STATISTICAL ANALYSIS PLAN
PHASE I

NCT02259231

DATE OF PLAN:

25-Oct-2019

BASED ON:

Protocol Version 5.0 (November 29, 2016)

STUDY DRUG:

RTA 408 (OMAVELOXOLONE)

PROTOCOL NUMBER:

408-C-1401

STUDY TITLE:

An Open-Label, Multicenter, Dose-Escalation, Phase 1b/2 Study of the Safety, Efficacy, Pharmacodynamics, and Pharmacokinetics of RTA 408 in Combination with Ipilimumab or Nivolumab in the Treatment of Patients with Unresectable or Metastatic Melanoma

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this statistical analysis plan.

Table 1: List of Abbreviations and Special Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical/Therapeutic/Chemical
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CM	concomitant medication
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
EAS	evaluable analysis set
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FDA	Food and Drug Administration (US)
GGT	gamma-glutamyl transferase
ICH	International Conference on Harmonization
iNOS	inducible nitric oxide synthase
Ipi	Ipilimumab
INR	International Normalized Ratio
LLD	lower limit of detection
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
Nivo	Nivolumab
ORR	overall response rate
PBMCs	peripheral blood mononuclear cells
PK	pharmacokinetic
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
PT	preferred term
PR	partial response
QTcF	Fridericia corrected QT interval

RECIST	Response Evaluation Criteria In Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SI	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
TBL	total bilirubin
ULN	upper limit of normal
WHO DD	World Health Organization Drug Dictionary
WOCBP	women of child bearing potential

2. REVISION HISTORY AND RELEVANT DCOUMENTS

Below lists revision summaries of this statistical analysis plan.

Version	Date	Document Owner	Revision Summary
1.0	DD-OCT-2019	Megan O'Grady	Initial version.

The analysis plan is based on the information from the following document:

Protocol Version 5.0, 29 November 2016.

3. PURPOSE OF THE ANALYSIS PLAN

The purpose of this statistical analysis plan (SAP) is to describe the rules and conventions to be used in the presentation and analysis of efficacy and safety data for supporting the completion of the clinical study report (CSR) of the Phase 1b portion of Protocol 408-C-1401 for the investigational product RTA 408. This SAP will be used to analyze the safety, tolerability, and efficacy data collected during Phase 1b portion of the study. Any pharmacokinetic and pharmacodynamic analyses not described in this plan will be described in a separate analysis plan.

Preliminary safety and efficacy results for the Phase 1b portion of the study will be performed as appropriate for reasons such as, but not limited to, regulatory interactions, scientific meetings or publications, and clinical development program support. The final analysis for the Phase 1b portion will be performed after database lock following the last enrolled patient having completed the study. The study database was locked on August 20, 2018. The SAP was finalized after database lock, but changes to the SAP after database lock did not meaningfully affect safety or efficacy results.

This plan may be amended for reasons such as, but not limited to, protocol amendments, interim analysis results, and internal data reviews that take place of the Phase 1b portion of the study. Exploratory analyses, which are not defined in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses, which are performed for the CSR, but not defined in this SAP, will be clearly identified and documented in the CSR as will any changes from the planned analyses as stated in the study protocol.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objective(s)

The objectives are as follows:

4.1.1. Primary Objectives

- To determine the safety of RTA 408 in combination with ipilimumab or nivolumab
- To evaluate the efficacy of the Phase 2 dose of RTA 408 in combination with nivolumab using overall response rate (ORR; complete plus partial responses)

4.1.2. Exploratory Objectives

- [redacted]
- [redacted]
- [redacted]

4.2. Study Endpoint(s)

4.2.1. Efficacy Endpoints

Overall response rate (ORR), complete response rate, partial response rate, and percent reduction in tumor biopsy inducible nitric oxide synthase (iNOS) expression.

4.2.2. Safety Endpoints

Results of physical examinations, laboratory test results, electrocardiograms (ECGs), vital sign measurements, concomitant medications, adverse events, and serious adverse events.

4.2.3. Pharmacokinetic Endpoints

Analysis of pharmacokinetic endpoints will be described in a separate document.

4.2.4. Pharmacodynamic Endpoints

Analysis of pharmacodynamic endpoints will be described in a separate document. All peripheral blood mononuclear cells (PBMC) biomarker and PBMC myeloid-derived suppressor cell (MDSC) analyses will be analyzed separately.

5. STUDY DESIGN

5.1. Overall Study Design

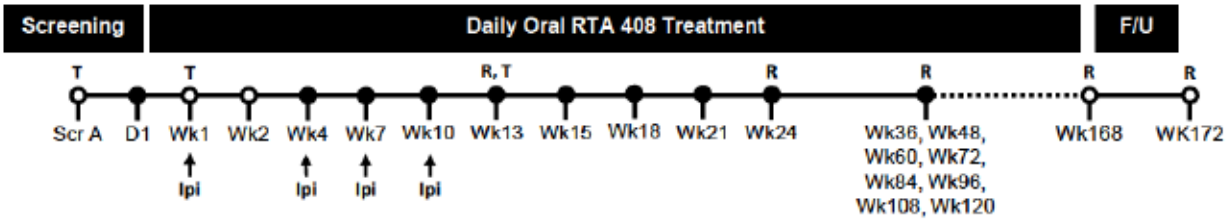
In this open-label, multicenter, dose-escalation, Phase 1b/2 study, patients with unresectable or metastatic melanoma who qualify will receive RTA 408 at the assigned dose level in combination with ipilimumab (3 mg/kg) or nivolumab (240 mg). The Phase 1b portion of the study will enroll cohorts of three to six patients at each dose level of RTA 408. Cohorts 1 to 3 will be used to assess combination therapy with ipilimumab separately from the combination with nivolumab. Cohorts 4 to 10 will only be used to assess combination therapy with nivolumab. A Phase 2 dose will be selected based on review of safety, efficacy, and pharmacodynamic data from the Phase 1b portion of the study.

5.2. Randomization and Dosing

The Phase 1b portion of the study will be open-label without randomization.

