RTA 408

408-C-1401

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

VERSION 5.0 – 29 NOVEMBER 2016

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SPONSOR APPROVAL AND SIGNATURE PAGE

[redacted]

Date

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Date

[redacted]

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for RTA 408. I have read the 408-C-1401 clinical study protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

2. SYNOPSIS

Name of Sponsor/company:
Reata Pharmaceuticals, Inc.

Name of investigational products:
RTA 408 Capsules

Name of active ingredient:
RTA 408

Title of study:
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

Study center(s): Up to 15 study centers in the United States

Studied period (years): <3	**Phase of development:**
Estimated date first patient enrolled: September 2014	1b/2
Estimated date last patient completed: March 2018	

Objectives:

Primary:

- 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)

Exploratory:

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

Methodology:

In this open-label, multicenter, dose-escalation, Phase 1b/2 study, patients who qualify will receive RTA 408 at the assigned dose level in combination with ipilimumab (3 mg/kg) or nivolumab (240 mg).

Cohorts 1 to 3:

Twelve patients will be enrolled at each dose level, with six patients administered RTA 408 + ipilimumab and the remaining six administered RTA 408 + nivolumab. Selection of therapy to be used in combination with RTA 408 (i.e., ipilimumab or nivolumab) should be determined by the investigator as clinically indicated.

Cohorts 4 to 10:

Three (3) to six (6) patients will be enrolled at each dose level, and patients will receive RTA 408 + nivolumab.

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. 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. 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 7.4.4). Patients will return 4 weeks after RTA 408 treatment completion for a follow-up visit.

A traditional 3+3 dose escalation design will be implemented for the Phase 1b portion of the study to evaluate RTA 408 for safety and tolerability within each cohort and select a target dose for the Phase 2 portion of the study. Dose selection in the Phase 1b portion of the study will be based on available safety and pharmacodynamic data from this study, as well as additional data from other studies with RTA 408 in other patient populations (NCT02255435 and NCT02255422). Dose escalation may proceed until a maximum tolerated dose (MTD) or maximum feasible pharmacodynamic response has been reached.

The dose-limiting toxicity (DLT) observation period will last until the Week 7 visit for patients receiving RTA 408 in combination with ipilimumab, which is 6 weeks after initiation of ipilimumab therapy. 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. DLT is defined as any toxicity Grade $\geq$ 3 (using CTCAE, version 4.03), except as noted in protocol Section 7.4.3 or toxicity that requires ipilimumab or nivolumab delay or discontinuation as detailed in protocol Section 9.1.

After the first 3 patients have completed the DLT observation period, all available safety and pharmacodynamic information for all enrolled patients will be reviewed by the protocol safety review committee (PSRC) to make a decision regarding escalation to the subsequent RTA 408 dose level or of the need to evaluate safety data from additional patients treated at the current RTA 408 dose level. If additional safety evaluation is needed as determined by the rules for dose escalation, another review of the data will occur once the next 3 patients (for a total of 6 patients) have completed the DLT observation period. The PSRC may also elect to add 3 patients at the dose-level under review to gain additional pharmacodynamic data. Additionally, the PSRC may recommend enrolling a cohort at a lower dose level based on safety data or review of available inducible nitric oxide synthase (iNOS) expression changes observed in enrolled patients so that appropriate dose levels are enrolled for selection of the Phase 2 dose.

A Phase 2 dose of RTA 408 will be selected based on safety and pharmacodynamic data from the dose-escalation cohorts. The Phase 2 portion of the study will include a separate expansion cohort consisting of patients who have received prior treatment with anti-PD-1 or anti-PD-L1 therapies. Patients enrolled in the expansion cohort will be treated with the selected Phase 2 dose of RTA 408 in combination with nivolumab. The Phase 2 expansion cohort will include an additional 24 or 27 patients to achieve a total of 30 patients at that RTA 408 dose in combination with nivolumab. Tumor response will be assessed at Week 13 and approximately every 12 weeks thereafter.

Number of patients (planned):

Up to 102 patients are expected to enroll in this study.

Inclusion criteria:

Patients must:

1. Provide written informed consent for study participation, approved by the appropriate institutional review board
2. Be ≥ 18 years of age
3. Have advanced, unresectable (Stage III) or metastatic (Stage IV) melanoma
4. Be eligible for commercial receipt of therapy to be used in this study in combination with RTA 408 (i.e., ipilimumab or nivolumab in the Phase 1b cohorts and nivolumab only in the Phase 2 cohort)
5. Have received prior treatment with anti-PD-1 or anti-PD-L1 therapy (including experimental therapies) if enrolling in the Phase 2 portion of the study. This criteria does not apply to patients enrolling in the Phase 1b portion of the study. Subjects who are currently taking nivolumab and have stable disease (SD) per investigator assessment will be eligible to participate provided SD has been present for at least 3 months
6. Have >5% of tumor cells from the screening biopsy stained positive for iNOS expression in an immunochemistry assay
7. Have an Eastern Cooperative Oncology Group performance status ≤2
8. Have a life expectancy of ≥ 3 months at the time of screening in the investigator's opinion
9. Have discontinued previous treatments for cancer and recovered from all acute toxic effects of prior systemic therapy to Grade ≤1. Exempted are effects that are often non-reversible or require a prolonged time for reversal (e.g., alopecia, hypothyroidism, neuropathy)
10. Have discontinued previous experimental therapies and checkpoint inhibitor antibodies at least 28 days prior to the Randomization Visit. This does not apply to subjects for Phase 2 who are currently receiving nivolumab and have SD
11. Have adequate bone marrow reserve and organ function at the Screening Visit as follows:
    a. Hematologic: Absolute neutrophil count >1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin ≥9 g/dL (patients may receive erythrocyte transfusions to achieve this hemoglobin level, at the discretion of the investigator, but the first dose of study drug must not begin until 5 days after the erythrocyte transfusion)
    b. Hepatic: Total bilirubin ≤1.5X the upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase ≤ 2.5X ULN for patients without liver metastasis or ≤ 5X ULN for patients with liver metastasis
    c. Renal: Estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula ≥60 mL/min/1.73 m^2
12. Be able to swallow capsules
13. Be willing and able to cooperate with all aspects of the protocol
14. Be willing to practice the following medically acceptable methods of birth control (both women of childbearing potential and men who have partners of childbearing potential) from the Screening Visit through 3 months after taking the final dose of RTA 408: spermicide with double barrier, oral contraceptive, vaginal ring, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, surgical sterilization of partner, or abstinence (for non–sexually active patients). Women of childbearing potential include all females who have experienced menarche and have not experienced menopause (defined as amenorrhea for >12 consecutive months) or have undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy)

15. Women of childbearing potential must not be pregnant or lactating and must agree to have pregnancy testing performed at each visit except at Week 1 and Week 2 (Visits 3 and 4)

Exclusion criteria:

Patients must not:

1. Have ocular melanoma
2. Have prior malignancy active within the previous 2 years except for localized cancers that are considered to have been cured and, in the opinion of the investigator, present a low risk for recurrence (e.g., basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma *in situ* of the prostate, cervix, or breast)
3. Have any active autoimmune disease or a history of known or suspected autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for patients with vitiligo or resolved childhood asthma/atopy or other syndromes which would not be expected to recur in the absence of an external trigger. Patients with type 1 diabetes mellitus are permitted to enroll. Diseases that are considered autoimmune related include the following:
    a. Inflammatory bowel disease, including ulcerative colitis and Crohn's disease
    b. Symptomatic diseases (e.g., rheumatoid arthritis, systemic progressive sclerosis, systemic lupus erythematosus, autoimmune vasculitis)
    c. Motor neuropathies considered of autoimmune origin (e.g., Guillain-Barré syndrome)
4. Have had brain metastases (screening not required), unless they have met all of the following criteria:
    a. Had a resection and/or completed a course of cranial irradiation, and
    b. Have no worsening central nervous system symptoms, and
    c. Have no magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration, and
    d. Have discontinued all corticosteroids for that indication for at least 2 weeks
5. Have the following cardiovascular abnormalities:
    a. Evidence of poor cardiovascular function, defined as B-type natriuretic peptide (BNP) >200 pg/mL or NT-proBNP > 2X the upper limit of normal (ULN)
    b. History of congestive heart failure, unstable angina, or uncontrolled hypertension
    c. Clinically significant ventricular arrhythmias at the Screening Visit
    d. Myocardial infarction within 6 months prior to the Screening Visit
    e. Corrected QTc interval on electrocardiogram (ECG) at the Screening Visit >500 msec
6. Have known hepatic impairment, including cirrhosis
7. Have known renal impairment, including glomerulonephritis
8. Have severe cerebral or peripheral vascular disease
9. Have pre-existing chronic diarrhea CTCAE (Common Terminology Criteria for Adverse Events) Grade ≥2 of any etiology (including malabsorption disorders and surgical procedures that, in the opinion of the investigator, may affect absorption of study drug)
10. Have known active fungal, bacterial, and/or viral infection, including human immunodeficiency virus (HIV) or hepatitis virus (A, B, or C)

11. Have had major surgery within 21 days before the Randomization Visit (Day 1 Visit)

12. Have taken any of the following drugs within 7 days before the Randomization Visit (Day 1 Visit):
    a. Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
    b. Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin), OCT1 transporter (e.g., metformin), OAT1 transporter (e.g., captopril, furosemide, methotrexate), or OATP1B3 transporter (e.g., atorvastatin, rosuvastatin, valsartan)
    c. CYP3A inhibitors and strong inducers
13. Have known or suspected active drug or alcohol abuse
14. Have any abnormal laboratory test value or serious pre-existing medical condition that, in the opinion of the investigator, would put the patient at risk by trial enrollment
15. Be unable to comply with the requirements of the study protocol or be unsuitable for the study for any reason, in the opinion of the investigator

Investigational product, dosage and mode of administration:

RTA 408 capsules will be administered orally at the starting dose level and subsequent dose levels defined by the PSRC.

Duration of treatment:

RTA 408 will be administered orally once daily for up to 168 weeks in combination with ipilimumab (3 mg/kg) given intravenously at Weeks 1, 4, 7, and 10 or up to 169 weeks in combination with nivolumab (240 mg) given intravenously every 2 weeks for 168 weeks.

Reference therapy, dosage, and mode of administration:

None.

Endpoints:

Safety: Results of physical examinations, laboratory test results, ECGs, vital sign measurements, concomitant medications, adverse events, and serious adverse events

Efficacy: ORR, complete response rate, partial response rate, progression-free survival, and percent reduction in tumor biopsy iNOS expression

Pharmacokinetics: RTA 408 plasma concentration-time data and possible metabolite concentration-time data for each analyte

Pharmacodynamics: Change from baseline in PBMC biochemical markers, in myeloid-derived suppressor cell (MDSC) function, and in tumor biopsy biomarkers, including the proportion of iNOS-positive tumor cells

Statistical methods:

Sample size: 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) selection of a Phase 2 dose based on review of safety, efficacy, and pharmacodynamic data, and (3) assessment of 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 as well as other pharmacodynamic markers from the Phase 1b dose-escalation portion of the study will provide information for selecting the Phase 2 expansion dose.

The Phase 2 portion of the study allows for assessment of ORR at the selected Phase 2 dose of RTA 408 with nivolumab. Since the Phase 2 portion will only enroll patients previously treated with anti-PD-1 or anti-PD-L1 therapy (including experimental therapies), the ORR for nivolumab monotherapy is assumed to be 0%. A sample size of 24 patients for the expansion cohort achieves at least 80% power to detect an improvement of 20% in ORR from the assumed nivolumab ORR as the null hypothesis using a 1-sided binomial test at alpha=0.10.

