MYTX-011-01 CSR

Appendix III. Statistical Analysis Plan

This Appendix includes the final (draft) statistical analysis plan at the time of study termination.

STATISTICAL ANALYSIS PLAN

Study 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
Name of Test Drug:	MYTX-011
Study Number:	MYTX-011-01
IND Number	IND 159721
CTIS Number:	2023-504630-22-00
Protocol Version:	Version 6.0
Protocol Date:	15 January 2025
Analysis Plan Version:	Draft Version 0.7
Analysis Plan Date:	15 May 2025
Analysis Type:	Final Analysis
Analysis Plan Author:	TJ Risoli

SPONSOR APPROVAL

_____	_____	_____
Printed Name	**Signature**	**Date**
_____	_____	_____
Printed Name	**Signature**	**Date**

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

SAP	statistical analysis plan
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
AEs	adverse events
AESIs	adverse events of special interest
ATC	anatomical therapeutic class
AUC	area under the curve
BMI	body mass index
BOIN	Bayesian optimal interval design
BOP2	Bayesian Optimal Phase II design
BOR	best overall response
CDVA	corrected distance visual acuity
CI	confidence interval
CL	total clearance
Clast	last measurable concentration
cm	centimeter
Cmax	maximum concentration
CR	complete response
CRF	case report form
CS	clinically significant
CSR	clinical study report
ctDNA	circulating tumor DNA
CTMS	clinical trial management system
DCR	disease control rate
DLTs	dose limiting toxicities
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture system
EGFR	epidermal growth factor receptor; estimated glomerular filtration rate
EOT	end of treatment
HLGT	MedDRA high level group term
HLT	MedDRA high level term
IHC	immunohistochemistry
in	inches
IRRs	infusion related reactions
kg	kilogram
lbs	pounds

LLT	MedDRA low level term
LOQ	lower limit of quantitation
LVEF	left ventricular ejection fraction
M	distant metastasis
MET	mesenchymal-epithelial transition factor
mg	milligram
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	number of subjects
N	regional lymph node
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	not clinically significant
NE	not evaluable
NSCLC	non-small cell lung cancer
NSQ	non-squamous
ORR	overall response rate
OS	overall survival
PD	progression disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	MedDRA preferred term
Q1	25th percentile
Q3	75th percentile
Q3W	every three weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAEs	serious adverse events
SAS	Statistical Analysis Software Inc.
SD	stable disease
SD	standard deviation
SOC	MedDRA system organ class
SQ	squamous
SRC	safety review committee
T	primary tumor
TEAEs	treatment-emergent adverse events
Tlast	time of last measurable concentration
TLFs	tables, listings, and figures
Tmax	time to maximum concentration
TTR	time to response
VA	visual acuity

Vd	volume of distribution
Vss	volume of distribution at steady state

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, listings, and figures (TLFs) to be implemented during the analyses of data collected within the scope of Part 1: Dose Escalation and Part 2: Dose Expansion of Protocol MYTX-011-01 [A Phase 1 Multicenter Dose Escalation and Dose Expansion Study of Antibody-Drug Conjugate MYTX-011 in Subjects with Non-Small Cell Lung Cancer] sponsored by Mythic Therapeutics. This SAP will be finalized before database lock. Any deviations from the SAP after database lock will be documented in the clinical study report (CSR).

1.1. Study Objectives and Endpoints

Part 1: Dose Escalation		
	Objective	**Endpoint**
Primary	1) To evaluate the safety and tolerability of MYTX-011. 2) To determine the recommended Phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) of MYTX-011.	1) Incidence and severity of treatment-emergent adverse events (TEAEs), AEs, and clinically significant changes from baseline in vital signs, ECGs, and laboratory parameters. 2) 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). 3) MTD will be determined by dose-limiting toxicities (DLTs) during Cycle 1 (the observation period for DLTs is Cycle 1).
Secondary	1) To characterize the pharmacokinetic (PK) profile of MYTX-011, including total antibody-drug conjugate (ADC), total antibody, and free MMAE.	1) 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}),

	2) 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. 3) To assess the incidence and persistence of anti-drug antibodies (ADA) to MYTX-011. 4) To determine preliminary antitumor activity of MYTX-011.	last measurable concentration (C_{last}), time of 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}). 2) Presence of ADAs at multiple timepoints during the study. 3) Overall response rate [ORR; confirmed complete response (CR) + confirmed partial response (PR)] by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. 4) Duration of response (DOR) for subjects who achieve CR or PR. 5) Disease control rate (DCR; CR + PR + stable disease (SD), best overall response, and time to response. 6) Progression free survival (PFS) and Overall survival (OS).
Exploratory	1) To measure the level of protein product of the MET gene (cMET) expression in tumor tissue and presence of alterations in mesenchymal-epithelial transition factor (MET).	1) Levels of cMET expression. 2) Presence of alterations in MET.
	1) To assess biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein.).	1) Biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, proteins, etc.).

Part 2: Dose Expansion (Cohorts A-F)		
	Objective	**Endpoint**
Primary	1) To evaluate preliminary anti-tumor activity of MYTX-011 in subjects with the following: a) Cohort A: Advanced non-squamous non-small cell lung cancer (NSCLC), without actionable epidermal growth factor receptor (EGFR) mutations, with high cMET expression; subjects to be randomized to 1 of 2 doses (1 of which will be RP2D). b) Cohort B: Advanced non-squamous NSCLC, without actionable *EGFR* mutations, with intermediate cMET expression. c) Cohort B2: Advanced non-squamous NSCLC, without actionable *EGFR* mutations, with intermediate cMET expression; subjects to be randomized to 1 of 2 doses [1 of which will be RP2D]; this cohort may open if Cohort B passes interim analysis for futility (i.e., futility criteria are not met). d) Cohort C: Advanced squamous cell NSCLC, without actionable *EGFR* mutations, with cMET expression. e) Cohort D: Advanced non-squamous or adenosquamous NSCLC, without actional *EGFR*	1) ORR (confirmed CR + PR) in each expansion cohort according to RECIST v1.1.

	mutations, with low cMET expression, that does not meet inclusion criteria for Cohorts A, B, or B2. f) Cohort E: Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression. g) Cohort E2: Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression. Subjects to be randomized to 1 of 2 doses (1 of which will be RP2D); this cohort may open if Cohort E passes interim analysis for futility (i.e. if futility criteria are not met). h) Cohort F: Advanced non-squamous or adenosquamous NSCLC without actionable *EGFR* mutations, with ultra-low cMET expression, that does not meet inclusion criteria for Cohorts A, B, B2 or D.	
Secondary	1) To evaluate the safety and tolerability of MYTX-011. 2) To characterize the PK profile of MYTX-011, including total ADC, total antibody, and free monomethyl auristatin E (MMAE). 3) To characterize anti-tumor activity of MYTX-011. 4) To explore the optimal biological dose of MYTX-011 in Cohort A, B2, and E2.	1) Efficacy assessments according to RECIST v1.1 in each expansion cohort, including: a) DOR for subjects who achieve confirmed CR or PR b) Time to response c) Best overall response d) DCR (confirmed CR + PR + SD) e) PFS f) OS