Patients will start receiving their assigned dose of RTA 408 orally on Day 1. Patients will receive RTA 408 monotherapy orally once daily during a run-in period for 1 week prior to initiation of combination therapy. For patients treated with ipilimumab (Cohorts 1 to 3 only), the run-in period will be followed by RTA 408 orally once daily in combination with ipilimumab administered at Weeks 1, 4, 7, and 10 (Figure 1). After Week 10, patients will receive maintenance treatment with RTA 408 alone once daily. For patients treated with nivolumab therapy, the run-in period will be followed by RTA 408 orally once daily in combination with nivolumab administered every two weeks as clinically indicated (Figure 2). After Week 24 (patients treated with RTA 408 + ipilimumab) or Week 25 (patients treated with RTA 408 + nivolumab), patients will return for study visits every 12 weeks. Each patient will continue at the assigned RTA 408 dose level until disease progression occurs, toxicity requiring discontinuation from study drug (i.e., RTA 408) is experienced, the patient has completed 168 weeks (patients treated with RTA 408 + ipilimumab) or 169 weeks (patients treated with RTA 408 + nivolumab) of treatment, the patient is discontinued from the study drug for another reason, the patient withdraws consent, or the patient is eligible for dose escalation (Section 7.4). Patients will return 4 weeks after RTA 408 treatment completion (or early termination) for a follow-up visit.

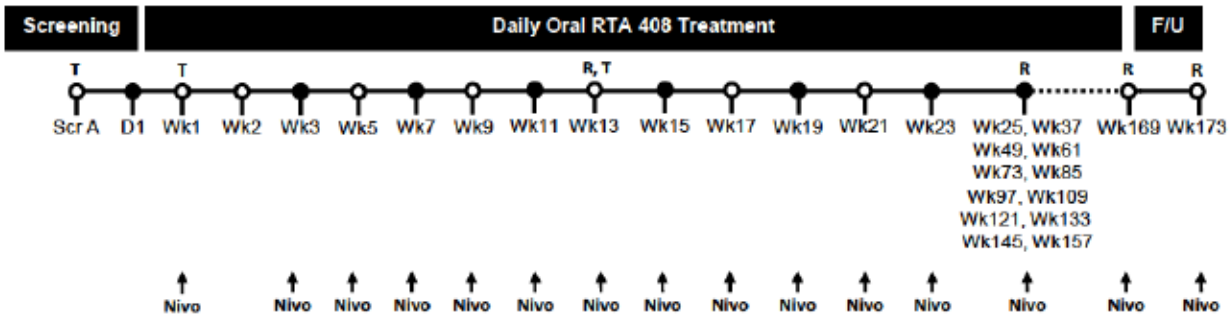
Figure 1: Schema for Study of RTA 408 in Combination with Ipilimumab in Patients with Metastatic Melanoma



● Visits at which drug is dispensed
Ipi Intravenous administration of Ipilimumab (3 mg/kg)
T Tumor biopsy
R Response (RECIST) assessed at Weeks 13, 24 and every 12 weeks thereafter, or at early termination

Abbreviations: D=day, F/U=follow up, Wk=week

Figure 2: Schema for Study of RTA 408 in Combination with Nivolumab in Patients with Metastatic Melanoma



● Visits at which drug is dispensed
Nivo Intravenous administration of Nivolumab (240 mg)
T Tumor biopsy
R Response (RECIST) assessed at Weeks 13 and every 12 weeks thereafter, or at early termination

Abbreviations: D=day, F/U=follow up, Wk=week

5.3. Assessments

Table 2 and Table 3 list the schedule of assessments for patients receiving RTA 408 and ipilimumab or nivolumab, respectively.

Table 2: Overall Schedule of Assessments for Patients Receiving RTA 408 + Ipilimumab

Visit Number	Visit 1 Screening	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Relative to RTA 408 and IPI		Start of RTA 408	Start of IPI				End of IPI					
Study Day/Week	Day -21 to -1[1]	Day 1[b]	Week 1 (Day 8) (±2 days)	Week 2 (Day 15) (±2 days)	Week 4 (Day 29) (±2 days)[c]	Week 7 (Day 50) (±3 days)	Week 10 (Day 71) (±3 days)	Week 13 (Day 92) (±3 days)	Week 15 (Day 106) (± 3 days)	Week 18 (Day 127) (±3 days)	Week 21 (Day 148) (± 3 days)	Week 24 (Day 169) (±3 days)
Informed consent	X											
Inclusion/Exclusion criteria	X	X										
Demographics and baseline disease characteristics	X											
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X											
ECOG performance status	X				X	X	X	X		X		X
Height	X											
Weight and BMI	X				X	X	X	X		X		X
Electrocardiogram	X	X			X	X	X	X		X		X
Vital sign measurements	X	X	X	X	X	X	X	X		X		X
Physical examination	X				X	X	X	X		X		X
Pregnancy test for WOCBP	X[c]	X[d]			X[d]	X[d]	X[d]	X[d]		X[d]		X[d]
Randomization		X										
Study drug dispensation		X			X	X	X	X	X	X	X	X
Study drug return/Pill count					X	X	X	X	X	X	X	X
Study drug administration		----------X[e]----------										
Ipilimumab administration			X		X	X	X					
Tumor biopsy	X		X[f]					X[g]				
Tumor burden evaluation[h]	X							X[i]				X[i]
Adverse event collection		X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X	X	X	X	X	X	X	X		X		X
Hematology	X	X	X	X	X	X	X	X		X		X
Coagulation	X	X	X	X	X	X	X	X		X		X
Virus serology	X											
PBMC biomarker analysis	X	X	X[j]					X[j]				
PBMC MDSC analysis	X	X	X[j]					X[j]				
PK analysis		X[k]	X[k]					X[k]				
Urinalysis and microscopy	X	X			X	X	X	X		X		X
End of study												

Visit Number	Visit 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23	Visit 24[a] (Early termination)	Visit 25 End of study/4-week follow-up
Relative to RTA 408 and IPI		End of RTA 408	4 weeks after end of RTA 408
Study Day/Week	Week 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156 (Day 253, 337, 421, 505, 589, 673, 757, 841, 925, 1009, 1093) (±3 days)	Week 168 (Day 1177) (±3 days)	Week 172 (Day 1205) (±3 days)
Informed consent			
Inclusion/Exclusion criteria			
Demographics and baseline disease characteristics			
Prior and concomitant medications	X	X	X
Medical history			
ECOG performance status	X	X	X
Height			
Weight and BMI	X	X	X
Electrocardiogram	X	X	X
Vital sign measurements	X	X	X
Physical examination	X	X	X
Pregnancy test for WOCBP	X[d]	X	X
Randomization			
Study drug dispensation	X		
Study drug return/Pill count	X	X	
Study drug administration	----------X----------		
Ipilimumab administration			
Tumor biopsy			
Tumor burden evaluation[a]	X[f]	X[f]	
Adverse event collection	X	X	X
Clinical chemistry	X	X	X
Hematology	X	X	X
Coagulation	X	X	X
Virus serology			
PBMC biomarker analysis			
PBMC MDSC analysis			
PK analysis			
Urinalysis and microscopy	X	X	X
End of study			X

[a] The Week 168 procedures should be completed for patients who terminate participation in the study early.

