NCT #NCT03323398

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CLINICAL TRIAL PROTOCOL

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

Protocol Number:	mRNA-2416-P101
Sponsor:	ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 USA Phone: +1-617-714-6500
Protocol Version:	7.0
Amendment Version:	6.0
Date released:	10 Jun 2019

1 SPONSOR SIGNATURE PAGE

Sponsor: ModernaTX, Inc.

Protocol Number: mRNA-2416-P101

Study Medication: mRNA-2416

Protocol 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

Protocol Version: 7.0

Amendment Version: 6.0

Date released: 10 Jun 2019

Approved by:

Date

PPD

ModernaTX, Inc.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. This trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States federal regulations and International Council for Harmonisation (ICH) guidelines.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by the Sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for this study.

I agree that the Sponsor or its representatives shall have access to any source documents from which case report form information may have been generated. I agree that regulatory authorities (FDA, EMA, and other local and country-related agencies) can audit and review source documents.

I further agree not to originate or use the name of ModernaTX, Inc. or any of its employees, in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to his protocol, to any amendment hereto, or to the performance hereunder, without the prior written consent of ModernaTX, Inc.

Investigator's Signature	Date

Name of Investigator (Typed or Printed)

Institution Name

Institution Address

Version History and Summary of Changes

Amendment 6.0

Amendment rationale

The main purpose of this amendment is to include a new treatment arm for mRNA-2416 in combination with durvalumab. This includes new primary study objectives in Phase I to determine the MTD/RDE for mRNA-2416 in combination with durvalumab and in Phase II to assess the objective response rate of the combination therapy in ovarian cancer based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Changes to the protocol

Section 2 Tabulated Protocol Summary: Updated to reflect main text revisions noted below.

Section 6 Background and Rationale: Added background information regarding combination treatment with CPIs.

Section 6.2 mRNA-2416 Background: Added results from preclinical efficacy testing of OX40L mRNA in combination with αPD-L1. Added summary of safety observed on this study as of 08-Feb-2019.

Section 6.3 Durvalumab Background: New section added including details of the proposed durvalumab mechanism and a summary of findings from pre-clinical and clinical studies.

Section 6.5 Durvalumab Dosing Rationale: New section added providing rationale for the 1500mg fixed dose of durvalumab planned for this study

Section 7 Study Objectives and Endpoints: Updated study endpoints and objectives to be applicable for mRNA-2416 alone as well as in combination with durvalumab.

Section 8.1 Number of Patients: Updated to account for treatment Arm B.

Section 8.2 Study Design: Updated section and Figure 1 to include treatment Arm B. Also revised to include patients with all solid tumors or lymphoma in the Dose Confirmation cohorts.

Section 8.2.2 Arm A Dose Escalation Biopsy Cohort Enrichment: Specified treatment Arm A.

Section 8.2.3 Arm B Dose Escalation Period: New section added describing Arm B Dose Escalation procedures including the dose levels to be tested.

Section 8.2.4 Dose Confirmation in Visceral Lesions: Revised to increase clarity.

Section 8.2.6 Arm B Dose Expansion Period: New section added describing the Arm B Dose Expansion period.

Section 8.3 Study Flow and Expected Duration of Patient Participation: In alignment with the safety profile observed during the dose escalation study period, the safety follow-up period has been decreased to 90 days following last treatment. Also added details on duration of participation in each phase and for each treatment arm.

Section 8.4.2 Definition of Dose-Limiting Toxicities: Added criteria applicable for treatment Arm B.

Section 8.4.4 Added durvalumab exposure criteria for patients evalubable for dose determination.

Section 9.1 Inclusion Criteria: Added criteria for thyroid function, expansion lesion requirements, life expectancy and body weight.

Section 9.2 Exclusion Criteria: Added several new criteria regarding: prior autoimmune or inflammatory disorders, immunodeficiency or immunosuppression, toxicities from prior therapies, active infections, pneumonitis, carcinomatosis, and involvement in study conduct.

Section 10.1 Intratumoral Injections: Clarified lesion requirements for Dose Expansion, specified dosing regimen for visceral lesions, and specified that no intrapatient dose escalation may occur.

Section 10.2 Durvalumab Administration: New section added for durvalumab administration.

Section 10.3 mRNA-2416 Dose Modification: Consolidated details previously contained in other sections.

Section 10.4 Durvalumab Dose Modification and Toxicity Management Guidelines: New section added.

Section 10.5 – 10.7, and 10.9: Sections relocated for clarity.

Section 10.8 Concomitant Therapy: Added new prohibited concomitant medications for both treatment arms.

Section 10.10 Radiologic Assessments: Clarified baseline imaging requirements and added that imaging data may be centrally collected and reviewed.

Section 10.12.1 Durvalumab Pharmacokinetics: New section added for durvalumab PK.

Section 10.13 Biomarkers: Specified RNA sequencing will be performed on biopsy samples, added collections for durvalumab PK to Table 6.

Section 10.13.1 Tumor Biopsies: Request for 4-6 passes for optimal results.

Section 10.13.2 Dose Escalation Biopsy Collection Plan: Organized for clarity.

Section 10.13.3 Dose Expansion Biopsy Collection Plan: Added groups F, G, and H for patients in treatment Arm B.

Section 10.14.1 Instructions for Male Patients: Added requirements for methods and timing of contraception.

Section 10.14.1 Instructions for Female Patients: Added requirements for methods and timing of contraception.

Section 10.14.3 Pregnancy Reporting: Added sponsor contact for reporting of pregnancies.

Section 10.15 Overdose Management: Specified that guidance is also applicable for durvalumab.

Section 12.1.4 Unexpected Adverse Reactions: Specified that expectedness is defined in the Investigator Brochures for mRNA-2416 and durvalumab.

Section 12.1.5 Durvalumab Adverse Events of Special Interest: New section added defining durvalumab AESIs.

Section 13.2 Sample Size Considerations: Added information for Arm B sample sizes.

Section 13.4.4 PK and Pharmacodynamic Analyses: Details added to align with biomarker section.

Section 20 References: Added reference.

Appendix E Dose Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion Related, and Non Immune-Mediated Reactions: New guidance added.

IRB/FDA Review/Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/FDA.

The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 5.0

Amendment rationale

The main purpose of this amendment is to include a Dose Confirmation period and a Phase II Expansion period for patients with ovarian cancer of epithelial origin.

Changes to the protocol

Section 2 Tabulated Protocol Summary: Updated to reflect main text revisions noted below.

Section 3 Schedule of Events: Cytokine profile sampling added. PK and Serum Immunogenicity sampling details moved from the footnote to new sections 10.4 and 10.5.

Section 5 Investigators and Study Administrative Structure: Updated Moderna address and CRO contact.

Section 6.1 Indication Background: Added background information for ovarian cancer.

Section 6.4 Dosing Rationale: Specified the dosing regimen and rationale for patients that are to receive intratumoral injections to visceral lesions.

Section 6.5 Patient Population: Revised to specify that patients with ovarian cancer of epithelial origin will be enrolled during the Dose Confirmation and Expansion periods.

Section 7 Study Objectives and Endpoints: Primary and Secondary objectives for efficacy per RECIST 1.1 added for Phase II. Removed details of PK sample type which is contained in Study Lab Manual.

Section 8.1 Number of Patients: Adjusted in accordance with Study Design.

Section 8.2 Study Design: Revised to include a Dose Confirmation period and a Phase II Expansion period. Removed information now contained in other sections.

Section 8.2.2 Dose Confirmation in Visceral Lesions: Section revised to describe new study part.

Section 8.2.3 Phase II Dose Expansion Period: Section added to describe new study part.

Section 9.1 Inclusion Criteria: Eligibility criteria regarding disease state and prior therapies for patients in Dose Confirmation and Phase II Expansion period added. Criteria for visceral lesions added. Criteria for TSH removed (Thyroid abnormalities from prior therapies still excluded per criteria 3).

Section 9.2 Exclusion Criteria: Washout period for chemotherapy, radiation, hormonal anti-cancer treatment and biologic therapy revised to 14 days. Washout for any other investigational agent or treatment with any anti-cancer monoclonal antibody, immunostimulant, or vaccine unchanged as <28 days prior to C1D1

Section 9.3.1 Dose Omissions and Discontinuation of Study Drug Administration: Clarified that disease progression or receiving alternate anticancer therapy are reasons for discontinuation of study treatment instead of discontinuation from all study procedures.

Section 10.1 Intratumoral Injections: Added details for intratumoral injections to visceral lesions.

Section 10.4 Pharmacokinetics and Immunogenicity: Details of PK and IG assessments relocated from Schedule of Events table footnote for clarity.

Section 10.5 Biomarkers: Section revised to contain additional details on sampling and assessments. Cytokine profile sampling added.

Section 10.5.3 Dose Expansion Biopsy Collection Plan: New section added.

Section 10.7.3 Pregnancy Reporting: Added guidance to also report pregnancies to the CRO.

Section 10.8 Overdose Management: New section added.

Section 12.1.1 Adverse Events and Section 12.1.3 Serious Adverse Events: Revised reporting for AE/SAEs that are due to disease progression.

Section 12.5 Follow-up for AEs: Clarified AE follow-up requirements.

Section 13.2 Sample Size Considerations: Details added for Phase II Dose Expansion.

Section 13.4.3 Efficacy Analysis: Details added for Phase II efficacy objectives.

Amendment 4.0

Amendment rationale

The main purpose of this amendment is to add information regarding injection related reactions and recommendations for additional monitoring by investigators to ensure patient safety and updated ancillary treatments if reactions are observed.

Changes to the protocol

Section 10.1 Intratumoral Injections: updated to include careful monitoring for possible injection related reactions and a recommendation to observe all patients for a minimum of 1 hour after administration of each mRNA-2416 injection.

Section 10.1.1: Ancillary Treatments: to allow the use of premedications prior to administration of mRNA-2416 at the discretion of the treating investigator. If the treating physician decides to premedicate their patients, it is recommended to do so prior to the second and subsequent injections, and to follow local institutional guidelines for premedication with montelukast, H-1 and H-2 antagonists.

Amendment 3.0

Amendment rationale

The main purpose of this amendment is to clarify pre-treatment biopsy collection details, define study visit windows for the Safety and Disease Progression Follow-up visits, and adjust the schedule for certain study procedures as described below.

Changes to the protocol

Section 2 Tabulated Protocol Summary, Section 7.3 Secondary Objectives: updated pharmacodynamic objective to emergence of antibodies against the drug product as well as OX40L, the protein translated by the drug product.

Section 2 Tabulated Protocol Summary, Section 7.4 Secondary Endpoints: removed duplicate mention of duration of response per RECIST/Cheson and removed cytokine levels.

Section 3: Schedule of Events: Added +7 day visit window for the Safety Follow-up visits

Section 3: Schedule of Events, Section 10.2 Radiological Assessments: Defined Disease Progression Follow-up visit timing as 90 and 180 days following end of treatment and added ± 30 day visit window

Section 3: Schedule of Events: Added ± 24-hour window for C1D8 PK sample

Section 3: Schedule of Events: Updated occurrence of symptom-directed physical examination to beyond cycle 2.

Section 3: Schedule of Events: Removed sample collection for cytokine analysis

Section 6.4 Dosing Rationale, Section 8.2.1 Dose Escalation Period: Clarified that dosing occurs on day 1 and day 15 of 28-day cycles.

Section 8.2.1 Dose Escalation Period: Clarified that biopsy enrichment cohorts are separate from the 3+3 escalation model

Section 8.2.1.1 Biopsy Cohort Enrichment: Added updates to biopsy site information in Table 2

Section 9.3 mRNA-2416 Dose Modification: Clarified that requirements apply to study-treatment related toxicities.

Section 12 Assessment of Safety: Clarified that the AE reporting period is defined as after a patient signs the ICF through the patient's last Safety Follow-up visit or study discontinuation, whichever is later. Guidance added that from the time of ICF signing to first dose of mRNA 2146, only AEs related to study procedures will be collected. Also, once a patient has ended study treatment and has initiated any new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected.

Section 12.1.3 Serious Adverse Events: Clarified that lack of efficacy of study treatment is not considered an SAE.

Section 13.4.3: Efficacy Analyses: Added that following completion of the study, best response will be determined for each patient in accordance with RECIST 1.1 and Cheson guidelines.

Section 13.4.4 PK and Pharmacodynamic Analyses: Removed reference to cytokine profiling.

IRB/FDA/NIH Review/Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/FDA/NIH.