Statistical analysis: A statistical analysis plan (SAP) detailing the analyses will be developed prior to the database lock. The SAP will include analysis of all safety, pharmacokinetic, pharmacodynamic, and response variables. All statistical analyses and data summaries will be performed using SAS® (version 9.1 or higher) or other similar software. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages.

3. TABLE OF CONTENTS AND LISTS OF TABLES AND FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 2: List of Abbreviations

Abbreviation	Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CPK	creatine phosphokinase
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	good clinical practice
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GLP	good laboratory practice
HDL-C	high-density lipoprotein cholesterol
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
ICF	informed consent form

Abbreviation	Explanation
ICH E6(R1)	International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6(R1)
IFNγ	interferon-gamma
iNOS	inducible nitric oxide synthase
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MDSC	myeloid-derived suppressor cell
MRI	magnetic resonance imaging
Na_2SO_3	sodium sulfate
NAD(P)H	nicotinamide adenine dinucleotide
NCI	National Cancer Institute
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
Nrf2	nuclear factor erythroid-derived 2-related factor 2
NO	nitric oxide
NOAEL	no-observed-adverse-effect level
NQO1	nicotinamide adenine dinucleotide (NAD(P)H) quinone oxidoreductase 1
NSCLC	non-small cell lung cancer
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PD-1	programmed cell death-1
PK	pharmacokinetic
PSRC	protocol safety review committee
PT	prothrombin time

Abbreviation	Explanation
PTT	partial thromboplastin time
QTc	corrected QT interval
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumours
ROS	reactive oxygen species
RNS	reactive nitrogen species
SAE	serious adverse event
SAP	statistical analysis plan
STD10	severely toxic dose in 10%
ULN	upper limit of normal
US	United States
US CFR Title 21	Title 21 of the US Code of Federal Regulations
VLDL-C	very-low-density lipoprotein cholesterol
WBC	white blood cell
WOCBP	women of childbearing potential

5. INTRODUCTION

5.1. Background on RTA 408

Natural triterpenoids, such as oleanolic acid and ursolic acid derived from plant extracts, have been used extensively in Asian medicine for their anti-inflammatory and anticancer properties (Liu, 1995). In an attempt to increase the potency of these compounds, Michael Sporn and colleagues tested over 280 semi-synthetic oleanane triterpenoids for their ability to inhibit the induction of nitric oxide (NO) in primary mouse macrophages treated with interferon-gamma (IFNγ; Honda, 1999). RTA 408 is a novel oleanane triterpenoid and is part of this class of compounds. Subsequent mechanistic studies have revealed that RTA 408 and the semi-synthetic triterpenoids are potent inhibitors of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and inducers of nuclear factor erythroid-derived 2-related factor 2 (Nrf2), and thus induce an anti-inflammatory and antioxidant phenotype.

Activation of Nrf2 induces the expression of a battery of cytoprotective genes, including the prototypical Nrf2 target gene, NQO1 (nicotinamide adenine dinucleotide (NAD(P)H) quinone oxidoreductase 1), enzymes involved in glutathione synthesis, and enzymes involved in detoxification (Wu, 2011). Induction of these genes results in a coordinated cellular effort to protect against oxidative insult, highlighted by increased antioxidative capacity, induction of glutathione synthesis, and conjugation of potentially harmful molecules. The protective role of the Keap1-Nrf2 pathway in carcinogenesis has been studied extensively and is the subject of recent review papers (Sporn, 2012; Lee, 2013). Because of the role Nrf2 plays in cellular protection, Nrf2 activation has multiple potentially beneficial effects in cancer treatment. Importantly, semi-synthetic oleanane triterpenoids have been shown to be highly effective in treating a wide variety of established tumors in multiple models (Deeb, 2009; Hyer, 2008; Jutooru, 2010; Konopleva, 2006; Kress, 2007; Lapillonne, 2003; Ling, 2007; Nagaraj, 2010; Place, 2003). As a class, the semi-synthetic oleanane triterpenoids have also been studied extensively in numerous models of cancer prevention, including both chemically and genetically induced carcinogenesis. In these studies, treatment with semi-synthetic oleanane triterpenoids extended lifespan and reduced tumor burden (Kim, 2011; Liao, 2011; Liby, 2007; Liby, 2010; Yates, 2006).

On the basis of these data, RTA 408 is currently being evaluated as a monotherapy in a Phase 1 study in patients with advanced solid tumors (Study 408-C-1303). Study 408-C-1303 is the first-in-human study with RTA 408 designed to assess the safety, maximum tolerated dose, pharmacodynamics, and pharmacokinetics of RTA 408 in patients with incurable non-small cell lung cancer (NSCLC) or melanoma that is relapsed, refractory after standard-of-care therapy, or for which standard-of-care therapy is not appropriate. Available data from Study 408-C-1303 will provide additional clinical and safety information for the conduct of the proposed clinical study.

Regarding the safety profile of RTA 408, no adverse effects were observed in the safety pharmacology studies. The genotoxicity potential of RTA 408 was investigated in 2 *in vitro* genetic toxicity tests and 2 *in vivo* genotoxicity studies in rats. The overall weight of evidence from the genotoxicity studies indicates that RTA 408 has a low genotoxicity risk to human subjects.

Overall, considering the large body of toxicity data generated to date with RTA 408, rats are more sensitive to the toxicologic effects of RTA 408 than mice or monkeys. In rats, the highest dosage tested (30 mg/kg/day) in the 28-day good laboratory practice (GLP) toxicity study did not produce severe toxicity; however, severe toxicity (i.e., mortality, decrease in weight gain, marked reduction in food consumption, and adverse clinical signs) was observed at 100 mg/kg/day in a non-GLP 14-day study, suggesting that 30 mg/kg/day may provide a conservative estimate of the severely toxic dosage in 10% (STD10) of rats. In monkeys, the highest dosage tested in the 28-day GLP study was 100 mg/kg/day, as higher dosages evaluated in a separate pharmacokinetic (PK) study were not associated with increased exposure. Although no signs of toxicity were observed with 100 mg/kg/day in monkeys, this dose is conservatively identified as the highest non-severely toxic dose (HNSTD) in non-rodents.

At doses below those required to produce severe toxicity, the primary systemic effects observed after oral administration of RTA 408 to rats and, to a much lesser extent, to monkeys were considered to be mostly due to the known pharmacologic activity of RTA 408 in animal models and likely do not reflect off-target toxicity. The rat was the most sensitive preclinical species, and the no-observed-adverse-effect level (NOAEL) in the GLP 28-day study with RTA 408 was 3 mg/kg/day, based on adverse liver and kidney findings at the higher dosages. The NOAEL in rats decreases with increased treatment duration, and in the 6-month chronic toxicity study, adverse findings were noted in the lowest dosage group studied (0.3 mg/kg/day). In contrast, a 30-mg/kg/day dose in monkeys was not associated with adverse liver or kidney findings regardless of the treatment duration. The adverse liver findings in rats were reversible upon drug discontinuation and were associated with moderate to marked increases in serum gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. With short treatment duration (i.e., 14 days), tubular degeneration/regeneration in rats was reversible with a 28-day treatment-free period in a non-GLP study. Although the kidney findings in rats after 28 days of treatment were not reversible after a 4-week recovery period, they were mild, were not associated with evidence of an effect on renal function (i.e., no increase in blood urea nitrogen [BUN] or serum creatinine), and were not present in monkeys at doses up to 30 mg/kg/day after up to 9 months of daily administration.

5.2. Rationale

Malignant melanoma is a leading cause of death from cutaneous malignancies, accounting for approximately three-fourths of all skin cancer deaths (Hall, 1999). Surgical excision is the standard treatment for localized melanomas, which are highly curable. For metastatic or unresectable melanomas, standard treatment options include checkpoint inhibitors (e.g., ipilimumab), interleukin-2, signal transduction inhibitors, chemotherapy, or palliative local therapy (NCCN Melanoma Guidelines, 2014). However, approved therapies are rarely curative.

It is now well accepted that tumors are able to evade detection and eradication by the immune system, even though many tumor types, particularly melanoma, are capable of eliciting a strong immune response (Swann, 2007). Ipilimumab is an approved monoclonal antibody that targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) activity. CTLA-4 is an immune checkpoint molecule that prevents autoimmunity and enables tolerance to self-antigens by downregulating T-cell activation. Nivolumab is another approved therapy for metastatic melanoma that targets the PD-1 protein on the surface of activated T cells, which regulates T-cell

activation and proliferation at the tumor site. Thus through blockade of CTLA-4 or PD-1/PD-L1 signaling, ipilimumab and nivolumab aim to amplify T-cell-mediated immunity, which theoretically enhances the patient's capacity to mount an antitumor immune response. However, although treatment with ipilimumab or nivolumab has been shown to reduce the risk of disease progression, response to therapy may be further augmented. Only 6% to 11% of melanoma patients treated with ipilimumab achieved a partial or complete response, and median overall survival was only 10 months (Hodi, 2010). While the overall response rate for nivolumab is higher than for ipilimumab, more than half of patients don't respond to nivolumab (Romano, 2015; Weber, 2014).

Substantial mechanistic work in recent years has revealed the key role of myeloid-derived suppressor cells (MDSCs) in masking the tumor environment from the immune system, which in turn contributes to both tumor progression and resistance to cancer immunotherapy. MDSCs represent the major population of antigen-presenting cells responsible for the induction of antigen-specific CD8+ T-cell tolerance in cancer (Gabrilovich, 2012). The immune-suppressive effect of MDSCs is dependent on the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). One mechanism by which MDSCs elicit T-cell tolerance is through nitrosylation of tyrosine residues in the T-cell receptor-CD8 complex, which prevents antigen-dependent T-cell activation (Nagaraj, 2007). As a result, inhibition of MDSC activity and reduction of ROS and RNS levels in the tumor microenvironment have been shown to be effective in restoring immune recognition of tumor-specific antigens. Conversely, the frequency of MDSCs correlate with disease progression and decreased overall survival in Stage IV melanoma patients (Jordan, 2013), and increased tumor levels of inducible nitric oxide synthase (iNOS) and nitrotyrosine expression have been correlated with decreased survival in patients with metastatic melanoma (Ekmekcioglu, 2000; Ekmekcioglu, 2006).

RTA 408 inhibits tumor growth in mouse tumor xenograft models and has multiple anticancer effects, including direct induction of apoptosis in cancer cells and suppression of ROS production by MDSCs *in vitro*. In addition, RTA 408 significantly reduces tumor nitrotyrosine burden, inhibits the activity of MDSCs, and augments T-cell anticancer activity *in vivo*. These effects of RTA 408 are consistent with the inhibition of MDSCs that has been observed with another semi-synthetic oleanane triterpenoid, bardoxolone methyl (Nagaraj, 2010). Specifically, treatment with bardoxolone methyl has been shown to abrogate the immune-suppressive effect of MDSCs with a corresponding improvement in immune response in tumor-bearing mice and in patients with cancer (Nagaraj, 2010). Thus, through inhibition of MDSC activity and suppression of tumor ROS/RNS, RTA 408 may work in combination with T-cell-activating therapeutics such as ipilimumab and nivolumab to enhance the natural immune anticancer response.