[b] Day 1 procedures should be performed within 1 hour prior to dose administration.

[c] WOCBP must have negative serum pregnancy test results to be eligible for the study.

[d] WOCBP must have negative urine pregnancy test results to continue in the study.

[e] Study drug should be administered in the presence of study staff in the clinic at Day 1, Week 1, and Week 13 after the predose PK blood collection. All other doses can be administered at home.

[f] Week 1 tumor biopsy must be collected prior to first administration of ipilimumab but may be collected 1 day prior to the scheduled visit. Week 1 tumor biopsy is optional for patients enrolled in the Phase 2 portion of the study.

Footnotes continued next page.

[g] The Week 13 tumor biopsy may be collected ±1 week from scheduled visit. Week 13 tumor biopsy is optional for patients enrolled in the Phase 2 portion of the study.

[h] Imaging studies for tumor size/burden evaluation as appropriate to assess disease burden or tumor size. The assessment done at the Screening Visit should be the same method used throughout the study. Spiral CT with contrast is appropriate unless otherwise specified by the principal investigator or designee. Assessments performed within 28 days preceding administration of the first dose may be used.

[i] Response (RECIST) assessment should include chest and abdomen and any area that is being monitored.

[j] Blood samples for PBMC (biomarker and MDSC) analysis should be taken prior to study drug administration.

[k] Blood samples for PK analysis should be taken prior to and 2 hours after dose administration.

[l] With approval of the Sponsor, or designee, screening may be increased to 28 days on an individual patient basis.

Abbreviations: BMI=body mass index, CT=computed tomography, ECOG=Eastern Cooperative Oncology Group, MDSC=myeloid-derived suppressor cell, PBMC=peripheral blood mononuclear cell, PK=pharmacokinetic, RECIST= Response Evaluation Criteria In Solid Tumours, WOCBP=women of childbearing potential.

Table 3: Overall Schedule of Assessments for Patients Receiving RTA 408 + Nivolumab

Visit Number		Visit 1 Screening	Visit 2 Random-ization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
Relative to RTA 408 and NIVO			Start of RTA 408	Start of NIVO													
Study Day/Week		Day -21 to -1[a]	Day 1[b]	Week 1 (Day 8) (±2 days)	Week 2 (Day 15) (±2 days)	Week 3 (Day 22) (±2 days)[c]	Week 5 (Day 36) (±3 days)	Week 7 (Day 50) (±3 days)	Week 9 (Day 64) (±3 days)	Week 11 (Day 78) (±3 days)	Week 13 (Day 92) (±3 days)	Week 15 (Day 106) (± 3 days)	Week 17 (Day 120) (±3 days)	Week 19 (Day 134) (± 3 days)	Week 21 (Day 148) (±3 days)	Week 23 (Day 162) (± 3 days)	Week 25 (Day 176) (± 3 days)
Informed consent		X															
Inclusion/Exclusion criteria		X	X														
Demographics and baseline disease characteristics		X															
Prior and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history		X															
ECOG performance status		X				X	X		X		X		X		X		X
Height		X															
Weight and BMI		X				X	X		X		X		X		X		X
Electrocardiogram		X	X			X	X		X		X		X		X		X
Vital sign measurements		X	X	X	X	X	X		X		X		X		X		X
Physical examination		X				X	X		X		X		X		X		X
Pregnancy test for WOCBP		X[c]	X[d]			X[d]	X[d]		X[d]		X[d]		X[d]		X[d]		X[d]
Randomization			X														
Study drug dispensation			X			X		X		X		X		X		X	
Study drug return/Pill count						X		X		X		X		X		X	
Study drug administration			X[e]														
Nivolumab administration				X		X	X	X	X	X	X	X	X	X	X	X	X
Tumor biopsy		X		X[f]							X[g]						
Tumor burden evaluation[h]		X									X[i]						X[i]
Adverse event collection			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry		X	X	X	X	X	X	X	X	X	X		X		X		X
Hematology		X	X	X	X	X	X		X		X		X		X		X
Coagulation		X	X	X	X	X	X		X		X		X		X		X
Virus serology		X															
PBMC biomarker analysis		X	X	X[j]							X[j]						
PBMC MDSC analysis		X	X	X[j]							X[j]						
PK analysis			X[k]	X[k]							X[k]						
Urinalysis and microscopy		X	X			X	X		X		X		X		X		X
End of study																	

Visit Number(s)	Visit 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27	Visit 28[a] (Early termination)	Visit 29 End of study/4-week follow-up
Relative to RTA 408 and Nivolumab		End of RTA 408	4 weeks after end of RTA 408
Study Day/Week	Week 37, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157 (Day 260, 344, 428, 512, 596, 680, 764, 848, 932, 1016, 1100) (±3 days)	Week 169 (Day 1184) (±3 days)	Week 173 (Day 1212) (±3 days)
Informed consent			
Inclusion/Exclusion criteria			
Demographics and baseline disease characteristics			
Prior and concomitant medications	X	X	X
Medical history			
ECOG performance status	X	X	X
Height			
Weight and BMI	X	X	X
Electrocardiogram	X	X	X
Vital sign measurements	X	X	X
Physical examination	X	X	X
Pregnancy test for WOCBP	X[d]	X	X
Randomization			
Study drug dispensation	X		
Study drug return/Pill count	X	X	
Study drug administration	----------X----------		
Nivolumab administration[m]	X	X	X
Tumor biopsy			
Tumor burden evaluation[h]	X[i]	X[i]	
Adverse event collection	X	X	X
Clinical chemistry	X	X	X
Hematology	X	X	X
Coagulation	X	X	X
Virus serology			
PBMC biomarker analysis			
PBMC MDSC analysis			
PK analysis			
Urinalysis and microscopy	X	X	X
End of study			X

[a] The Week 169 procedures should be completed for patients who terminate participation in the study early.
[b] Day 1 procedures should be performed within 1 hour prior to dose administration.
[c] WOCBP must have negative serum pregnancy test results to be eligible for the study.
[d] WOCBP must have negative urine pregnancy test results to continue in the study.
Footnotes continue next page.
[e] Study drug should be administered in the presence of study staff in the clinic at Day 1, Week 1, and Week 13 after the predose PK blood collection. All other doses can be administered at home.
[f] Week 1 tumor biopsy must be collected prior to first administration of nivolumab but may be collected 1 day prior to the scheduled visit. Week 1 tumor biopsy is optional for patients enrolled in the Phase 2 portion of the study.
[g] The Week 13 tumor biopsy may be collected ±1 week from scheduled visit. Week 13 tumor biopsy is optional for patients enrolled in the Phase 2 portion of the study.
[h] Imaging studies for tumor size/burden evaluation as appropriate to assess disease burden or tumor size. The assessment done at the Screening Visit should be the same method used throughout the study. Spiral CT with contrast is appropriate unless otherwise specified by the principal investigator or designee. Assessments performed within 28 days preceding administration of the first dose may be used.
[i] Response (RECIST) assessment should include chest and abdomen and any area that is being monitored.
[j] Blood samples for PBMC (biomarker and MDSC) analysis should be taken prior to study drug administration.
[k] Blood samples for PK analysis should be taken prior to and 2 hours after dose administration.
[l] With approval of the Sponsor, or designee, screening may be increased to 28 days on an individual patient basis.
[m] Nivolumab should continue to be administered every 2 weeks according to the package insert.