The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 2.0

Amendment rationale

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Section 2 Tabulated Protocol Summary, Section 7.5 Exploratory Objectives, Section 7.6 Exploratory Endpoints and Section 13.4.4 PK and Pharmacodynamic Analyses: removed

- Mutational (neoantigen) load of tumors prior to treatment
- T-cell clonality emergent in tumors and in whole blood during study therapy
- Cytokine (other than TNF and IL-6) analysis

Section 2 Tabulated Protocol Summary, Section 9.1 Inclusion Criteria and Section 10.6.1 Instructions for Male Patients: Modified the use a highly reliable method of birth control from the Screening visit through 12 weeks to 120 days after the last dose of study drug

Section 3: Schedule of Events: Added the assessment of height, removed "Serum Sample for Exploratory Biomarker", removed "T-cell Clonality in Whole Blood"

Section 5 Investigator and Study Administrative Structure: changed CRO from PSI to PPD and Sponsor primary contact information

Section 6.2 mRNA-2416 Background: included results of the in vivo genotoxicity study in Sprague Dawley rats and the in vivo toxicology study in the Cynomolgus Monkey

Table 2 Group A: included OX40/OX40L expression for analysis

Section 8.2.1.1 Biopsy Cohort Enrichment, Section 10.1 Intratumoral Injections and Section 10.4 Tumor Biopsies: removed the option of visceral tumor injection

Section 10.7 Additional Biomarker Assessments: Added Additional Biomarker Assessments section stating exploratory biomarker analysis may be conducted on any remaining tumor and/or blood samples with patient consent

Administrative corrections for document consistency, typographical corrections and minor clarifications were made throughout the document.

IRB/FDA/NIH Review/Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/FDA/NIH.

The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1.0

Amendment rationale

This amendment addresses the following revision requested by a regulatory authority:

Section 3 Schedule of Events: Corrected tumor assessment requirement from C4 to C3 and C5

Section 8.2.2.1 Expansion Period Stopping Rules, Section 12 Assessment of Safety and Section 12.2 AE Collecting and Reporting: Added language to clarify all SAEs/SUSARs and deaths will be reported to FDA per 21 CFR 312.32

Section 8.4.2 Dose-Limiting Toxicities: Clarified the definition of a dose limiting toxicity

Section 2 Tabulated Protocol Summary and Section 9.1 Inclusion Criteria: Included the following inclusion criteria:

> Histologically- or cytologically-confirmed advanced/metastatic solid tumor or lymphoma by pathology report and who has received, or been intolerant to, all approved therapies. Advanced solid tumors (i.e. including but not limited to melanoma, breast, head and neck squamous cell) and lymphomas (i.e. including by not limited to diffuse large B cell lymphoma) of any type are eligible for enrollment.
>
> No limit to the number of prior therapies
>
> a. Patients who refuse standard treatments may also be considered provided that he/she has been made aware of all therapeutic options and it is documented in the study records.
>
> A minimum of one lesion that is easily accessible for injection, where easily accessible is defined as a cutaneous or subcutaneous mass that is palpable and/or visualizable by ultrasound
>
> a. ***Biopsy Cohort Enrichment and biopsy component of the Expansion Period only***: Patients must have a tumor lesion amenable to biopsy and consent to pre-treatment and on-treatment biopsies
>
> All lesion(s) targeted for the initial injection must be ≥ 0.5 cm on longest diameter, be at least 5 mm thick, and have distinct borders based on exam or imaging, not close to critical structures such as major vessels, nerves, or airways

Section 9.3.1 Dose Omissions and Discontinuation of Study Drug Administration: Decreased the recovery window for a DLT from 28 days to 14 days and added the following requirement: Patients who experience a Grade 3 hypersensitivity reaction or autoimmune events must discontinue from study treatment.

Section 10.2 Radiologic Assessments: Clarified the criteria for continuation of treatment for a patient that has disease progression per RECIST 1.1

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Section 2 Tabulated Protocol Summary: Simplified summary by including key protocol information only. In addition, all changes made throughout the protocol were reflected in the protocol summary.

Section 3 Schedule of Events:

- Added end of treatment visit
- Clarified safety follow-up visit and added a 180-day safety follow-up visit
- Corrected disease progression follow-up visit – visits at 3 months and 6 months post EOT
- Streamlined footnotes
- Corrected “symptom-directed physical exam” C2-C6 to indicate C2 only
- Consolidated tumor assessment procedure to one line
- Removed “baseline” – baseline assessments are done pre-dose on C1D1 or during screening

Section 7.1 Primary Objectives: Modified "recommended phase 2 dose" to "recommended dose for expansion" – this change was made throughout the document as appropriate

Section 7.5 Exploratory Objectives: Changed "irCheson" to "lymphoma response to immunomodulatory therapy (LYRIC)" to assessment of overall response rate – this change was made throughout the document as appropriate

Section 7.7 Safety Parameters: Antibodies against OX40L as a safety assessment for dose escalation will be reviewed as data are available

Section 8.1 Number of Patients: Revised total enrollment from 60 to 75 and escalation period maximum enrollment from 30 to 55

Section 8.2 Study Design: Clarified the study design; simplified study schema (Figure 1)

Section 8.2.1 Dose Escalation Period: Clarified process for escalating a dose and added a provisional dose table

Section 8.2.2.1 Expansion Period Stopping Rules: Revised DLT rate from > 33% to ≥ 33 % and revised text for clarification

Section 8.4.1 Safety Review Committee: Revised text for clarification

Section 8.4.4 Dose Escalation Procedure: Revised text to clarify the dose escalation procedure and adjusted the -1 provisional dose to 0.5 mg, a 50% reduction from the starting dose. Additional dosing below the -1 0.5 mg dose will be addressed in a protocol amendment.

Section 9.1 Inclusion Criteria: Reference section 10.14.1 and 10.14.2 as required male and female methods of contraception

Section 9.3 mRNA-2416 Dose Modification: Revised text for clarification

Section 9.3.1 Dose Omissions and Discontinuation of Study Drug Administration: Revised text for clarification and added an End of Treatment visit

Section 9.3.2 Discontinuation from the Study: Revised to include the required End of Treatment visit and 30 and 180-day Safety Follow-up visits. In addition, moved the language regarding permitted radiation to Section 9.4 Prior and Concomitant Medication

Section 10.1 Intratumoral Injections: Clarified superficial tumor requirements

Section 10.12 Tumor Biopsies: Revised clearly defined requirements of Group A, Group B and Group C

Administrative corrections for document consistency and typographical corrections were made throughout the document.

IRB/FDA/NIH Review/Approval

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The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

2 TABULATED PROTOCOL SUMMARY

Protocol Number	mRNA-2416-P101
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
Phase	I/II
Indication	Dose Escalation: Relapsed or refractory advanced solid tumor malignancies or lymphoma. Dose Expansion: Ovarian cancer of epithelial origin.
Introduction	Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immune-oncology for both solid tumors and hematologic malignancies. The cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) receptor and its ligand (programmed death ligand 1 [PD-L1]) are important cellular targets that play complementary roles in regulating adaptive immunity. Checkpoint inhibitors have induced regressions and improved survival in melanoma and non-small cell lung cancer (Robert et al 2015; Borghaei et al 2015). However, checkpoint inhibitors alone are not sufficient to induce significant tumor regressions in the majority of patients. Generating optimal T-cell responses also requires T-cell receptor activation and co-stimulation, which can be provided via ligation of tumor necrosis factor (TNF) receptor family members, such as OX40. The OX40 receptor (TNFRSF4, cluster of differentiation [CD]134) is expressed on activated immune effector cells such as T-cells and natural killer (NK) cells (Mallett et al 1990). The ligand for OX40, OX40L, is a homo-trimeric protein expressed on antigen-presenting cells (Compaan and Hymowitz 2006); binding of OX40 by OX40L in the presence of a recognized antigen, such as a tumor neoantigen, enhances the expansion of CD4+ and CD8+ T-cells and increases T-cell memory effects while inhibiting T regulatory cells. OX40 ligation with agonist antibodies boosts cytokine production and enhances anti-tumor immunity (Sugamura et al 2004). As a result, induction of expression of OX40L by tumor cells, or other cells presenting tumor antigens to immune effector cells, is an attractive method of enhancing local anti-tumor immunity and may trigger a specific cell-mediated immune response with systemic anti-tumor effects. Durable tumor regressions have been observed in murine mouse models treated with single-agent anti-OX40. Several agonists of OX40 have entered early-phase clinical trials. Preliminary results demonstrate only low-grade adverse events (AEs) coupled with minimal activity as a single agent. In a Phase 1 study, the preliminary safety and efficacy of PF04518600 was assessed with doses ranging from 0.01 to 3.0 mg/kg administered intravenously (IV) every 2 weeks. Treatment-emergent AEs (TEAEs) were Grades 1 to 2 and were observed in 67.7% of patients; fatigue and decreased appetite were the most common TEAEs. One partial response was observed at 0.1 mg/kg, and 14 patients experienced stable disease across the dose ranges (Diab et al 2016). Similar effects were seen in the Phase 1 trial of MOXR0916 (0.2 to 1200 mg IV every 3 weeks) in which only Grade 1 and 2 TEAEs were observed; the most common TEAEs included fatigue, gastrointestinal (GI) symptoms, and infusion reactions. Minimal activity was demonstrated, but initial reports indicate that increased

	immune activation and efficacy may be seen in combination with a PD-L1 inhibitor (Infante et al 2016). However, most agents currently being tested are administered systemically and can activate immune effector cells at sites of active inflammation or immune reactivity outside the tumor. Local induction of OX40L within the tumor milieu via intratumoral injection may restrict the immune response to the tumor. A resulting T-memory effect might then have anti-tumor effects at sites distant to the tumor lesion directly injected. Agents such as talimogene laherparepvec (Imlygic™, T-VEC) have demonstrated that intralesional injections can lead to durable responses (Andtbacka et al 2015). mRNA-2416 is a novel messenger ribonucleic acid (mRNA)-based immuno-oncological treatment for solid tumors that encodes the wild type human OX40L (hOX40L), a transmembrane T-cell costimulatory protein normally expressed on antigen presenting cells upon immune stimulation. Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1, kappa (IgG1, kappa) subclass that blocks the interaction of PD-L1 (but not programmed cell death - ligand 2 [PD-L2]) with programmed cell death protein 1 (PD-1) on T-cells and cluster of differentiation (CD) 80 proteins on immune cells. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. The population for Dose Escalation was selected as those patients with locally advanced, recurrent or metastatic incurable solid malignancy or lymphoma that has progressed after standard therapy or for which standard therapy has proven to be ineffective or intolerable or is considered inappropriate and are therefore considered to be appropriate candidates for clinical trials exploring new forms of treatment. In the Dose Expansion period, patients with ovarian cancer of epithelial origin will be enrolled at the MTD and/or RDE.
Planned Number of Patients	The planned study enrollment is approximately 117 patients. Approximately 57 patients will be enrolled during the Dose Escalation and Dose Confirmation Periods of the study. During the Expansion Period of the study, approximately 60 patients will be enrolled at the maximum tolerated dose/recommended dose for expansion (MTD/RDE).
Planned Number of Sites	Approximately 15 sites in the United States

Study Objectives	Primary: 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 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 Secondary: • To assess mRNA pharmacokinetics (PK) of mRNA-2416 alone and in combination with durvalumab • To assess emergence of antibodies against the drug product as well as OX40L, the protein translated by the drug product • 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 of mRNA-2416 monotherapy based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or Cheson 2014 criteria (lymphomas) • Phase II only: To assess disease control rate and duration of response of mRNA-2416 alone and in combination with durvalumab based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Exploratory: • 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 pharmacokinetics (PK) of durvalumab in combination with mRNA-2416
Study Outcome Measures	Primary: Phase I • Incidence and nature of dose-limiting toxicities (DLTs) with mRNA-2416 alone and in combination with durvalumab

	• Incidence, nature, and severity of AEs/serious AEs, 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 of mRNA-2416 alone and in combination with durvalumab in patients with ovarian cancer based on RECIST v1.1 Secondary: • Presence and/or concentration of antibodies against the drug product as well as OX40L, the protein translated by the drug product • PK parameters for mRNA-2416 alone and in combination with durvalumab: maximum observed concentration and area under the concentration-time curve • Phase I only: Assessment of objective response rate and duration of response (progression-free survival) of mRNA-2416 monotherapy and combination with durvalumab based on RECIST v1.1 or Cheson 2014 criteria (lymphomas) • Phase II only: Assessment of disease control rate and duration of response of mRNA-2416 alone and in combination with durvalumab in patients with ovarian cancer based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Exploratory: • 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: o Expression of OX40 and OX40L and change in expression over the treatment period o Expression of other immune-related markers, including PD-1 and PD-L1 o Infiltration of tumor with immune effector cells, including T-cells • PK parameters for durvalumab in combination with mRNA-2416: maximum observed concentration and area under the concentration-time curve
Study Design	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 periods in patients with ovarian cancer in each treatment arm. The study includes the following 2 treatment arms:

	• Arm A: mRNA-2416 alone • Arm B: mRNA-2416 in combination with durvalumab (PD-L1 inhibitor) Each arm of the study consists of a Dose Escalation and Dose Confirmation part followed by a Dose Expansion part 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 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 visceral lesions injectable with ultrasound or CT guidance. Dose Confirmation will be conducted in the same fashion as Dose Escalation, as described in Section 8.2.1 and Section 8.4. For both Arms, once the MTD and/or RDE has been determined in Dose Escalation/Confirmation, patients will be enrolled in an Expansion cohort in order to assess the preliminary anti-tumor activity of mRNA-2416 in ovarian cancer of epithelial origin The Dose Expansion will consist of 2 investigational groups across the treatment arms summarized as follows and shown in Figure 1: Arm A: mRNA-2416 alone • Group 1: Ovarian cancer Arm B: mRNA-2416 in combination with durvalumab • Group 2: Ovarian cancer Prior to enrollment, all patients will undergo screening to determine study eligibility. All patients completing study therapy with an overall tumor assessment of stable disease (SD) or better will be followed for 6 months or until disease progression, whichever occurs first.
Study Duration	Approximately 3.5 years
Study Population	**<u>Inclusion Criteria</u>** All patients must meet all of the following inclusion criteria: 1. Males or females ≥18 years of age who have provided written informed consent prior to completing any study-specific procedure 2. Disease state and prior therapies: a. Dose Escalation and Dose Confirmation Periods: Histologically- or cytologically-confirmed advanced/metastatic solid tumor or lymphoma by pathology report and who has received, or been intolerant to, all approved therapies. Advanced solid tumors (i.e. including but not limited to melanoma, breast, head and neck

	squamous cell) and lymphomas (i.e. including by not limited to diffuse large B cell lymphoma) of any type are eligible for enrollment. b. Dose Expansion Period: Histologically or cytologically confirmed diagnosis of: epithelial cancer of the ovary, fallopian tube, or peritoneum which is platinum resistant or platinum refractory. Patients must have received at least 2 prior lines of therapy. Patients with known BRCA mutation positive must have been treated with and progressed on at least 1 prior PARPi (poly(ADP-ribose) polymerase inhibitor). 3. No limit to the number of prior therapies a. Patients who refuse standard treatments may also be considered provided that he/she has been made aware of all therapeutic options and it is documented in the study records. 4. Lesions for intratumoral injection and biopsies: a. Dose Escalation: A minimum of one non-visceral lesion that is easily accessible for injection where easily accessible is defined as a cutaneous or subcutaneous mass that is palpable and/or visualizable by ultrasound b. Dose Confirmation: A minimum of one visceral lesion injectable with ultrasound or computer tomography (CT) guidance and that is not encasing or abutting major vascular structures or are in a location that are considered high risk for AEs by the enrolling physician c. Dose Expansion: A minimum of one lesion amenable to injection (either non-visceral or visceral). Patients must have a tumor lesion amenable to biopsy and consent to a pre-treatment and an on-treatment biopsy. For patients with only one lesion amenable to injection, biopsy, and RECIST assessment, the lesion must be ≥ 2 cm. d. Biopsy Cohort Enrichment: Patients must have a tumor lesion amenable to biopsy and consent to a pre-treatment and an on-treatment biopsy 5. All lesion(s) targeted for the initial injection must be ≥ 0.5 cm on longest diameter, be at least 5 mm thick, and have distinct borders based on exam or imaging, not close to critical structures such as major vessels, nerves, or airways 6. Patients must have measurable disease as determined by RECIST v1.1 (solid tumors) or Cheson 2014 criteria (lymphomas). a. Dose Expansion: Patients must have at least 1 measurable lesion per RECIST v1.1 which has not been previously irradiated. 7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 8. Adequate hematological and biological function, confirmed by the following laboratory values: Bone marrow function

a. Absolute neutrophil count ≥1.5 × 10^9/L
b. Hemoglobin ≥9 g/dL or ≥6.2 mmol/L
c. Platelets ≥100 × 10^9/L without transfusion support

Hepatic function

d. Aspartate aminotransferase and alanine aminotransferase ≤2.5 × upper limit of normal (ULN) (≤5 × ULN, if hepatic involvement of tumor)
e. Bilirubin ≤1.5 × ULN (<3.0 mg/dL if patient has Gilbert's disease)

Renal function

f. Serum creatinine ≤1.5 × ULN or creatinine clearance of >50 mL/min (using Cockcroft-Gault formula)

$$eC_{Cr}[mL/min] = \frac{(140 - Age\ [yrs]) \times Body\ Weight\ [kg] \times [0.85\ if\ Female]}{72 \times Serum\ Creatinine\ [mg/dL]}$$

Coagulation function

g. Protime/international normalized ratio and activated partial thromboplastin time ≤1.5 × ULN

Thyroid function

h. Thyroid-stimulating hormone within normal range

9. Female patients of childbearing potential must have a negative serum pregnancy test during screening. Male and female patients must agree to use a highly reliable method of birth control (expected failure rate less than 1% per year) from the Screening visit through 120 days after the last dose of study drug. Patients must consent to following the contraception requirements in Section 10.14.1 and 10.14.2
10. Must have a life expectancy of at least 12 weeks
11. Body weight >30 kg.

Exclusion Criteria

Any of the following criteria will exclude patients from study participation:

1. Active central nervous system tumors or metastases
2. Treatment with chemotherapy, radiation (local radiation for palliative care is permitted), hormonal anti-cancer treatment, or biologic therapy <14 days prior to the first day of study treatment (Cycle 1 Day 1 [C1D1])

    a. Treatment with any other investigational agent or treatment with any anti-cancer monoclonal antibody, immunostimulant, or vaccine <28 days prior to C1D1.

3. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

	4. History of severe allergic reactions to any of the study drug components 5. Has active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion: • Patients with vitiligo or alopecia • Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement • Patients with any chronic skin condition that does not require systemic therapy • Patients without active disease in the last 5 years may be included but only after consultation with the Moderna medical monitor • Patients with celiac disease controlled by diet alone. 6. Has a history of primary immunodeficiency, allogenic solid organ transplantation, or tuberculosis. 7. Immunosuppressive doses of systemic steroids or absorbed topical steroids (doses >10 mg prednisone daily equivalent) within 2 weeks before study drug administration 8. Local infection at site of a tumor lesion amenable to injection requiring anti-infective therapy within 2 weeks of the first dose of study drug 9. Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment. Note: Patients, if enrolled, should not receive live vaccine whilst receiving study treatment and up to 30 days after the last dose of study treatment. 10. History of human immunodeficiency virus infection 11. Active/chronic hepatitis B or C 12. Major surgical procedures ≤28 days or non-study-related minor procedures ≤7 days prior to C1D1. In all cases, the patient must be sufficiently recovered and stable before treatment administration. 13. Any of the following cardiac abnormalities: a. Medically uncontrolled hypertension b. New York Heart Association Class III or IV cardiac disease c. Myocardial infarction within prior 6 months d. Unstable angina e. Unstable arrhythmias or mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart) 14. History of another primary malignancy except for: • Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

	• Adequately treated carcinoma in situ without evidence of disease 15. Patients requiring active systemic anticoagulation at the time of intratumoral injection or biopsy 16. Active GI bleeding 17. Females who are pregnant or breastfeeding 18. Any other unstable or clinically significant concurrent medical condition (eg, substance abuse, psychiatric illness/social situations, uncontrolled intercurrent illness including active infection, arterial thrombosis, symptomatic pulmonary embolism, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea etc) that would, in the opinion of the investigator, jeopardize the safety of a patient, impact their expected survival through the end of the study participation, and/or impact their ability to give written informed consent or comply with the protocol. 19. For patients who have received prior anti-PD-1 or anti PD-L1 therapy, a patient must not have experienced any of the following: a. Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy. b. All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study. 20. Must not have experienced a ≥ Grade 3 immune-related AE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy. Note: Patients with endocrine AEs of ≤ Grade 2 are permitted to enroll if they are stable while maintained on appropriate replacement therapy and are asymptomatic. 21. Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day. 22. Has an active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBV surface antigen [HBsAg] result), hepatitis C, or human immunodeficiency virus (positive HIV-1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. 23. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis. 24. Has a history of leptomeningeal carcinomatosis. 25. Has involvement in the planning and/or conduct of the study.
Study Drug, Dosage and Route of Administration	mRNA-2416 will be administered to patients as intratumoral injections on Days 1 and 15 of each 28-day cycle (±2 days). All patients in Arm B and Arm A patients that are to receive intratumoral injections to visceral lesions will reduce dosing frequency to every 4 weeks after completing 1 cycle of therapy (Day 1 and Day 15 for Cycle 1, then Day 1 only for Cycles 2-6).

	The starting dose is 1.0 mg mRNA-2416 for Arm A and 4.0mg mRNA-2416 in combination with 1500mg of durvalumab for Arm B; other dose levels may be evaluated during this trial.
Randomization	Not applicable
Efficacy Assessments	Best response will be determined for each patient in accordance with RECIST/Cheson and irRC/LYRIC guidelines.
Safety Assessments	Safety measures will include: • AEs (including imAEs and AESIs) • Hematology, clinical chemistry, and liver function tests • 12-Lead electrocardiograms • Physical examination • Vital signs and body weight • Concomitant medications/procedures • ECOG performance status • Antibodies against OX40L, the protein translated by the drug product, will be reviewed with investigators as data are available Where applicable, AEs will be classified according to the NCI CTCAE Version 4.03.
Biomarker & Pharmacodynamic Assessments	The biomarker analysis will be used to investigate the effect of mRNA-2416 alone and in combination with durvalumab, as well as to determine how the markers are associated with clinical outcome. Immune responses will be studied in the peripheral circulation and in tumor biopsy specimens. Tumor biopsies will be examined using methods such as immunohistochemistry, quantitative immunofluorescence, RNA sequencing, and/or electrochemiluminescence (ECL) assays to evaluate changes in key immune pathway axes, such as PD-L1/PD-1 and OX40L/OX40, as well as characterization (eg, phenotype, distribution, and activation) of tumor infiltrating lymphocyte and myeloid populations. Cytokines will also be examined in both tumor and blood tissues using methods such as RNA sequencing and enzyme-linked immunosorbent assay (ELISA)/ ECLassays respectively.
Patient Reported Outcome Assessments	None
Statistical Procedures	Described in Section 13 and in the Statistical Analysis Plan

3 SCHEDULE OF EVENTS

Study Procedure	**Screening**	**Cycle 1**				**Cycle 2 - Cycle 6**		**End of Treatment**	**Follow-up**	
Study Days	**-14 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**Within 14 days of Treatment Discontinuation**	**30 and 90 Day Safety F/U**	**90 and 180 Day Disease Progression F/U Period**
Visit Window	-	-	**+1 day**		**±2 days**	**±2 days**		**±2 days**	**-2/+7 days**	**±30 days**
Clinical Assessments										
Informed Consent	X									
Inclusion/exclusion criteria	X									
Demographics[1]	X									
Medical/Surgical/Cancer Histories[2]	X									
Vital Signs[3]	X	X	X	X	X	X	X	X	X	
Height	X									
Body Weight	X	X				X		X	X	
Physical Exam[4]	X							X		
Symptom-directed Physical Exam		X	X	X	X	X	X		X	
ECOG Performance Status	X					X		X	X	
Concomitant Medications[5]	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments										
Full Blood Count[6]	X	X	X	X	X	X	X	X	X	
Coagulation[6]	X	X				X				
Serum Chemistry Panel[6]	X	X	X	X	X	X	X	X	X	
Thyroid Function [12]	X	X			X	X		X	X	
Urinalysis[6]	X							X		
Pregnancy Test [10]	X	X				X		X	X	
12-Lead Electrocardiogram	X							X	X	
HIV, Hepatitis B & C Tests[6,11]	X									
Study Drug Administration										

Study Procedure	**Screening**	**Cycle 1**				**Cycle 2 - Cycle 6**		**End of Treatment**	**Follow-up**	
Study Days	**-14 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**Within 14 days of Treatment Discontinuation**	**30 and 90 Day Safety F/U**	**90 and 180 Day Disease Progression F/U Period**
Visit Window	-	**-**	**+1 day**		**±2 days**	**±2 days**		**±2 days**	**-2/+7 days**	**±30 days**
mRNA-2416 intratumoral injection[7]		X			X	X	X[7]			
Durvalumab infusion		X				X				
Tumor Assessments										
Tumor assessment[8]	X					C3 & C5		X		X
PK/Pharmacodynamic Assessments										
PK Sampling[9]		X	X	X		C2				
Cytokine Profile Sampling[9]		X	X	X		C2				
Serum Immunogenicity Sample[9]		X			X	X	C3 & C6	X		
Tumor Biopsy	X	Refer to Section 10.5								