	5) To assess the incidence and persistence of ADA to MYTX-011.	2) Incidence and severity of TEAEs, treatment-related AEs, and clinically significant changes from baseline in vital signs, ECGs, and laboratory parameters. 3) 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}). 4) Presence of ADA at multiple timepoints during the study.
Exploratory	1) To measure the level of cMET expression in tumor tissue and presence of alterations in MET.	1) Levels of cMET expression. 2) Presence of alterations in MET. 3) Correlation to response.
	1) To assess biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, protein, etc.).	1) Biomarkers and predictors of response and resistance to MYTX-011 in tumor and blood (e.g., molecular, genetics, proteins, etc.).

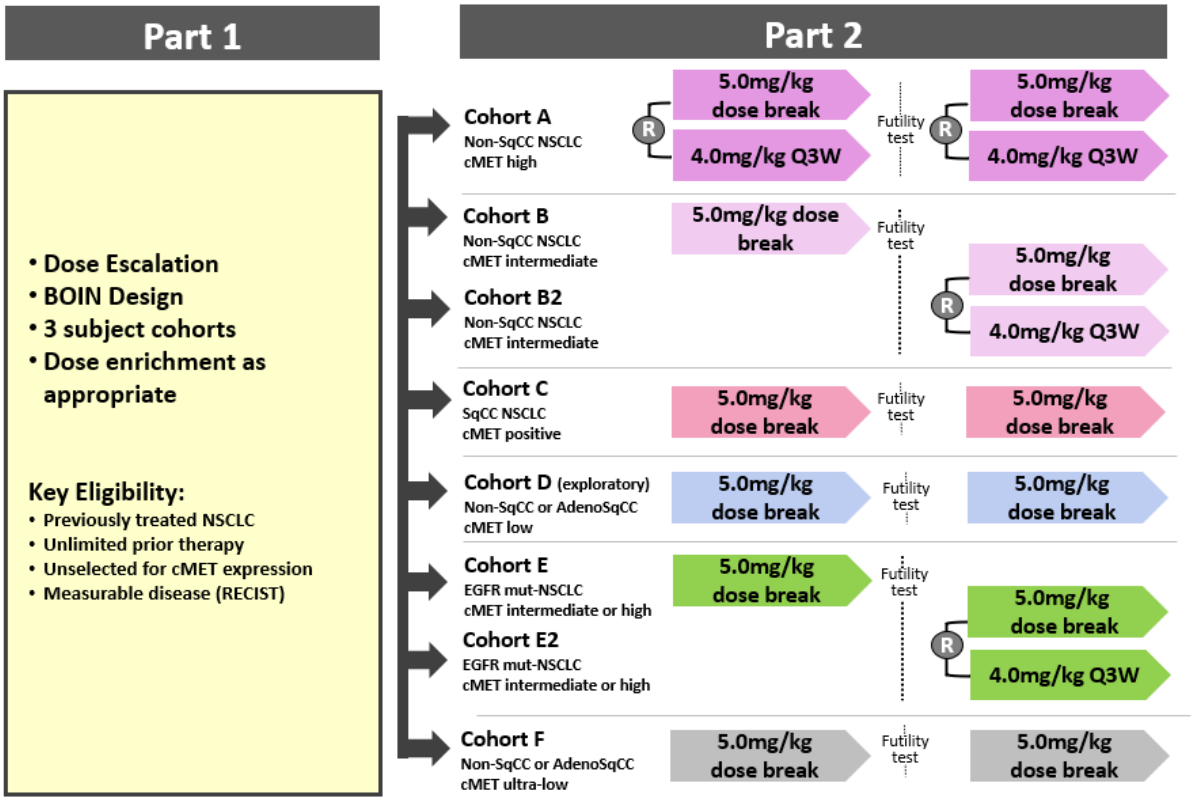
1.2. Study Design

This is a FIH, Phase 1, multicenter, open-label, dose escalation, and dose expansion study designed to evaluate the safety, tolerability, and PK of MYTX-011, to determine the R2PD and/or MTD, and to evaluate the preliminary anti-tumor activity in subjects with previously treated NSCLC with cMET expression.

The study will be conducted in 2 parts:

- Part 1: Dose Escalation
- Part 2: Dose Expansion

Figure 1: Study Design Schematic



1.2.1. 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 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 which 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. Part 1 will initially consider a series of 6 escalating dose levels (plus dose "level -1" if needed), with no

skipping, however, additional intermediate dose levels may be introduced based on review by the Safety Review Committee (SRC). DLTs occurring during Cycle 1 (e.g., 21 days) will be considered when implementing the dosing algorithm and decisions. The SRC will review and assess data collected during the study to guide dose escalation and the determination of the RP2D.

1.2.1.1. 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 before or while proceeding with further dose escalation.

1.2.1.2. 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.

1.2.1.3. Intra-subject Dose Escalation to the RP2D

Once the RP2D is identified, subjects assigned to a dose level lower than the RP2D in Part 1 may be considered for intra-subject dose escalation to the RP2D with Sponsor Medical Monitor or designee approval. To be considered for intra-subject 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.

1.2.2. 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 5mg/kg dose-break regimen throughout the protocol).
- Alternative dose for randomized cohorts A, B2, E2 is 4 mg/kg every 21 days.

Cohorts A-E may be opened for enrollment simultaneously or in a staggered manner at the discretion of the Sponsor, with exception of Cohorts B2 and E2, which will open if Cohorts

B or E, respectively, pass interim analysis for futility (i.e., if futility criteria are not met). Cohorts are defined as follows:

1) 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.
2) 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.
3) 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. if futility criteria are not met). Subjects will be randomized 1:1 to 1 of 2 dose levels.
4) 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.
5) 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.
6) Cohort E: Advanced NSCLC harboring actionable *EGFR* mutation, with high or intermediate cMET expression by IHC (3+ with tumor cell positivity of ≥25%).
7) 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 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 subjects in Cohort F after all necessary country and site level diagnostic approvals are in place. Cohort F is defined as follows:

1) 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.

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 subjects and all newly enrolled subjects to the dose regimen that appears to have the more favorable benefit:risk ratio, and no longer assign doses via randomization.

1.2.3. Study Drug Administration

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 ± 10 minutes or longer. If there are no infusion-associated reactions with the first dose, subsequent doses may be administered over 60 minutes ± 5 minutes. 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.