Abbreviations: BMI=body mass index, CT=computed tomography, ECOG=Eastern Cooperative Oncology Group, MDSC=myeloid-derived suppressor cell, PBMC=peripheral blood mononuclear cell, PK=pharmacokinetic, RECIST= Response Evaluation Criteria In Solid Tumours, WOCBP=women of childbearing potential.

5.3.1. Efficacy Measurement and Variables

Overall response rate (ORR), defined as the proportion of patients with complete or partial tumor size reduction according to RECIST 1.1 criteria, will be summarized. Stable disease is not a component of ORR.

Efficacy variables are tumor response rates (overall, complete, and partial) according to RECIST 1.1 criteria, and percent reduction in tumor biopsy iNOS expression.

5.3.2. Pharmacodynamic Measurement and Variables

The pharmacodynamic variables include tumor biopsy biomarkers and PBMC assessments. Augmented immune-mediated effects with combined RTA 408 and ipilimumab or RTA 408 and nivolumab treatment, as assessed by tumor biopsy and PBMC parameters, are expected to correlate with decreased iNOS expression in tumors.

5.3.3. Safety Measurements and Variables

The safety variables include ECGs, vital sign measurements, results of physical examinations, laboratory test results (clinical chemistry, hematology, and urinalysis and microscopy), concomitant medications, adverse events (AEs), and serious adverse events (SAEs).

5.3.4. Pharmacokinetics Measurements and Variables

Pharmacokinetic (PK) samples will be collected on Day 1, Day 8 (±2 days), and Day 92 (±3 days). Samples will be collected prior to study drug dosing (pre-dose), and 2 hours after dose administration. The PK variables include RTA 408 plasma concentration-time data, and estimated PK parameters.

6. SAMPLE SIZE AND POWER

The sample size (n = up to 102) for this study was selected to serve 3 purposes: (1) assess the safety of RTA 408 combined with ipilimumab and RTA 408 combined with nivolumab, (2) select Phase 2 dose based on review of safety, efficacy, and pharmacodynamic data, and (3) assess ORR for iNOS-positive melanoma patients in combination with nivolumab at the selected Phase 2 dose of RTA 408. This sample size permits enrollment of 57 to 78 patients in dose-escalation cohorts (Phase 1b) and 24 to 27 patients in the expansion cohort (Phase 2).

The Phase 1b portion of the study allows for assessment of safety and selection of a Phase 2 dose. The sample size for reviewing safety of RTA 408 combined with an additional therapy was selected based on a traditional 3+3 design for a dose-escalation study with up to 6 patients on each combination therapy. In addition to the safety profile, selection of an appropriate Phase 2 dose is based on changes observed in iNOS expression measured in tumor biopsies at baseline and after 1 week of monotherapy of RTA 408 (i.e., prior to starting combination therapy). Evaluation of the descriptive summaries (including 95% confidence intervals) for change from baseline in percentage of iNOS-positive tumor cells from the Phase 1b dose-escalation portion of the study will provide information for selecting the Phase 2 expansion dose.

7. GENERAL CONSIDERATIONS

The analysis sets, as defined in Section 8, will be used for efficacy, safety, and tolerability. Patient listings of all analysis data that support summary tables and/or figures will be provided along with their source data from the electronic case report forms (eCRFs). Measurements from patients excluded from the pre-defined analysis sets or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise but will be included in the patient listings. Missing data will not be imputed, unless otherwise specified. In general, patient listings will be sorted by patient number and assessment date (time and parameter, as applicable).

Unless otherwise specified, descriptive statistics for continuous variables will include the number of patients with data (N), mean, standard deviation (SD), median, minimum, and maximum. For all analyses except clinical chemistry, hematology, and urinalysis data, the same number of decimal places as in the observed value will be presented when reporting minimum and maximum; 1 more decimal place than in the observed value will be presented when reporting mean and median; and 2 more decimal places than in the observed value will be presented when reporting SD. Clinical chemistry, hematology, and urinalysis data must be converted to conventional units before any analyses are performed. For clinical chemistry, hematology, and urinalysis data, the same number of decimal places as in the value in SI units will be presented when reporting minimum and maximum; 1 more decimal place than the value in SI units will be presented when reporting mean and median; and 2 more decimal places than the value in SI units will be presented when reporting SD.

Clinical chemistry, hematology, and urinalysis data must be converted to International System of Units (SI units) before any analyses are performed.

All categorical/qualitative data will be presented using frequency counts and percentages. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100 will be presented as 100% and no percentages will be presented for zero frequencies. Where individual variable values are missing, categorical data will be summarized based on reduced denominators (i.e., only patients with available data will be included in the denominators). For summaries of AEs and concomitant medications (CM), the percentages will be based on the number of patients who received study drug.

The following data collected from patients enrolled in the RTA 408 + ipilimumab cohorts will be summarized separately from data collected from patients enrolled in the RTA 408 + nivolumab cohorts:

- Demographics and Baseline Characteristics
- Efficacy summaries (Section 11)
- Treatment-emergent adverse events (Section 12)

- Laboratory values of interest, including:
  - Alanine transaminase (ALT)
  - Aspartate transaminase (AST)
  - Alkaline phosphatase
  - Ferritin
  - Gamma-glutamyl transferase (GGT)
  - Total bilirubin

Results of statistical analyses will be reported using summary tables, listings, and figures (TLFs). The ICH numbering convention will be used for all TLFs. The following conventions will be followed:

- Unless otherwise noted, all statistical testing will be two-sided and will be performed at the 0.05 significance level
- Tests will be declared statistically significant if the calculated p-value is <0.05

All analyses and summaries will be produced using SAS® version 9.3 (or higher).

7.1. Derived Variables

7.1.1. Age

Age (years) will be calculated as the number of years between date of birth and date of informed consent, expressed as an integer.

