N, Raimbourg J, Cho BC, Gottfried M, et al. 2024. 1257MO ABBV-400, a c-Met protein-targeting antibody-drug conjugate (ADC), in patients (Pts) with advanced EGFR wildtype (WT) non-squamous (NSQ) non-small cell lung cancer (NSCLC): Results from a phase I study. NSCLC, metastatic. 35:2;S805-S806.

Eisenhauer, E. A., P. Therasse, J. Bogaerts, L. H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, and J. Verweij. 2009. 'New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)', *Eur J Cancer*, 45: 228-47.

ELAHERE® [package insert]. 2022. ImmunoGen, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761310s000lbl.pdf.

FDA. 2022. 'Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers'. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Fernandes, M., P. Jamme, A. B. Cortot, Z. Kherrouche, and D. Tulasne. 2021. 'When the MET Receptor Kicks in to Resist Targeted Therapies', *Oncogene*, 40: 4061-78.

Fisher, J. E., Jr. 2021. 'Considerations for the Nonclinical Safety Evaluation of Antibody-Drug Conjugates', *Antibodies (Basel, Switzerland)*, 10.

Johnson, M., T. F. Burns, J. Thompson, A. Spira, M. Alexander, G. R. Blumenschein, J. Michalski, S. Bilic, A. Teh, K. C. Lai, S. McGann, H. Chalk, L. Haystrand, T-H. Wu, G. Gallant, and R. S. Heist. 2024. Abstract 8558: 'MYTX-011 in patients with previously treated locally advanced or metastatic NSCLC: Initial dose escalation results in the phase 1 KisMET-01 study', 2024 Annual ASCO Meeting, *J Clin Oncol*, 42 (16Suppl.): 8558. https://mythictx.com/wp-content/uploads/2024/06/ASCO-2024-MYTX-011-01-poster.pdf

Kim, S. K., P. Ursell, R. L. Coleman, B. J. Monk, and I. Vergote. 2022. 'Mitigation and Management Strategies for Ocular Events Associated with Tisotumab Vedotin', *Gynecol Oncol*, 165: 385-92.

Lee, J. J., and D. D. Liu. 2008. 'A Predictive Probability Design for Phase II Cancer Clinical Trials', *Clin Trials*, 5: 93-106.

Masters, J. C., D. J. Nickens, D. Xuan, R. L. Shazer, and M. Amantea. 2018. 'Clinical Toxicity of Antibody Drug Conjugates: a Meta-analysis of Payloads', *Invest New Drugs*, 36: 121-35.

Matulonis, U. A., M. J. Birrer, D. M. O'Malley, K. N. Moore, J. Konner, L. Gilbert, L. P. Martin, T. M. Bauer, A. M. Oza, K. Malek, J. Pinkas, and S. K. Kim. 2019. 'Evaluation of Prophylactic Corticosteroid Eye Drop Use in the Management of Corneal Abnormalities Induced by the Antibody-Drug Conjugate Mirvetuximab Soravtansine', *Clin Cancer Res*, 25: 1727-36.

Mithoowani, H., and M. Febbraro. 2022. 'Non-Small-Cell Lung Cancer in 2022: A Review for General Practitioners in Oncology', *Curr Oncol*, 29: 1828-39.

National Cancer Institute. 2023. 'Cancer Stat Facts: Lung and Bronchus Cancer', National Cancer Institute. https://seer.cancer.gov/statfacts/html/lungb.html.

PADCEV® [package insert]. 2021. Astellas Pharma US, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761137s000lbl.pdf.

POLIVY® [package insert]. 2023. Genentech, Inc. https://www.gene.com/download/pdf/polivy_prescribing.pdf.

Heist, R Shum E, Garcia E, Itchins M, Gao B, et al. 2025. MYTX-011, a cMET-targeting antibody-drug conjugate (ADC), in patients with previously treated, advanced NSCLC: Updated dose escalation results in the phase 1 KisMET-01 study. JCO 43, 8613-8613.

Saber, H., and J. K. Leighton. 2015. 'An FDA Oncology Analysis of Antibody-Drug Conjugates', *Regul Toxicol Pharmacol*, 71: 444-52.

Salgia, R. 2017. 'MET in Lung Cancer: Biomarker Selection Based on Scientific Rationale', *Mol Cancer Ther*, 16: 555-65.

Sierra, J. R., and M. S. Tsao. 2011. 'c-MET as a Potential Therapeutic Target and Biomarker in Cancer', *Ther Adv Med Oncol*, 3: S21-35.