Study drug will administered via 10 mL single-use vials, 100 mg/vial (10.0 mg/mL concentration). Dosing of study drug will be on a mg/kg basis for subjects weighing up to 100 kg. Subjects > 100 kg will receive a fixed dose, matching that of subjects who weigh 100 kg. If during the study a subject's weight changes by ≥10% of the initial weight, their dose will be recalculated based on the updated weight.

Dose levels for Part 1: Dose Escalation are summarized below in Table 1a.

Table 1a: 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] mg/kg dose for subjects weight 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 pharmacokinetics (PK), safety, and preliminary anti-tumor activity data during the study, the Safety Review Committee (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 recommended by the SRC to assess the safety PK and preliminary anti-tumor activity data.
[3] If a dose de-escalation is needed in at dose level 1 based on the Bayesian Optimal Interval (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.

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.

Dose modification levels are provided in Table 1b. For dose reductions "1 dose level lower" does not include intermediate doses. (For example, to dose reduce by 1 dose level from 5 mg/kg, the new reduced dose would be 3.3 mg/kg).

Intermediate dose levels can be considered as an option for dose reduction only with the approval of the Sponsor Medical Monitor or designee.

Table 1b: 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**	**8.3***	**10.0***
1st dose modification (1 dose level lower)	0.3	1.0	*1.5*	2.0	*2.6*	3.3	*4.0*	*4.0*	*5.0*	5.0	6.7	8.3
2nd dose modification (2 dose levels lower)		0.3	1.0	*1.5*	2.0	*2.6*	3.3	3.3	4.0	*4.0*	5.0	6.7
3rd dose modification (3 dose levels lower)						2.0	*2.6*	*2.6*	*3.3*	3.3	*4.0*	5.0

*For dose levels not tested in the study by the time of Protocol version 6.0, the dose modification scheme may change depending on emerging clinical and pharmacokinetic data.
Note: Intermediate dose levels are in *italics*.

For subjects enrolled in Part 1 5.0 mg/kg dose-break regimen, it is recommended to follow Part 2 dose modification levels, shown below in Table 1c.

Table 1c: Part 2 Dose Modification Levels for MYTX-011

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

Note: Rechallenge of the same dose level may be considered for the first episode ocular AE with Gr.1/Gr.2 blurred vision and/or mild/moderate corneal surface changes. Do not rechallenge the same dose level if subject experiences ≥Gr.3 blurred vision or severe/very severe corneal surface changes or had a second episode of ocular AE at the same dose level. Reducing more than 3 dose levels lower would require approval from the Sponsor Medical Monitor.

Note: 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 resume treatment to maintain dose intensity. Please reach out the Sponsor Medical Monitor for questions related to dose-break regimen.

Note: Ongoing Part 1 subjects have the option to follow Part 2 dose modification guidance.

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. 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, the subject will be withdrawn from the study treatment, unless the subject is deriving clinical benefit form the treatment in the opinion of the Investigator and further dose modification is approved by the Sponsor Medical Monitor. Study treatment dose increases are not allowed in the study.

Subjects enrolled in Part 2 should follow the dose modification defined in Table 1c. Ongoing subjects in Part 1 enrolled in 5.0mg/kg with dose-break after every 2 cycles cohort and 4.0 mg/kg cohort may choose to follow the dose modification in Table 1c per the investigator's discretion.

Once enrolled in the study, MYTX-011 will be administered intravenously 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, or voluntary withdrawal of consent, or up to 2 years, 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.

Figure 2: Q3W Dosing Regimen

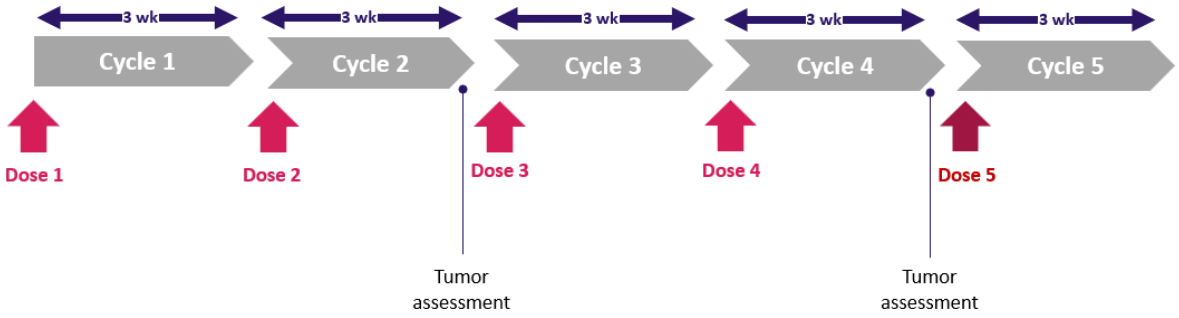
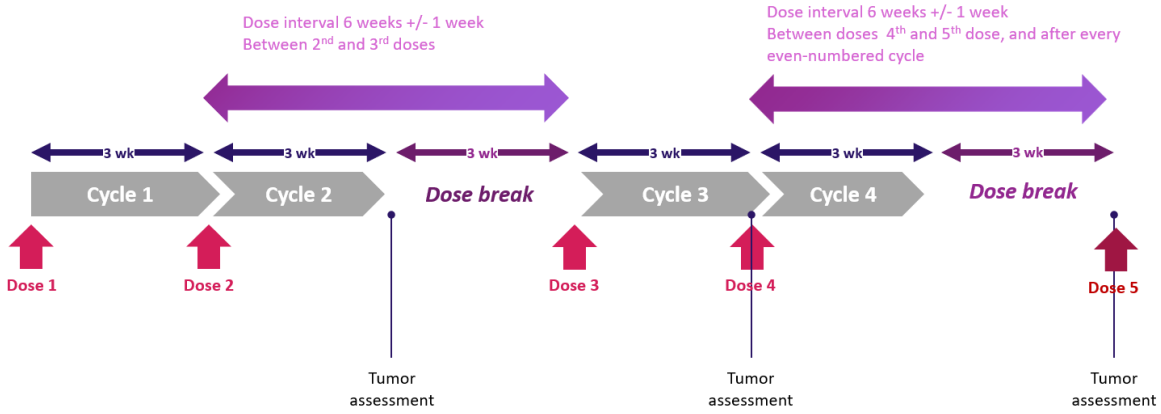


Figure 3: Dose-Break Regimen



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 of the protocol).

1.2.4. Study Duration

The study will run for approximately 4 years with the general timeline below:

- Screening: up to 28 days
- Treatment: up to 2 years
- Long-term follow-up: up to 2 years after End of Treatment (EOT)

1.2.5. Schedule of Assessments

For full detail of the Schedule of Assessments for this study please refer to Section 6.