This study is designed to assess the safety, efficacy, pharmacodynamics, and pharmacokinetics of RTA 408 in combination with ipilimumab or nivolumab in patients with unresectable or metastatic melanoma. The results of this study will help provide clinical information for the design and conduct of further clinical studies with RTA 408 in patients with cancer.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. 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)

6.2. Exploratory Objectives

[redacted]

7. INVESTIGATIONAL PLAN

7.1. 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).

Cohorts 1 to 3:

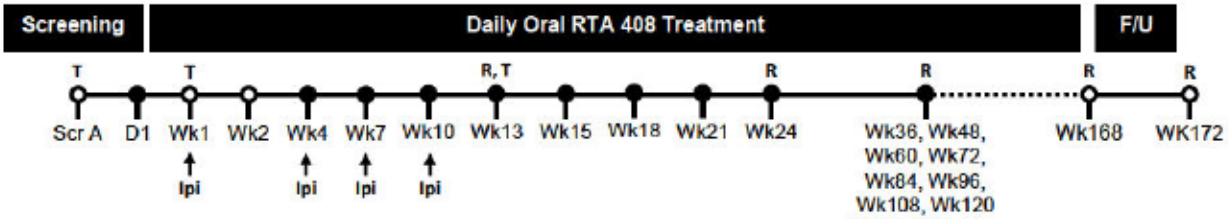
Twelve patients will be enrolled at each dose level, with six patients administered RTA 408 + ipilimumab and the remaining six administered RTA 408 + nivolumab. Selection of therapy to be used in combination with RTA 408 (i.e., ipilimumab or nivolumab) should be determined by the investigator as clinically indicated. Subsequent cohorts will assess escalating doses of RTA 408 administered in combination with ipilimumab or nivolumab. A starting RTA 408 dose level of 5 mg was selected for the first dose-escalation cohort in this study based on available safety and pharmacodynamic data from a separate Phase 1 study of RTA 408 monotherapy in patients with advanced solid tumors (Study 408-C-1303).

Cohorts 4 to 10:

Three (3) to six (6) patients will be enrolled at each dose level, and patients will receive RTA 408 + nivolumab.

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 7.4.4). Patients will return 4 weeks after RTA 408 treatment completion (or early termination) for a follow-up visit.

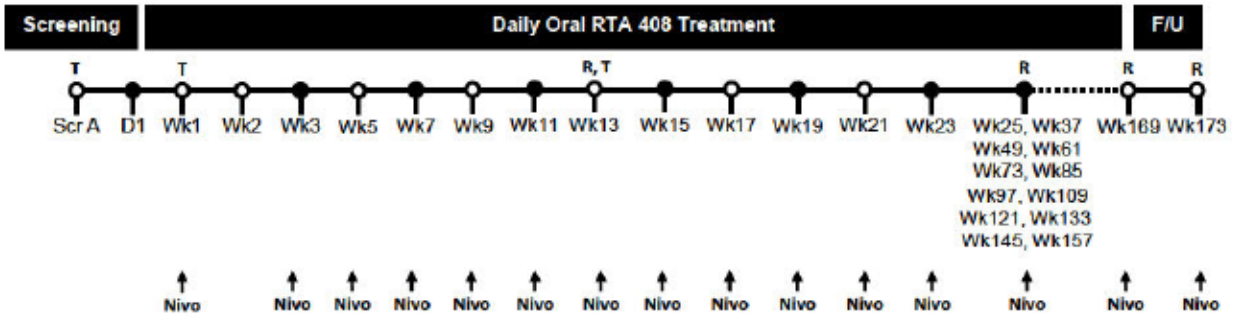
Figure 1: Schema for Study of RTA 408 in Combination with Ipilimumab in Patients with Metastatic Melanoma



● 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

A traditional 3+3 dose escalation design will be implemented for the Phase 1b portion of the study to evaluate RTA 408 for safety and tolerability within each cohort and select a target dose for the Phase 2 portion of the study (Figure 3). Dose selection in the Phase 1b portion of the study will be based on available safety and pharmacodynamic data from this study, as well as additional data from other studies with RTA 408 in other patient populations (NCT02255435 and NCT02255422). Dose escalation may proceed until a maximum tolerated dose (MTD) or maximum feasible pharmacodynamic response has been reached.

The dose-limiting toxicity (DLT) observation period will last until the Week 7 visit for patients receiving RTA 408 in combination with ipilimumab, which is 6 weeks after initiation of ipilimumab therapy. 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. DLT is defined as any toxicity Grade ≥3 (using Common Terminology

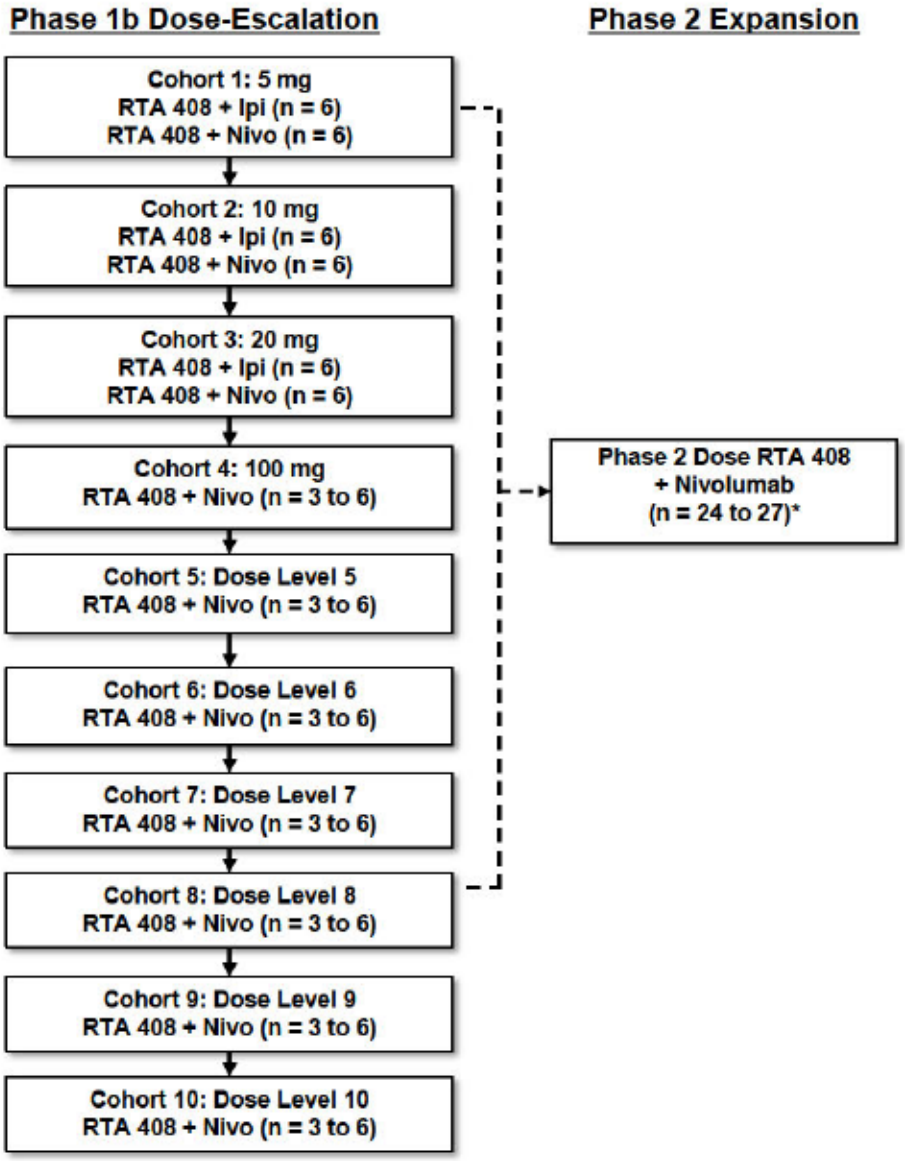
Criteria for Adverse Events [CTCAE], version 4.03) related to RTA 408 treatment, except as noted in protocol Section 7.4.3 or toxicity that requires ipilimumab or nivolumab delay or discontinuation as detailed in protocol Section 9.1.

After the first 3 patients have completed the DLT observation period, all available safety and pharmacodynamic information for all enrolled patients will be reviewed by the protocol safety review committee (PSRC) to make a decision regarding escalation to the subsequent RTA 408 dose level or of the need to evaluate safety data from additional patients treated at the current RTA 408 dose level. If additional safety evaluation is needed as determined by the rules for dose escalation, another review of the data will occur once the next 3 patients (for a total of 6 patients) have completed the DLT observation period. The PSRC may also elect to add 3 patients at the dose level under review to gain additional pharmacodynamic data. Additionally, the PSRC may recommend enrolling a cohort at a lower dose level based on safety data or review of available iNOS expression changes observed in enrolled patients so that appropriate dose levels are enrolled for selection of the Phase 2 dose.

A Phase 2 dose of RTA 408 will be selected based on safety and pharmacodynamic data from the dose-escalation cohorts. The Phase 2 portion of the study will include a separate expansion cohort consisting of patients who have received prior treatment with anti-PD-1 or anti-PD-L1 therapies treated with RTA 408 in combination with nivolumab. The Phase 2 expansion cohort will include an additional 24 or 27 patients to achieve a total of 30 patients at that RTA 408 dose in combination with nivolumab. Tumor response will be assessed at Week 13 and approximately every 12 weeks thereafter.

A detailed schedule of assessments for the study is shown in Table 3 (ipilimumab) and Table 4 (nivolumab). The study consists of up to a 21-day screening period, up to approximately 168 weeks (patients treated with RTA 408 + ipilimumab) or 169 weeks (patients treated with RTA 408 + nivolumab) of RTA 408 treatment, which includes 4 doses of ipilimumab or intravenous administration of nivolumab every two weeks, and a 4-week post-treatment follow-up.

Figure 3: RTA 408 Dose-Escalation and Expansion Schema



*Total number of patients enrolled at the Phase 2 dose for a RTA 408 + nivolumab will be 30.

7.2. Number of Patients

Up to 102 patients are expected to enroll in this study.

7.3. Treatment Assignment

Patients who qualify for the study will be assigned to the dose of RTA 408 open for enrollment in the dose-escalation or expansion cohorts as described in Section 7.4.2.

7.4. Dose Selection and Escalation Scheme

7.4.1. Selection of Starting Dose

The starting RTA 408 dose level that will be combined with ipilimumab or nivolumab will be 5 mg based on available safety and efficacy data from an ongoing Phase 1 study of RTA 408 monotherapy in patients with advanced solid tumors (Study 408-C-1303).

7.4.2. Dose-Escalation Scheme

A traditional 3+3 dose escalation design will be implemented for the Phase 1b portion of the study to evaluate RTA 408 for safety and tolerability within each cohort and select a target dose for the Phase 2 portion of the study.