1. Demographics include age, sex, race, and ethnicity.
2. Prior cancer history includes (i) date of diagnosis, (ii) staging, (iii) all previous therapies (ie, chemotherapy, immunotherapy, biologic or targeted agents, experimental therapies, radiotherapy, and surgery), (iv) previous therapy details (ie, regimen, start and stop dates), and (v) best response for each regimen.
3. Vital signs include temperature, blood pressure, preferably in seated position, and pulse rate. Pre-dose and as clinically indicated before every infusion or administration.
4. Complete physical examination should include evaluation of the HEENT and neck and dermatologic, cardiovascular, respiratory, gastrointestinal (including assessments of liver and spleen), musculoskeletal, neurological, and lymphatic systems.
5. Please refer to Section 10.8 for additional detail regarding prior and concomitant medications
6. Please reference Appendix B Safety Laboratory Tests and Hepatitis Serology
7. Only for Arm A patients receiving treatment to superficial lesions. All patients in Arm B and patients in Arm A receiving treatment to visceral lesions are to receive intratumoral injections on Day 1 and Day 15 for Cycle 1, and on Day 1 only for Cycles 2-6. Please refer to Section 8.2 Study Design and Section 10.1 Intratumoral Injections for mRNA-2416 dosing requirements.
8. Please refer to Section 10.2 and 10.3 for tumor assessment imaging requirements
9. Please refer to Table 6 for PK, Cytokine Profile, and Serum Immunogenicity sampling details.
10. Females of child bearing potential only.
11. Testing for HIV and Hepatitis B or C is to be done locally. It is not required if a documented negative test within 6 months is available.
12. TSH and reflex free T3 or free T4g. If measured within 14 days prior to C1D1, it does not need to be repeated at C1D1.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definitions
ADR	adverse drug reaction
AE	adverse event
ALT/GPT	Alanine aminotransferase
AST/GOT	Aspartate aminotransferase
ATA	Anti-therapeutic antibody
AUC	area under the concentration-time curve
BUN	blood urea nitrogen
CXDX	Cycle X Day X
CD	cluster of differentiation
CD4	cluster of differentiation 4: a glycoprotein that is found primarily on the surface of helper T-cells
CFR	Code of Federal Regulations
Cmax	maximum observed concentration
CR	complete response
CRF	case report form
CRO	Contract Research Organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
EOT	End of Treatment
FDA	Food and Drug Administration
F/U	Follow Up
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice

Abbreviation	Definitions
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C antibody
hrs	hours
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IND	Investigational New Drug
IR	Immune response
IRB	Institutional Review Board
irRC	Immune-related Response Criteria
IV	intravenous(ly)
kg	kilogram
L	liter
LDH	lactic dehydrogenase
LNP	lipid nanoparticle
LYRIC	lymphoma response to immunomodulatory therapy criteria
MedDRA	Medical Dictionary for Regulatory Activities
min	minute(s)
mg	milligram
mL	milliliter
mmol	millimoles
mM	millimolar
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NIH	National Institute of Health
NK	natural killer
OX40L	OX40 ligand
PARPi	poly(ADP-ribose) polymerase inhibitor
PD	progressive disease

Abbreviation	Definitions
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PI	Principal Investigator
PK	pharmacokinetics
PR	partial response
QIF	quantitative immunofluorescence
RECIST	Response Evaluation Criteria in Solid Tumors
RDE	recommended dose for expansion
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Stable Disease
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
US / USA	United States of America
WBC	white blood cell

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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6 BACKGROUND AND RATIONALE

Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immune-oncology for both solid tumors and hematologic malignancies. The cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) receptor and its ligand (programmed death ligand 1 [PD-L1]) are important cellular targets that play complementary roles in regulating adaptive immunity. Checkpoint inhibitors have induced regressions and improved survival in melanoma and non-small cell lung cancer (Robert et al 2015; Borghaei et al 2015). However, checkpoint inhibitors alone are not sufficient to induce significant tumor regressions in the majority of patients.

Generating optimal T-cell responses also requires T-cell receptor activation and co-stimulation, which can be provided via ligation of tumor necrosis factor (TNF) receptor family members, such as OX40. The OX40 receptor (TNFRSF4, cluster of differentiation [CD]134) is expressed on activated immune effector cells such as T-cells and natural killer (NK) cells (Mallett et al 1990). The ligand for OX40, OX40L, is a homo-trimeric protein expressed on antigen-presenting cells (Compaan and Hymowitz 2006); binding of OX40 by OX40L in the presence of a recognized antigen, such as a tumor neoantigen, enhances the expansion of CD4+ and CD8+ T-cells and increases T-cell memory effects while inhibiting T regulatory cells. OX40 ligation with agonist antibodies boosts cytokine production and enhances anti-tumor immunity (Sugamura et al 2004). As a result, induction of expression of OX40L by tumor cells, or other cells presenting tumor antigens to immune effector cells, is an attractive method of enhancing local anti-tumor immunity and may trigger a specific cell-mediated immune response with systemic anti-tumor effects. Durable tumor regressions have been observed in murine mouse models treated with single-agent anti-OX40.

Several agonists of OX40 have entered early-phase clinical trials. Preliminary results demonstrate only low-grade adverse events (AEs) coupled with minimal activity as a single agent. In a Phase 1 study, the preliminary safety and efficacy of PF04518600 was assessed with doses ranging from 0.01 to 3.0 mg/kg administered intravenously (IV) every 2 weeks. Treatment-emergent AEs (TEAEs) were Grades 1 to 2 and were observed in 67.7% of patients; fatigue and decreased appetite were the most common TEAEs. One partial response was observed at 0.1 mg/kg, and 14 patients experienced stable disease across the dose ranges (Diab et al 2016). Similar effects were seen in the Phase 1 trial of MOXR0916 (0.2 to 1200 mg IV every 3 weeks) in which only Grade 1 and 2 TEAEs were observed; the most common TEAEs included fatigue, gastrointestinal (GI) symptoms, and infusion reactions. Minimal activity was demonstrated, but initial reports indicate that increased immune activation and efficacy may be seen in combination with a PD-L1 inhibitor (Infante et al 2016).

However, most agents currently being tested are administered systemically and can activate immune effector cells at sites of active inflammation or immune reactivity outside the tumor. Local induction of OX40L within the tumor milieu via intratumoral injection may restrict the immune response to the tumor. A resulting T-memory effect might then have anti-tumor effects at sites distant to the tumor lesion directly injected. This can improve outcomes from systemically delivered antibodies, such as CPIs, and have an improved tolerability profile compared to systemic therapy alone. Intratumoral administration of immune-mediated therapies have primarily included oncolytic viruses, DNA-based gene delivery, small molecules, and antibodies (Aznar et al 2017; Van Lint et al 2016). More recently, mRNA-based therapies have been studied in this setting. Moderna's platform enables the local delivery of several mRNAs formulated in LNPs that can encode various proteins that have distinct functions yet work synergistically in mediating anti-cancer responses.

Based on the afore-mentioned research, ModernaTX, Inc. is proposing to conduct a clinical study using mRNA-2416 encoding for OX40L as a monotherapy and in combination with an anti-PD-L1 antibody.

6.1 INDICATION BACKGROUND

Cancer immunotherapy attempts to stimulate the immune system to recognize and destroy tumor cells. To date, a variety of methods have been utilized. Most recently, the advent of checkpoint inhibitors has demonstrated activity in a multitude of tumor types. Although ipilimumab has been approved for melanoma only (metastatic and adjuvant treatment), PD-1/PD-L1 inhibitors have expanded use into additional tumor types including non-small cell lung cancer, renal cell carcinoma, Hodgkin's disease, and urothelial carcinoma. In addition, a multitude of tumor types are currently under investigation including both solid tumors and hematologic malignancies. Likewise, use of an immunostimulatory molecule such as an OX40L should have activity in a wide variety of tumors.

Ovarian cancer is the leading cause of death from gynecological malignancies in the United States with an incidence rate of approximately 22,000 and 14,000 deaths per year (Meehan et al 2016). The five-year survival rate remains dismal especially for later stage disease. While great strides have been made with immunotherapy, ovarian carcinoma hasn't seen much benefit from these advances. Recent phase I and II studies demonstrate limited monotherapy activity of PD-1/PD-L1 pathway inhibition in recurrent ovarian cancer, yielding 11% to 17% response rates, with a few durable complete responses in a subset of heavily pretreated patients (Bourla et al 2016). During the dose escalation period of this trial, 2 epithelial ovarian cancer patients were enrolled and had stable disease per RECIST1.1 with noted response in injected lesions (SITC annual meeting 2018 poster P295).

6.2 mRNA-2416 BACKGROUND

mRNA-2416 is a novel mRNA-based therapeutic agent containing 2 mg/mL of CX-000006, mRNA Drug Substance, that encodes the wild type human OX40 ligand (OX40L), a transmembrane protein normally expressed on antigen presenting cells upon immune stimulation. mRNA-2416 is intended for intratumoral injection.

Modified mRNA is less immunogenic than unmodified mRNA and results in increased protein translation. Both the murine and human OX40L mRNA constructs that have been tested encode the wild type transmembrane OX40L protein. Each construct also contains a miR-122 recognition site in the 3' untranslated region, which significantly reduces protein expression by normal hepatocytes, a potentially undesirable location for immune activation. The mRNA is then encapsulated in lipid nanoparticles and may be used for direct injection.

Transfection of mRNA encoding both murine and human OX40L has been shown to induce functionally active surface-bound OX40L protein both in vitro and in vivo. Expression is stable in vitro for up to 5 days. After injection of the murine analog of OX40L mRNA to murine tumors, expression of OX40L protein peaks at around 24 hours and is still detectable at 7 days. Pharmacodynamic studies demonstrate rapid increase of NK cells within the tumor following injection of OX40L mRNA, followed at 7 to 14 days by an increase in CD8+ T-cells. Non-translated mRNA has no effect.

The efficacy of murine OX40L mRNA has been tested in subcutaneous murine models of cancer in immunocompetent mice. Injection of OX40L mRNA encapsulated in a lipid nanoparticle (LNP) directly into established tumors induces tumor regressions and tumor growth delay. Mice in whom tumors completely regress did not grow tumors when challenged with re-implantation, suggesting an immune memory response was induced, which resulted in tumor rejection. Weekly injection of OX40L mRNA for 6 to 8 doses resulted in efficacy, which appears to be superior to 2 doses. There was also a dose-dependent effect; 12.5 µg of mRNA weekly was more efficacious than 6.25 µg or 3.25 µg.

The efficacy of murine OX40L mRNA in combination with anti-PD-L1 checkpoint inhibitor has been tested in the syngeneic MC38S colon carcinoma tumor model. Weekly injection of OX40LmRNA encapsulated in LNP combined with αPD-L1 antibody administered via IP injection twice weekly resulted in 8/15 complete responders (CRs) (53%) at the end of the study period. In contrast, treatment with OX40L mRNA combined with Isotype control antibody resulted in 1/15 CRs (7%). Treatment with a nontranslated control mRNA in combination with αPD-L1 resulted in 1/15 CRs (7%). As with OX40L mRNA monotherapy therapy, mice treated with the combination that were complete responders, did not grow tumors when challenged with re-implantation suggesting an immune memory response.

Biodistribution studies have been performed in tumor-bearing mice. Twenty-four hours following a single intratumoral injection of OX40L mRNA, the highest concentration of mRNA was detected in the injected tumor. Substantially lower and nearly equal concentrations of mRNA were detected in the liver, heart, proximal lymph node, lung, kidney, and brain. Considering the very high sensitivity of the branched DNA assay used to quantify mRNA levels, it was stipulated that these results are possibly due to incomplete PBS perfusion to clear blood from tissues before collection or other artifacts of the method.

OX40L protein levels in the liver, spleen, and MC38 tumor tissue were determined by an OX40L-specific enzyme-linked immunosorbent assay. Although the highest concentration of OX40L protein was observed in the liver, a lack of dose response and similarly high levels of OX40L in animals administered a nontranslating construct, suggest that it is an endogenous protein. Hence, it was concluded that dose-related OX40L was reliably detected only in tumor and spleen samples.

The safety and tolerability of mRNA-2416 were evaluated in repeat-dose toxicity studies in Sprague-Dawley rats and cynomolgus monkeys. In two 1-month, Good Laboratory Practice (GLP) compliant, repeat-dose toxicity studies with a 14-day post-study recovery period, mRNA-2416 was administered subcutaneously (SC), using lipid nanoparticle containing mRNA encoding wild type human OX40L, once per week for a total of 5 doses in the outbred Sprague-Dawley rat and cynomolgus monkey.

Results of the repeat-dose toxicity study in rats via the SC route demonstrated no mRNA-2416-related effects on survival, ocular findings and urinalysis parameters. All animals survived until the scheduled necropsy. Weekly administration of mRNA-2416 to Sprague-Dawley rats at dose levels of 0.1, 0.3, and 1.0 mg/kg was associated with dose-dependent injection site lesions that were considered adverse at 1.0 mg/kg. Histology indicated minimal to mild hepatocellular single cell necrosis with subcapsular localization in females at ≥0.1 mg/kg. Secondary to injection site inflammatory changes, systemic inflammation changes were observed at ≥0.1 mg/kg. Possible stress-related findings were observed at ≥0.3 mg/kg. All changes were either totally or partially resolved following a 14-day recovery period.

