NCT #NCT03323398

ModernaTX, Inc.

mRNA-2416-P101

A Phase I/II, Open-label, Multicenter, Dose Escalation and Efficacy Study of mRNA-2416, a Lipid Nanoparticle Encapsulated mRNA Encoding Human OX40L, for Intratumoral Injection Alone and in Combination with Durvalumab for Patients with Advanced Malignancies

29NOV2021

Statistical Analysis Plan

Version 1.0

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List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLQ	below the level of quantification
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence intervals
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irRC	immune-related Response Criteria
irSD	immune-related stable disease
ITT	Intent-to-treat
LYRIC	lymphoma response to immunomodulatory therapy criteria
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable

ORR	overall response rate
OX40L	OX40 ligand
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PEG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
QIF	quantitative immunofluorescence
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. Introduction

The purpose of the statistical analysis plan (SAP), which is based on most recent version of clinical study protocol amendment version 6 dated 10-JUN-2019, and the case report form (CRF) version 14.0 dated 12-MAR-2021, is to describe the analyses and data presentations for the Sponsor's protocol mRNA-2416-P101. This SAP outlines the types of analyses that will address the study objectives, and explains in detail how the data will be handled and analyzed. It contains the definitions of analysis sets and statistical methods for the analysis of safety, efficacy, pharmacokinetics (PK), and pharmacodynamics.

In addition to the information presented in the statistical methods section of the protocol (Section 13) which provides the principal features of planned analyses for this study, this SAP provides appropriate statistical analysis methodologies in details. It also documents modifications or additions (if applicable) to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

PPD Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the efficacy, safety, pharmacokinetic, and pharmacodynamics; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the clinical database lock for primary analysis. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

2. Study Objectives

2.1. Primary Objectives

The primary objectives of the study are as follows:

Phase I

- To determine safety and tolerability of escalating intratumoral doses of mRNA-2416 alone and in combination with durvalumab in patients with relapsed/refractory solid tumor malignancies or lymphoma
- To define the maximum tolerated dose (MTD) and recommended dose for expansion (RDE) and schedule for intratumoral injections of mRNA-2416 alone and in combination with durvalumab in patients with relapsed/refractory solid tumor malignancies or lymphoma

Phase II

- To assess objective response rate of mRNA-2416 alone and in combination with durvalumab in ovarian cancer based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

2.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To assess emergence of antibodies against the drug product as well as OX40 ligand (OX40L), the protein translated by the drug product
- To assess mRNA PK alone and in combination with durvalumab
- To assess anti-tumor effects of mRNA-2416 alone and in combination with durvalumab
- Phase I only: To assess objective response rate and duration of response (DOR) of mRNA-2416 alone and in combination with durvalumab based on RECIST v1.1 or Cheson 2014 criteria (lymphomas)
- Phase II only: To assess disease control rate (DCR) and DOR of mRNA-2416 alone and in combination with durvalumab based on RECIST v1.1

2.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- To assess objective response rate of mRNA-2416 alone and in combination with durvalumab based on Immune-related Response Criteria (irRC) or lymphoma response to immunomodulatory therapy criteria (LYRIC)
- To assess the correlation of other investigational serum-based proteins (eg, anti-drug antibodies) with PK, efficacy, and safety endpoints
- To assess biomarkers of immunological response in tumor and blood of mRNA-2416 alone and in combination with durvalumab
- To assess PK of durvalumab in combination with mRNA-2416

3. Investigational Plan

3.1. Overall Study Design and Plan

This is an open-label, multicenter, Phase I/II Dose Escalation study of repeated intratumoral injections of mRNA-2416 alone (Arm A) and in combination with intravenously administered durvalumab (Arm B) in patients with advanced relapsed/refractory solid tumor malignancies or lymphoma, followed by Expansion period in patients with ovarian cancer in each treatment arm. Each arm of the study consists of a Dose Escalation Period in non-visceral lesions and a Dose Confirmation period in visceral lesions followed by a Dose Expansion Period in ovarian cancer.

Each dose level in the Dose Escalation Period will be conducted using a standard 3+3 study design in order to determine the safety and tolerability of each dose. For Arm A Dose Escalation, once a dose level has been cleared for safety, that dose level is open to enrollment of up to 9 additional patients who are willing and eligible to undergo tumor biopsy.

Once the expected MTD/RDE has been cleared in Dose Escalation for Arm A, Dose Escalation in Arm B will begin with mRNA-2416 at 1 dose level lower than the Arm A MTD/RDE according to the protocol Table 1.

For both arms, once the expected MTD/RDE has been cleared in Dose Escalation, Dose Confirmation of the MTD/RDE will be conducted in at least 3 patients with ovarian cancer with visceral lesions injectable

with ultrasound or computer tomography (CT) guidance. Dose Confirmation will be conducted in the same fashion as Dose Escalation.

For both arms, once the MTD and/or RDE has been determined in Dose Escalation/Confirmation, patients will be enrolled in the Expansion cohort in order to assess the preliminary anti-tumor activity of mRNA-2416 in ovarian cancer of epithelial origin.

Prior to enrollment, all patients will undergo screening to determine study eligibility. Arm A patients will receive mRNA-2416 for 6 cycles with 28 days in each cycle. Arm B patients will receive mRNA-2416 in combination with durvalumab for 6 cycles with 28 days in each cycle. Following completion of 6 cycles of combination dosing, patients may continue with durvalumab as a single-agent until disease progression, unacceptable toxicity, or 24 months of treatment (total), whichever is sooner. Patients completing study therapy with an overall tumor assessment of stable disease (SD) or better will be followed for efficacy for 6 months or until disease progression, whichever occurs first. Schedule of events can be found in the protocol.