1.3. Sample Size Determination

1.3.1. Part 1: Dose Escalation

The dose escalation process will be supported by a BOIN design with a target toxicity rate of 0.3. Subjects will be enrolled and treated in cohorts of size 3. DLTs occurring during Cycle 1 will be considered when implementing the dosing algorithm and decisions. 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 below in Table 2 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 until the maximum sample size of 36 is reached, at which point 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 2: Dose Escalation Rules

Number of Evaluable Subjects

Number of Subjects with DLTs	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

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.

No more than 10 subjects will be enrolled per enrichment cohort. Enrollment in the enrichment cohorts may continue throughout the conduct of the study until all slots are filled or it is determined 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, or low cMET expression as defined in Part 2) in enrichment cohorts or intermediate dose levels in which preliminary anti-tumor activity is observed.

1.3.2. Part 2: Dose Expansion

1.3.2.1. Cohort A

Cohort A will be monitored for efficacy using the Bayesian Optimal Phase II (BOP2) design (Zhou, Lee, and Yuan 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 the uninformative prior Beta (0.5, 0.5) distribution. For Cohort A, the reference rate is 15% and the assumed efficacy rate is 55%. Initially, 20 subjects will be randomized to 2 dose levels (10 subjects each).

The interim analysis for futility will be performed after 10 subjects per dose level are available for evaluation of response. 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 terminated if fewer than 2 responses are observed.

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 ORR is ≥40%, the study will have at least 80% power to reject the reference rate of 15%.

1.3.2.2. Cohorts B and B2

Cohort B will be monitored for efficacy using the BOP2 design (Zhou, Lee, and Yuan 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 activated (Figure 2). 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%, 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.

1.3.2.3. Cohort C

Cohort C will be assessed for efficacy using 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 the prior distribution for the efficacy response rate. For Cohort C, the reference response rate is assumed to be 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. Cohort C will be terminated for futility if 1 or fewer responses are observed among 15 evaluable subjects. Early efficacy may be declared if 7 or more responses are observed in 15 subjects.

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 with a response observed. The above decision rule assumes a 91% threshold for declaring efficacy at the final analysis, with 99% threshold for early stopping for efficacy and 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 for a prior on the efficacy

response rate. The study has 90% power to declare efficacy, with a Type I error rate controlled at 0.10 (simulations indicate that the type I error rate is approximately 5.6%).

1.3.2.4. Cohort D

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 the 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, an 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.

1.3.2.5. Cohorts E and E2

Cohort E will be monitored for efficacy using the BOP2 design (Zhou, Lee, and Yuan 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.

1.3.2.6. Cohort F

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.

2. TYPE OF PLANNED ANALYSIS

This SAP provides technical documentation and detailed specifications for the final analysis to be conducted at the end of the study. Per protocol, there are planned interim and primary analyses, that may warrant an addendum of this SAP.

Ongoing review will occur for each dosing cohort in Part 1 prior to dose escalation, determination of the MTD or RP2D, and initiation of enrollment into Part 2. These reviews will be conducted by the SRC and the Sponsor based on all data available at the time of the meetings.

Interim analyses for futility will be performed according to the individual cohort details described in section 1.3.2 of this SAP.

Primary efficacy analysis will be completed per each expansion cohort when all treated subjects 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.

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.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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.

3.1. Analysis Populations

3.1.1. Safety Analysis Population

All subjects who receive at least 1 dose of MYTX-011. All safety analyses will be performed using this analysis set.

3.1.2. 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 set.

3.1.3. Efficacy Analysis Population

All subjects who receive at least 1 dose of MYTX-011 (with a complete infusion on C1D1), have a measurable disease on the baseline tumor assessment, and either have at least one post-infusion disease assessment or have discontinued treatment for any reason prior to the first response assessment.

3.1.4. Response Evaluable Population

All subjects who receive at least 1 dose of MYTX-011 (with a complete infusion on C1D1), have a measurable disease on the baseline tumor assessment, and either have at least one post-infusion disease.

3.1.5. PK Analysis Population

All subjects who receive at least 1 dose of MYTX-011 and have at least one evaluable post-infusion PK sample. This set will be used for summaries of PK parameters.

3.1.6. Immunogenicity Analysis Population

All subjects who receive at least 1 dose of MYTX-011 and have at least one post-infusion immunogenicity sample. This set will be used for summaries of ADAs.

3.2. Subject Groups

Unless otherwise specified, data will be described and summarized by study part (i.e., Part 1: Dose Escalation and Part 2: Dose Expansion).

For Part 1, data will be presented by dose level, where subjects are summarized under the original dose level received, unless otherwise specified.

For Part 2, data will be summarized by the defined cohorts.

For analyses specifically regarding Cohort A, analysis will be conducted and data summarized by randomized groups, i.e. the RP2D and an alternative dose that was tested during Part 1 that is at or below the MTD (or the highest dose tested during dose escalation if the MTD is not determined).

Data will similarly be summarized in Cohort B2 as in Cohort A, with the added stratification by number of prior lines of therapy (≥3 previous lines of therapy or ≥2 previous lines of palliative systemic therapy versus < 3 previous lines of therapy or < 2 previous lines of palliative systemic therapy).

3.3. Missing Data

In general, missing data will not be imputed and will be treated as missing. Refer to Appendix 1 for details on partial date imputation.

3.4. Data Handling Conventions and Transformations

All analyses will be performed using SAS ® version 9.4 or higher. The following data conventions are applied to all data presentations and summaries:

- The following conversion factors will be used to convert days into weeks, months, or years: 1 week = 7 days, 1 month = 30.4375 days (i.e., 365.25 days/12 months), 1 year = 365.25 days.

- Height entries made in inches (in) are converted to centimeters (cm) using the following formula: height (cm) = height (in) * 2.54.

- Weight entries made in pounds (lbs) are converted to kilograms (kg) using the following formula: weight (kg) = weight (lbs) / 2.2046.

- Body mass index (BMI) is calculated using height (in) and weight (lbs) using the following formula: BMI (kg/m^2) = 703 x weight (lbs) / [height (in)]^2.

- Categorical variables (e.g., race) are summarized using counts and percentages. Percentages are calculated using the total subjects in the analysis set, unless otherwise noted.

- Continuous variables (e.g., age) are summarized using the following descriptive statistics: N (number of subjects in the analysis set), n (number of subjects with data), mean, standard deviation (SD), median, Q1 and Q3 (25^{th} and 75^{th} percentile), minimum, and maximum.

- When estimating proportions, the denominator to be used in the calculation will be the total number of subjects in the indicated analysis set for a specific dose level or cohort.

- Measurements from unscheduled visits will be included in listings, but not by nominal visit summary tables.

- Wherever possible, data will be decimally aligned. For continuous variables, all mean, median, Q1, and Q3 values are formatted to one more decimal place than the measured value. SD are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.