Results of the repeat-dose toxicity study in monkeys via the SC route appear to support the safe delivery of mRNA-2416 in monkeys. Following 5 repeated SC doses of up to 0.6 mg/kg, no significant systemic toxicity was observed and there were no deaths. Treatment-related findings were generally limited to the SC injection site where a dose-related inflammatory reaction was noted at all doses. Moderate edema of the SC tissue was only observed in a single 0.6 mg/kg male, and mild arterial necrosis was only observed in a single 0.6 mg/kg female. Systemic inflammation and changes in endocrine organs were also observed and considered consistent with a secondary response to inflammation associated with the administration sites. Decreased body weights, decreased red blood cell count, and increased liver weights were also observed in some animals at the 0.6 mg/kg dose but all changes were partially resolved (microscopic changes at the injection site and in the spleen) or fully resolved following a 14-day recovery period. The monkey was determined to be the most sensitive species, and the highest non-severely toxic dose was judged to be 0.3mg/kg.

In the rat and monkey, ATA analysis indicated a dose-dependent increase in antibodies (IgM and IgG) directed against human OX40L on Day 29 in all groups dosed with mRNA-2416. Since all animals treated with mRNA-2416 developed anti-hOX40L response (and homology of cyno and human OX40L is considered high = 99%), seroconversion may occur in patients. Published studies in knock-out animals have indicated that there is no or only minor contribution of this protein to immunity since it is part of a redundant signaling system (Boettler et al 2012, Kopf et al 1999, Murata et al 2000, Salek-Ardakani et al 2008). Therefore, seroconversion in patients is not anticipated to cause significant risk.

The safety of mRNA-2416 was evaluated in an in vivo genotoxicity study in Sprague Dawley rats using the bone marrow micronucleus test. In addition, the concentrations of mRNA-2416 in the plasma were determined. Refer to the Investigator's Brochure for study details.

Results showed mRNA-2416 induced chromosome damage in rat bone marrow immature erythrocytes, when administered intravenously at up to 2 and 3 mg/kg, the estimated maximum tolerated doses for male and female Sprague Dawley rats, respectively. These results were considered weakly positive. Based on the relative lack of response in females at the higher dose (3 mg/kg), the mild nature of response (< 3-fold), the high doses administered by the IV route, and the lack of in vitro response of SM-86, the risk of genotoxicity in patients is considered low.

The safety of SM-86, a novel lipid excipient of the mRNA-2416, was evaluated in 2 in vitro genotoxicity studies. SM-86 did not show any evidence of genotoxic activity in either assay.

This study represents the first-in-human clinical study for mRNA-2416. As of 08-Feb-2019, 32 patients with advanced relapsed/refractory malignancies have been enrolled. General adverse reactions, reported in 3 or more subjects, included site pain, injection site reaction (erythema, edema, itching), pyrexia, flushing, fatigue, chills, and nausea with all the events being mild to moderate in severity except for one Grade 3 injection-related reaction. Refer to the current mRNA-2416 and durvalumab investigator's brochures (IB) for a complete summary of pre-clinical and clinical information.

6.3 Durvalumab Background

Durvalumab (MEDI4736) is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1, kappa (IgG1, kappa) subclass that blocks the interaction of PD-L1 (but not programmed cell death - ligand 2 [PD-L2]) with programmed cell death protein 1 (PD 1) on T-cells and cluster of differentiation (CD) 80 proteins on immune cells. Durvalumab is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action for durvalumab is interference in the interaction of PD L1 with PD 1 and CD80. Blockade of PD-L1/PD-1 and PD L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrated that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T-cells resulting in the restored proliferation of interferon-gamma ([IFN γ] Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's anti-tumor immune response by binding to PD L1 and shifting the balance toward an anti-tumor response. Durvalumab has been engineered to reduce antibody dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis, adrenal insufficiency, hypo- and hyper thyroidism, and type I diabetes mellitus), hepatitis/increases in

transaminases, nephritis/increases in creatinine, pancreatitis/increases in serum amylase and lipase, rash/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

In monotherapy clinical studies, very commonly AEs reported included events such as fatigue, diarrhea, nausea and vomiting, decreased appetite, and muscle and joint pain. A total of 5% to 10% of patients discontinued the drug due to an AE. Refer to the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs, and Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Appendix E).

For information on all identified and potential risks with durvalumab, please refer to the current version of the durvalumab IB.

6.4 mRNA-2416 Dosing Rationale

The planned starting dose is 1.0 mg (0.5 mL) of mRNA-2416 on Day 1 and Day 15 of 28-day cycles.

Antibody agonists of OX40 have been tested in Phase 1 trials in cancer patients. Preliminary results demonstrate only low-grade AEs. In a Phase 1 study, the preliminary safety and efficacy of PF04518600 was assessed with doses ranging from 0.01 to 3.0 mg/kg administered IV every 2 weeks. TEAEs were Grades 1 to 2 and were observed in 67.7% of patients; fatigue and decreased appetite were the most common TEAEs (Diab et al 2016). Similar effects were seen in the Phase 1 trial of MOXR0916 (0.2 to 1200 mg IV every 3 weeks) in which only Grade 1 and 2 TEAEs were observed; the most common TEAEs included fatigue, GI symptoms, and infusion reactions.

The dose of mRNA injected may be limited by either local or systemic tolerability or by the maximum volume of mRNA that can be injected. mRNA-2416 has been formulated at 2 mg/mL. Experience with intratumoral injection of the oncolytic viral product talimogene laherparepvec (Imlygic™, T-VEC) suggests that 5 mL is the maximal intratumoral volume per injection. Toxicology studies in non-human primates suggest that a safe starting dose for mRNA-2416, including a 6 times margin of error, is 0.017 mg/kg, or approximately 1 mg in a 70 kg patient.

In the first clinical study of mRNA-2416 it is proposed that the study drug is administered by intratumoral injection on Days 1 and 15 of a 28-day cycle, repeated for a maximum of 6 cycles. The selection of a 14-day dosing regimen is based upon the following:

- The observed pharmacodynamic effects of OX40L may extend to 14 days given that there was an increase in T-cells in tumors 14 days after injection of mRNA encoding murine OX40L (Section 6.2).
- Any local toxicity observed in the GLP toxicology studies after subcutaneous injection of mRNA-2416 was either partially resolved (microscopic changes at the injection site and in the spleen) or fully resolved 14 days after injection (Section 6.2).
- This dosing regimen enables convenient combination in future studies of mRNA-2416 with an anti-PD-1 or anti-programmed death ligand 1 (PD-L1) antibody in accordance with their approved dosing regimens (Planchard et al 2016).

The proposal to repeat administration of mRNA-2416 is justified by the nonclinical efficacy data demonstrating that repeated doses of murine OX40L into tumor-bearing mice are more efficacious than a single administration. Patients who do not experience dose-limiting or other unacceptable toxicity after the first cycle of therapy, and who are otherwise adjudged to benefit from study therapy at the end of Cycle 2 tumor assessment, may continue on study treatment. Repeated dosing for up to 6 cycles (approximately 6 months) is justified on the basis that other immune therapies for cancer, such as PD-1 inhibitors, may not show clinical efficacy immediately. Median time to first response for patients with melanoma treated with the PD-1 inhibitor pembrolizumab was 3 months, with some patients fulfilling the definition of tumor response for the first time after 6 months of therapy (Robert et al 2016).

All patients in Arm B and patients that are to receive intratumoral injections to visceral lesions will reduce dosing frequency to every 4 weeks after completing 1 cycle of therapy (Day 1 and Day 15 for Cycle 1, then Day 1 only for Cycles 2-6). The choice for this regimen is a balance between the dosing rationale described above and consideration for the clinical feasibility of repeat injections in patients with visceral lesions that require additional utilization of limited institutional resources such as imaging and procedural time by interventional radiology.

6.5 DURVALUMAB DOSING RATIONALE

The planned dose of durvalumab for this study is 1500 mg every 4 weeks (Q4W). A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (Study D4190C00002). A fixed dose of 1500 mg Q4W is supported by results of a population PK analysis.

Pharmacokinetic/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks (Q3W), durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, refer to the current durvalumab IB.)

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC at steady state (AUCss) (calculated over 4 weeks). Median Cmax,ss is expected to be higher with 20 mg/kg Q4W (approximately 1.5-fold) and median Ctrough,ss is expected to be higher with 10 mg/kg Q2W (approximately 1.25-fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W and is expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal anti-tumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting the use of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK for the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens for durvalumab. Based on an average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (for a body weight-based dose of 20 mg/kg Q4W) is included in the current study.

6.6 PATIENT POPULATION

The population for Dose Escalation was selected as those patients with locally advanced, recurrent or metastatic incurable solid malignancy or lymphoma that has progressed after standard therapy or for which standard therapy has proven to be ineffective or intolerable or is considered inappropriate and are therefore considered to be appropriate candidates for clinical trials exploring new forms of treatment. In the Dose Expansion periods, patients with ovarian cancer of epithelial origin will be enrolled at the MTD and/or RDE.

6.7 STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 PRIMARY OBJECTIVES

The primary objectives of the study are as follows:

Phase 1

- 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

7.2 PRIMARY ENDPOINTS

The primary endpoints of the study are as follows:

Phase 1

- Incidence and nature of dose-limiting toxicities (DLTs) with mRNA-2416 alone and in combination with durvalumab
- Incidence, nature, and severity of 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 of mRNA-2416 alone and in combination with durvalumab in patients with ovarian cancer based on RECIST v1.1

7.3 SECONDARY OBJECTIVES

The secondary objectives of the study are as follows:

- To assess emergence of antibodies against the drug product as well as OX40L, the protein translated by the drug product
- To assess mRNA pharmacokinetics (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 of mRNA-2416 monotherapy based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 / or Cheson 2014 criteria (lymphomas)

- Phase II only: To assess disease control rate and duration of response of mRNA-2416 alone and in combination with durvalumab based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

7.4 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 and duration of response (progression-free survival) of mRNA-2416 monotherapy based on RECIST v1.1 or Cheson 2014 criteria (lymphomas); See Appendix C and Appendix D
- Phase II only: Assessment of disease control rate and duration of response of mRNA-2416 alone and in combination with durvalumab in patients with ovarian cancer based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- PK parameters for mRNA-2416 alone and in combination with durvalumab: maximum observed concentration (Cmax) and area under the concentration-time curve (AUC)

7.5 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 pharmacokinetics (PK) of durvalumab in combination with mRNA-2416.

7.6 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 PD-1 and PD-L1
    - Infiltration of tumor with immune effector cells, including T cells

- PK parameters for durvalumab in combination with mRNA-2416: maximum observed concentration and area under the concentration-time curve

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.

7.7 SAFETY PARAMETERS

The parameters that will be used to assess safety in this study include the following:

- AEs
- Hematology, clinical chemistry, and liver function tests
- 12-Lead electrocardiogram (ECG)
- Physical examination
- Vital signs and body weight
- Concomitant medications/procedures
- Eastern Cooperative Oncology Group (ECOG) performance status
- Antibodies against OX40L, the protein translated by the drug product, will be reviewed with investigators as data are available.

Where applicable, AEs will be classified according to the NCI CTCAE Version 4.03.

8 STUDY DESIGN

8.1 NUMBER OF PATIENTS

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

8.2 STUDY DESIGN

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 periods in patients with ovarian cancer in each treatment arm. The study includes the following 2 treatment arms:

- Arm A: mRNA-2416 alone
- Arm B: mRNA-2416 in combination with durvalumab (PD-L1 inhibitor)

Each arm of the study consists of a Dose Escalation and Dose Confirmation part followed by a Dose Expansion part 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 a dose of 4mg mRNA-2416, 1 dose level lower than the Arm A MTD/RDE according to 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 visceral lesions injectable with ultrasound or CT guidance. The purpose of the Dose Confirmation part is to confirm that the dose level determined for patients with accessible lesions is also appropriate for patients with visceral lesions. Dose Confirmation will be conducted in the same fashion as Dose Escalation, as described in Section 8.2.1 and Section 8.4.