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary endpoints of the study are as follows:

Phase I

- Incidence and nature of dose-limiting toxicities (DLTs) with mRNA-2416 alone and in combination with durvalumab
- Incidence, nature, and severity of adverse events (AEs)/serious adverse events (SAEs), graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for mRNA-2416 alone and in combination with durvalumab

Phase II

- Assessment of objective response rate mRNA-2416 alone and in combination with durvalumab in patients with ovarian cancer based on RECIST v1.1

3.2.2. Secondary Endpoints

The secondary endpoints of the study are as follows:

- Presence and/or concentration of antibodies against the drug product as well as OX40L, the protein translated by the drug product
- Phase I only: Assessment of objective response rate, DOR, and progression-free survival (PFS) of mRNA-2416 alone and in combination with durvalumab based on RECIST v1.1 or Cheson 2014 criteria (lymphomas)

- Phase II only: Assessment of DCR, DOR, and PFS of mRNA-2416 alone and in combination with durvalumab in patients with ovarian cancer based on RECIST v1.1
- PK parameters for mRNA-2416 alone and in combination with durvalumab: maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC)

3.2.3. Exploratory Endpoints

The exploratory endpoints of the study are as follows:

- Assessment of objective response rate of mRNA-2416 alone and in combination with durvalumab based on irRC or LYRIC
- Assessment of the correlation of other investigational serum-based proteins (eg, anti-drug antibodies) with PK, efficacy, and safety
- Evaluation of plasma will include assessment of pro-inflammatory cytokines and interferons
- Evaluations of tumor tissue will include:
    - Expression of OX40 and OX40L and change in expression over the treatment period
    - Expression of other immune-related markers, including programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1)
    - Infiltration of tumor with immune effector cells, including T cells
- PK parameters for durvalumab in combination with mRNA-2416: C_{max} and AUC

The on-treatment biopsy timing may be adjusted based on emerging data.

Where possible, outcome measures will be correlated with clinical characteristics such as tumor histotype, dose of mRNA administered, and clinical outcomes.

3.3. Treatment

Two investigational products, mRNA-2416 and durvalumab, are tested on patients with advanced relapsed/refractory solid tumor malignancies or lymphoma. mRNA-2416 is a novel mRNA encoding human OX40L encapsulated in a lipid nanoparticle, administered through repeated intratumoral injections on tumor lesions. Durvalumab in combination with mRNA-2416 in arm B is administered to study patients through intravenous infusion.

Arm A patients receiving treatment to superficial lesions will receive mRNA-2416 on Day 1 and Day 15 of a 28-day cycle for 6 cycles. Arm A patients receiving treatment to visceral lesions and all Arm B patients will receive mRNA-2416 on Day 1 and Day 15 for Cycle 1, and on Day 1 only for Cycles 2-6. All Arm B patients will receive durvalumab in combination with mRNA-2416 on Day 1 in each cycle. Dose levels of mRNA-2416 can be found in the protocol Table 1 and Table 2. In the event that ≥ 2 of the first 6 DLT-evaluable patients in the 8.0 mg cohort experience a DLT, an intermediate dose cohort may be opened at 6.0 mg mRNA-2416. Per protocol, the potential dose cohorts are 0.5 mg, 1.0 mg, 2.0 mg, 4.0

mg, 6.0 mg, and 8.0 mg of mRNA-2416 alone, and 2.0 mg, 4.0 mg, 6.0 mg, and 8.0 mg of mRNA-2416 in combination with durvalumab. Some cohorts may not have any patients enrolled during the course of the study. Only the dose cohorts that have patients enrolled will be analyzed. If the dose level of mRNA-2416 that a patient received at the first dose is different from the dose cohort that the patient was enrolled in, the patient may be analyzed in the dose level of mRNA-2416 that the patient received as specified in the analysis.

Following are the potential treatment arms and dose cohorts for Phase I and Phase II.

- Arm A
    - mRNA-2416 0.5 mg
    - mRNA-2416 1.0 mg
    - mRNA-2416 2.0 mg
    - mRNA-2416 4.0 mg
    - mRNA-2416 6.0 mg
    - mRNA-2416 8.0 mg
- Arm B
    - mRNA-2416 2.0 mg + Durvalumab
    - mRNA-2416 4.0 mg + Durvalumab
    - mRNA-2416 6.0 mg + Durvalumab
    - mRNA-2416 8.0 mg + Durvalumab

4. General Statistical Considerations

This document will provide details regarding the definition of analysis variables and analysis methodology to address all study objectives.

Unless otherwise specified, the first/last dose refers to the first/last dose of study drug (mRNA-2416 or durvalumab). Study day for events on or after the date of the first dose will be defined as the number of days from the date of the first dose, plus 1 day, so that the date of the first dose will be defined as Day 1. For events before the date of the first dose, study day will be calculated as the difference in days between the date of the first dose and the date of interest. Thus, the day before the date of the first dose will be defined as Day -1. This means there will be no study Day 0.

Baseline is defined as the last assessment prior to the first dose. All baseline measurements must have been collected prior to administration of the first dose. Measurements obtained after the first dose will be considered as post-baseline values. If the measurement of a variable is not made on a given patient prior to the first dose, that patient will be considered not to have a baseline value for that variable. Change from baseline is defined as post-baseline assessment minus baseline assessment.