7.1.2. Study Day

Study Day will follow the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standard and is defined as follows:

- assessment date – date of first study drug dosing + 1, where the assessment date is on or after the date of first study drug dosing
- assessment date – date of first study drug dosing, where the assessment date is before the date of first study drug dosing

7.1.3. Overall Response Rate

Best overall response rate (ORR) is defined as the proportion of evaluable patients with the best reported tumor response of complete response (CR) or partial response (PR) according to RECIST version 1.1 criteria. The first occurrence of a response is considered an unconfirmed

response. A CR or PR which persists to the next tumor burden assessment is then considered a confirmed response.

7.1.4. Electrocardiogram Fridericia Corrected QT Interval

Electrocardiogram intervals, including Fridericia corrected QT interval (QTcF), will be assessed locally at each site. In the event that QTcF interval is not provided, it can be calculated from QT and RR intervals using the following formula:

- $QTcF = QT/\sqrt[3]{RR}$

Where RR = 60 / (Heart Rate).

7.1.5. Total Number of Doses

Total number of doses received will be calculated from information on the eCRF of Study Drug Return and Study Drug Dispensation, as the total number of doses dispensed – total number of doses returned. The total dose (mg) received can be calculated in similar way. The average daily dose (mg) will be calculated as total dose (mg) / (total number of days of exposure – the withdrawal periods). Study drug compliance (%) will be calculated as 100 × total number of doses received / total number of doses dispensed.

7.2. Baseline Values

Baseline values are defined as the last non-missing assessment prior to the first study drug dosing, unless otherwise specified below.

7.2.1. Height

Baseline height is the last non-missing assessment prior to the first study drug dosing regardless of study day prior to date of first dose.

7.3. Analysis Windows

Because clinical visits may occur outside protocol specified windows, instead of relying solely on visit labels in the clinical database, analysis visits and their windows are defined using Study Day (Section 7.1.2). For the purposes of data analysis and summary, on-treatment assessments and/or measurements will be flagged based on the collection date/time that is closest to the protocol scheduled time point (or target Study Day). Off-treatment assessments will be flagged based on days since last dose of RTA 408. Analysis visit windows are presented in Table 4 by type of assessments and/or measurements.

Table 4: Analysis Visit Windows for Patients Receiving RTA 408 + Ipilimumab

Protocol Scheduled Time Point	Target Study Day	Analysis Visit Windows
Screening	-1	All pre-dose value
Day 1	1	1
Week 1	8	2 to 11
Week 2	15	12 to 22
Week 4	29	23 to 35
Week 7	50	36 to 57
Week 10	71	58 to 78
Week 13	92	79 to 99
Week 15	106	100 to 113
Week 18	127	114 to 134
Week 21	148	135 to 155
Week 24	169	156 to 176
Week 36	253	177 to 260
Week 48	337	261 to 343
Week 60	421	344 to 428
Week 72	505	429 to 512
Week 84	589	513 to 596
Week 96	673	597 to 680
Week 108	757	681 to 764
Week 120	841	765 to 848
Week 132	925	849 to 934
Week 144	1009	935 to 1016
Week 156	1093	1017 to 1100
Week 168	1177	1101 to 1184
Week 172	1205	> 1185
Follow-up	28 days after last dose	14 ≤ days after last dose ≤ 35

Table 5: Analysis Visit Windows for Patients Receiving RTA 408 + Nivolumab

Protocol Scheduled Time Point	Target Study Day	Analysis Visit Windows
Screening	Study Day	All pre-dose values
Day 1	1	1
Week 1	8	2 to 11
Week 2	15	12 to 18
Week 3	22	19 to 28
Week 5	36	29 to 42
Week 7	50	43 to 56
Week 9	64	57 to 70
Week 11	78	71 to 84
Week 13	92	85 to 99
Week 15	106	100 to 113
Week 17	120	114 to 126
Week 19	134	127 to 140
Week 21	148	141 to 154
Week 23	162	155 to 168
Week 25	176	169 to 182
Week 37	260	183 to 266
Week 49	344	267 to 350
Week 61	428	351 to 434
Week 73	512	435 to 518
Week 85	596	519 to 602
Week 97	680	603 to 686
Week 109	764	687 to 770
Week 121	848	771 to 854
Week 133	932	855 to 938
Week 145	1016	939 to 1022
Week 157	1100	1023 to 1106
Week 169	1184	1107 to 1190
Week 173	1212	>1190
Follow-up	28 days after last dose	14 ≤ Days after last dose ≤ 35

Note: Study Day is relative to the first date of study drug administration (Study Day 1). Protocol Scheduled Time Point = Analysis Visit (AVISIT), after applying the analysis windows described above. The Week 172 (RTA 408 + ipilimumab) and Week 173 (RTA 408 + nivolumab) visits have the additional restriction that assessments must be collected after final dose of RTA 408 during the 4-week follow-up visit. For patients who terminated treatment prior to Week 168 (RTA 408 + ipilimumab) or Week 169 (RTA 408 + nivolumab), use Week 172 (RTA 408 + ipilimumab) or Week 173 (RTA 408 + nivolumab) as follow-up visit, otherwise Week 172 (RTA 408 + ipilimumab) or Week 173 (RTA 408 + nivolumab).

The follow-up is based on days since last dose. If more than one assessment exists during the follow-up after last dose, the one closest to 28 days following the date of the last study drug administration is used for analysis and summary.

If more than one measurement is collected equidistant to the target Study Day and on different collection date, the first measurement will be flagged for analysis and summary. If more than one measurement is closest to the target Study Day and collected on the same date, the average of those measurements will be used for analysis and summary. If multiple nominal study visit assessments fall within the same analysis visit, the assessment closest to the target visit day specified in the protocol study procedures will be used.

7.4. Incomplete Diagnosis or Treatment Date

Incomplete diagnosis and treatment dates are imputed as follows:

- If day is missing, day will be set to 15th of the month
- If month and day are missing, month and day will be set to July 1st
- If year, month, and day are missing, date will be set to missing

If treatment dates occur after study completion or termination, then the treatment dates are imputed as the date of study completion or termination.

8. ANALYSIS SETS

8.1. Safety Analysis Set

Safety analysis set is defined as all patients who received any amount of study drug. The safety analysis set will be used for evaluation of safety variables.

8.2. Evaluable Analysis Set

Evaluable analysis set (EAS) is defined as all enrolled patients having received at least two weeks of study drug before disease progression and excludes patients who discontinued from study for reasons other than an adverse event prior to first tumor restaging. The EAS will be used for evaluation of all efficacy parameters.

8.3. Pharmacokinetics Analysis Set

Pharmacokinetics (PK) analysis set is defined as all patients who received any amount of study drug and had at least one RTA 408 plasma concentration measurement. The PK analysis set will be used for evaluation of pharmacokinetics.