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

The Dose Expansion will consist of 2 investigational groups across the treatment arms summarized as follows and shown in Figure 1:

Arm A: mRNA-2416 alone

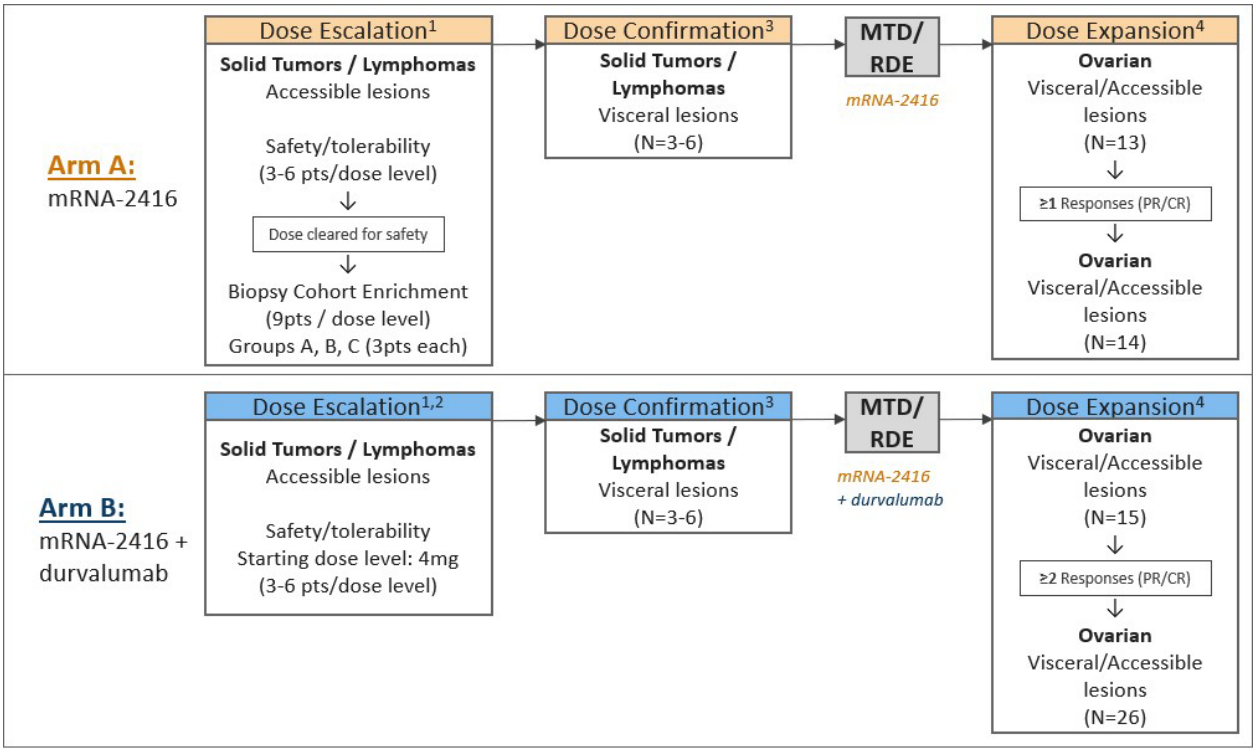
- Group 1: Ovarian cancer

Arm B: mRNA-2416 in combination with durvalumab

- Group 2: Ovarian cancer

The study schema is presented in Figure 1.

Figure 1: mRNA-2416-P101 Study Schema



1 - Dose Escalation: 3+3 model. DLT window = 1 cycle (28D)
2 - Dose Escalation in Arm B: To begin once the expected MTD/RDE has been cleared in Arm A Dose Escalation
3 - Dose Confirmation: To confirm the MTD/RDE in visceral lesions after clearance of MTD/RDE in accessible lesions
4 - Dose Expansion: Simon two-stage model

8.2.1 ARM A DOSE ESCALATION PERIOD

Dose escalation will be conducted using a standard 3+3 study design in order to determine safety and tolerability of the study therapy (see Section 8.4 for further details). The planned mRNA-2416 starting dose is 1.0 mg (0.5 mL) on Day 1 and Day 15 of 28-day cycles. Patients will be evaluated at the end of the first 28-day period (Cycle 1). A sentinel patient will receive their initial dose of mRNA-2416 1.0 mg intratumoral injection per intratumoral injection criteria (Section 10.1). Following a 7-day observation period, additional patients may be enrolled in the 1.0 mg cohort. Table 1 describes the 1.0 mg starting dose and other dose levels that may be evaluated during this trial. Subsequent dose cohorts may enroll up to 3 patients at a time. No intra-patient dose escalations may occur.

Table 1: Arm A Provisional Dose Levels

Dose level	Proposed mRNA-2416 Q2W dose
-1	0.5 mg (0.25 mL)
1 (starting dose)	1.0 mg (0.5 mL)
2	2.0 mg (1.0 mL)
3	4.0 mg (2.0 mL)
4	8.0 mg (4.0 mL)

Once a dose level has been cleared for safety, the dose level is open to enrollment of up to an additional 9 patients who are willing and eligible to undergo tumor biopsy for analysis (see details in Section 8.2.2). Any adverse events among patients in the biopsy enrichment cohorts would be considered in determining an appropriate RDE but will not affect the determination of the MTD. These cohorts are only opened at doses cleared for safety and are separate from the 3 + 3 escalation model described in Section 8.4.4.

Patients must have a superficial tumor lesion amenable to injection. A tumor lesion amenable to injection during the Dose Escalation Period is defined as a superficial tumor lesion that is

- clearly visible or palpable
- can be easily injected without the use of imaging guidance, and
- All lesion(s) targeted for the initial injection must be ≥ 0.5 cm on longest diameter, be at least 5 mm thick, and have distinct borders based on exam or imaging, not close to critical structures such as major vessels, nerves, or airways.

8.2.2 ARM A DOSE ESCALATION BIOPSY COHORT ENRICHMENT

For Arm A Dose Escalation, once a dose level has been cleared for safety, the dose level is open to enrollment of additional patients who are willing and eligible to undergo tumor biopsy. Eligible patients should be enrolled into the highest dose level that has been cleared for safety, providing their injectable tumor volume permits the necessary dose of mRNA-2416 according to Section 10.1 Table 3. For patients whose tumor volume does not support dosing at the highest cleared dose level, participation in a lower dose level is acceptable.

Up to 9 patients can be enrolled into the biopsy cohort at each dose level: 3 patients in Group A, 3 in Group B and 3 in Group C. Enrollment in the Biopsy Cohort Enrichment will continue throughout the conduct of the study until all slots are filled or it is determined additional enrollment is not required. Refer to Section 10.12 for further details on the enrollment in Biopsy Cohort Enrichment.

8.2.3 ARM B DOSE ESCALATION PERIOD

Dose escalation will be conducted using a standard 3+3 study design in order to determine safety and tolerability of the study therapy (see Section 8.4 for further details). In combination with a fixed dose of 1500 mg durvalumab every 4 weeks, the planned mRNA-2416 dose is 4.0 mg (2 mL) on Day 1 and Day 15 of 28-day cycles for Cycle 1, and on Day 1 only for Cycles 2-6. Patients will be evaluated at the end of the first 28-day period (Cycle 1). A sentinel patient will receive their initial dose of mRNA-2416 in combination with durvalumab. Following a 7-day observation period, additional patients may be enrolled in the 4.0 mg cohort. Table 2 describes the 4.0 mg starting dose and other dose levels that may be evaluated during this trial. Subsequent dose cohorts may enroll up to 3 patients at a time. No intra-patient dose escalations may occur.

Table 2: Arm B Provisional Dose Levels

Dose level	Proposed mRNA-2416 dose	Durvalumab dose level
-1	2.0 mg (1.0 mL)	1500 mg
1 (starting dose)	4.0 mg (2.0 mL)	1500 mg
2	8.0 mg (4.0 mL)	1500 mg

8.2.4 DOSE CONFIRMATION IN VISCERAL LESIONS

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 visceral lesions injectable with ultrasound or CT guidance. The purpose of the Dose Confirmation part is to confirm that the dose level determined for patients with accessible lesions is also appropriate for patients with visceral lesions. Dose Confirmation will be will be conducted in the same fashion as Dose Escalation as described in Section 8.2.1 and Section 8.4. A sentinel patient will receive their initial dose of mRNA-2416 intratumoral injection per intratumoral injection criteria (Section 10.1). Following a 7-day observation period, additional patients may be enrolled in the Dose Confirmation cohort.

8.2.5 ARM A PHASE II DOSE EXPANSION PERIOD

Once the MTD and/or RDE has been determined in Dose Escalation/Confirmation, patients will be enrolled in the Expansion period in order to assess the preliminary anti-tumor activity of mRNA-2416 in ovarian cancer of epithelial origin. The Expansion period will initially enroll 13 evaluable patients, unless enrolling 13 patients is not logistically feasible, in which case enrollment may be stopped before 13 patients are enrolled. If at least 1 patient has an objective response (partial response [PR] or complete response [CR]) per RECIST v1.1 or iRECIST, the sample size may be expanded to 27 evaluable patients. Details of the sample size calculations leading to the patient numbers are provided in Section 13.2.

8.2.6 ARM B PHASE II DOSE EXPANSION PERIOD

Once the MTD and/or RDE has been determined in Dose Escalation/Confirmation, patients will be enrolled in the Expansion period in order to assess the preliminary anti-tumor activity of mRNA-2416 in combination with durvalumab in ovarian cancer of epithelial origin. The Expansion period will initially enroll 15 evaluable patients, unless enrolling 15 patients is not logistically feasible, in which case enrollment may be stopped before 15 patients are enrolled. If at least 2 patients have an objective response (partial response [PR] or complete response [CR]) per RECIST v1.1 or iRECIST, the sample size may be expanded to 41 evaluable patients. Details of the sample size calculations leading to the patient numbers are provided in Section 13.2.

8.2.7 PHASE II DOSE EXPANSION PERIOD STOPPING RULES

Further computations of the DLT rate will be performed during the Expansion Period in order to incorporate study stopping rules. During the Expansion Period, the DLT rate will be calculated as events occur. The DLT rate will be defined as the ratio of the total number of patients with a DLT at the MTD/RDE divided by the total number of patients enrolled at that dose level who are evaluable for DLT (for evaluability see Section 8.4.4).

If the DLT rate is ≥33%, a temporary study suspension of enrollment at the MTD/RDE will be required in order to perform a thorough and in-depth review of the available safety information to determine whether additional patients should be enrolled at that dose level. The SRC may decide to enroll 3 more patients at the MTD/RDE and review the DLT rate again once those patients become evaluable for DLT. Alternatively, if the SRC determines that there is a reasonable probability that the DLT rate will remain higher than 33% with further enrollment of patients at that dose level, then the SRC may decide to stop enrollment at the MTD/RDE and permit expansion of a dose level lower than the MTD/RDE. Enrollment at the new RDE will be subject to the same enrollment and stopping rules as expansion at the MTD/RDE.

In addition, any Grade 4 toxicity related to mRNA-2416 during the Expansion Period will require a temporary suspension of expansion and review by the SRC. A drug-related death at any time during the study would result in study pause and expedited notification to FDA per 21 CFR 312.32

8.3 STUDY FLOW AND EXPECTED DURATION OF PATIENT PARTICIPATION

All patients will participate in a Screening Phase, Treatment Phase, and Follow-up Phase.

Screening Phase:

- A 14-day screening period before enrollment (≤ 28 days for baseline biopsy and imaging)
- Patients will be evaluated against study inclusion and exclusion criteria. Patients must meet all inclusion criteria and none of the exclusion criteria at screening in order to be eligible for the study. Assessments required on C1D1 that are performed as part of the screening evaluations and within 72 hours prior to the first dose of study treatment, do not need to be repeated on C1D1.

Treatment Phase:

- Arm A: mRNA-2416 administered for 6 cycles
- Arm B: Combination dosing of mRNA-2416 with durvalumab for 6 cycles. 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.

Safety Follow-up:

- Patients will be followed up for safety evaluation 30 and 90 days after their last dose of study treatment.

Disease Progression Follow-up:

Patients who complete study treatment with an overall tumor assessment of stable disease (SD) or better will be followed for tumor assessment 60 and 180 days after their last dose of study treatment, or until disease progression, whichever occurs first.

8.4 DOSE ESCALATION PROCEDURES

8.4.1 SAFETY REVIEW COMMITTEE (SRC)

A SRC composed of the study Medical Monitor, Sponsor representatives, and enrolling Principal Investigators (PIs) will hold teleconferences at the completion of each dose cohort in the Dose Escalation Period and during the Expansion Period, as needed, to review and assess all available safety data and the treatment status of all patients.

A written summary documenting the results, and recommendations of each review, including SRC consensus regarding recommended dose escalations or MTD/RDE, will be provided to the investigator(s) and maintained on file with the Sponsor. Additional personnel may participate in reviews as indicated.

Following a cohort review, the mRNA-2416 SRC may recommend proceeding with enrollment in the next dose cohort, enrolling additional patients in the current cohort, dropping back to a lower cohort, or not enrolling any additional patients. The dose escalation guidelines outlined in Section 8.4.4, as well as the study stopping rules outlined in Section 8.2.6, will be used as the basis for all SRC decisions.

While the SRC is expected to reach a consensus opinion regarding any premature discontinuation or significant modification of the study, the Sponsor may independently stop the study.

8.4.2 DEFINITION OF DOSE-LIMITING TOXICITIES

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications and at least possibly related to the study therapy and that occurs within the first 28 days of study therapy. The investigator must notify the Sponsor immediately of any DLTs.

For patients in Arm A receiving mRNA-2416, the following toxicities will be considered a DLT:

- 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.