Continuous data will be described using the following descriptive statistics: the number of patients (n), mean, standard deviation, median, minimum and maximum, where appropriate. Categorical data will be summarized using the frequency count (n) and percentage (%) of patients for each category, where appropriate. Percentages will be based on non-missing data unless specified otherwise.

Unless otherwise specified, all statistical tests will be 2-sided and conducted at the 0.05 significance level.

No imputation will be applied for missing data unless otherwise specified.

All collected data used for safety and efficacy evaluations will be presented in listings. Data will be displayed in all listings sorted by treatment arm, cohort (dose escalation/confirmation/expansion), dose cohort, and patient identifier unless otherwise specified.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding AEs and medical histories. Prior or concomitant medication data will be coded using the World Health Organization (WHO) Drug Dictionary.

4.1. Sample Size

No formal sample-size estimation will be performed. The choice of the number of patients will be based on a standard, Phase 1, 3+3 dose escalation design in which 3 to 6 patients are enrolled into each dose cohort.

For the Arm A dose expansion period, the sample size estimation is based on Simon's minimax two-stage design (Richard S, 1989). The null hypothesis that the true overall response rate (ORR) is 0.05 will be tested, and the sample size of 13 and 14 for the first and second stage, respectively, will provide an overall one-sided alpha value of 0.05 and statistical power of 0.80 when the true ORR is 0.20. If there is 1 or more response observed from the 13 patients in first stage, the study will proceed to the second stage. To account for potential patient drop-out, a total of approximately 30 patients will be enrolled in order to obtain evaluable data from 27 patients.

For the Arm B dose expansion period, the sample size estimation is based on Simon's two-stage design (Richard S, 1989). The null hypothesis that the true ORR is 0.1 will be tested, and the sample size of 15 and 26 for the first and second stage, respectively, will provide an overall one-sided alpha value of 0.05 and statistical power of 0.80 when the true ORR is 0.25. If there are 2 or more responses observed from the 15 patients in first stage, the study will proceed to the second stage. To account for potential patient drop-out, a total of approximately 45 patients will be enrolled in order to obtain evaluable data from 41 patients.

The planned study enrollment is approximately 117 patients. Approximately 57 patients will be enrolled during the Dose Escalation Period and Dose Confirmation Periods of the study. During the Expansion Period of the study, approximately 60 patients will be enrolled at the MTD/RDE.

4.2. Randomization and Blinding

Not applicable. It is an open-label study.

4.3. Analysis Set

4.3.1. Intent-to-Treat Set

The intent-to-treat (ITT) set will consist of all patients who are enrolled (i.e. signed inform consent form). Patients will be included in the dose cohort to which they were enrolled.

4.3.2. Safety Set

The safety set will consist of all enrolled patients who received any amount of study drug. Patients will be included in the dose cohort corresponding to the dose level which they actually received.

4.3.3. Activity Evaluable Set

The activity evaluable set will consist of all enrolled patients who received any amount of study drug and have at least 1 tumor response evaluation. Patients will be included in the dose cohort to which they were enrolled.

4.3.4. PK Analysis Set

The PK analysis set is a subset of the safety set for patients who have at least one baseline and post-baseline serum PK concentration result. Patients with protocol deviations, or who experience dosing or other issues which are deemed to affect the PK data, will be considered for exclusion from the PK analysis set on a case-by-case basis. Patients will be included in the dose cohort corresponding to the dose level which they actually received.

5. Patient Disposition

Patient disposition data will be summarized using the safety set by treatment arm and dose cohort of mRNA-2416 (as specified in Section 3.3), total for each treatment arm combining Phase I and Phase II, and overall of Arm A and Arm B, unless otherwise specified.

5.1. Disposition

A summary of analysis sets will be presented for the ITT set, the safety set, the activity evaluable set, and PK analysis set. Analysis set will also be presented in a listing using the ITT set.

The patient disposition summary will present the number and percentage of patients for the following categories:

- End of treatment: patients who received mRNA-2416, patients who completed mRNA-2416, patients who discontinued mRNA-2416, the reasons for discontinuation of mRNA-2416, patients who received durvalumab, patients who completed durvalumab, patients who discontinued durvalumab, and the reasons for discontinuation of durvalumab.
- End of study: patients who completed the follow-up period, patients who discontinued from the follow-up period, and the reasons for discontinuation of the follow-up period.

The reasons for discontinuation of mRNA-2416 will be summarized based on the following categories:

- Adverse event
- Patient no longer has lesions that meet injection criteria
- Pregnancy
- Investigator decision
- Withdrawal of consent
- Death
- Disease progression
- Symptomatic deterioration/clinical progression
- Non-compliance
- Receiving alternate anticancer therapy
- Other

The reasons for discontinuation of durvalumab will be summarized based on the following categories:

- Adverse event
- Pregnancy
- Investigator decision
- Withdrawal of consent
- Death
- Disease progression
- Symptomatic deterioration/clinical progression
- Non-compliance
- Receiving alternate anticancer therapy
- Completed 2 years of durvalumab treatment
- Other

Patients who completed 6 cycles of durvalumab treatment are considered for completion of durvalumab treatment. Patients who discontinued durvalumab treatment after completing 6 cycles of durvalumab treatment are not considered for discontinuation of durvalumab treatment.

The reasons for discontinuation from the follow-up period will be summarized based on the following categories:

- Withdrawal of consent

- Patient received alternate anti-cancer therapy
- Death
- Lost to follow up
- Other

All patient disposition data will be provided in the listings.