9. STUDY POPULATION

9.1. Patient Disposition

Enrollment and disposition will be summarized. A patient will be defined as enrolled if they sign the informed consent form. The patient disposition summary will include the number of patients who:

- enrolled in the study
- are in the safety analysis set
- are in the evaluable analysis set
- are in the pharmacokinetics analysis set
- completed the Week 13 treatment period (RTA 408 + ipilimumab patients)
- completed the Week 13 treatment period (RTA 408 + nivolumab patients)
- completed the Week 24 treatment period (RTA 408 + ipilimumab patients)
- completed the Week 25 treatment period (RTA 408 + nivolumab patients)
- completed the Week 36 treatment period (RTA 408 + ipilimumab patients)
- completed the Week 37 treatment period (RTA 408 + nivolumab patients)
- completed the Week 48 treatment period (RTA 408 + ipilimumab patients)
- completed the Week 49 treatment period (RTA 408 + nivolumab patients)
- completed the Week 60 treatment period (RTA 408 + ipilimumab patients)
- completed the Week 61 treatment period (RTA 408 + nivolumab patients)
- permanently discontinued from the study
- completed the study

The disposition summary will also include the primary reason for withdrawal from the study. Patients who received study drug for entire studied period are defined as those who received study drug through Week 108 in the RTA 408 + Ipilimumab cohorts or received study drug through Week 109 in the RTA 408 + Nivolumab cohorts. A listing of disposition will be provided for all enrolled patients.

9.2. Protocol Deviations

Where available, protocol deviations in the Safety Analysis Set will be listed by deviation category (e.g., eligibility criteria, out of window visit, serious adverse event (SAE) reporting, study procedures, treatment procedures). All deviations, including major protocol deviations that could potentially affect the efficacy or safety conclusions of the study, will be identified prior to database lock. Protocol deviations will be listed in a data listing and summarized by deviation category.

9.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Safety Analysis Set. Demographic characteristics will include age, gender, race, and ethnicity. The baseline characteristics include: baseline weight, height, and body mass index (BMI), iNOS staining (%); ECOG performance status, Melanoma related information—melanoma history, current disease stage, and prior checkpoint inhibitor therapy use. Demographics and Baseline Characteristics will be listed.

9.4. Medical History

Medical history will be mapped to preferred terms (PT) and system organ classes (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA®) Dictionary (version 14.1). Medical history items will be summarized by MedDRA SOC and PT and patient listing will be provided for the Safety Analysis Set.

10. STUDY DRUG AND OTHER MEDICATIONS

10.1. Prior and Concomitant Medications

Prior and concomitant medication verbatim terms on eCRFs will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and preferred names using the World Health Organization Drug Dictionary (WHO DD) Enhanced version, September 2011, B2 format.

A prior medication is any medication that is taken and stopped prior to the first dose of study drug. Medications that are stopped on the date of first study drug administration are prior medications. A concomitant medication is any medication taken at the time of first study treatment or a medication that was started after the start of study drug dosing. Specifically, concomitant medications are medications that are continued from screening and continued after the first study drug dosing, or that have start dates or stop dates within the treatment period. Prior and concomitant medications will be summarized for each treatment group by WHO DD ATC class and preferred name. These summaries will present the number and percentage of patients using each medication. Patients may have more than one medication per ATC class and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class.

In addition, patients who take excluded medications (defined in the Protocol Section 9.2.1) during the study will be listed.

10.2. Duration of Study Treatment and Exposure to Study Drug

The duration of study drug exposure is defined as the number of days on treatment from the first dose of study drug until the last dose of study drug (last dose – first dose + 1). Study drug exposure will be summarized by descriptive statistics. Summaries will include the number of doses received (or dispensed), total dose (mg) received (or dispensed), average daily dose (mg), study drug compliance, and duration (days) of exposure during the study treatment period.

Total number of doses dispensed and total dose (mg) dispensed will be calculated from total number of kits (bottles) recorded on the Study Drug Dispensation eCRF.

The Safety Analysis Set is used to summarize the duration of study treatment and exposure to study drug.

Patients will return all unused pills at each visit and will be dispensed a new bottle of pills to take until the next visit. Compliance will be measured by counting pills to determine the number of missed doses from one visit to the next. To be considered compliant with study drug, patients can miss no more than 25% of the total planned doses during the study. Patients who exceed the number of allowed missed doses will be considered noncompliant with dosing. Patients will not be discontinued from the study for treatment noncompliance, but protocol deviations should be recorded for dosing noncompliance.

All study drug dispense, and accountability data will be listed in patient listing.

10.3. Combination Therapy Exposure

Patients enrolled in the study will administer RTA 408 in combination with either ipilimumab (Ipi) or nivolumab (Nivo), according to the package insert (Ipi x 4 doses or Nivo q2 weeks (and 240 mg after 2017)):

Ipilimumab 3 mg/kg will be administered to the patient intravenously

Nivolumab 240 mg will be administered to the patient intravenously

The duration of combination therapy exposure is defined as the number of days from the first administration until the last administration (last administration – first administration + 1). Combination therapy exposure will be summarized by descriptive statistics. Summaries will include the number of doses administered dose (mg).

The package insert for Ipi indicates four doses should be administered. For patients receiving Ipi, the proportion of patients receiving all four of the expected doses will be summarized.

The package insert for Nivo indicates doses should be administered every two weeks, unless a delay is necessary (e.g., skin related AE, immune related AE, lab abnormality). For patients receiving Nivo, the proportion of patients with a delayed treatment will be tabulated.

All combination therapy administration data will be listed in patient listing.

11. EFFICACY ANALYSES

11.1. Primary Efficacy Analysis

With only 3 to 6 patients per dose, the Phase 1b portion of the study is not powered for efficacy. The phase 1b portion of the study is intended to identify an optimal dose for phase 2. Complete and partial tumor responses will be evaluated by radiographic assessment using the standardized response criteria developed by the RECIST (Response Evaluation Criteria In Solid Tumours) Working Group, version 1.1. Overall response rate (ORR), defined in Section 5.1.3, as well as the number and proportion of partial and complete responses, will be summarized descriptively within each dose and overall. ORR will be summarized as confirmed, unconfirmed, and confirmed+unconfirmed. Summaries of ORR, CR and PR will be tabulated by dose and for all doses within each combination with RTA 408 (i.e., ipilimumab or nivolumab).