After the first 3 patients have completed the DLT observation period, all available safety and pharmacodynamic information for all enrolled patients will be reviewed by the PSRC to make a decision regarding escalation to the subsequent RTA 408 dose level or of the need to evaluate additional patients at the current RTA 408 dose level. The PSRC may include the investigator(s), Sponsor representative(s), and independent physician(s). Any PSRC decision requires unanimous agreement among the members of the PSRC. A separate charter for the PSRC is not required for this study. If there are no general safety concerns noted from the overall assessment of safety based on available data from all enrolled patients, then the following rules for additional safety evaluation or dose escalation will be applied within each combination therapy type based on assessment of DLTs after completing the specified DLT observation period:

1. If no patients (0 of 3) experience a DLT, then dose escalation may occur
2. If 1 patient (1 of 3) experiences a DLT, then 3 additional patients at the same dose level will be evaluated after completing the DLT observation period and the following rules will be applied:
    a. If none of the additional patients experience a DLT (i.e., 1 of 6 patients experience a DLT at the current dose level), then RTA 408 dose escalation may occur
    b. If ≥1 additional patients experience a DLT (i.e., ≥2 of 6 patients experience a DLT at the current dose level), then dose escalation will not occur. The PSRC may recommend dose reduction and enrollment of additional cohorts at a lower dose between the previously well-tolerated dose level and the current dose level. The PSRC may recommend no further patients be enrolled at the dose under evaluation
3. If ≥2 patients (≥2 of 3) experience a DLT, then dose escalation will not occur; however, the PSRC may recommend dose reduction and enrollment of additional cohorts at a lower dose

between the previously well-tolerated dose level and the current dose level. The PSRC may recommend no further patients be enrolled at the dose under evaluation

If all 6 patients have completed the DLT observation period at the current dose level and a decision is not determined by the above rules, then dose escalation will not occur; however, the PSRC may recommend dose reduction and enrollment of additional cohorts at a lower dose level.

Subsequent cohorts will be enrolled at dose levels based on available safety and pharmacodynamic data from this study, as well as additional data from other studies with RTA 408 in other patient populations (NCT02255435 and NCT02255422). Dose escalation may proceed until a maximum tolerated dose (MTD) or maximum feasible pharmacodynamic response has been reached.

7.4.3. Criteria for Determining Dose-Limiting Toxicity

Because the timecourse 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. Furthermore, during safety review, the PSRC will also consider safety data obtained from prior cohorts treated at lower doses of RTA 408 in combination with ipilimumab or nivolumab to determine if latent AEs occur outside of the DLT observation period. The CTCAE (version 4.03) will be used to assess AEs that may be considered a DLT, except where related to transaminase laboratory values. Nrf2 activation by RTA 408 and related analogs has been shown to upregulate the production of transaminases. The transaminase upregulation is a pharmacologic response related to increased glucose utilization and has not been shown to be associated with liver toxicity in animal studies or clinical studies with a related analog (Hong, 2012; Pergola, 2011). Therefore, the determination of DLT will be defined in each patient as all toxicity Grade ≥3 (using CTCAE, version 4.03) related to RTA 408 treatment, except as noted below:

- Nausea and vomiting will be considered a DLT if Grade 3 toxicity persists 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 Section 9.1.2.1 or 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.

7.4.4. Intrapatient Dose Escalation

Intrapatient dose escalation of the selected Phase 2 dose (to a higher dose level that has proven tolerable in the study) will be allowed at the discretion of the investigator once a patient has completed Week 13 assessments.

7.5. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If the Sponsor discontinues the study, all study treatment will be discontinued and the investigator will be responsible to prescribe any additional therapy to be administered.

7.6. Schedule of Assessments

Table 3 and Table 4 list the schedule of assessments for patients receiving RTA 408 and ipilimumab or nivolumab, respectively.

Table 3: 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[i]**	**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[b]	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.
[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 4: 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[f]	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[l]							X[l]						
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[e]	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.
[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.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

All patients must meet all of the following criteria to be included in the study:

1. Provide written informed consent for study participation, approved by the appropriate institutional review board (IRB)
2. Be ≥18 years of age
3. Have advanced, unresectable (Stage III) or metastatic (Stage IV) melanoma
4. Be eligible for commercial receipt of therapy to be used in this study in combination with RTA 408 (i.e., ipilimumab or nivolumab in the Phase 1b portion and nivolumab only in the Phase 2 portion)
5. Have received prior treatment with anti-PD-1 or anti-PD-L1 therapy (including experimental therapies) if enrolling in the Phase 2 portion of the study. This criteria does not apply to patients enrolling in the Phase 1b portion of the study. Subjects who are currently taking nivolumab and have stable disease (SD) per investigator assessment will be eligible to participate provided SD has been present for at least 3 months
6. Have >5% of tumor cells from the screening biopsy stained positive for iNOS expression in an immunochemistry assay
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2
8. Have a life expectancy of ≥ 3 months at the time of screening in the investigator's opinion
9. Have discontinued previous treatments for cancer and recovered from all acute toxic effects of prior systemic therapy to Grade ≤1. Exempted are effects that are often non-reversible or require a prolonged time for reversal (e.g., alopecia, hypothyroidism, neuropathy)
10. Have discontinued previous experimental therapies and checkpoint inhibitor antibodies at least 28 days prior to the Randomization Visit. This does not apply to subjects who are currently receiving nivolumab and have SD
11. Have adequate bone marrow reserve and organ function at the Screening Visit as follows:
    a. Hematologic: Absolute neutrophil count >1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin ≥9 g/dL (patients may receive erythrocyte transfusions to achieve this hemoglobin level, at the discretion of the investigator, but the first dose of study drug must not begin until 5 days after the erythrocyte transfusion)
    b. Hepatic: Total bilirubin ≤1.5X ULN, ALT and AST ≤ 2.5X ULN for patients without liver metastasis or ≤ 5X ULN for patients with liver metastasis
    c. Renal: Estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula ≥60 mL/min/1.73 m^2
12. Be able to swallow capsules
13. Be willing and able to cooperate with all aspects of the protocol

14. Be willing to practice the following medically acceptable methods of birth control (both women of childbearing potential (WOCBP) and men who have partners of childbearing potential) from the Screening Visit through 3 months after taking the final dose of RTA 408: spermicide with double barrier, oral contraceptive, vaginal ring, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, surgical sterilization of partner, or abstinence (for non–sexually active patients). WOCBP include all females who have experienced menarche and have not experienced menopause (defined as amenorrhea for >12 consecutive months) or have undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy)
15. WOCBP must not be pregnant or lactating and must agree to have pregnancy testing performed at each visit except at Week 1 and Week 2 (Visits 3 and 4)

8.2. Patient Exclusion Criteria

All patients with any of the following conditions or characteristics must be excluded from the study:

1. Have ocular melanoma
2. Have prior malignancy active within the previous 2 years except for localized cancers that are considered to have been cured and, in the opinion of the investigator, present a low risk for recurrence (e.g., basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma *in situ* of the prostate, cervix, or breast)
3. Have any active autoimmune disease or a history of known or suspected autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for patients with vitiligo or resolved childhood asthma/atopy or other syndromes which would not be expected to recur in the absence of an external trigger. Patients with type 1 diabetes mellitus are permitted to enroll. Diseases that are considered autoimmune related include the following:
    a. Inflammatory bowel disease, including ulcerative colitis and Crohn's disease
    b. Symptomatic diseases (e.g., rheumatoid arthritis, systemic progressive sclerosis, systemic lupus erythematosus, autoimmune vasculitis)
    c. Motor neuropathies considered of autoimmune origin (e.g., Guillain-Barré syndrome)
4. Have had brain metastases (screening not required) unless they have met all of the following criteria:
    a. Had a resection and/or completed a course of cranial irradiation, and
    b. Have no worsening central nervous system symptoms, and
    c. Have no magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration, and
    d. Have discontinued all corticosteroids for that indication for at least 2 weeks

5. Have the following cardiovascular abnormalities:
    a. Evidence of poor cardiovascular function, defined as B-type natriuretic peptide (BNP) >200 pg/mL or NT-proBNP > 2X the upper limit of normal (ULN)
    b. History of congestive heart failure, unstable angina, or uncontrolled hypertension
    c. Clinically significant ventricular arrhythmias at the Screening Visit
    d. Myocardial infarction within 6 months prior to the Screening Visit
    e. Corrected QT interval (QTc) on electrocardiogram (ECG) at the Screening Visit >500 msec
6. Have known hepatic impairment, including cirrhosis
7. Have known renal impairment, including glomerulonephritis
8. Have severe cerebral or peripheral vascular disease
9. Have pre-existing chronic diarrhea CTCAE Grade ≥2 of any etiology (including malabsorption disorders and surgical procedures that, in the opinion of the investigator, may affect absorption of study drug)
10. Have known active fungal, bacterial, and/or viral infection, including human immunodeficiency virus (HIV) or hepatitis virus (A, B, or C)
11. Have had major surgery within 21 days before the Randomization Visit (Day 1 Visit)
12. Have taken any of the following drugs within 7 days before the Randomization Visit (Day 1 Visit):
    a. Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
    b. Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin), OCT1 transporter (e.g., metformin), OAT1 transporter (e.g., captopril, furosemide, methotrexate), or OATP1B3 transporter (e.g., atorvastatin, rosuvastatin, valsartan)
    c. CYP3A inhibitors and strong inducers
13. Have known or suspected active drug or alcohol abuse
14. Have any abnormal laboratory test value or serious pre-existing medical condition that, in the opinion of the investigator, would put the patient at risk by trial enrollment
15. Be unable to comply with the requirements of the study protocol or be unsuitable for the study for any reason, in the opinion of the investigator

8.3. Patient Rescreening

Patients may repeat the screening procedures to qualify for the study with approval from the medical monitor.

8.4. Patient Withdrawal and Discontinuation

Patients have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug or terminate the patient from the study. The reason for a patient's withdrawal or discontinuation from the study will be recorded in the case report form (CRF).

8.4.1. Patient Discontinuation Criteria

Discontinuation refers to a patient stopping administration of study drug (RTA 408 only). Reasons for study drug discontinuation include the following:

- Disease progression
- DLT
- Occurrence of an AE or change in medical status that leads the investigator to be concerned about the patient's welfare
- Noncompliance with study procedures
- Pregnancy during the study

Subjects with RECIST progressive disease may continue on study at the discretion of the Investigator if pseudo-progression is suspected and the patient consents to continued treatment. Pseudo-progression is defined as apparent disease progression that may be due to T-cell infiltration of the tumor site, which could cause an increase in tumor size or new lesions to appear upon imaging. When pseudo-progression is suspected, patients may continue to participate in the study and continue to receive protocol-specified treatment if the following criteria are met:

- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in WHO/ECOG performance status
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention
- No significant, unacceptable or irreversible toxicities related to protocol-specified treatment

Subjects with subsequent reduction in tumor diameter will have CT results compared to baseline for calculation of RECIST response. Patients who are discontinued from study drug should still continue to receive ipilimumab or nivolumab as indicated (according to ipilimumab or nivolumab prescribing information), attend all study visits, and undergo all study assessments, if possible. Patients who are discontinued prior to the assessment of potential toxicity may be replaced, except when the discontinuation is due to a patient experiencing a DLT.

8.4.2. Patient Termination Criteria

Termination refers to a patient stopping study drug and all study assessments and visits. Reasons for study termination include the following:

- Failure to return for follow-up
- Adverse event, which results in death
- Withdrawal of consent

Patients who terminate RTA 408 for any reason may not re-initiate RTA 408 at any time.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug, Ipilimumab, and Nivolumab

9.1.1. Study Drug: RTA 408

RTA 408 drug product information is shown in Table 5. Reata Pharmaceuticals will provide sufficient quantities of RTA 408 Capsules to allow for completion of the study. References in this document to study drug are specifically referring to RTA 408.

Table 5: RTA 408 Drug Product Information

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

9.1.1.1. Study Drug Treatment Interruption

In the case of serious toxicities that do not meet the definition of a DLT (Section 7.4.3), the investigator may choose to interrupt treatment with RTA 408. RTA 408 treatment may be restarted with approval from the medical monitor. Dose reductions are not permitted.