5.2. Protocol Deviations

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits.

The number and percentage of the patients with each major protocol deviation type will be provided for the safety set by treatment arm and dose cohort of mRNA-2416 (as specified in Section 3.3), total for each treatment arm combining Phase I and Phase II, and overall of Arm A and Arm B. All protocol deviation data will be provided in a listing.

5.3. COVID-19 Impact

A listing will be provided for the impact of coronavirus disease 2019 (COVID-19) on the execution of the study.

6. Demographics and Baseline Characteristics

Demographics and baseline characteristics, as well as baseline disease characteristics, will be summarized using the safety set. Unless otherwise specified, summaries will be presented by treatment arm and dose cohort of mRNA-2416 (as specified in Section 3.3), total for each treatment arm combining Phase I and Phase II, and overall of Arm A and Arm B.

6.1. Demographics and Baseline Characteristics

Summary statistics will be provided descriptively for the following continuous variables:

- Age
- Baseline weight (kg)
- Baseline height (cm)
- Baseline body mass index (BMI) (kg/m^2)

Age will be calculated as the number of months between the birth date and the date of inform consent divided by 12. If the month of the birth date is the same as the inform consent date and the day of the birth date is greater than the date of informed consent, then the age calculated previously should minus 1.

BMI will be calculated as follows:

BMI = weight (kg) / $[\text{height (m)}]^2$.

The number and percentage of patients will be provided for the following categorical variables:

- Sex (Male, Female with or without childbearing potential)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Demographics and baseline characteristics data will be presented in a listing.

6.2. Baseline Disease Characteristics

Baseline disease characteristics and disease history will be summarized including, but not limited to, the following categories:

- Type of tumor
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2, 3, 4, 5)
- If solid tumor (Phase I):
    - Solid tumor diagnosis (eg, adrenal, anal, bladder, brain, breast, etc)
    - Time from initial solid tumor diagnosis to first dose of study drug (months)
    - Stage at initial diagnosis (I, II, III, IV)
    - Mutational status (ALK, EGFR, BRAF, BRCA, KRAS, P53, V600, Other)
    - Amplications (HER2+, MET, Other)
- If solid tumor (Phase II):
    - Solid tumor diagnosis (eg, adrenal, anal, bladder, brain, breast, etc)
    - Time from initial solid tumor diagnosis to first dose of study drug (months)
    - Stage at initial diagnosis (I, II, III, IV)
    - Microsatellite instability (high, intermediate, low, other)
    - Homologous recombination deficiency (positive, negative, other)
    - Tumor mutational burden (high, low, other)
    - Human papillomavirus (positive, negative, other)
    - Estrogen receptor (positive, negative, other)
    - Progesterone receptor (positive, negative, other)
    - HER2/NEU/ERBB2 (positive, negative, other)
- If lymphoma:

- Lymphoma type (Hodgkin lymphoma, Non-Hodgkin lymphoma B-cell lymphoma, Non-Hodgkin lymphoma T-cell lymphoma)
- Lymphoma diagnosis
- Time from initial lymphoma diagnosis to first dose of study drug

Time from initial diagnosis to first dose in months will be calculated as: (Date of first dose - date of initial diagnosis + 1)/30.4375. If the day of initial diagnosis is missing, it will be imputed as the first day of that month. If the day and month of initial diagnosis are missing, it will be imputed as the first day of that year. If all day, month, and year are missing then set to the day before the first dose date.

All disease-specific history data will be presented in a listing.

6.3. Medical History

6.3.1. General Medical History

All medical history data will be presented in a listing as collected on the electronic case report form (eCRF).

6.3.2. Prior Therapies/Surgeries

Prior systemic therapies will be coded using the WHO Drug dictionary.

Prior radiation therapy, prior systemic therapy, and prior cancer related surgeries will be presented in separate listings.

7. Treatments and Medications

Treatments and medications will be summarized based on the safety set. Descriptive statistics will be calculated for continuous variables and frequency counts and percentages will be applied to categorical variables. No inferential statistical analysis will be performed.

7.1. Prior and Concomitant Medications

All medications taken at any time from the time of informed consent to the last safety follow up visit must be recorded in the patient's eCRF. Any changes in concomitant medications will also be recorded in the patient's eCRF.

Prior medications are defined as medications that ended before the start of first dose. Concomitant medications are defined as medications started before first dose and continued or ended on or after first dose, or started between first dose and last dose date (inclusive) of study drug.

Missing start dates for concomitant medications data will be handled as follows:

- Missing day only:
  - If the month and year are the same as the first dose month and year, then it will be imputed as the date of the first dose.

  - If the month and year are prior to the first dose month and year, then it will be imputed as the last day of the collected month.
  - If the month and year are after the first dose month and year, then it will be imputed as the first day of the collected month.

- Missing day and month:
  - If the year is the same as the first dose year, then it will be imputed as the date of the first dose.
  - If the year is prior to the year of the first dose, then it will be imputed as December 31st of the collected year.
  - If the year is after the year of the first dose, then it will be imputed as January 1st of the collected year.
- Missing day, month, and year:
  - It will be imputed as the date of the first dose.

Missing stop dates for concomitant medications data will be handled as follows:

- Missing day only:
  - It will be imputed as the last day of the collected month or the death date, whichever is earlier.
- Missing day and month:
  - It will be imputed as December 31st of the collected year or the death date, whichever is earlier.
- Missing day, month, and year:
  - No imputation is needed.