- Due to the small sample size and exploratory nature of the study, no inferential statistics will be provided.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be displayed as-is in listings but will be imputed as follows for summaries:

- If the recorded value is of the form "< X" (where x is considered the lower LOQ), then the value will be $X-(10)^{-n}$ where n is the number of decimals in the result "<X". For example, if the values are reported as < 50 and < 5.0, values of $50-(10)^{0}=49$ and $5.0-(10)^{-1}=4.9$, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, etc. a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- Similarly, results for the form "> X" will be imputed to $X + (10)^{-n}$ where n is the number of decimals in the result.

- The LOQ will be used to calculate descriptive statistics if the result is reported in the form of "≤ X" or "≥ X" (where x is considered the LOQ).

The TLFs document to this SAP provides the expected layout and titles of the TLFs. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP, nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation.

3.5. Data Coding Plan

Coding will be performed on an ongoing basis during the study within the electronic data capture (EDC) system. The following dictionaries will be used for the specified case report forms (CRFs):

Table 3: Data Coding Plan

CRF Page Form	Dictionary
Adverse Event Details	MedDRA v25.1
Medical History Details	MedDRA v25.1
Prior Cancer Surgery Details	MedDRA v25.1
Concomitant Medications Details	WHODrug Global B3 Sep2022
Prior Cancer Therapy Details	WHODrug Global B3 Sep2022

3.6. General Definitions

3.6.1. Definition of Study Day

Study day will be calculated as (date of clinical event – treatment start date) + 1 if the date of the event is on or after the treatment start date, and as (date of clinical event – treatment start date) if the date of the event is before the date of first dose.

The day of treatment start will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0, in alignment with international data standards for clinical trials. Unless specified otherwise, study day will be calculated only for complete dates. In subject listings, study day will only be displayed for complete dates even if date imputation is implemented.

3.6.2. Definition of Baseline and Change from Baseline

Baseline is defined as the last non-missing observation prior to the first dose of study drug. This includes any sample collected during screening as well as any time prior to receiving the first dose of the study drug.

The change from baseline is defined as the post-baseline observed value minus the baseline value for continuous data:

$$\text{Change from Baseline} = \text{Observed value} - \text{Baseline value}$$

The percent change from baseline is defined as change from baseline divided by baseline value:

Percent Change from Baseline = [(Observed value – Baseline value) / Baseline value]*100

The change from baseline will be analyzed descriptively for safety endpoints where applicable, and other endpoints or assessments, if specified. The percent change from baseline will be analyzed optionally, when specified.

4. SUBJECT DISPOSITION

4.1. Disposition of Subjects

A tabulation of subject disposition will be provided by dose level (Part 1) and by study cohort (Part 2) for all subjects.

Counts and percentages of subjects who are in each of the following disposition categories will be presented:

- Number screened (count only)
- Number enrolled (count only)
- Number included in each analysis population
- Number that discontinued treatment and reasons for treatment discontinuation
- Number that withdrew from study and reasons for withdrawal

A listing of disposition for all enrolled subjects will be included. The disposition listing will indicate whether a subject belongs to any of the analysis sets as well as all the disposition categories mentioned above with associated dates and study days where applicable. A separate listing of subject deaths will also be provided.

4.2. Extent of Exposure

The cumulative dose (mg) of study drug administered, the total number of doses of study drug administered, duration of exposure (weeks), dose intensity (mg/week and mg/kg/3-weeks) and relative dose intensity (%) will be summarized using descriptive statistics. Additionally, the number and percentage of dose delays, reductions, interruptions, and incomplete infusions will be summarized.

Duration of exposure to study drug will be defined as (last dose date – first dose date + 21) / 7, regardless of temporary interruptions in study drug administration.

Dose intensity is calculated as Cumulative Dose (mg) / Duration of Exposure (weeks) and 3 * Cumulative Dose Administered per kg / Duration of Exposure (weeks), respectively.

Relative dose intensity is calculated as Actual cumulative dose / Planned cumulative dose * 100.

4.3. Protocol Deviations

Protocol deviations will be documented by Clinical Research personnel in the clinical trial management system (CTMS). A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol.

Protocol deviations are classified as major or minor. Major protocol deviations may significantly impact the completeness, accuracy, and/or reliability of key study data or significantly affect a subject's rights, safety, efficacy, or well-being.

Counts and percentages of subjects with major protocol deviations by deviation category will be summarized by the specified subject groups. A listing of all protocol deviations will also be provided.

4.4. Inclusion/Exclusion Criteria

Subjects that met/did not meet inclusion/exclusion criteria (along with an identification of each criterion met for exclusion criteria and not met for inclusion criteria) will be listed for all screened subjects.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate for the safety population:

- Age
    - Age will be derived as (informed consent date – birth date +1)/365.25 rounded down to the nearest integer.
- Age categories (<65 vs ≥ 65 years of age)
- Race
- Ethnicity
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline body mass index (BMI) (kg/m2)
- Baseline Eastern Cooperative Oncology Group (ECOG) status
- Smoking History (Y/N)
- Baseline left ventricular ejection fraction (LVEF) (%)
- Baseline QTcF Interval (ms)
- Follow-up Time (days)
    - Last visit date or End of study date – Treatment start date + 1
- Number of prior lines of therapy
    - ≥3 previous lines of therapy or ≥2 previous lines of palliative systemic therapy
    - < 3 previous lines of therapy or < 2 previous lines of palliative systemic therapy

Demographic and baseline characteristics data will also be presented in by-subject listings.

5.2. Medical History

A complete medical history will be recorded at screening. Medical history will include any significant conditions, diseases, and prior surgical procedures, other than those related to the target disease, which stopped at or prior to screening. A summary of medical history will be presented by MedDRA system organ class (SOC) and MedDRA preferred term (PT).

Medical history will also be presented in by-subject listings.

5.3. Prior Cancer Therapies and Surgeries

Prior cancer therapies and surgeries will be recorded at screening and listed for the Safety Analysis Population.

Listings for prior radiation therapies will indicate the start and stop dates of therapy, the total dose administered (unit), the site of radiation (anatomical), and the purpose for the radiation therapy (curative or palliative).

Listings for prior cancer surgeries will indicate the surgical procedure performed, date of surgery, surgery type (e.g. biopsy, primary resection, metastatic site resection), surgery location (anatomical), and purpose of the surgery (curative or palliative).

Listings for prior systemic anti-cancer therapies will indicate name of therapy, start and stop dates of therapy, line of therapy, treatment context/setting (adjuvant, neoadjuvant, palliative, or maintenance), reason for discontinuation, and best response.

Summaries will include the number and proportion of subjects that had prior radiation therapies, surgeries, and systemic anti-cancer therapies. Summaries will also include counts and percentages for the number of prior regimens and reason for discontinuation as well as best response to the last regimen of prior systemic drug therapy.