Sung, H., J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, and F. Bray. 2021. 'Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries', *CA Cancer J Clin*, 71: 209-49.

Swain, S. M., M. Nishino, L. H. Lancaster, B. T. Li, A. G. Nicholson, B. J. Bartholmai, J. Naidoo, E. Schumacher-Wulf, K. Shitara, J. Tsurutani, P. Conte, T. Kato, F. Andre, and C. A. Powell. 2022. 'Multidisciplinary Clinical Guidance on Trastuzumab Deruxtecan (T-DXd)-Related Interstitial Lung Disease/Pneumonitis-Focus on Proactive Monitoring, Diagnosis, and Management', *Cancer Treat Rev*, 106: 102378.

Tarantino, P., S. Modi, S. M. Tolaney, J. Cortes, E. P. Hamilton, S. B. Kim, M. Toi, F. Andre, and G. Curigliano. 2021. 'Interstitial Lung Disease Induced by Anti-ERBB2 Antibody-Drug Conjugates: A Review', *JAMA Oncol*, 7: 1873-81.

TIVDAK® [package insert]. 2021. Seagen Inc. and Genmab US, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761208Orig1s000lbledt.pdf.

Yuan, Y., K. R. Hess, S. G. Hilsenbeck, and M. R. Gilbert. 2016. 'Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials', *Clin Cancer Res*, 22: 4291-301.

Zhou, H., J. J. Lee, and Y. Yuan. 2017. 'BOP2: Bayesian Optimal Design for Phase II Clinical Trials with Simple and Complex Endpoints', *Stat Med*, 36: 3302-14.

# APPENDIX A. CONTRACEPTION GUIDELINES

### Definition of Females Not of Childbearing Potential

A woman is considered of childbearing potential, i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

### Definition of, and Contraception Guidelines for, Females of Childbearing Potential

Females of childbearing potential, defined as all females physiologically capable of becoming pregnant, must use a highly effective method of contraception for the duration of the study and for at least 6 months after the last dose of study drug.

Females of childbearing potential must have a negative serum pregnancy test ≤72 hours prior to initiating treatment and a negative urine or serum pregnancy test prior to each administration of study drug in compliance with local requirements.

### Contraception Guidelines for Male Subjects

Male subjects with partners of childbearing potential must use a highly effective method of contraception for the duration of the study and for at least 6 months after the last dose of study drug.

Male subjects should not donate sperm starting at screening and until at least 6 months after the last dose of study drug.

### Definition of Highly Effective Contraception

A highly effective method of contraception, as per Clinical Trials Facilitation and Coordination Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials v1.1, is defined as any of the following:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation
- Vasectomized partner

- Sexual abstinence
  - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with MYTX-011 treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

The following are **unacceptable** forms of contraception:

- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

# APPENDIX B. NEW YORK HEART ASSOCIATION CLASSIFICATIONS

New York Heart Association (NYHA) Classifications

| Class | Functional Capacity | Objective Assessment |
|---|---|---|
| I | Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. | No objective evidence of cardiovascular disease. |
| II | Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of minimal cardiovascular disease. |
| III | Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of moderately severe cardiovascular disease. |
| IV | Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

Source: The Criteria Committee of New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* 9th ed. Boston, MA: Little, Brown & Co; 1994:253-256.

# APPENDIX C. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS 1.1 (RECIST 1.1)

Tumor response will be assessed according to RECIST 1.1 (Eisenhauer et al. 2009), as described below.

**Measurability of Tumor at Baseline**

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows:

Measurable

*Tumor lesions*: Must be accurately measured in ≥1 dimension (longest diameter in the plane of measurement to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)

20 mm by chest X-ray

*Malignant lymph nodes*: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm)

Nonmeasurable

- All other lesions (or disease sites), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis)
- Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly, identified by physical examination, but not measurable by reproducible imaging techniques
  - Lesions in a previously irradiated area or in an area subjected to locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion

**Tumor Response Evaluation**

Baseline Documentation of Target and Nontarget Lesions

*Target Lesions*

- When >1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions
- It may be the case that, on occasion, the largest lesion that can be measured reproducibly should be selected

*Nontarget Lesions*

- All other lesions (or disease sites), including pathological lymph nodes, should be identified as nontarget lesions
- It is possible to record multiple nontarget lesions involving the same organ as a single item (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")

Evaluation of Target Lesions

Target lesions will be evaluated, and response recorded as defined in Table 16.