If the imputed start date is after the stop date, then the start date will be imputed as the stop date.

Prior and concomitant medications will be coded using the WHO Drug dictionary. The dictionary will be updated throughout the life of the project to allow for the most recent version of the dictionary to be used.

Prior and concomitant medications will be summarized in separate tables by treatment arm and dose cohort of mRNA-2416 (as specified in Section 3.3), and total for each treatment arm combining Phase I and Phase II. The number and percentage of patients receiving at least one medication will be presented. In addition, the tables will present the number and percentage of patients by drug class and preferred term. Drug classes will be sorted alphabetically, while preferred terms within each drug class will be presented in descending order of frequency based on the total of Arm B combining Phase I and Phase II. At each level of patient summarization, a patient is counted once if the patient reported one or more medications.

All prior and concomitant medications will be presented in a listing.

7.2. Medical Procedures/Surgeries

Medical procedures/surgeries will be presented in data listings.

7.3. Study Treatments

Study treatments will be summarized by treatment arm and dose cohort (as specified in Section 3.3) for Phase I and Phase II, and total for each treatment arm combining Phase I and Phase II. Descriptive statistics will be provided in the following categories.

- Arm A: treatment duration, number of dosing cycles, and cumulative dose of mRNA-2416 during the treatment period.
- Arm B: treatment duration, number of dosing cycles, and cumulative dose of mRNA-2416; treatment duration, number of dosing cycles, and cumulative dose of durvalumab during the treatment period (including combination treatment with mRNA-2416 and continuation treatment as a single agent), separately.

All study treatment data will be presented in a listing.

7.3.1. Extent of Exposure

Treatment duration of mRNA-2416 (weeks) is defined as:

[(last dose date of mRNA-2416) – (first dose date of mRNA-2416) + 1]/7.

Treatment duration of durvalumab (weeks) is defined as:

[(last dose date of durvalumab) – (first dose date of durvalumab) + 1]/7.

7.3.2. Cumulative Dose

Cumulative dose of mRNA-2416 is defined as the sum of all mRNA-2416 doses (mg) taken during the treatment period. Cumulative dose of durvalumab is defined as the sum of all durvalumab doses (mg) taken during the treatment period.

7.3.3. Number of Dosing Cycles

Number of dosing cycles is defined as the total number of cycles at which the patient received non-zero mRNA-2416 doses. Number of dosing cycles is defined as the total number of cycles at which the patient received non-zero durvalumab doses.

7.3.4. Treatment Modifications

Number of patients with mRNA-2416 injection administered, number of patients without mRNA-2416 injection administered, reason for mRNA-2416 injection not administered, number of patients who had dose modified, categories of dose modification, reason for dose modified, number of lesion injected, and

lesion type will be summarized by scheduled visits, treatment arm and dose cohort for Phase I and Phase II, and total for each treatment arm combining Phase I and Phase II.

Number of patients with durvalumab administered, number of patients without durvalumab administered, action taken with durvalumab, and reason for action on durvalumab will be summarized by scheduled visits and dose cohort for Phase I and Phase II, and total for Arm B combining Phase I and Phase II.

8. Efficacy Analysis

All tables and figures for efficacy evaluations will be conducted using the activity evaluable set by treatment arm and dose cohort (as specified in Section 3.3) for Phase I and Phase II, and total for each treatment arm combining Phase I and Phase II. Listings will be based on the safety set.

Solid tumor response will be assessed by investigators based on RECIST 1.1 (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or not evaluable [NE]), and based on irRC (immune-related complete response [irCR], immune-related partial response [irPR], immune-related stable disease [irSD], immune-related progressive disease [irPD], or not evaluable [NE]). Lymphoma response will also be assessed by investigators based on Cheson 2014 criteria (positron emission tomography [PET]-CT-based complete metabolic response, partial metabolic response, no metabolic response, or progressive metabolic response; CT-based complete radiologic response, partial radiologic response, SD, or PD), and based on LYRIC (PET-CT-based complete metabolic response, partial metabolic response, no metabolic response, progressive metabolic response, or indeterminate response; CT-based complete radiologic response, partial radiologic response, SD, PD, or indeterminate response). Best overall response is determined from time-point overall response. When SD for RECIST 1.1 or irSD for irRC is believed to be the best overall response, it must meet the minimum time (at least 55 days between the first dose date and the last SD assessment date, and no PD between). Death may be considered in determination of best overall response.

Listings will be provided for tumor assessment of target lesions, non-target lesions, new lesions, and overall response evaluation. Waterfall plots of best percent change from baseline in sum of diameters of target lesions based on investigator assessments (per RECIST 1.1 and irRC, respectively) will be provided by treatment arm, and by treatment arm and injection status, respectively.

The following efficacy endpoints will be analyzed:

- ORR based on RECIST 1.1/Cheson 2014 criteria
- ORR based on irRC/LYRIC
- DOR based on RECIST 1.1/Cheson 2014 criteria
- PFS based on RECIST 1.1/Cheson 2014 criteria
- PFS based on irRC/LYRIC
- DCR based on RECIST 1.1

All derived efficacy parameters will be displayed in a data listing.

8.1. Overall Response Rate

ORR is defined as the proportion of patients whose best overall response is partial response or better based on each corresponding criterion. If data allow, ORR may be summarized with Clopper-Pearson 95% confidence intervals (CI). No confirmation is required for partial response or better.

8.2. Duration of Response

DOR is defined as the time from first response (partial response or better) to first occurrence of a disease progression.