5.4. Disease History

Disease history will be recorded at screening and listed for the Safety Analysis Population.

Summaries of disease history will include counts and percentages for the following: primary tumor location, T, N, M classification at initial diagnosis, molecular subtype, histological grade differentiation at initial diagnosis, NSCLC histology, current disease status, stage of disease at initial diagnosis, cMET amplification, and exon 14 skipping mutations.

Disease history will also be presented in by-subject listings.

6. 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. During the course of the study, any changes in concomitant medications should be recorded.

Medications will be coded to WHO Drug Dictionary anatomical therapeutic classes (ATC), ATC1 to ATC4, and WHO Drug Dictionary preferred name.

Medications are considered prior if they stopped prior to the treatment start date and concomitant if they were taken at any time on or after the treatment start date (i.e., including medications that started prior to treatment start date and were ongoing as well as those started after the treatment start date) and up to and including treatment end date. In case of partial or missing start and end date where it cannot be inferred with absolute certainty that a medication is prior; the medication will be considered concomitant.

Counts and percentages of subjects taking concomitant medications by ATC2 class and preferred term will be summarized based on the safety population. At each level of summary (ATC2, preferred term), multiple drug use will be counted only once per subject.

Concomitant medications will be presented in by-subject listings.

7. EFFICACY ANALYSES

Efficacy data will be presented by dose level (Part 1) or cohort (Part 2) for the response evaluable population.

Efficacy endpoints will be based on RECIST 1.1 criteria (Appendix 2). The primary analysis will be based on the Investigators assessment of response. Confirmation of Investigator-assessed ORR and DOR may be performed retrospectively through an Independent Review Committee.

7.1. Response Endpoints

Best overall response (BOR) is defined as the best result obtained among all tumor assessment visits from baseline until determination of progressive disease (PD) or the initiation of subsequent anti-cancer therapy. Confirmed response (CR) and partial response (PR) must be confirmed by 2 tumor imaging assessments conducted at least 4 weeks apart. Overall response of stable disease (SD) must meet the minimum criteria of occurring at least 5 weeks from start of study treatment.

7.1.1. Overall Response Rate

Overall response rate (ORR) is defined as the proportion of subjects with the BOR of CR or PR.

ORR=100×(Number of subjects with BOR of CR or PR)/(Total number of subjects (including those with a BOR of NE))

7.1.2. Disease Control Rate

Disease Control Rate (DCR) is defined as the proportion of subjects who achieve a BOR of CR, PR, or SD. SD must occur at least ≥ 5 weeks following the first dose of MYTX-011 administration.

DCR = 100 × (Number of subjects with BOR of CR, PR, or SD) / (Total number of subjects (including those with a BOR of NE))

7.1.3. Analysis of Response Endpoints

The ORR and DCR will be presented for each dose (Part 1) or cohort (Part 2) along with exact Clopper-Pearson 90% binomial confidence intervals (CIs). DCR will also be summarized by counts and percentages at 6, 12, and 18 weeks, with corresponding 90% CIs.

BOR will be summarized with counts and percentages of CR, PR, SD, PD, and not evaluable (NE). BOR will also be summarized by NSCLC histology in the following groups:

- All non-squamous (NSQ): adenocarcinoma, large cell carcinoma, sarcomatoid carcinoma
    - EGFR-mutated
    - EGFR-wild type
- Squamous (SQ): squamous cell carcinoma
- Other (adenosquamous, other)

Waterfall and spider plots will be used to display maximum decrease from baseline (minimum increase if no decline) in the sum of target lesions. Swimmer plots will be used to display the duration of treatment and tumor responses at each assessment. Waterfall, spider, and swimmer plots will be displayed at the subject level and will be summarized by NSCLC histology and cMET status in the following groups:

- NSQ EGFR-wild type, cMET high, intermediate, low
- NSQ EGFR-mutated, cMET high, intermediate
- SQ, cMET high, intermediate, low
- Other histology/cMET grouping

Target lesion response, non-target lesion response, occurrence of new lesions, and overall response data will be presented in a by-subject listing.

7.2. Time to Event Endpoints

7.2.1. Time to Response (for subjects who achieve CR or PR)

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 a BOR of CR or PR and summarized using descriptive statistics.

TTR = Date of response - Date of first dose

7.2.2. Duration of Response (for subjects who achieve CR or PR)

Duration of response (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 cut-off date, DOR will be censored at the date of last available tumor assessment.

DOR = min(Date of PD, Date of death) - Date of response + 1

7.2.3. Progression-free Survival

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 or the date of death (in the absence of progression) whichever comes first. For subjects who have not

progressed or died before the analysis cut-off date, PFS will be censored at the date of the last available tumor assessment.

PFS = min(Date of PD,Date of death) - Date of first dose + 1

7.2.4. Overall Survival

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 known alive date.

OS = Date of death - Date of first dose + 1

Table 4: Censoring Rules

Situation	Date of Progression or Censoring	Outcome
No Progressive Disease and no death - Study discontinuation happens before the first on-study radiographic assessment	Date of the first treatment dose.	Censored
No Progressive Disease and no death - Withdraws consent	Date of last adequate disease response assessment before withdrawal	Censored
No Progressive Disease and no death; new anti-cancer treatment not initiated	Date of last adequate disease response assessment	Censored
No Progressive Disease and no death; subsequent anti-cancer treatment is initiated	Date of last adequate disease response assessment before subsequent anti-cancer treatment	Censored
Progressive Disease or death documented after ≤1 missed disease assessment	Date of documented Progressive Disease or death	Progressed or Death
Progressive Disease or death documented after ≥2 missed disease assessments	Censored at last adequate disease response assessment prior to the >=2 missed disease response assessments	Censored

7.2.5. Analysis of Time-to-Event Endpoints

Time-to-event endpoints (DOR, OS, PFS) will be summarized with medians, ranges, and 90% CIs using Kaplan-Meier methods with the censoring rules defined above. These endpoints will also be summarized by NSCLC histology as described in the analysis of response endpoints.

Kaplan-Meier plots will be used to display events and censoring for PFS.

Time-to-event endpoints will be presented in a by-subject listing.

8. SAFETY ANALYSES

The primary objective of the study is to evaluate the safety and tolerability of MYTX-011. Safety data will be presented by dose level (Part 1) or cohort (Part 2) for the safety analysis population. No inferential statistics will be generated for safety summaries.

8.1. Adverse Events

8.1.1. Adverse Event Coding Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v25.1. System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

8.1.2. Adverse Event Severity

AEs are graded by the investigator using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/disabling), or Grade 5 (death) according to toxicity criteria specified in the study protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings and will be considered the least severe for the purposes of sorting for data presentation.

8.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator answers possibly related, probably related, or definitely related to the question pertaining to the causal relationship of any AE to the study drug. Events for which the investigator did not record relationship to study drug will be considered related to study drug. By-subject listings will present the relationship as it is recorded in the database.