For patients in Arm B receiving mRNA-2416 in combination with durvalumab, the following toxicities will be considered a DLT:

Adverse Event (AE)+C2:F16	DLT Criteria		
	Grade 2 Events	Grade 3 Events	Grade 4 events
Diarrhea/colitis	none	Events that do not resolve to Grade 1 or baseline within 14 d (whether or not it is immune-mediated)	DLT
Pneumonitis	Non-infectious pneumonitis that does not resolve to Grade ≤1 within 10 days	Non-infectious pneumonitis is a DLT	DLT
Hepatitis	none	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8×ULN or total bilirubin (TBL) >5×ULN OR events meeting Hy's Law (AST or ALT ≥3×ULN with concurrent increase in TBL ≥2×ULN without evidence of cholestasis or alternative explanations)	DLT
Rash	Any grade rash with bullous formation.	Rash not resolving to Grade 1 or baseline within 30d. Any rash with bullous formation.	DLT
Peripheral neuromotor syndromes such as Guillain-Barre or myasthenia gravis	Events not resolving to Grade 1 within 30d. Events with any signs of respiratory insufficiency or autonomic instability.	Events that do not resolve to Grade 1 within 30d. Events with any signs of respiratory insufficiency or autonomic instability.	DLT
Myocarditis	Events that do not resolve to Grade 1 within 3d OR a biopsy confirms immune-mediated myocarditis.	All Grade 3 myocarditis.	DLT
Myositis/polymyositis	Events that do not resolve to Grade 1 within 30d OR exhibit signs of respiratory insufficiency regardless of optimal medical management	Events that do not resolve to Grade 1 within 30d OR exhibit signs of respiratory insufficiency regardless of optimal medical management	DLT
Endocrinopathies involving thyroid or pituitary glands or adrenal insufficiency	none	Excludes events that are managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic	
Type I diabetes mellitus	none	Events that are not managed with appropriate diabetic therapy	
Nephritis	none	Any immune-mediated increase in creatinine >3×ULN, or >3×baseline for patients with a baseline creatinine elevated above ULN	DLT
Elevated amylase or lipase/ pancreatitis	none	Elevations in amylase or lipase >2.0×ULN with signs or symptoms of pancreatic inflammation	
All other imAEs OR non-imAEs	none	Events that do not resolve to Grade 1 or baseline within 30d	DLT
Infusion-related reactions	none	Events that do not resolve within 6h despite appropriate medical management.	DLT

- Any Grade ≥3 immune or non-immune adverse event (AE) that is at least possibly related to the investigational product (IP) or investigational regimen (IR) with two exceptions: Any grade of vitiligo or alopecia
- Hematologic toxicity:
  - Grade ≥3 neutropenia complicated by fever >38.3°C
  - Grade 4 neutropenia (lasting more than 7 days)
  - Grade ≥3 thrombocytopenia with significant bleeding
  - Grade 4 thrombocytopenia (regardless of duration)
  - Grade 4 anemia (regardless of duration)

8.4.3 DEFINITION OF MTD

The MTDs will be defined as the highest dose of mRNA-2416 alone and in combination with durvalumab at which a DLT has been seen in less than 2 of 6 patients (<33%) during the first 28-days of study therapy.

If 2 or more adverse events that meet the definition of a DLT as defined in Section 8.4.2, are observed beyond the first 28 days of study therapy within a dose escalation cohort, further enrollment may be held, pending safety analysis of the events by the SRC. These events will not affect the determination of the MTD but will be used in determining the appropriate RDE.

8.4.4 DOSE ESCALATION PROCEDURE

In order to be evaluable for dose determination, a patient must have received ≥50% of the planned mRNA-2416 dose and ≥75% of the planned durvalumab dose (Arm B) for Cycle 1 and must either have been followed ≥ 28 days following the first dose or have experienced a DLT within 28 days of the first dose. Patients who are not evaluable for dose determination may be replaced.

Dose escalation determination will not occur until the third patient in a cohort has completed their first 28-day study therapy.

- If no patient (0 of 3) in a dose cohort experiences a DLT during the first 28 days, then the next dose cohort of 3 patients will be enrolled at the next dose level per Table 1 following consensus of the SRC.
- If 1 of 3 patients in a dose cohort experiences a DLT, an additional 3 patients will be enrolled in that dose cohort.
  - Provided that no more than 1 of 6 patients in the expanded dose cohort experiences a DLT within 28 days of the first dose, then a dose cohort of 3 patients will be enrolled at the next dose level per Table 1 following consensus of the SRC.
- If ≥ 2 patients in a dose cohort experience a DLT within 28 days of the first dose, that cohort will have exceeded the MTD. No additional patients will be dosed at that level, and 3 patients will be enrolled in the preceding dose cohort, unless 6 patients have already been treated at that dose level. Using the same criteria, lower dose cohorts will be explored as the MTD until ≤ 1 of 6 patients experiences a DLT.

In the event that ≥ 2 of the first 6 DLT-evaluable patients in the 1.0 mg cohort experience a DLT, then the next cohort will be dosed with 0.5 mg mRNA-2416.

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.

9 SELECTION OF PATIENTS

9.1 INCLUSION CRITERIA

All patients must meet all of the following inclusion criteria:

1. Males or females ≥18 years of age who have provided written informed consent prior to completing any study-specific procedure
2. Disease state and prior therapies:
    a. Dose Escalation and Dose Confirmation Periods: Histologically- or cytologically-confirmed advanced/metastatic solid tumor or lymphoma by pathology report and who has received, or been intolerant to, all approved therapies. Advanced solid tumors (i.e. including but not limited to melanoma, breast, head and neck squamous cell) and lymphomas (i.e. including by not limited to diffuse large B cell lymphoma) of any type are eligible for enrollment.
    b. Dose Expansion Period: Histologically or cytologically confirmed diagnosis of: epithelial cancer of the ovary, fallopian tube, or peritoneum which is platinum resistant or platinum refractory. Patients must have received at least 2 prior lines of therapy. Patients with known BRCA mutation positive must have been treated with and progressed on at least 1 prior PARPi (poly(ADP-ribose) polymerase inhibitor)
3. No limit to the number of prior therapies
    a. Patients who refuse standard treatments may also be considered provided that he/she has been made aware of all therapeutic options and it is documented in the study records.
4. Lesions for intratumoral injection and biopsies:
    a. Dose Escalation: A minimum of one lesion that is easily accessible for injection where easily accessible is defined as a cutaneous or subcutaneous mass that is palpable and/or visualizable by ultrasound
    b. Dose Confirmation: A minimum of one visceral lesion injectable with ultrasound or computer tomography (CT) guidance and that is not encasing or abutting major vascular structures or are in a location that are considered high risk for AEs by the enrolling physician
    c. Dose Expansion: A minimum of one lesion amenable to injection (either non-visceral or visceral). Patients must have a tumor lesion amenable to biopsy and consent to a pre-treatment and an on-treatment biopsy. For patients with only one lesion amenable to injection, biopsy, and RECIST assessment, the lesion must be ≥ 2 cm.
    d. Biopsy Cohort Enrichment: Patients must have a tumor lesion amenable to biopsy and consent to a pre-treatment and an on-treatment biopsy
5. All lesion(s) targeted for the initial injection must be ≥ 0.5 cm on longest diameter, be at least 5 mm thick, and have distinct borders based on exam or imaging, not close to critical structures such as major vessels, nerves, or airways
6. Patients must have measurable disease as determined by RECIST v1.1 (solid tumors) or Cheson 2014 criteria (lymphomas).

a. Dose Expansion: Patients must have at least 1 measurable lesion per RECIST v1.1 which has not been previously irradiated.

7. Easter Cooperative Oncology Group (ECOG) performance status of ≤1
8. Adequate hematological and biological function, confirmed by the following laboratory values:

   Bone marrow function

   a. Absolute neutrophil count ≥1.5 × 10^9/L
   b. Hemoglobin ≥9 g/dL or ≥6.2 mmol/L
   c. Platelets ≥100 × 10^9/L without transfusion support

   Hepatic function

   d. Aspartate aminotransferase and alanine aminotransferase ≤2.5 × upper limit of normal (ULN) (≤5 × ULN, if hepatic involvement of tumor)
   e. Bilirubin ≤1.5 × ULN (<3.0 mg/dL if patient has Gilbert's disease)

   Renal function

   f. Serum creatinine ≤1.5 × ULN or creatinine clearance of >50 mL/min (using Cockcroft-Gault formula)

$$eC_{Cr}[mL/min] = \frac{(140 - Age\ [yrs]) \times Body\ Weight\ [kg] \times [0.85\ if\ Female]}{72 \times Serum\ Creatinine\ [mg/dL]}$$

   Coagulation function

   g. Protime/international normalized ratio and activated partial thromboplastin time ≤1.5 × ULN

   Thyroid function

   h. Thyroid-stimulating hormone within normal range.

9. Female patients of childbearing potential must have a negative serum pregnancy test during screening. Male and female patients must agree to use a highly reliable method of birth control (expected failure rate less than 1% per year) from the Screening visit through 120 days after the last dose of study drug. Patients must consent to following the contraception requirements in Section 10.14.1 and 10.14.2.
10. Must have a life expectancy of at least 12 weeks
11. Body weight > 30 kg

9.2 EXCLUSION CRITERIA

Any of the following criteria will exclude patients from study participation:

1. Active central nervous system tumors or metastases
2. Treatment with chemotherapy, radiation (local radiation for palliative care is permitted), hormonal anti-cancer treatment, or biologic therapy <14 days prior to the first day of study treatment (Cycle 1 Day 1 [C1D1]).

   b. Treatment with any other investigational agent or treatment with any anti-cancer monoclonal antibody, immunostimulant, or vaccine <28 days prior to C1D1.

3. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

- Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

4. History of severe allergic reactions to any of the study drug components
5. Has active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
   - Patients with vitiligo or alopecia
   - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
   - Patients with any chronic skin condition that does not require systemic therapy
   - Patients without active disease in the last 5 years may be included but only after consultation with the Moderna medical monitor
   - Patients with celiac disease controlled by diet alone.
6. Has a history of primary immunodeficiency, allogenic solid organ transplantation, or tuberculosis.
7. Immunosuppressive doses of systemic steroids or absorbed topical steroids (doses >10 mg prednisone daily equivalent) within 2 weeks before study drug administration
8. Local infection at site of a tumor lesion amenable to injection requiring anti-infective therapy within 2 weeks of the first dose of study drug
9. Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment. Note: Patients, if enrolled, should not receive live vaccine whilst receiving study treatment and up to 30 days after the last dose of study treatment.
10. History of human immunodeficiency virus infection
11. Active/chronic hepatitis B or C
12. Major surgical procedures ≤28 days or non-study-related minor procedures ≤7 days prior to C1D1. In all cases, the patient must be sufficiently recovered and stable before treatment administration.
13. Any of the following cardiac abnormalities:
    a. Medically uncontrolled hypertension
    b. New York Heart Association Class III or IV cardiac disease
    c. Myocardial infarction within prior 6 months
    d. Unstable angina
    e. Unstable arrhythmias or mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart)
14. History of another primary malignancy except for:
    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease

15. Patients requiring active systemic anticoagulation at the time of intratumoral injection or biopsy
16. Active GI bleeding
17. Females who are pregnant or breastfeeding
18. Any other unstable or clinically significant concurrent medical condition (eg, substance abuse, psychiatric illness/social situations, uncontrolled intercurrent illness including active infection, arterial thrombosis, symptomatic pulmonary embolism, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, etc.) that would, in the opinion of the investigator, jeopardize the safety of a patient, impact their expected survival through the end of the study participation, and/or impact their ability to give written informed consent or comply with the protocol.
19. For patients who have received prior anti-PD-1 or anti PD-L1 therapy, a patient must not have experienced any of the following:
    a. Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.
    b. All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.
20. Must not have experienced a ≥ Grade 3 immune-related AE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy. Note: Patients with endocrine AEs of ≤ Grade 2 are permitted to enroll if they are stable while maintained on appropriate replacement therapy and are asymptomatic.
21. Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.
22. Has an active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBV surface antigen [HBsAg] result), hepatitis C, or human immunodeficiency virus (positive HIV-1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
23. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
24. Has a history of leptomeningeal carcinomatosis.
25. Has involvement in the planning and/or conduct of the study.
26. Must not plan to donate blood or blood components while participating in this study and through 90 days after the last dose of study treatment.

10 STUDY PROCEDURES

10.1 INTRATUMORAL INJECTIONS

Patients in the Dose Escalation period of the study must have a superficial tumor lesion amenable to injection. A tumor lesion amenable to injection during the Dose Escalation period of the study is defined as a superficial tumor lesion which is:

- Clearly visible or palpable,
- Can be easily injected without the use of imaging guidance, and
- All lesion(s) targeted for the initial injection must be ≥ 0.5 cm on longest diameter, be at least 5 mm thick, and have distinct borders based on exam or imaging, not close to critical structures such as major vessels, nerves, or airways.

Patients in the Dose Confirmation part of the study must have a visceral tumor lesion amenable to injection which is defined as:

- Visceral lesion injectable with ultrasound or computer tomography (CT) guidance
- Must not be encasing or abutting major vascular structures or are in a location that are considered high risk for AEs by the enrolling physician

Patients in the Dose Expansion part of the study must have an injectable lesion which may be either a superficial lesion or a visceral lesion which is not encasing or abutting major vascular structures or is in a location that is considered high risk for AEs by the enrolling physician.