9.1.2. Ipilimumab

Ipilimumab product will be administered according to the package insert (Appendix A) to the patient intravenously at the times indicated in Table 3. The following guidelines will be applied regarding delay of dose administration or discontinuation of ipilimumab therapy. Modifications to ipilimumab therapy during the study do not impact patient participation in the study, except where specifically noted below.

Decisions to delay an ipilimumab dose must be made on specified safety criteria. Treatment with ipilimumab will be delayed or discontinued if the patient experiences at least 1 AE, specified below, considered by the investigator to be "possibly," probably," or "definitely" related to ipilimumab treatment.

9.1.2.1. Delay of Ipilimumab

The following criteria will be used to determine dose delay of ipilimumab:

- Any Grade ≥3 skin-related AE regardless of causality

- Any Grade ≥2 non–skin-related AE (including immune-related adverse reactions), except for easily corrected laboratory abnormalities that do not reflect underlying organ pathology
- Any Grade ≥3 laboratory abnormality
- Any AE or laboratory abnormality that, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing
- It may be necessary to hold study drug to evaluate Grade 1 events that suggest ongoing or incipient autoimmune disease, including gastrointestinal (GI) toxicity, diarrhea, pancreatitis, hepatitis, pituitary insufficiency, early evidence of neurologic events, and skin toxicity, until diagnosis and progression are determined

9.1.2.2. Restarting Ipilimumab

Ipilimumab may be restarted if/when the AE(s) resolve(s) or returns to baseline severity within 2 weeks of last dose administration.

If the AE has been determined not be related to ipilimumab or is not an autoimmune/inflammatory event. If >1 dose is to be held or >2-week delay is expected due to current events not related to study, the dosing schedule modifications must be discussed with the principal investigator prior to implementation.

If the AE has resolved to Grade ≤1, ipilimumab dosing may be restarted at the next scheduled timepoint per protocol. Please follow guidelines for specific events. Please note that re-initiating treatment may be associated with recurrence or exacerbation of autoimmune or inflammatory events. In some instances, clinical resolution of events such as colitis may be associated with residual pathologic changes and should require evaluation of complete resolution prior to restarting therapy.

Events that require intervention with immunosuppressant therapy, steroids, surgery, or hormone replacement generally require permanently discontinuation of ipilimumab.

Autoimmune/inflammatory events are presumably related to the mechanisms of action of ipilimumab and potentially to a therapeutic effect. The incidence and severity of these events may be dose related, but once initiated, there is no evidence that lowered doses can be administered without continued autoimmune activity and there has so far been no demonstrable benefit to continuing ipilimumab after an autoimmune event during the initial treatment. As such, no dose modification is used for ipilimumab.

9.1.2.3. Ipilimumab Discontinuation

Patients must be discontinued from ipilimumab therapy and discontinued from study drug for the following reasons:

- Persistent adverse reactions that require holding more than 2 treatment doses
- Any motor neurologic toxicity Grade ≥3 regardless of causality
- Any Grade ≥3 treatment-related sensory neurologic toxicity
- Other Grade 3 or 4 events, including the following:

- Any event that requires systemic steroids or immunosuppressive treatment
- Severe or life-threatening adverse reactions, including any of the following:
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more per day over baseline), stool incontinence, need for intravenous (IV) hydration for more than 24 hours, GI hemorrhage, or GI perforation
- AST or ALT >5X ULN or total bilirubin >3X ULN
- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
- Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
- Severe immune-related reactions involving any organ system (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
- Immune-related ocular disease that is unresponsive to topical immunosuppressive therapy
- Any AE or laboratory abnormality that, in the judgment of the investigator, presents organ specific injury and/or a substantial clinical risk to the patient with continued dosing

Exceptions to ipilimumab discontinuation include:

- Potentially reversible inflammation (Grade <4), attributable to a local antitumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for but not diagnostic of metastasis
- Hospitalization for Grade ≤2 AEs where the primary reason for hospitalization is to expedite the clinical work-up
- The following conditions where, in the investigator's opinion, continuing study drug administration is justified based on the potential for continued clinical benefit:
  - Treatment with systemic steroids for <2 weeks without evidence of autoimmune disease requiring steroid treatment
  - Grade 2 skin rash treated with topical steroids for <4 weeks
  - Grade 2 ocular toxicity that has completely responded to topical therapy within 4 weeks
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. **Note:** Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy, such as hydrocortisone

9.1.2.4. Immune-Related Adverse Events and Reactions with Ipilimumab

Immune-related AEs or reactions are defined as adverse reactions of unknown etiology associated with ipilimumab exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an event an immune-related AE. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented on an AE or serious adverse event (SAE) form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-related adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune-related adverse reaction (e.g., rash, colitis, uveitis, hepatitis, or thyroid disease). If an immune-related adverse reaction is noted, appropriate work-up (including biopsy, if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical antitumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient.

Guidelines for treatment and monitoring of specific immune-related adverse reactions should follow the ipilimumab package insert (Appendix A). These recommendations should be utilized as clinically appropriate for the treatment of individual patients.

9.1.3. Nivolumab

Nivolumab will be administered according to the package insert (Appendix B) to the patient intravenously. The following guidelines will be applied regarding delay of dose administration or discontinuation of nivolumab therapy. Modifications to nivolumab therapy during the study do not impact patient participation in the study, except where specifically noted below.

Decisions to delay an nivolumab dose must be made on specified safety criteria. Treatment with nivolumab will be delayed or discontinued if the patient experiences at least 1 AE, specified below, considered by the investigator to be "probably" or "definitely" related to nivolumab treatment. Decisions to delay or discontinue nivolumab due to transaminase elevations should be discussed with the medical monitor.

9.1.3.1. Delay of Nivolumab

The following criteria will be used to determine dose delay of nivolumab:

- Any Grade 2 pneumonitis
- Grade 2 or 3 colitis
- ALT or AST > 3X ULN (or ALT or AST >8X ULN in patients taking liver medications at baseline) and up to 5X ULN or total bilirubin > 1.5X ULN and up to 3X ULN
- Creatinine > 1.5X and up to 6X ULN or greater than 1.5X baseline
- Any other severe or Grade ≥3 adverse reaction attributed to nivolumab administration

- Any AE or laboratory abnormality attributed to nivolumab that, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing

9.1.3.2. Restarting Nivolumab

Patients may resume treatment with nivolumab unless the criteria for permanent discontinuation are met (Section 9.1.3.3). Nivolumab may be restarted in patients whose adverse reactions recover to Grade 0 to 1. If the AE has resolved to Grade ≤1, nivolumab dosing may be restarted at the next scheduled time point per protocol. Please note that re-initiating treatment may be associated with recurrence or exacerbation of autoimmune or inflammatory events.

If >1 dose is to be held or >2-week delay is expected due to current events not related to study, the dosing schedule modifications must be discussed with the Medical Monitor prior to implementation.

9.1.3.3. Nivolumab Discontinuation

Patients must be discontinued from nivolumab therapy and discontinued from study drug for the following reasons:

- Persistent adverse reactions that require holding more than 2 treatment doses of nivolumab
- Any life-threatening or Grade 4 adverse reaction
- Grade 3 or 4 pneumonitis
- Grade 4 colitis
- AST or ALT > 5X ULN or total bilirubin > 3X ULN
- Creatinine greater than 6X ULN
- Any Grade ≥ 3 bronchospasm, hypersensitivity reaction, or infusion reaction
- Any severe or Grade ≥ 3 adverse reaction related to nivolumab treatment that recurs
- Persistent Grade 2 or 3 treatment-related adverse reactions that do not recover to Grade 1 or resolve within 12 weeks after last dose of nivolumab
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Any AE or laboratory abnormality that, in the judgment of the investigator, presents organ specific injury and/or a substantial clinical risk to the patient with continued dosing

9.1.3.4. Immune-Related Adverse Events and Reactions with Nivolumab

Immune-related AEs or reactions are defined as adverse reactions of unknown etiology associated with nivolumab exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an event an immune-related AE. Suspected immune-related adverse reactions must be documented on an AE or SAE form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-related adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune-related adverse reaction (e.g., pneumonitis, colitis, hepatitis). If an immune-related adverse reaction is noted, appropriate work-up should be performed, and steroid therapy may be considered if clinically necessary.

Guidelines for treatment and monitoring of specific immune-related adverse reactions should follow the nivolumab package insert (Appendix B). These recommendations should be utilized as clinically appropriate for the treatment of individual patients.

9.2. Concomitant Medications

9.2.1. Excluded Medications

Patients who have taken any of the following drugs within 7 days prior to the Randomization Visit (Day 1 Visit) will be excluded from the study:

- Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
- Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin), OCT1 transporter (e.g., metformin), OAT1 transporter (e.g., captopril, furosemide, methotrexate), and OATP1B3 transporter (e.g., atorvastatin, rosuvastatin, valsartan)

Please refer to the label of each medication for substrate information.

Administration of these medications will not be considered protocol deviations:

- Single dose administration of analgesics, anesthetics, or anxiolytics required for study-related biopsies
- Loperamide (Imodium®) to treat cancer treatment-induced diarrhea

The following medications and medication classes are not permitted during this study, except as noted in Section 9.2.2. Thus, patients taking these medications or treatments will be ineligible for continuation in the study:

- Any other investigational drug
- Any other agent intended for the treatment of cancer
- Herbal preparations or over-the-counter medication, except as identified in Section 9.2.2
- Granulocyte-stimulating factors, except for intermittent treatment of neutropenia
- Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
- Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin), OCT1 transporter (e.g., metformin), OAT1 transporter (e.g., captopril, furosemide, methotrexate), and OATP1B3 transporter (e.g., atorvastatin, rosuvastatin, valsartan)

9.2.2. Permitted Medications

Prophylactic antiemetics will be allowed, at the discretion of the treating physician. The following concomitant medications are permitted, as authorized by the treating physician:

- Antibiotics, except as noted above (Section 9.2.1)
- Daily multivitamins
- Daily supplements, vitamins, and minerals (e.g., calcium, magnesium, vitamin D, B-complex vitamins, vitamin E, etc.)
- Pain medication, except as noted above (Section 9.2.1)
- Other medications intended to manage concurrent diseases, except as noted above (Section 9.2.1)
- Oral, implantable, or injectable contraceptives

Patients taking medication chronically should be maintained on those same doses and dose schedules throughout the study period, as medically feasible. Patients taking medications with intermittent or as-needed schedules should try to avoid taking the concomitant medication on days when PK samples will be collected (i.e., Visits 2, 3, and 8), as medically feasible.

9.3. Compliance with Study Drug

The investigator or designee will only dispense study drug (RTA 408) to patients enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Beginning with the Week 4 Visit (Visit 5), 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.

9.4. Randomization and Blinding

No blinding or randomization procedures will be employed in this open-label study.

9.5. Protocol Safety Review Committee

As detailed in Section 7.4.2, for each combination therapy (i.e., RTA 408 + ipilimumab or RTA 408 + nivolumab), after the first 3 patients have completed the DLT observation period, all available safety and pharmacodynamic information will be reviewed by the PSRC to make a decision regarding escalation to the subsequent RTA 408 dose level or of the need to evaluate additional patients at the current RTA 408 dose level in combination with ipilimumab or nivolumab. The PSRC will include at a minimum a Sponsor representative, an oncologist, and a statistician. Should issues arise requiring expertise not represented by the current members, the PSRC may appoint additional clinical specialists.