8.1.4. Dose-Limiting Toxicity (DLT)

The DLT observation period is the time of 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 AE that occurred during the DLT observation period that meets the criteria listed in section 4.3 of the protocol.

8.1.5. Serious Adverse Events (SAEs)

Serious adverse events are those identified in the clinical database as serious.

8.1.6. Treatment-Emergent Adverse Events (TEAEs)

8.1.6.1. Definition of Treatment-Emergent

Any AE starting or worsening after first treatment of study drug and within 30 days of the last treatment of study drug will be considered a TEAE.

8.1.6.2. Incomplete Dates

If the date of onset is incomplete, then the month and year (or year alone if month is not recorded) of onset determine treatment-emergent as follows. The event is treatment-emergent if the month and year of onset (or year of onset) of the event is the same as or after the month and year (or year) of the first dose of study drug. AEs that had no recorded start date and the stop date is not before the first dose of the study drug will also be defined as a TEAE.

8.1.7. Adverse Events of Special Interest (AESIs)

Adverse events of special interest (AESI) include the following:

- Infusion related reactions (IRRs)
- Ocular AEs identified according to a pre-specified search list of MedDRA preferred terms.
- Clinically significant pulmonary AEs
- 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.

8.1.8. Ocular AE Grouping

AEs that fall under the SOC of Eye Disorders will be further grouped into categories to be used in summaries as follows:

Blepharitis	Blepharitis
Vision blurred	Blurred Vision
Visual acuity reduced	

Visual impairment	
Cataract	Cataract
Cataract nuclear	Cataract nuclear
Conjunctival haemorrhage	Conjunctival haemorrhage
Corneal cyst	Corneal epithelial microcysts
Corneal epithelial microcysts	
Corneal oedema	Corneal oedema
Diplopia	Diplopia
Dry eye	Dry eye
Eye pain	Eye Pain
Eye paraesthesia	Eye paresthesia
Floppy eyelid syndrome	Floppy eyelid syndrome
Keratitis	Keratitis
Punctate keratitis	
Cornea verticillata	Keratopathy
Corneal deposits	
Corneal disorder	
Corneal erosion	
Corneal lesion	
Corneal opacity	
Keratopathy	
Lacrimation increased	Lacrimation increased
Maculopathy	Maculopathy
Miosis	Miosis
Photophobia	Photophobia
Pterygium	Pterygium
Retinal drusen	Retinal drusen
Vitreous detachment	Vitreous detachment
Vitreous floaters	Vitreous floaters

8.1.9. Summaries of Adverse Events and Deaths

An overview of TEAEs will be provided including counts and percentages of subjects with an event for the following:

- Any TEAE
- Any study drug related TEAE
- Any Grade 3 or higher TEAE

- Any study drug related grade 3 or higher TEAE
- Any serious TEAE
- Any study drug related serious TEAE
- Any TEAE leading to drug discontinuation
- Any study drug related TEAE events leading to drug discontinuation
- Any TEAE leading to dose reduction
- Any study drug related TEAE leading to dose reduction
- Any TEAE leading to dose delay
- Any study drug related TEAE leading to dose delay
- Any serious TEAE leading to dose delay
- Any serious study drug related TEAE leading to dose delay
- Any TEAE leading to death
- Any DLT (Part 1 only)

Counts and percentages of subjects will also be presented by SOC and PT for the following categories: TEAEs, serious TEAEs, study drug related TEAEs, serious study drug related TEAEs. A separate group of summaries by SOC, PT, and maximum severity will also be presented for the above categories.

An overview of AESIs will be provided including counts and percentages of subjects with an event for the following:

- Any AESI
- Any related AESI
- Any Grade 3 or higher AESI
- Any Grade 3 or higher related AESI
- Any serious AESI
- Any related serious AESI

Counts and percentages of subjects will also be presented by SOC and PT for the above categories.

Summaries of AESI by SOC, PT, and maximum severity will also be presented for the following categories: AESI, related AESI, serious AESI, and related serious AESI.

At each level of summary, multiple occurrences of the same event will only be counted once per subject in each summary. For data presentation, SOC and PT will be ordered by decreasing total frequency, alphabetically in case of ties. For summaries by severity grade, the most severe event will be selected.

By-subject listings will also be provided for all TEAEs, serious TEAEs, TEAEs leading to death, TEAEs leading to study drug discontinuation, and DLTs.

8.2. Laboratory Evaluations

Laboratory assessments will be collected as specified in of the relevant assessment schedule in the protocol. The Investigator should assess out of range clinical laboratory values for clinical significance. Clinically significant abnormalities should be reported as an AE.

Summaries of chemistry and hematology data overall and by dose level (Part 1) or cohort (Part 2) data will be provided for the safety analysis population.

By-subject listings of laboratory results will be provided for each of the following laboratory categories: hematology, chemistry, coagulation, urinalysis, serology, and urine or serum pregnancy test.

8.2.1. Numeric Laboratory Values

All continuous laboratory parameters will be summarized descriptively by value at baseline and each post-baseline analysis visit, together with the corresponding change from baseline.

8.2.2. Graded Laboratory Values

Laboratory values will be graded per NCI-CTCAE Version 5.0 as applicable. Laboratory values considered to be normal by CTCAE criteria, meaning they do not qualify as Grade 1-4, will be assigned a severity grade of 0. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (i.e., increased, decreased) will be presented separately.

Shift tables demonstrating change from baseline to worst post-baseline grade will be displayed in cross-tabulations. For parameters that cannot be graded using the NCI-CTCAE, number and percentage of subjects with shifts from baseline normal to at least one result above normal and one result below normal during on-treatment period will be used for summaries.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will be shown in a data listing.

8.3. Vital Signs and Physical Examinations

Vital signs (temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation) will be measured prior to study drug administration and at time points noted in the relevant assessment schedule in the protocol. Height and weight will be recorded at timepoints noted in Schedule of Assessments of the protocol.

All vital signs parameters will be summarized descriptively by value at baseline and each post-baseline analysis visit, together with the corresponding change from baseline.

By-subject listings will also be provided for vital sign data.

8.4. 12-Lead Electrocardiogram (ECG) Results

Triplicate 12-lead ECGs will be read locally at screening and at time points noted in relevant sampling schedule in the protocol and will include measurement of heart rate and intervals for PR, QT, QRS, RR and QTc. The QTc will be calculated using the Fridericia's correction formula. The investigator can assess the ECG results for abnormalities of clinical significance. ECGs may be collected for retrospective independent review.

A shift table of overall ECG interpretation (Normal, Abnormal-Not Clinically Significant (NCS), and Abnormal-Clinically Significant (CS)) from baseline to each post-baseline visit and timepoint will be provided. If the ECG visits selected for summary is from a triplicate recording, the worst interpretation among the triplicate will be selected for summary. The order of worsening of ECG interpretation is: Normal, Abnormal-NCS, and Abnormal-CS.