For patients who do not experience any of these events by the last date of study participation, death date, or the time of data cutoff, whichever is the earliest, the following censoring rule will be used for DOR:

- Patients who do not experience disease progression and have an adequate post-baseline tumor assessment will be censored at the date of the last adequate tumor assessment that is SD or better.
- Patients who do not experience disease progression and do not have any adequate post-baseline tumor assessment that is SD or better will be censored at Day 1.

Patients who never achieve a response will be excluded from this analysis.

DOR (days) = date of event/censoring - date of first response + 1.

If data allow, swimmer plots of tumor assessment over time such as time to response and DOR (per RECIST 1.1 and irRC, respectively) may be provided for each patient by treatment arm.

8.3. Progression-free Survival

PFS is defined as the time from first dose to first occurrence of a disease progression or death, whichever comes first.

For patients who do not experience one of these events by the last date of study participation or the time of data cutoff, the following censoring rule will be used for PFS:

- Patients who do not experience disease progression or death and have an adequate post-baseline tumor assessment will be censored at the date of the last adequate tumor assessment that is SD or better.
- Patients who do not experience disease progression or death and do not have any adequate post-baseline tumor assessment that is SD or better will be censored at Day 1.

PFS (days) = date of event/censoring - date of first dose + 1.

PFS will be summarized by descriptive statistics (mean, standard deviation, minimum and maximum). The Kaplan-Meier method will be used to estimate the distribution functions of PFS per RECIST 1.1 and irRC, respectively. The quartiles, median along with 95% CI of PFS, and probability of being event free at selected time points will be provided. Kaplan-Meier plot of PFS (per RECIST 1.1 and irRC, respectively) will be provided for Arm A regardless of mRNA 2416 dose level in each study phase.

Kaplan-Meier plot of PFS (per RECIST 1.1 and irRC, separately) will be provided for Arm B regardless of mRNA 2416 dose level in each study phase.

8.4. Disease Control Rate

DCR is defined as the proportion of patients whose best overall response is CR, or PR, or had durable SD which is defined as there is at least 55 days between the first dose date and the last SD assessment date, and no PD between. All tumor response will be based on the investigators' assessment RECIST v1.1. DCR will be summarized with Clopper-Pearson 95% CI calculated for Phase II.

9. Safety Analysis

Safety evaluations will be based on the incidence, severity, and type of AE; serious AE; laboratory results; vital signs; electrocardiogram (ECG); ECOG performance status; and analysis of anti-drug antibodies. All safety analyses will be conducted on the safety set by treatment arm and dose cohort of mRNA-2416 (as specified in Section 3.3), and total for each treatment arm combining Phase I and Phase II. All safety data will be presented in listings based on the safety set.

9.1. Adverse Events

An AE is any adverse experience in a patient administered a pharmaceutical product, whether or not it is considered drug related, that occurs during a patient's study participation (defined as after a patient signs the informed consent form through the patient's last safety follow up visit or study discontinuation, whichever is later). A treatment-emergent AE (TEAE) is defined as any AE that newly appeared, increased in frequency, or worsened in severity occurring on or after the first dose of study drug.

Missing or partial start dates for AE data will be handled following the imputation rules of missing or partial start dates for concomitant medications data (Section 7.1). No imputation will be applied to the missing or partial stop dates for AEs. If the AE end date is complete and the partial AE start date imputed by the rules above is after the AE end date, then the start date will be imputed by the AE end date.

All AEs will be coded according to the latest version of MedDRA at the time of coding. The severity will be defined according to the NCI CTCAE version 4.03. If a patient experiences the same AE more than once with different toxicity grades, then the event with the highest grade will be tabulated in "by grade" tables. In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of "Missing" only if the same event category has no other valid grades. AEs with missing relationship to the treatment will be imputed as treatment-related and summarized in the tables.

The incidence of AEs will be summarized in tables with the number and percentage of patients with AEs by system organ class (SOC) and preferred term (PT). Unless otherwise specified, at each level of SOC or PT, a patient with multiple events will only be counted once per SOC or PT. Percentages of patients with AEs will be calculated out of the number of patients in the safety set. Tables will be sorted by SOC in internationally agreed order, and PT within each SOC will be presented in descending frequency based on the total of Arm B combining Phase I and Phase II.

The following categories of AE will be summarized by SOC and PT:

- TEAEs
- TEAEs by maximum NCI CTCAE grade
- mRNA-2416-related TEAEs
- Durvalumab-related TEAEs
- TEAEs by relationship with mRNA-2416
- TEAEs by relationship with durvalumab
- Serious TEAEs
- TEAEs leading to discontinuation of mRNA-2416
- TEAEs leading to discontinuation of durvalumab
- TEAEs of special interest for durvalumab

An overview table of the following categories will also be provided:

- TEAEs
- TEAEs with NCI CTCAE grade ≥ 3
- mRNA-2416-related TEAEs
- Durvalumab-related TEAEs
- Serious TEAEs
- TEAEs leading to discontinuation of mRNA-2416
- TEAEs leading to discontinuation of durvalumab
- TEAEs of special interest for durvalumab
- TEAEs leading to death

All AEs will be presented in a data listing and TEAEs will be flagged in the listings. AEs leading to discontinuation of mRNA-2416, AEs leading to discontinuation of durvalumab, AEs leading to death, and SAEs will be presented in separate listings.