Based on the number of evaluable patients and number of DLTs experienced outlined in Section 7.4.2, the PSRC will recommend one of the following: (1) patients enrolled in the subsequent cohort may be treated at the next higher dose level; (2) safety evaluation after 3 additional patients have completed the DLT observation period at the current dose level; (3) dose escalation will not occur; or (4) patients enrolled in the subsequent cohort may be treated at a lower dose between a previously well-tolerated dose level and the current dose level. The PSRC will also recommend one of the following: (1) enrollment will continue at the current dose level to a maximum of 6 patients; or (2) enrollment will not continue at the current dose level.

Additionally, the PSRC will also evaluate data for signs of pharmacodynamic activity and efficacy to recommend a Phase 2 dose.

9.6. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- Patient rescreening
- Management of an AE or SAE
- Performance of additional laboratory tests for clinically abnormal test values or to confirm a possible pregnancy
- Imaging studies for tumor size/burden evaluation as appropriate to assess disease burden or tumor size in patients with pseudo-progression
- Any time the investigator feels that it is clinically appropriate for patient safety

9.7. Pregnancy

9.7.1. Women of Childbearing Potential

WOCBP are female patients who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy), do not have fallopian inserts with confirmed blockage, have not had reproductive potential terminated by radiation, and are not postmenopausal for at least 1 year.

9.7.2. Methods of Birth Control

From the Screening Visit, while taking study drug, and until 3 months after taking the final dose of study drug, WOCBP must agree to practice one of the following methods of birth control:

- Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method
- Use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration
- Use of an intrauterine device
- Complete abstinence from sexual intercourse

From the Screening Visit, while taking study drug, and until 3 months after taking the final dose of study drug, males who have female partners of childbearing potential must agree to practice one of the following methods of birth control:

- Have had a vasectomy (at least 6 months earlier)
- Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method
- Partner use of hormonal contraceptives (oral, parenteral, vaginal or transdermal) for at least 3 months prior to study drug administration
- Partner use of an intrauterine device
- Complete abstinence from sexual intercourse

9.7.3. Suspected Pregnancy

During the study, all WOCBP must be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., late or missed menstrual period). Male patients must be instructed to contact the investigator if a sexual partner suspects she may be pregnant.

If a patient or investigator suspects that the patient may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If pregnancy is confirmed with a serum pregnancy test, the patient must discontinue taking study drug but continue to attend all study visits and undergo all study assessments. The patient should also follow the guidance on the ipilimumab or nivolumab prescribing information regarding continuation of ipilimumab or nivolumab. The investigator must immediately report a pregnancy associated with study drug exposure and record the event.

Pregnancy is not considered an AE; however, the investigator must follow a pregnant patient or the pregnant female partner of a male patient (if consenting), and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. Reata Pharmaceuticals or its designee may contact the investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the electronic CRF and on an SAE form:

- Congenital anomaly/birth defect
- Stillbirth
- Spontaneous miscarriage

9.8. Serious Toxicities

In the case of serious toxicities that do not meet the definition of a DLT (Section 7.4.3), the investigator may choose to interrupt treatment with RTA 408. RTA 408 treatment may be restarted with approval from the medical monitor. Dose reductions are not permitted. As stated in Section 9.3, if a patient misses more than 25% of the total planned doses during the study, protocol deviations should be recorded in the CRF. Recommended guidelines for treatment and

monitoring of specific immune-related adverse reactions are included in the ipilimumab package insert (Appendix A) and the nivolumab package insert (Appendix B), and specified safety criteria detailed in Sections 9.1.1.1 and 9.1.3 will be used to determine dose delay, restarting doses, or discontinuation of ipilimumab and nivolumab therapy, respectively.

Previous clinical experience in oncology patients with a related compound, bardoxolone methyl, suggests that transient elevations in transaminase (ALT or AST) and GGT levels may occur and then spontaneously resolve while continuing treatment with RTA 408. Furthermore, the DLT for bardoxolone methyl in oncology patients was transaminase elevations (Hong, 2012).

Any increase in transaminase (ALT or AST) levels to >3X ULN should be followed by repeat testing of ALT, AST, and total bilirubin within 48 to 72 hours. If the elevations persist above 3X ULN, the transaminase and total bilirubin tests should be repeated 2 to 3 times weekly. Patients must be discontinued from the study drug if they meet any of the following criteria :

- ALT or AST >3X ULN **and** (total bilirubin >2X ULN **or** 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%)

If a patient is discontinued from study drug due to one of the above criteria, the hepatobiliary tree must be visualized (e.g., ultrasound) and assessed. Additional tests or studies may be warranted depending on the clinical presentation.

9.9. Study Procedures

- To avoid interobserver variability, every effort should be made to ensure that the same individual who made the initial baseline determination completes all subsequent assessments.
- With approval of the Sponsor, or designee, screening may be increased to 28 days on an individual patient basis.

9.9.1. Informed Consent

Written informed consent (Section 16.3) must be obtained from the patient before any study-related procedures are performed, and if there is a change in the study procedures that could affect the patient's willingness to participate. Informed consent must also be obtained from the patient if RECIST progressive disease is observed that the Investigator suspects is due to pseudo-progression and the patient wishes to continue protocol-specified treatment (Section 8.4.1).

9.9.2. Inclusion/Exclusion Criteria

Inclusion and exclusion criteria should be reviewed at the times indicated in Table 3 and Table 4. Patients must meet all of the inclusion criteria and none of the exclusion criteria for entry into the study.

9.9.3. Demographics and Baseline Disease Characteristics

Demographic data, including sex, age, race, and ethnicity, and baseline disease characteristics, including documentation of prior antineoplastic therapy, will be collected at the time indicated in Table 3 and Table 4.

9.9.4. Prior and Concomitant Medications

Information on prior and concomitant medications will be collected at the times indicated in. The name, dose, and frequency of all medications that the patient is taking or has taken within 30 days prior to Study Day 1 must be recorded. All allowed and excluded medications should be recorded, including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Trade or generic drug names should be used whenever possible.

9.9.5. Medical History

A complete medical history (e.g., per patient report) that includes all medical history within the past 5 years will be collected and recorded at the time indicated in Table 3 and Table 4.

9.9.6. ECOG Performance Status

ECOG performance status will be assessed using the grading scale shown below (Table 6; Oken, 1982) and recorded at the times indicated in Table 3 and Table 4.

Table 6: ECOG Performance Status

ECOG Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

9.9.7. Height

Height in centimeters should be measured without footwear, head coverings, or prosthetics at the time indicated in Table 3 and Table 4.

9.9.8. Weight and Body Mass Index

Weight in kilograms should be measured at the times indicated in Table 3 and Table 4. Body mass index (BMI) will be automatically calculated each time the weight is recorded.

9.9.9. Electrocardiogram

A 12-lead ECG will be recorded at the times indicated in Table 3 and Table 4 after the patient has rested for approximately 10 minutes in a supine position. The heart rate from the ECG machine should not be used as part of the vital sign measurements.

9.9.10. Vital Sign Measurements

Vital sign measurements should be taken at the times indicated in Table 3 and Table 4 and include the patient's heart rate (beats/minute), blood pressure (mm Hg), and body temperature (°C). Blood pressure should be taken after the patient has rested in a sitting position for approximately 5 minutes. The same arm (usually the non-dominant arm) and the appropriate size cuff should be used for each measurement.

9.9.11. Physical Examination

A comprehensive physical examination must be performed by a physician, physician assistant, or registered nurse practitioner at the times indicated in Table 3 and Table 4. If possible, the same individual should perform each physical exam on a patient during the study. The examination must include the following organ or body system assessments: head, eyes, ears, nose, throat, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, skin, extremities, and neurological. Assessments of any specific signs or symptoms reported by the patient must also be performed and documented along with any other findings of note. Findings at the Screening Visit must be characterized as either normal or abnormal, and, if abnormal, a description of the abnormality must be provided. Following the examination at the Screening Visit, the assessments must be classified as unchanged, new, worsened, or improved from the last time the body system was assessed.

9.9.12. Pregnancy Test

WOCBP (Section 9.7.1) will provide a blood or urine sample for a pregnancy test at the times indicated in Table 3 and Table 4. Negative serum test results are required at the Randomization Visit (Day 1 Visit) before study drug administration, and negative urine test results are required at all other times indicated in Table 3 and Table 4 for continued participation in the study. Any patient who becomes pregnant during the study must discontinue taking study drug immediately. See Section 9.7.3 for a description of procedures to be followed in case of pregnancy.

9.9.13. Study Drug Dispensation

Adequate quantities of RTA 408 capsules will be dispensed to the patient at the times indicated in Table 3 and Table 4 to last the patient until the next visit, along with instructions for use.

9.9.14. Study Drug Return/Pill Count

Capsules returned by the patient will be counted by the study doctor or the study staff at the times indicated in Table 3 and Table 4 to determine treatment compliance. Criteria for noncompliance and instructions for recording compliance on the CRF are included in Section 9.3.

9.9.15. Study Drug Administration

Patients should self-administer the assigned number of RTA 408 Capsules orally once daily in the morning on an empty stomach (approximately 1 hour before or 2 hours after eating) with water at the times indicated in Table 3 and Table 4, except on days when PK samples are collected (Day 1, Week 1, and Week 13 [Visits 2, 3, and 8]), at which time study staff will administer RTA 408 at the clinic following collection of the first (predose) PK sample.

A vomited dose should not be replaced. Missed doses may be taken in the afternoon or evening of the same day approximately 1 hour before or 2 hours after a meal. A double dose (e.g., missed dose from previous day and dose for current day) should not be taken.

9.9.16. Ipilimumab Administration

Ipilimumab 3 mg/kg will be administered to the patient intravenously at the times indicated in Table 3 according to the package insert (Appendix A).

9.9.17. Nivolumab Administration

Nivolumab 240 mg will be administered to the patient intravenously at the times indicated in Table 4 according to the package insert (Appendix B).

9.9.18. Tumor Biopsy

Three tumor biopsies will be collected at the Screening Visit, at Week 1, and at Week 13 (Table 3 and Table 4) for analysis of the following biomarkers: NF-κB, iNOS, nitrotyrosine, arginase, and other markers of immune status and inflammation. All tumor biopsies are mandatory for patients enrolling in the Phase 1b dose-escalation portion of the study. The Screening visit tumor biopsy is mandatory for patients enrolling in the Phase 2 portion of the study, but the Week 1 and Week 13 tumor biopsies are optional for these patients. Additionally, immunohistochemical staining will be used to quantify tumor cell populations (e.g., tumor infiltrating lymphocytes and MDSCs). These biopsies should include adequate tissue for sample analysis, as detailed in the study manual. Detailed processing instructions will be provided for isolation, storage, and shipment of tumor biopsy samples.

The date and time of collection of all tumor biopsy samples should be recorded; however, any deviations from the protocol-specified sampling times will not be considered protocol deviations. Sample time deviations will be summarized in the study report.

9.9.19. Tumor Burden Evaluation

Complete and partial tumor responses will be evaluated by radiographic assessment at the times indicated in Table 3 and Table 4 using the standardized response criteria developed by the RECIST (Response Evaluation Criteria In Solid Tumours) Working Group, version 1.1 (Eisenhauer, 2009), which will be provided to the investigator. Spiral computed tomography (CT) with contrast is preferred unless otherwise specified by the principal investigator or designee. Assessments performed within 28 days preceding administration of the first dose may be used for baseline tumor burden evaluation. If tumor assessments are performed for any reason prior to Week 13, investigators should consider that transient increase of tumor burden on

radiographic assessments has been reported with ipilimumab that may subsequently resolve on continued therapy, and discontinuation of protocol therapy is not required based on such results.