QTcF severity will be classified according to the NCI-CTCAE criteria version 5.0. Grade as follows:

- Grade 0: QTcF < 450 msec
- Grade 1: 450 msec ≤ QTcF < 480 msec
- Grade 2: 480 msec ≤ QTcF < 500 msec
- Grade 3: 500 ≤ QTcF or 60 msec change from baseline

The average value of the triplicate within timepoints will be used for summaries. A shift table demonstrating change from baseline to worse post-baseline value grade will be provided.

ECG data will be presented in by-subject listings.

8.5. Ophthalmic Examinations

Ocular symptom assessment (e.g., blurred vision, redness, dryness or excessive watering, itching, burning sensation, light sensitivity, eye pain) will be performed by the Investigator prior to the administration of each dose of MYTX-011. Full ophthalmic examination with dilation by an ophthalmologist will be conducted at baseline (prior to first administration of study drug), at 1 year post Cycle 1 Day 1, at EOT visit, and as clinically indicated. The EOT ophthalmic evaluation may be performed 21 days after the last dose.

Full ophthalmic examination should include slit lamp examination, intraocular pressure measurement, corneal photography, visual acuity (VA), and dilated fundoscopic examination.

Partial ophthalmic examinations during the study consisting of slit lamp examination and corrected distance visual acuity (CDVA) will be conducted prior to Cycle 2, and then prior to dosing on an every other cycle basis (i.e., Cycles 4, 6, 8, etc.) until the EOT visit or TEAE resolution, and as clinically indicated. Subjects on a dose-break regimen complete a partial ophthalmic examination during each dose-break as indicated in the Part 2 scheduled of assessments in the protocol. A full ophthalmic examination may be done in place of the partial examinations if clinically indicated. 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).

Summariesof each ophthalmic parameter will be presented by laterality and visit for abnormal findings.

Listings of ophthalmic parameters will include visit, collection data/time and the assessment result.

9. PK ANALYSIS

Pharmacokinetic data will be summarized overall and by dose level and will include subjects in the PK Analysis Population. 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) will be performed.

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}, $AUC_{0\text{-}last}$ (ex. AUC_{504h}), volume of distribution (Vd), CL, and $t_{½}$.

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 (i.e. n=number of subjects, arithmetic mean, standard deviation, median, Q1, Q3, geometric mean).

10. IMMUNOGENICITY ANALYSIS

Immunogenicity data will be summarized overall and by dose level and will include subjects from the Immunogenicity Analysis Population.

ADAs will be assessed at multiple time points during the study. The number of screened positive subjects will be captured. A confirmation assessment will be conducted on subjects who screened positive. Titers will be reported for confirmed positive subjects. Results will be summarized for each test by visit. A listing of subjects showing screened positivity and confirmed positivity will be generated by visit and titers will be provided for the confirmed positive subjects. A descriptive analysis providing the transient vs persistent occurrence of confirmed ADA samples from an individual subject may be included based upon the overall incidence of confirmed positives. Transient will be defined as one or more confirmed positives followed by a sample determined negative. Similarly, persistent will be when a subject remains confirmed positive over multiple samples not followed by a negative sample. If a subject is found confirmed positive for the subject final sample taken. Transient vs persistent status will not be reported but can be considered when or if additional samples are taken.

The relationship between PK profile and titers by visit will be depicted using a scatter and line plot, with two y-axes (PK profile and titer) and visit as the x-axis.

11. 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 in the tumor and/or blood, and predictors of response or resistance to MYTX-011 and subject outcomes (e.g., anti-tumor activity) may be explored. This may include changes in biomarkers and predictors of response or resistance to MYTX-011 from baseline. Examples of biomarkers include but may not be limited to molecular, genetics, or protein analytes.

11.1. Immunohistochemistry (IHC)

A listing of IHC markers will be presented for the pre-dose visit.

11.2. Soluble cMET

Soluble cMET will be summarized and listed by visit. A spider plot by visit will be created.

11.3. Circulating Tumor DNA (ctDNA)

ctDNA will be summarized and listed by visit. A plot will also be used to depict the expression over time.

11.4. Exploratory PK Exposure Response Analyses

11.4.1. Exposure: Dose-Efficacy

The concentration/dose−efficacy relationship will be explored graphically, and if appropriate, evaluated by a mixed effects model in order 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.

11.4.2. 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.

11.4.3. Immunogenicity: Exposure and/or Adverse Event Relationship

The concentration/AE – immunogenicity relationship will be also explored graphically and tabulated to characterize any potential relationship between the observed changes in immunogenicity and serum concentration of MYTX-011 from screening to repeat dosing. 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.

12. REFERENCES

Lee JJ, Liu DD. A predictive probability design for Phase II cancer clinical trials. Clinical Trials 2008;5:93-106.

Yuan Y, Hess KR, Hilsenbeck SG, et al. Bayesian optimal interval design: a simple and well-performing design for Phase I oncology trials. Clin Cancer Res 2016;22(17):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.

13. SAP REVISIONS

Revision Date (dd month, yyyy)	Version	Section	Summary of Revision

14. APPENDIX 1: HANDLING OF PARTIAL DATES

An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. The data fields contain month, day, and year. A date is incomplete if at least one of these three fields is not known. In such case, incomplete dates will be imputed.

Adverse Events

The imputed adverse event dates will be used to determine the treatment-emergent adverse events (TEAEs). The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both Month and Day are missing and Year = Year of treatment start date, then set to treatment start date, as long as adverse event end date is not prior to treatment start date
- If both Month and Day are missing and Year ≠ Year of treatment start date, then set to January 1
- If Day is missing and Month and Year=Month and Year of treatment start date, then set to treatment start date, as long as adverse event end date is not prior to treatment start date
- If Day is missing and Month and Year ≠ Month and Year of treatment start date, then set to first of the month
- If start date is completely missing, set to treatment start date, as long as adverse event end date is not prior to treatment start date

If end date of an adverse event is partially missing, impute as follows:

- If both Month and Day are missing, then set up December 31
- If only Day is missing, then set to last day of the month
- If end date is completely missing, do not impute

Concomitant Medications

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both Month and Day are missing, then set to January 1
- If only Day is missing, then set to the first of the month

If end date of a medication is partially missing, impute as follows:

- If both Month and Day are missing, then set to December 31 or EOS, whichever is earlier.
- If only Day is missing, then set to last day of the month

If start date or end date of a medication is completely missing, do not impute.

15. APPENDIX 2: 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)

Non-measurable

- 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 non-measurable 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 2a.

Table 2a: 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 2b.

Table 2b: 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 2c.

Table 2c: 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
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

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
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.