9.1.1. Dose-limiting Toxicity

The DLT window of observation will be the first 28 days of mRNA-2416 treatment and meets the following criteria:

- All Grade 3 AEs with the exception of the following:
    - Grade 3 thrombocytopenia lasting <7 days

- Grade 3 neutropenia without fever or lasting <7 days

- Any Grade 4 or Grade 5 toxicity

Death due to disease progression is not considered a DLT.

A summary table of DLTs will be presented, including number and percentage of patients for each PT based on the safety set and will be sorted in descending frequency based on the total of Arm B combining Phase I and Phase II.

All DLT events will be presented in a listing.

9.2. Clinical Laboratory Evaluations

Clinical laboratory tests (including hematology, clinical chemistry, coagulation, urinalysis, hepatitis serology, thyroid function, and pregnancy test) will be collected per the timing presented according to the protocol. Clinical laboratory values will be graded according to NCI CTCAE for applicable tests. International System of Units (SI) will be used in the summaries.

All laboratory data will be presented in listings by patient and visit for each panel.

9.2.1. Hematology

The hematology tests will include hemoglobin, hematocrit, white blood cell, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, and platelets.

Descriptive statistics of observed and change from baseline values for hematology tests will be presented at the scheduled visits and for the overall worst value post-baseline. A shift table representing the change from the baseline grade to the worst post-baseline grade will also be provided. The number and percentage of patients with at least a 2-grade increase from baseline will be summarized treatment arm and dose cohort for Phase I and Phase II, and total for each treatment arm combining Phase I and Phase II.

A listing for hematology tests will be provided by patient and visit.

9.2.2. Clinical Chemistry

The clinical chemistry tests will include magnesium, bicarbonate, sodium, potassium, phosphorus, chloride, calcium (corrected), alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total bilirubin, glucose, total protein, albumin, creatinine, blood urea nitrogen (BUN), uric acid, lipase, and amylase and thyroid-stimulating hormone.

Descriptive statistics of observed and change from baseline values for clinical chemistry tests will be presented at the scheduled visits and for the overall worst value post-baseline. A shift table representing the change from the baseline grade to the worst post-baseline grade will also be provided. The number and percentage of patients with at least a 2-grade increase from baseline will be summarized.

A listing for clinical chemistry tests will be provided by patient and visit.

9.2.3. Coagulation

The coagulation tests will include prothrombin time, partial thromboplastin time, and fibrinogen.

Descriptive statistics of observed and change from baseline values for coagulation tests will be presented at the scheduled visits and for the overall worst value post-baseline. A shift table representing the change from the baseline grade to the worst post-baseline grade will also be provided.

A listing for coagulation tests will be provided by patient and visit.

9.2.4. Urinalysis

A listing for urinalysis will be provided by patient and visit.

9.2.5. Hepatitis Serology

A listing for hepatitis serology will be provided by patient at screening.

9.2.6. Pregnancy Testing

A listing for pregnancy test will be provided by patient and visit.

9.3. Vital Signs

Vital sign measurements include pulse (beats per minute), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C), and weight (kg). Descriptive statistics will be provided for observed values and change from baseline values at the scheduled visits.

Patients with abnormal post-baseline vital sign values, identified by values outside the threshold values defined below, will be summarized by visit, treatment arm and dose cohort for Phase I and Phase II, and total for each treatment arm combining Phase I and Phase II.

Vital Signs	**Abnormality**
Pulse	<45 beats per minute or >90 beats per minute
Systolic blood pressure	<90 mmHg or >140 mmHg
Diastolic blood pressure	<40 mmHg or >90 mmHg
Temperature	<36.5°C or >37.3°C

All vital signs will be presented in a listing.

9.4. Electrocardiogram

Twelve-lead ECG assessments include ECG heart rate (beats per minute), PR interval (milliseconds), QRS duration (milliseconds), QT interval (milliseconds), and RR interval (milliseconds). Descriptive statistics will be provided for observed values and change from baseline values at the scheduled visits.

The number and percentage of patients with each ECG overall interpretation will be summarized at scheduled visits.

All ECG assessments will be presented in a listing.

9.5. ECOG Performance Status

The number and percentage of patients with each ECOG status will be summarized at scheduled visits. All ECOG data will be presented in a listing.

10. Pharmacodynamics and Biomarker Analysis

Summary of the number and percentage of patients with screening status and confirmatory status of presence of anti-OX40L, the screening and confirmatory status of the presence of anti-polyethylene glycol (PEG), as well as the titer information of anti-OX40L and anti-PEG will be summarized by visit based on the safety set for treatment arm and dose cohort (as specified in Section 3.3) for Phase I and Phase II, and total for each treatment arm combining Phase I and Phase II.

All pharmacodynamic data will be presented in listings based on the safety set.

Tumor biopsies will be examined using quantitative immunofluorescence (QIF) and/or an orthogonal method (i.e. enzyme-linked immunosorbent assay [ELISA]) for changes in OX40L/OX40 and PD-L1/PD-1 expression levels, as well as characterization of tumor infiltrating lymphocyte populations (e.g., phenotype, distribution, and activation). Descriptive statistics for each parameter may be provided for observed values and change from baseline values by scheduled visit, treatment arm, dose cohort, and total, and biopsy cohort group for Phase I, and by scheduled visit, treatment arm, dose cohort, and biopsy cohort group for Phase II based on the safety set.

All biomarker data will be presented in listings. Biomarker data (summary table and listing) will be provided in the Biomarker Report.