9.9.20. Adverse Event Collection

Patients should be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness at the times indicated in Table 3 and Table 4. Patients should be instructed to volunteer any information regarding AEs at any time during the study. The study doctor or the study staff should also query patients with an open question regarding any AEs they may be experiencing (e.g., "How do you feel?" or "How have you been feeling since your last visit?"). Any findings are to be documented and will be evaluated by the investigator or designee according to the CTCAE criteria per Section 12.5.

9.9.21. Clinical Chemistry

Blood samples will be collected for clinical chemistry analyses at the times indicated in Table 3 and Table 4. Clinical chemistry analyses are listed in Table 7. For calculation of the eGFR, the 4-variable MDRD equation must be used. The equation is as follows:

$$eGFR = 175 \times \text{standardized serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ [if black]} \times 0.742 \text{ [if female]}$$

Table 7: Clinical Chemistry Assessments

Clinical Chemistry Assessments
B-type natriuretic peptide (BNP)
N-Terminal-proBNP (NT-proBNP)
Blood urea nitrogen (BUN)
Creatinine
Total bilirubin
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Alkaline phosphatase (ALP)
Ferritin
Sodium
Potassium
Calcium
Inorganic phosphorus
Magnesium
Chloride
Bicarbonate
Uric acid
Cholesterol
Total protein
Glucose
Triglycerides
Albumin
Creatine phosphokinase (CPK)
Lactate dehydrogenase (LDH)
High-density lipoprotein cholesterol (HDL-C)
Low-density lipoprotein cholesterol (LDL-C)
Very-low-density lipoprotein cholesterol (VLDL-C) (direct measurement or calculation per local lab standards)
Gamma-glutamyl transpeptidase (GGT)
Estimated glomerular filtration rate (eGFR) using the MDRD formula

9.9.22. Hematology

Blood samples will be collected for hematology assessments at the times indicated in Table 3 and Table 4. Hematology assessments are listed in Table 8.

Table 8: Hematology Assessments

Hematology Assessments
Hematocrit
Hemoglobin
Red blood cell (RBC) count
White blood cell (WBC) count
Neutrophils
Bands (if detected)
Lymphocytes
Monocytes
Basophils (if detected)
Eosinophils (if detected)
Absolute platelet count
Mean corpuscular hemoglobin (MCH)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin concentration (MCHC)
Reticulocyte count

9.9.23. Coagulation

Blood samples will be collected for coagulation assessments at the times indicated in Table 3 and Table 4. Coagulation assessments are listed in Table 9.

Table 9: Coagulation Assessments

Coagulation Assessments
Prothrombin time (PT)
Partial thromboplastin time (PTT)
International normalized ratio (INR)

9.9.24. Virus Serology

Blood samples will be collected for testing for hepatitis A, B, and C viruses, and anti-HIV type 1 or 2 antibodies at the time indicated in Table 3 and Table 4.

9.9.25. Peripheral Blood Mononuclear Cell Biomarker Analysis

Blood samples for PBMC biomarker analysis will be collected at the times indicated in Table 3 and Table 4. These biomarkers include, but are not limited to, the following genes: Nrf2, NF-κB, NQO1, SRXN1, GCLC, GSR, GLRX, PRDX1, TXN, TXNRD1, PGD, and G6PD. Blood samples (2 x 8 mL each) will be collected within cell preparation tubes containing sodium citrate. The date and time of collection of all PBMC blood samples should be recorded; however, any deviations from the protocol-specified sampling times will not be considered protocol deviations. Sample time deviations will be summarized in the study report. Dates in the CRF should be recorded in an unambiguous format (e.g., DD MMM YYYY) and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples not collected should be recorded as such. Detailed sample processing instructions will be provided for isolation, storage, and shipment of PBMC samples.

9.9.26. Peripheral Blood Mononuclear Cell Myeloid-Derived Suppressor Cell Analysis

Blood samples will be collected for PBMC MDSC analysis at the times indicated in Table 3 and Table 4. Multiple tests will be performed, including analysis of ROS and peroxynitrite levels in

myeloid cells, analysis of the functional activity of MDSCs, and assessing the response of mononuclear cells to stimulation with recall antigen (tetanus toxoid). Because RTA 408 influences the transcription of genes that result in reduced peroxynitrite levels, MDSCs recovered from the blood of patients treated with RTA 408 are expected to have reduced functional capacity to suppress T-cell function.

Blood samples (30 mL each) will be collected within cell preparation tubes containing sodium citrate. The date and time of collection of all PBMC samples should be recorded; however, any deviations from the protocol-specified sampling times will not be considered protocol deviations. Sample time deviations will be summarized in the study report. Dates in the CRF should be recorded in an unambiguous format (e.g., DD MMM YYYY) and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples not collected should be recorded as such. Detailed sample processing instructions will be provided for isolation, storage, and shipment of PBMC samples.

9.9.27. Pharmacokinetic Analysis

Blood samples for PK analysis will be collected at the times indicated in Table 3 and Table 4. Blood sample collection instructions are detailed in the lab manual.

The date and time of collection of all PK blood samples should be recorded; however, any deviations from the protocol-specified sampling times will not be considered protocol deviations. Sample time deviations will be summarized in the study report. Dates in the CRF should be recorded in an unambiguous format (e.g., DD MMM YYYY) and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples not collected should be recorded as such. Detailed sample processing instructions will be provided for isolation, storage, and shipment of PK samples.

9.9.28. Urinalysis and Microscopy

Urine samples will be collected for urinalysis and microscopy assessments at the times indicated in Table 3 and Table 4. Urinalysis and microscopy assessments are listed in Table 10.

Table 10: Urinalysis/Microscopy Assessments

Urinalysis/Microscopy Assessments
Specific gravity
Ketones
pH
Protein
Blood
Glucose
Urobilinogen
Bilirubin
Microscopic examination (if indicated based on laboratory procedures)
Nitrate
Leukocyte esterase

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

RTA 408 capsules, in 2.5-mg, 10-mg, and/or 50-mg strengths, will be used in this study.

10.2. Study Drug Packaging and Labeling

RTA 408 will be supplied in 75-cc white high-density polyethylene (HDPE) bottles with foil induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 30 capsules and each capsule will contain 2.5 mg, 10 mg, or 50 mg of RTA 408. Each bottle will also contain a desiccant insert that must not be ingested. The label on each bottle will contain the following information:

- Protocol 408-C-1401
- Lot number
- Dose strength (one of the following):
    - RTA 408 Capsules, 2.5 mg
    - RTA 408 Capsules, 10 mg
    - RTA 408 Capsules, 50 mg
- Contents: 30 capsules. Bottle also contains one desiccant insert; do not ingest the desiccant insert.
- Direction for use: Take capsule(s) as directed orally once a day in the morning on an empty stomach (1 hour before or 2 hours after eating) with water
- Caution Statement: New Drug – Limited by Federal Law to Investigational Use
- FOR ORAL USE ONLY
- Storage: Store at 20°C to 25°C (68°F - 77°F), excursions allowed to 15°C to 30°C (59°F - 86°F).
- Reata Pharmaceuticals, Inc., Irving, TX

To accommodate multiple dose levels, the study drug will be provided to the site pharmacy. The pharmacist will provide an adequate number of bottles to each patient with clear instructions on the number and type of capsules to be taken each day.

10.3. Study Drug Storage

The stability of the drug product is being evaluated in ongoing studies.

Investigative sites must store the investigational product in a secure location with room temperature conditions of 20°C to 25°C (68°F - 77°F), excursions allowed to 15°C to 30°C (59°F - 86°F).

10.4. Study Drug Administration

Please refer to Section 9.9.15 for details on study drug administration. An appropriate number of capsules and/or bottles will be provided to each patient based on the number of capsules required for each dose level. Clear instructions will be provided to the patient regarding the number and type of capsules to be ingested at each study drug administration time point listed in Table 3 and Table 4.

10.5. Study Drug Accountability

The investigator or designee will maintain a record of all study drug received, dispensed, and returned to the Sponsor or its designee. No study drug shall be destroyed by the clinical site unless directed to do so by the Sponsor or its designee. Study drug bottles and any unused capsules should be returned by the patient to the study staff.

10.6. Study Drug Handling and Disposal

At the conclusion of the study, the Sponsor or its designee will direct the site regarding the final disposition of any remaining study drug.

11. PHARMACOKINETIC, PHARMACODYNAMIC, AND EFFICACY ASSESSMENTS

11.1. Pharmacokinetic Samples

PK samples will be analyzed for RTA 408 using a validated analytical method. Samples may be analyzed for potential metabolites of RTA 408 using nonvalidated analytical methods.

11.2. Tumor Biopsies

Tumor biopsies will be analyzed for biomarkers of NF-κB and to determine the immune status of tumors. These biomarkers include, but are not limited to, the following parameters: NF-κB, iNOS, nitrotyrosine, arginase, and other markers of immune status and inflammation. Additionally, immunohistochemical staining will be used to quantify tumor cell populations (e.g., tumor infiltrating lymphocytes and MDSCs).

11.3. Peripheral Blood Mononuclear Cells

PBMC samples will be analyzed for biomarkers of Nrf2 and NF-κB pharmacology using nonvalidated analytical methods. Additional biomarkers include, but are not limited to, the following genes: NQO1, SRXN1, GCLC, GSR, GLRX, PRDX1, TXN, TXNRD1, PGD, and G6PD.

PBMC samples will also be collected for MDSC analysis. Multiple tests will be performed, including analysis of ROS and peroxynitrite levels in myeloid cells, analysis of the functional activity of MDSCs, and assessing the response of mononuclear cells to stimulation with recall antigen (tetanus toxoid). Because RTA 408 influences the transcription of genes that result in reduced peroxynitrite levels, MDSCs recovered from the blood of patients treated with RTA 408 are expected to have reduced functional capacity.

11.4. Tumor Burden Evaluation

Spiral CT with contrast is preferred to evaluate tumor burden unless otherwise specified by the principal investigator or designee. Assessments performed within 28 days preceding administration of the first dose may be used to assess baseline tumor burden. The assessment performed at the Screening Visit should be the same method used throughout the study. Complete and partial responses to RTA 408 and ipilimumab or RTA 408 and nivolumab will be evaluated using the standardized response criteria developed by The RECIST Working Group, version 1.1 (Eisenhauer, 2009), which will be provided to the investigator.

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

Safety parameters include weight, BMI, ECG, vital sign measurements, physical examination, AEs, SAEs, and laboratory tests (clinical chemistry, hematology, urinalysis, and microscopy).

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be related to RTA 408 or ipilimumab or nivolumab. Included in this definition are any newly occurring events or previous condition that has increased in severity or frequency since the administration of study drug. Disease progression is a study endpoint and consequently, disease progression should not be reported as an AE. However, when a patient dies from disease progression with no other immediate causes, "disease progression" should be reported as an SAE (Section 12.2.1.2). Additionally, signs and symptoms that may be related to disease progression or the underlying disease (regardless of disease progression) should be reported as an AE or as an SAE if it meets the definition of an SAE in Section 12.2.1.2.

All AEs that are observed or reported by the patient during the study (from the time of the first dose of study drug until the final visit) must be reported, regardless of their relationship to study drug or their clinical significance.

12.2.1.2. Serious Adverse Event

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect in an offspring of a patient taking study drug
- Is an important medical event

The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may

jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time of first dose of study drug until the final visit). Certain pregnancy outcomes will require submission as an SAE (Section 9.7.3).