**Table 16: Response Based on Evaluation of Target Lesions at Each Assessment**

| | |
|---|---|
| **Complete response (CR)** | Disappearance of all target lesions; if a pathologic lymph node, reduction in the shortest axis to <10 mm[a] |
| **Partial response (PR)[b]** | ≥30% decrease in the sum of the diameters of target lesions relative to the baseline sum diameters[c] |
| **Stable disease (SD)[b,d]** | Neither a sufficient reduction to qualify as a PR nor a sufficient increase to qualify as progression[c] |
| **Progressive disease (PD)[b]** | ≥20% increase in the sum diameters relative to the smallest sum diameters recorded (including the baseline sum diameters) in conjunction with an increase of at least 5 mm in the smallest sum diameters or the appearance of 1 or more new lesions[c,e] |

[a] For each pathologic lymph node considered a target lesion, the node must have a short axis measuring < 10 mm to be considered as a CR. In such cases, the sum diameters may not be zero (as a normal lymph node can have a short axis of <10 mm).
[b] For each pathologic lymph node considered a target lesion, the measurement of the short axis of the node is to be included in the sum diameters when determining PR, stable disease, and progression.
[c] In this study, the "baseline sum diameter" is calculated based on the lesion measurements obtained at screening.
[d] Duration of stable disease is measured from the date of the first dose of study drug until criteria for progressive disease are met based on the smallest sum diameters recorded (including the baseline sum diameters).
[e] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDG-PET) scan may be useful in assessing new lesions apparent on computed tomography (CT) scan.

Evaluation of Nontarget Lesions

Nontarget lesions will be evaluated and response recorded as defined in Table 17.

**Table 17: Response Based on Evaluation of Nontarget Lesions at Each Assessment**

| | |
|---|---|
| **Complete response (CR)** | Disappearance of all nontarget lesions; all lymph nodes must be non-pathologic in size (i.e., <10 mm on the short axis) |
| **Not CR or not progressive disease (PD)** | Persistence of 1 or more nontarget lesions |
| **PD** | Unequivocal progression[a] of any existing nontarget lesion or the appearance of 1 or more new lesions[b] |

[a] The subject should stop investigational product, even in the presence of a PR or stable disease, based on an assessment of target lesions.
[b] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in assessing new lesions apparent on computed tomography (CT) scan.

New Lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

Timepoint Response

Timepoint response based on the evaluation of target and nontarget lesions will be determined as shown in Table 18.

**Table 18: Evaluation of Timepoint Response**

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response |
|---|---|---|---|
| Complete response | Complete response | No | Complete response |
| No target lesion[a] | Complete response | No | Complete response |
| Complete response | Not evaluable[b] | No | Partial response |
| Complete response | Not complete response/nonprogressive disease | No | Partial response |

**Table 18: Evaluation of Timepoint Response (Continued)**

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response |
|---|---|---|---|
| Partial response | Non-progressive disease and not evaluable[b] | No | Partial response |
| Stable disease | Non-progressive disease and not evaluable[b] | No | Stable disease |
| Not all evaluated | Non-progressive disease | No | Not evaluable |
| No target lesion[a] | Not all evaluated | No | Not evaluable |
| No target lesion[a] | Non-complete response/ non-progressive disease | No | Non-complete response/ non-progressive disease |
| Progressive disease | Any | Yes or No | Progressive disease |
| Any | Progressive disease | Yes or No | Progressive disease |
| Any | Any | Yes | Progressive disease |
| No target lesion[a] | Unequivocal progressive disease | Yes or No | Progressive disease |
| No target lesion[a] | Any | Yes | Progressive disease |

[a] Defined as no target lesions at baseline.
[b] Not evaluable is defined as when either no lesion measurements or only a subset of lesion measurements are made at an assessment.

# APPENDIX D. ECOG PERFORMANCE STATUS

| ECOG | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work) |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to a bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry out selfcare; totally confined to bed or chair |

# APPENDIX E. CREATININE CLEARANCE BY MODIFIED COCKCROFT-GAULT FORMULA

**Conventional–Serum Creatinine in mg/dL**

Male

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

**International System of Units (SI)–Serum Creatinine in µmol/L**

Male

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

Female

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113} \times 0.85$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
Online Calculator: The Calculator.co website. Creatinine Clearance Calculator.
https://www.thecalculator.co/health/Creatinine-Clearance-Calculator-258.html