11.1.1. Reporting Results

Tables will summarize the number and percent of patients with complete response, partial response, and disease progression by:

- Overall (all patients in evaluable analysis set)
- Patients with RTA 408 + ipilimumab treatment (all RTA 408 doses in evaluable analysis set)
- Patients with RTA 408 + nivolumab treatment (all RTA 408 doses in evaluable analysis set)
- Patients with RTA 408 + ipilimumab treatment (by RTA 408 dose in evaluable analysis set)
- Patients with RTA 408 + nivolumab treatment (by RTA 408 dose in evaluable analysis set)
- By prior therapy within RTA 408 + ipilimumab patients: CI-naïve, CI-refractory, PD-1/PD-L1 refractory in evaluable analysis set
- By prior therapy within RTA 408 + nivolumab patients: CI-naïve, CI-refractory, PD-1/PD-L1 refractory in evaluable analysis set

11.2. Additional Efficacy Analyses

11.2.1. Time to Response and Duration of Response

A listing of patients having reported a PR during the study will be provided which includes patient ID; study treatment and combination therapy; study week (day) of PR; study week (day) of CR; and duration of response (weeks).

The listing should be summarized by:

- Patients with RTA 408 + ipilimumab treatment (by RTA 408 dose in evaluable analysis set)
- Patients with RTA 408 + nivolumab treatment (by RTA 408 dose in evaluable analysis set)

11.2.2. Percent Change in iNOS

A listing of all patients will include iNOS expression at baseline, Day 8, and Week 13. The listing should be tabulated by RTA 408 dose group and cohort (RTA 408 + Ipilimumab or RTA 408 + Nivolumab). The analysis visits used for the Overall summaries are baseline, Day 8, and Week 13 analysis visits pooled. The listing should be summarized by:

- Overall (all patients in evaluable analysis set)
- Patients with RTA 408 + ipilimumab treatment (all RTA 408 doses in evaluable analysis set)
- Patients with RTA 408 + nivolumab treatment (all RTA 408 doses in evaluable analysis set)

11.2.3. ECOG Performance Status

The ECOG performance status will be summarized using descriptive statistics, including 95% CI for change from baseline. The tables and listings should be summarized by:

- Patients with RTA 408 + ipilimumab treatment (all RTA 408 doses in evaluable analysis set)
- Patients with RTA 408 + nivolumab treatment (all RTA 408 doses in evaluable analysis set)

11.3. Sensitivity Analyses

There is no pre-planned sensitivity analysis for the primary efficacy variable for the Phase 1b portion of the study.

11.4. Subgroups Analyses of Efficacy

The efficacy variables will be summarized using descriptive statistics, including 95% CI for change from baseline, will be reported for each subgroup of interest listed below:

- Checkpoint inhibitor naïve, prior checkpoint inhibitor treatment
  - A subject is considered 'CI-Naive' if he or she has no prior history of treatment with Ipilimumab, Nivolumab, or Pembrolizumab.

- A subject is considered 'PD-1/PD-L1 Refractory' if he or she has ever been treated with Nivolumab or Pembrolizumab.

- A subject is considered 'CI-Refractory' if he or she has ever been treated with Ipilimumab, Nivolumab, or Pembrolizumab.

For the Phase 1b portion of the study, no statistical testing will be performed for subgroups.

12. SAFETY ANALYSES

Safety and tolerability are evaluated by AEs, SAEs, clinical laboratory test results, body weight, vital signs, 12-lead ECG findings, and physical examination. All analyses of the safety data will be performed using the safety analysis set. Descriptive statistics (described in Section 7) will be presented by treatment group assignment in the safety analysis set.

Tables will summarize the safety results by:

- Patients with RTA 408 + ipilimumab treatment (all RTA 408 doses in evaluable analysis set)
- Patients with RTA 408 + nivolumab treatment (all RTA 408 doses in evaluable analysis set)
- Patients with RTA 408 + ipilimumab treatment (by RTA 408 dose in evaluable analysis set)
- Patients with RTA 408 + nivolumab treatment (by RTA 408 dose in evaluable analysis set)

12.1. Adverse Events and Serious Adverse Events

All adverse event verbatim terms on electronic case report forms (eCRFs) will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA®) Dictionary (version 14.1).

12.1.1. Treatment Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as any AEs, regardless of relationship to study drug, that have an onset or worsen in severity on or after the first dose of study drug. Treatment-emergent adverse events are events that either:

- Date of onset on or after the date of first dose and not more than 30 days after the date of the last dose of study drug, or
- Had no recorded date of onset with a stop date after the first dose of study drug, or
- Had no recorded date of onset or stop date

If it cannot be determined whether the AE is treatment-emergent due to a partial onset date, then it will be counted as a TEAE. Adverse events with incomplete start dates will be considered TEAEs, if:

- Onset time is missing but the onset date is on Study Day 1

- Day and month are missing and the year is equal to or after the year of the first date of study drug dosing
- Day is missing and the year is after the year of the first date of study drug dosing
- Day is missing and the year is equal to the year of the first date of study drug dosing and the month is equal to or after the month of the first date of study drug dosing; or
- Year is missing

Related AEs are those with relationship to study drug reported as "possibly related", "probably related", or "definitely related". If severity (relationship) of an AE to study drug is not recorded, the severity (relationship) will be imputed as 'severe' ('definitely related').

All reported AEs (including non-TEAEs), SAE, and deaths will be listed in separate patient listings.

12.1.2. Summary of Treatment-Emergent Adverse Events and Serious Adverse Events

All TEAE summary tables will include the number and percentages of patients reporting TEAEs. A summary of TEAEs by severity, seriousness, and relation to study drug will be tabulated. In addition, TEAEs will be summarized by MedDRA system organ class and preferred term. Patients can have more than one TEAE per system organ class and preferred term. These summaries will include the following:

- All TEAEs
- TEAEs by worst severity
- Related TEAEs
- TEAEs leading to study drug interruption (if any)
- TEAEs leading to study drug discontinuation (if any)
- All treatment-emergent SAEs
- Treatment-emergent SAEs by worst severity
- Related treatment-emergent SAEs

At each level of patient summarization, a patient is counted once if he/she reported one or more TEAE at that level. If a patient reported the same TEAE on multiple occasions, the highest severity (severe > moderate > mild) or study drug relationship (related > probable > possible > unlikely > unrelated) recorded for the event will be summarized. Each summary will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

TEAE listings should be summarized by:

- Safety analysis set
- Patients treated with RTA 408 + ipilimumab in safety analysis set (all doses)
- Patients treated with RTA 408 + nivolumab in safety analysis set (all doses)

12.1.3. Dose-Limiting Toxicities

A listing of potential dose-limiting toxicities (DLTs) will display all events meeting the following protocol-defined DLT criteria:

The determination of DLT will be defined in each patient as all toxicity Grade ≥3 (using Common Terminology Criteria for Adverse Events [CTCAE], version 4.03) related to RTA 408 treatment, except as noted below:

- Nausea and vomiting will be considered a DLT if the adverse events are severe or serious and the duration is greater than 48 hours until the Week 7 visit for patients receiving RTA 408 in combination with ipilimumab and until the Week 5 visit for patients receiving RTA 408 in combination with nivolumab after optimal medical therapy
- Any hepatobiliary disorders of Grade ≥2 (from CTCAE, version 4.03, pages 24-25) will be considered a DLT. Note that laboratory measurements are included in a separate section of the CTCAE
- Changes in ALT, AST, and total bilirubin levels must meet 1 of the following criteria to be considered a DLT:
    - ALT or AST >3X ULN and (total bilirubin >2X ULN or international normalized ratio [INR] >1.5)
    - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Any toxicity listed in protocol Section 9.1.2.1 or protocol Section 9.1.3.1 that requires ipilimumab or nivolumab delay that is considered related to RTA 408 treatment or any toxicity listed in Section 9.1.2.3 or Section 9.1.3.3 that requires ipilimumab or nivolumab discontinuation that is considered related to RTA 408 treatment will be considered a DLT

The final determination of a DLT is based on the event timing. Because the time course of any potential RTA 408 DLTs are expected to occur relatively soon after treatment initiation, the DLT observation period for patients receiving RTA 408 in combination with ipilimumab will last through Week 7 (i.e., 6 weeks from initiation of ipilimumab therapy, as opposed to 12 weeks). The DLT observation period will last until the Week 5 visit for patients receiving RTA 408 in combination with nivolumab, which is 4 weeks after initiation of nivolumab therapy. Therefore, in addition to event information, the DLT listing will also include event start week.

12.2. Clinical Laboratory Evaluation

Clinical laboratory tests are specified in the protocol: clinical chemistry in Section 9.9.21, hematology in Section 9.9.22, coagulation in Section 9.9.23, virus serology in Section 9.9.23, and urinalysis in Section 9.9.28. Samples will be analyzed at the local laboratory and recorded in the eCRF using local ranges and units. Laboratory results that are above or below normal limits will be flagged in the listings. All laboratory results (including pregnancy test results) will be presented in data listings, but descriptive summaries will be limited to clinical chemistry and hematology results. Local lab data will be converted to standard units for analysis. Clinical chemistry, hematology, and urinalysis data must be converted to International System of Units (SI units) before any analyses are performed. The standardized values will be summarized using descriptive statistics at each scheduled time point. Post-baseline laboratory assessments missing or below the lower limit of detection (LLD) will be imputed using the LLD values minus one order of magnitude in the first two decimal places. For instance, a LLD value of 20 are imputed as 19.90 and a LLD value <1 is imputed as 0.99. Changes from baseline will also be summarized by time point.

Listings for laboratory parameters of interest include the following items:

- Alanine transaminase (ALT)
- Aspartate transaminase (AST)
- Alkaline phosphatase
- Ferritin
- Gamma-glutamyl transferase (GGT)
- Total bilirubin

Listings for laboratory parameters of interest will be summarized by:

- Patients with RTA 408 + ipilimumab treatment (by RTA 408 dose in safety analysis set)
- Patients with RTA 408 + nivolumab treatment (by RTA 408 dose in safety analysis set)

In addition, a summary table will be provided for number and percentage of patients meeting the following pre-specified threshold level at any time during the study.

Table 6: Pre-Specified Threshold Levels for Laboratory Parameters

Lab Parameter	Pre-Specified Level
BNP	> 200 pg/mL
ALT, AST	> 3 × upper limit of normal (ULN)

Lab Parameter	Pre-Specified Level
ALT, AST	> 8 × ULN
ALT, AST	> 5 × ULN for more than 2 weeks
ALT, AST, TBL, INR	> 3 × ULN and (TBL > 2 × ULN or INR > 1.5 × ULN)

Categorical laboratory summaries using ULN thresholds in Table 6 will use the following limits:

Table 7: Pre-Specified Upper Limit of Normal (ULN) Levels for Laboratory Parameters

Lab Parameter	Sex	Age	ULN
ALT	Female	All	34 U/L
	Male	All	43 U/L
AST	Female	< 18	40 U/L
		≥ 18	34 U/L
	Male	< 18	40 U/L
		≥ 18	36 U/L
TBL			Central lab ULN
INR			Central lab ULN

Urinalysis results (other than pH and specific gravity) of ketones, protein, blood, glucose, clarity, color, leukocytes, nitrite, bilirubin, and microscopic examinations (if indicated based on laboratory results), urine microscopic findings, and pregnancy test results will not be summarized.

Laboratory results that are above or below normal limits will be flagged in the listings.

12.3. Vital Signs

Descriptive statistics for blood pressure, heart rate, and temperature including baseline values and change from baseline values, will be summarized by time point. All vital signs parameters will be listed.

12.4. Body Weight

Descriptive statistics for body weight that are collected on the eCRF and change from baseline values will be summarized and listed by time point. In addition, number and percentage of patients who experience a five pound (2.3 kg) or greater increase in weight versus baseline will be summarized by time point.

12.5. 12-lead ECG

Electrocardiogram (ECG) data, such as clinical interpretation of ECGs, ventricular rate and interval assessments of PR, QRS, and QT, will be collected on the eCRF. QT will be corrected to QTcF as described in Section 7.4.1. QTcF will be included in data summaries, while QT will only be listed. Descriptive statistics for observed values and change from baseline at each time point will be presented for these 12-lead ECG interval assessments. In addition, number and percentage of patients with any abnormal values (i.e., above a pre-specified threshold) will be summarized by time point and overall while on study drug. The pre-specified levels of ECG QTc thresholds are consistent with FDA guidance (See Table 8 below).

Table 8: Pre-Specified Threshold Levels for ECG Parameters

ECG Parameter	Pre-Specified Level
PR	>200 msec
QTcF	>450, >480 or >500 msec, >30 or >60 msec increase from baseline
Heart Rate	<40, >100 beats/min

All ECG parameters will be listed. Any results that exceed the above levels (provided in the above table) will be flagged in the listing.

12.6. Physical Examination

Abnormal clinically significant findings will be reported as Medical History or Adverse Events depending on day of onset. Abnormal non-clinically significant findings from physical examinations will be listed.

13. PHARMACOKINETICS ANALYSIS

Blood samples for determination of plasma RTA 408 and potential metabolite concentrations will be drawn as shown in Table 3. The PK profile of RTA 408 will be evaluated from plasma concentration data from individual patients.

14. DEVIATION FROM THE PROTOCOL SPECIFIED ANALYSIS

Progression free survival (PFS) is listed in the protocol as would be assessed, however, this endpoint will not be calculated or analyzed for the phase 1b portion of the study.