The investigator is responsible for reporting to Reata Pharmaceuticals or its designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of first dose of study drug until the final visit) according to designated Standard Operating Procedures, regardless of their relationship to study drug or their clinical significance. All SAEs reported or observed during the study must be followed to resolution or until the investigator deems the event to be chronic or the patient to be stable. Reata Pharmaceuticals or its designee may contact the investigator to obtain additional information on any SAE that has not resolved at the time the patient completes the study.

12.3. Eliciting Adverse Event Information

At every study visit, patients must be asked a standard, non-directed question, such as, "How do you feel?" or "How have you been feeling since your last visit?" to elicit any medically related changes in their well-being. They may also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses should be recorded in the source documents.

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, ECG abnormalities, or other documents that are relevant to patient safety.

12.4. Assessment of Causality

The investigator must use the following classifications and criteria to characterize the relationship or association of RTA 408 or ipilimumab or nivolumab, in causing or contributing to the AE:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration, and/or, follows a known response pattern to the study drug, but could have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based

on the investigator's clinical experience, the association of the event with study drug administration seems likely.

12.5. Assessment of Severity

The investigator will grade the severity of the AEs as Grades 1, 2, 3, 4, or 5 based on the National Cancer Institute (NCI) CTCAE, version 4.03. If the criteria in the CTCAE version 4.03 do not apply, severity should be defined as shown in Table 11.

Table 11: AE Severity Grades

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

The NCI CTCAE, version 4.03 will be provided to the investigator.

12.6. Recording Adverse Events

All conditions present prior to the first dose of study drug should be documented as medical history. All drug-related (characterized as possibly or probably related; Section 12.4) AEs and abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline or within normal limits). All other AEs will be followed through the final visit (i.e., end of study or early termination). Information to be collected includes type of event, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

While an AE is ongoing, changes in the severity (e.g., worsening or improving) should be noted in the source documents but when documenting the AE, only the total duration and greatest severity should be recorded in the CRF. AEs characterized as intermittent require documentation of onset and duration.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, or reactions to concurrent medications must also be reported. Worsening or complication of such a concurrent condition should also be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…"). Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. Disease progression is a study endpoint and consequently, disease progression should not be reported as an AE or SAE. However, when a subject dies from disease progression with no other immediate causes, "disease progression" should be reported as an SAE. Additionally, signs and symptoms that may be related to disease

progression or the underlying disease (regardless of disease progression) should be reported as an AE or as an SAE if it meets the definition of an SAE in Section 12.2.1.2.

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory test values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory test values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine levels in renal failure), only the diagnosis should be reported as an AE.

Elective procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs but should be documented in the patient's source documents as elective (e.g., elective periodontal surgery). However, if a preplanned procedure is performed early (e.g., as an emergency) because of a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE.

12.7. Reporting Serious Adverse Events

Any AE that meets the criteria of serious according to the previously described criteria must be reported within 24 hours from the time when site personnel first learn about the event. To report the SAE, fax the completed SAE form to Medpace (fax number listed below in Table 12) within 24 hours of awareness.

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., patient discharge summary or autopsy reports), should be faxed to Medpace Clinical Safety (Table 12).

Reata Pharmaceuticals or its designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For other SAEs that do not meet the fatal or life-threatening unexpected criteria, but are reported to be associated with the use of the study drug (that is, "possible" or "probable" in causality assessment), Reata Pharmaceuticals or its designee will notify the appropriate regulatory agencies in writing within the timeframe established by those regulatory agencies. Reata Pharmaceuticals or its designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the investigators for their information and submission to their IRB, as appropriate.

Principal investigators are responsible for informing their IRB of any SAEs at their site, as appropriate. SAE correspondence with regulatory authorities or IRBs must be submitted to Reata Pharmaceuticals or its designee for recording in the study file.

13. STATISTICS

13.1. Sample Size

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) selection of a Phase 2 dose based on review of safety, efficacy, and pharmacodynamic data, and (3) assessment of 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.

The Phase 2 portion of the study allows for assessment of ORR at the selected Phase 2 dose of RTA 408 with nivolumab. Since the Phase 2 portion will only enroll patients previously treated with anti-PD-1 or anti-PD-L1 therapy (including experimental therapies), the ORR for nivolumab monotherapy is assumed to be 0%. A sample size of 24 patients for the expansion cohort achieves approximately 80% power to detect an improvement of 20% in ORR from the assumed nivolumab ORR as the null hypothesis using a 1-sided binomial test at alpha=0.10.

13.2. Study Variables

13.2.1. Pharmacokinetic Variables

The PK variables include RTA 408 plasma concentration-time data and metabolite concentration-time data (if available) for each analyte.

13.2.2. Pharmacodynamic 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.

13.2.3. Efficacy Variables

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

13.2.4. Safety 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, AEs, and SAEs.

13.3. Statistical Analyses

A statistical analysis plan (SAP) detailing the analyses will be developed prior to the database lock. The SAP will include analysis of all safety, PK, pharmacodynamic (PD), and response variables. All statistical analyses and data summaries will be performed using SAS® (version 9.1 or higher) or other similar software. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages. Patients will be pooled from the Phase 1b dose-escalation cohorts with the Phase 2 expansion cohort by RTA 408 dose level for data analyses.

13.3.1. Primary Efficacy Analyses

The ORR for the Phase 2 dose will be compared to the null hypothesis of 0% for nivolumab monotherapy using a 1-sided binomial test.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

The study monitor, as a representative of the Sponsor, has the obligation to follow the study conduct closely. In doing so, the monitor will visit the principal investigator and study facilities periodically, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current knowledge of the study activity of the investigator and his/her staff through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigators and staff.

The Sponsor or its designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6(R1), abbreviated as ICH E6(R1), and current standard operating procedures.

Each principal investigator is expected to make a reasonable effort to accommodate the monitor when monitoring visits are necessary and to be available during the site visit. Furthermore, the monitor should be provided direct access to source data and documents for trial-related monitoring and to the internet during the visit.

14.2. Audits and Inspections

Principal investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), by providing direct access to all study records. In the event of an audit, the principal investigator agrees to allow the Sponsor, representatives of the Sponsor, the FDA, or other relevant regulatory authorities access to all study records.

The principal investigator or designee should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or its designee.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Reata Pharmaceuticals may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

15.2. Financial Disclosure

Principal investigators and sub-investigators are required to provide financial disclosure information prior to starting the study. In addition, the principal investigator and sub-investigators must provide the Sponsor or its designee with updated information, if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Any potential investigator who has a vested financial interest in the success of this study may not participate in this study.

15.3. Sponsor Obligations

The Sponsor or its designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor or its designee is not financially responsible for treatment of non-study-related fatalities, physical injuries, or damage to health that may occur during the clinical study, as well as the patient's underlying disease.

15.4. Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R1), Section 8.2 and Title 21 of the United States (US) Code of Federal Regulations (CFR), abbreviated as US CFR Title 21, by providing the essential documents to the Sponsor or its designee, which include but are not limited to the following:

- An original investigator-signed investigator agreement page of the protocol
- The IRB approval of the protocol
- The IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the principal investigator and each sub-investigator listed on Form FDA 1572. A curriculum vita and current licensure, as applicable, must be provided. The curriculum vitae must have been signed and dated by the principal investigators and sub-investigators within 2 years before study start-up to indicate the documents are accurate and current

- Completed financial disclosure forms (Section 15.2) to allow the Sponsor or its designee to submit complete and accurate certification or disclosure statements required under US CFR Title 21, Part 54. In addition, the investigators must provide to the Sponsor or its designee a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study
- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of this study

15.5. Clinical Study Insurance

In accordance with the respective national drug laws, the Sponsor has taken out patient liability insurance for all patients who give their consent and enroll in this study. This insurance covers potential study-related fatalities, physical injuries, or damage to health that may occur during the clinical study.

15.6. Use of Information

All information regarding RTA 408 supplied by the Sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Furthermore, the investigator is obligated to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of RTA 408 Capsules and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants, as required.

16. ETHICS

16.1. Institutional Review Board Review

The protocol and the proposed informed consent form (ICF) must be reviewed and approved by a properly constituted IRB before study start. Each site must provide the Sponsor or its designee a signed and dated statement that the protocol and informed consent have been approved by the IRB before consenting patients. Prior to study initiation, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee, and regulatory authorities, as required.

The IRB chairperson or designee must sign all IRB approvals and must identify the IRB by name and address, the clinical protocol, and the date approval and/or favorable opinion was granted.

The principal investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB, but not exceeding 1 year. The principal investigator must supply the Sponsor or its designee with written documentation of reviews of the clinical research.

16.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH E6(R1), with applicable local regulations (e.g., US CFR Title 21), and with the ethical principles of the Declaration of Helsinki.

The principal investigator agrees to conduct the study in accordance with the ICH E6(R1) and the principles of the Declaration of Helsinki. The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

16.3. Written Informed Consent

Because the study will be conducted under a US Investigational New Drug Application, a signed ICF, in compliance with US CFR Title 21, Part 50, will be obtained from each patient before the patient enters the study. An informed consent template may be provided by the Sponsor or its designee to the investigators. The consent must be reviewed by the Sponsor or its designee before IRB submission. Once reviewed, the consent will be submitted by the principal investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all participants affected by the revision must sign the revised IRB-approved consent form.

Before enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved ICF. Once the principal investigator or designee is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB, and a copy of the approved version and the notice of approval must be provided to the Sponsor's designated monitor after IRB approval.

The principal investigator or designee will provide a copy of the ICF (signed copy to be provided per applicable law) to the patient and/or legal guardian. The original form will be maintained in the patient's medical records at the site.

16.4. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB.

The principal investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

16.5. Modification of the Protocol

Any changes that arise after the approval of the protocol must be documented as protocol amendments. FDA must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the principal investigator, and the IRB. In cases where the protocol is modified to enhance patient safety, changes may be implemented and the amendment must be immediately submitted to the IRB.

The principal investigator is responsible for informing the IRB of all problems involving risks to patients according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify FDA in accord with US CFR Title 21, Part 312, Section 32.

16.6. Protocol Deviations

The principal investigator or designee must document any protocol deviation. The IRB must be notified of all protocol deviations in a timely manner by the investigator as appropriate. Protocol deviations will also be documented by the responsible monitor during monitoring visits, and those observations will be communicated to the investigator.

If there is an immediate hazard to a patient, the principal investigator may deviate from the protocol without prior Sponsor and IRB approval. The Sponsor and IRB must be notified of the deviation.

17. DATA HANDLING AND RECORDKEEPING

17.1. Retention of Records

The investigator will maintain all study records according to ICH E6(R1) and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application is approved or 2 years after formal discontinuation of the clinical development of the investigational product. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

17.2. Case Report Forms

All CRF data will be entered in electronic forms at the investigational site. The electronic data capture (EDC) system used to capture data electronically for all randomized patients will be US CFR Title 21, Part 11 compliant.

18. PUBLICATION POLICY

Reata Pharmaceuticals reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. Reata Pharmaceuticals supports communication and publication of study results whatever the findings of the study. Reata Pharmaceuticals also encourages disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication.

Those individuals who have contributed greatly to this study, as determined by Reata Pharmaceuticals, will serve on any publications committee for the study.

19. LIST OF REFERENCES

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APPENDIX A. IPILIMUMAB PACKAGE INSERT

APPENDIX B. NIVOLUMAB PACKAGE INSERT