11. Pharmacokinetic Analysis

11.1. General

The PK Analysis Set will serve as the primary analysis set for PK analyses. The analysis will be conducted by treatment arm and dose cohort of mRNA-2416 (as specified in Section 3.3) for Phase I and Phase II.

11.2. Values Below the Limit of Quantitation or Missing

Concentration values that are below the limit of quantification (BLQ) will be set to zero, with defined exceptions as follows:

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a pre-dose concentration is missing, these values may be set to zero.

11.3. Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in PK section of the Clinical Study Report.

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

Positive pre-dose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the pharmacokineticist.

11.4. Serum Concentration

Blood samples for determination of mRNA-2416 serum concentrations and durvalumab serum concentrations will be collected via venipuncture or an indwelling catheter in Cycle 1 at pre-dose (prior study drug administration), at 3, 6 and 24 (Cycle 1 Day 2) hours post-dose and at pre-dose on Cycle 1 Day 8 and Cycle 2 Day 1.

Serum concentration data of mRNA-2416 and durvalumab will be individually listed and summarized using descriptive statistics by nominal time point (n, mean, standard deviation, coefficient of variation [CV], geometric mean, median, minimum, and maximum). Geometric mean will not be calculated where the minimal concentration values include zero.

Geometric mean serum concentration by nominal time profiles by period and treatment both in linear and semi-logarithmic scale will be provided; individual serum concentration plots by actual sampling time for all patients combined within period and treatment will be provided on a linear and semi-logarithmic scale.

11.5. Serum Pharmacokinetic Parameters

The individual serum concentration versus actual time data for mRNA-2416 and durvalumab will be used to derive the PK parameters using non-compartmental PK analyses with Phoenix WinNonlin version 8.0 or higher.

The following serum PK parameters will be calculated for mRNA-2416 and durvalumab if data permit:

C_{max}	Maximum observed serum concentration, obtained directly from the observed concentration time data.
t_{max}	Time to maximum observed serum concentration, obtained directly from the observed concentration time data.
AUC_{0-t}	AUC from 0 hour to the time of the last observed quantifiable serum concentration (C_{last}); calculated by linear up log down trapezoidal method.
AUC_{0-inf}	AUC extrapolated to infinity; calculated as [AUC_{0-t} + (C_{last}/λ_z)]
%AUC	Percentage of estimated part of the calculation of AUC_{0-inf}, calculated as: ((AUC_{0-inf} - AUC_{0-t}) / AUC_{0-inf}) × 100; If %AUC extrapolated is higher than 30%, then AUC_{0-inf} and parameters derived from will be displayed in the listing (flagged) and excluded from descriptive statistics and statistical analysis.
λ_z	Apparent elimination rate constant, estimated by linear regression of the terminal portion of the log-concentration by time curve; a minimum of 3 non-BLQ data points in the elimination phase (not including C_{max}) will be used for the calculation. The λ_z will not be estimated if adjusted r-squared is less than 0.8.
t½	Apparent elimination half-life, calculated as [(ln 2)/λ_z]. If the length of the time interval used to determine λ_z is less than 2 times t½, then t½ will be flagged (i.e., t½ values that are more than half the time interval used to determine λ_z will be flagged).

Adjusted r-squared, number of points to calculate slope of terminal phase and start and end of the λ_z will be listed. Additional parameters may be calculated if deemed necessary.

11.6. Statistical Analysis of Pharmacokinetic Parameters

Pharmacokinetic parameters derived from serum concentrations will be individually listed and summarized. The PK parameters with the exception of t_{max} will display n, mean, standard deviation, CV, geometric mean, median, minimum, and maximum as descriptive statics. However, t_{max} will only display n, median, minimum and maximum.

For the listings, concentration data will be presented to the same precision as the data is received. All PK parameters will be presented in the listings to 3 significant figures with the exception of t_{max}, which will be presented to 2 decimal places.

For summary statistics, the following precisions should be used:

- n should be presented to zero decimal places
- CV% should be presented to 1 decimal place
- Mean, standard deviation, geometric mean, median, minimum, and maximum should be presented to the same precision as the listings

12. Interim Analysis

No formal interim analysis is planned.

13. Changes in the Planned Analysis

One of the exploratory endpoints, assessment of the correlation of other investigational serum-based proteins (e.g., anti-drug antibodies) with PK, efficacy, and safety, is not included in this statistical analysis plan.

14. References

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32(27):3059-68.

Eisenhauer EA et al. New response criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J of Cancer. 2009; 45(2):228-247.

Statistical Analysis Plan (SAP) Client Approval Form

Client:	ModernaTX, Inc.
Protocol Number:	mRNA-2416-p101
Document Description:	Final Statistical Analysis Plan
SAP Title:	A Phase I/II, Open-label, Multicenter, Dose Escalation and Efficacy Study of mRNA-2416, a Lipid Nanoparticle Encapsulated mRNA Encoding Human OX40L, for Intratumoral Injection Alone and in Combination with Durvalumab for Patients with Advanced Malignancies
SAP Version Number:	1.0
Effective Date:	29NOV2021

Author(s):

For PPD: PPD

For Moderna: PPD

Approved by:

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Date *(DD-MMM-YYYY)*

Biostatistics and programming, PPD

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Date *(DD-MMM-YYYY)*

Clinical Development, Moderna, Inc.

PPD

Date *(DD-MMM-YYYY)*

Biostatistics, Moderna, Inc.

Document Number: FORM-02894 v8.0
Effective Date: 22 Nov 2021

Page 1 of 1
Printed on: 24 November 2021