Patients in Arm A receiving treatment to superficial lesions are to receive intratumoral injections on Day 1 and Day 15 of 28-day cycles for up to 6 cycles. All patients in Arm B and patients receiving treatment to visceral lesions are to receive intratumoral injections on Day 1 and Day 15 of 28-day cycles for Cycle 1, and on Day 1 only for Cycles 2-6.

mRNA-2416 is injected directly into the tumor. A single injection is preferred, however, the prescribed dose of mRNA-2416 may be administered as several injections into different sites within the same lesion or split across several lesions if no single lesion is large enough to receive the entire dose per the maximum injection volume per lesion size (see Table 3). All patients must have tumor(s) of sufficient size to support injection of the first planned dose of mRNA-2416. No intra-patient dose escalations may occur. If the tumor at subsequent doses has regressed or shrunk and the size of the accessible tumor burden cannot support the planned dose, then the next lowest dose supported by the tumor size may be administered following documented approval of Moderna. Lesions displaying signs of local infection should not be injected.

After insertion of the needle into the tumor it is important that the syringe plunger is gently withdrawn a short distance to ensure that the needle tip is within tumor parenchyma and not in a blood vessel. There is no safety data to support administration of mRNA-2416 directly into a vein or artery. Formal toxicology studies have deployed subcutaneous dosing in rats and non-human primates. If mRNA-2416 appears to extravasate from the tumor injection site into surrounding subcutaneous tissue patients should be followed for adverse reactions according to the protocol but no additional immediate action needs to be taken.

For patients receiving mRNA-2416 in combination with durvalumab, the ITu injection of mRNA-2416 should be administered first with at least a 30 minute break between the two study treatments.

Table 3: Maximum Injection Volume per Lesion Size

Lesion Size (Longest Dimension)	Injection Volume
≤0.5 cm	up to 0.1 mL
>0.5 cm to 1.5 cm	up to 0.5 mL
>1.5 cm to 2.5 cm	up to 1.0 mL
>2.5 cm to 5 cm	up to 2.0 mL
>5 cm	up to 4.0 mL

Each patient should be carefully monitored for possible injection related reactions. It is recommended that investigators observe all patients for a minimum of 1 hour after administration of each mRNA-2416 injection, with continuous monitoring of pulse oximetry and vital sign assessment every 10 minutes for the first 30 minutes followed by every 15 minutes for the first hour. If an injection related reaction occurs, patients should be treated symptomatically as per standard of care and the Moderna Medical Monitor should be notified. Additionally, blood samples for complement activation of tryptase within 2 hours of the reaction are requested if feasible. The patient should be instructed to call the clinical site if any such reactions develop or don't resolve within 24 to 48 hours. All reactions will be recorded as an adverse event.

10.2 DURVALUMAB ADMINISTRATION

Durvalumab will be supplied by the Sponsor as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. Investigational product vials are to be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the investigator's or site's designated investigational product (IP) manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed the following:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

A dose of 1500 mg (for patients > 30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (ie, 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.
If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Vital Sign Monitoring

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the Schedule of Events. Body weight is also recorded at each visit along with vital signs.

First infusion

On the first infusion day, patients will be monitored and vital signs collected/recorded in eCRF prior to, during, and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from patients in the IO arms before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent infusions

BP, pulse, and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page

10.3 mRNA-2416 Dose Modification

Patients who experience study treatment-related toxicity that leads to a dose interruption, following recovery to at least Grade 1 or to baseline, continue to receive injections at 50% of the planned dose based on investigator discretion. Patients may not be rechallenged at the planned dose.

Patients with a lesion that has become inaccessible or has decreased in tumor volume during the study treatment period, such that the planned dose is no longer able to be administered, may continue with study therapy at a lower dose following documented approval from Moderna.

For patients who do not tolerate the protocol-specified dosing schedule of mRNA-2416, dose reductions may be permitted in order to allow the patient to continue study therapy. If a patient experiences an AE meeting the criteria for DLT as defined in Section 8.4.2, study therapy should be withheld. Following resolution of the toxicity to grade 1 or to the patient's baseline value, the patient may resume study therapy at 50% of the planned dose.

10.4 Durvalumab Dose Modification and Toxicity Management Guidelines

Dose delays are permitted for durvalumab (please see Appendix E for dose modification and toxicity management guidelines), however dose reductions are not permitted for durvalumab.

10.5 Dose Omissions and Discontinuation of Study Drug Administration

Study treatment may be interrupted for situations other than treatment-related AEs such as medical and/or surgical events or logistical reasons not related to study treatment. Patients should be placed back on study

treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Patients who have permanently discontinued study therapy will be scheduled for an End of Treatment visit within 14 days (±2 days) of the decision to permanently discontinue study therapy and assessments will be performed per the Schedule of Events table (Section 3). Patients who have permanently discontinued study therapy should not be considered withdrawn from the study. They should return for the 30-day and 90-day safety follow-up visit from last dose and the tumor assessment follow-up visits per the Schedule of Events table. If the patient fails to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them.

The following are reasons for discontinuing study therapy without necessarily requiring withdrawal from the study:

- Patients who have completed 6 cycles of study therapy and have an overall tumor assessment of SD or better
- Patients who have experienced a Grade 4 treatment-related AE at any time during study treatment must discontinue from study treatment
- Patients who, in the opinion of the investigator, have incurred a Grade 3 drug-related DLT that has not recovered to Grade 1 or less within 14 days, or has recurred following restarting study therapy at a modified dose level.
- Patients who, in the opinion of the investigator, have incurred unacceptable toxicity that does not meet the pre-determined criteria for DLT (eg, late-onset, treatment-emergent toxicity after the DLT assessment window, or Grade 2 toxicities that are sufficiently durable or unresponsive to supportive intervention as to render them unacceptable in the opinion of the investigator) which has not recovered to Grade 1 or less within 28 days, or has recurred following restarting study therapy at a modified dose level.
- Patients who experience a Grade 3 hypersensitivity reaction or autoimmune events must discontinue from study treatment
- Patients who no longer have lesions that meet criteria for injection
- Pregnancy
- Physician’s decision
- Patient/guardian decision
- Patients will be withdrawn from study due to progressive disease per irRC/LYRIC. Due to the possibility of pseudoprogression; patients should not be withdrawn from the study due to progressive disease per RECIST v1.1 or Cheson 2014 criteria.
- Patient has received alternative anti-cancer therapy
- Patient has symptomatic progression of disease, or other clinical conditions which, in the opinion of the investigator, render it in the interests of the patient to withdraw from the study.

The reason for discontinuation of study therapy should be recorded on the appropriate page(s) of the electronic case report form (eCRF).

10.6 DISCONTINUATION FROM THE STUDY

Patients will be permanently discontinued from the study following completion of the EOT, 30-day and 90-day safety follow-up visits. Additional reasons for discontinuation from the study include the following:

- Patient withdraws consent
- Unwillingness to comply with study requirements

10.6.1 HANDLING OF WITHDRAWALS OF CONSENT

Patients may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the patient is otherwise entitled. When a patient wishes to withdraw consent, it is important to distinguish between withdrawing their consent for a particular study procedure or visit versus withdrawing their consent from the study entirely. The Investigator should discuss with the Medical Monitor whether selective withdrawal of consent for specific procedures should disqualify the patient from further participation in the study.

10.7 ANCILLARY TREATMENTS

The use of premedications prior to administration of mRNA-2416 is at the discretion of the treating investigator. If the treating physician decides to premedicate their patients, it is recommended to do so prior to the second and subsequent injections, and to follow local institutional guidelines for premedication with montelukast, H-1 and H-2 antagonists. Per exclusion criteria 7, immunosuppressive doses of systemic steroids or absorbed topical steroids (doses >10 mg prednisone daily equivalent) are not allowed within 2 weeks before the start of study treatment.

If any patient develops an injection related reaction (IRR) despite premedication with montelukast, H-1 and H-2 antagonists, please contact the Moderna Medical Monitor regarding continued treatment with mRNA-2416. If treatment is to be continued, it is recommended to escalate the pretreatment regimen as per institutional guidelines.

If any patient develops a Grade 3 or above IRR, then that patient must be discontinued from further injections with mRNA-2416. If ≥ 2 patients experience Grade 3 or above IRR, then a mandatory primary prophylaxis premedication regimen including montelukast, H-1 and H-2 antagonists will be instituted after discussion and agreement among principal investigators and Moderna Medical Monitor.

Rescue Medications and Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined, along with the dose modification guidelines, in Section 10.3 and Appendix E. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. As a result of immune-mediated AEs that could potentially be experienced by patients on durvalumab, steroids and other immunosuppressant rescue medication has to be made available to this patient population.

10.8 CONCOMITANT THERAPY

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including the 90-day Safety Follow-up Period following the last dose of study drug.

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, pro-biotics, and/or herbal supplements that the patient is receiving at the time of enrollment or receives during the study must be recorded along with the following:

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

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Restricted, prohibited, and permitted concomitant medications are described in Table 4 and Table 5. Refer also to the Dose Modification and Toxicity Management Guidelines (see Section 10.4).

Table 4: Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage:**
For all treatment arms	
Any investigational anti-cancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAb against PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP

Prohibited medication/class of drug:	**Usage:**
Any substrates to CYP3A4, CYP2C19, and CYP1A2.	Should be used with caution through to 90 days after the last dose of study treatment
For the durvalumab treatment arm only	
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the infusions. The following are allowed exceptions: Use of immunosuppressive medications for the management of IP-related AEs, Use in patients with contrast allergies. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea).
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

Abbreviations: AE, adverse event; CYP, cytochrome P450; EGFR, epidermal growth factor receptor; IP, investigational product; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death - ligand 1; TKI, tyrosine kinase inhibitor

Table 5: Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

10.9 MANAGEMENT OF CLINICAL SUPPLIES

mRNA-2416 will be supplied by the Sponsor as solution for intratumoral injection in 2-mL glass vials. mRNA-2416 must be stored at -20°C. Detailed information regarding the storage and preparation of the mRNA-2416 will be provided in the Pharmacy Manual.

Durvalumab will be supplied by the Sponsor as a 500-mg vial solution for infusion after dilution (50 mg/mL). Durvalumab vials are to be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

mRNA-2416 and durvalumab must be stored in a restricted access area under the storage conditions indicated in the Pharmacy Manual.

10.10 RADIOLOGIC ASSESSMENTS

For the purpose of this clinical trial, the following imaging will be acquired at Screening for a baseline tumor assessment and on study:

- CT (with contrast) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis
- CT (with contrast) or MRI of the neck, if clinically indicated
- Bone scan if clinically indicated

- PET-CT (for lymphoma)

All patients will have tumor assessments performed within 28 days prior to C1D1, every 56 days from C1D1 (± 7 days), and during Disease Progression Follow-up Period at 90 and 180 days following the end of treatment (± 30 days).

At screening, all patients will undergo CT with IV contrast of the chest, abdomen and pelvis. MRI should only be used to evaluate sites of disease that are not adequately imaged by CT. If a patient is intolerant of iodine-based contrast agents, CTs may be performed without contrast. MRI may be used to evaluate sites of disease where a CT without IV contrast is not adequate. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Bone scans should be performed within past 60 days prior to Cycle 1 Day 1. If the baseline bone scan is positive, scans should be repeated at Cycle 3 Day 1, Cycle 5 Day 1, at the end of Cycle 6, and during Disease Progression Follow-up Period at 90 and 180 days following the end of treatment (± 30 days).

For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Target lesions should be selected and measured as per RECIST guidelines (see Appendix C and Appendix D).

At the investigator's discretion, imaging studies may be repeated at any time if disease progression is suspected. Due to the possibility of pseudoprogression, patients will be permitted to continue with treatment beyond initial RECIST 1.1 or Cheson defined disease progression as long as they meet the following criteria:

- If, in the opinion of the investigator, he/she is continuing to receive clinical benefit as defined by:
    - Absence of clinical symptoms and signs (including worsening of laboratory values) indicating disease progression
    - No decline in ECOG performance status
    - Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.
    - Subject is tolerating study drug

All decisions to continue treatment beyond disease progression must be discussed with the Sponsor/Medical Monitor and documented in the study records. Disease progression will be confirmed after at least 4 weeks per irRC/LYRIC. If disease progression is confirmed per irRC/LYRIC, the patient will discontinue study therapy. The local investigator's assessment will be used for the analysis of response according to both RECIST 1.1 and irRC/Lyric, and for treatment decision making (study discontinuation due to PD as per irRC). Patients experiencing progressive disease per RECIST v. 1.1 criteria may continue to be treated according to irRC guidelines until progression is documented via irRC. Imaging data may be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Moderna. The local investigator's assessment will be used for the data analysis and for treatment decision making. Central review of the imaging data may be performed if deemed necessary.

10.11 OPTIONAL DIGITAL PHOTOGRAPHY

In addition to radiological imaging techniques, photographs of visible cutaneous lesions are recommended. Optional digital photograph(s) will be taken of all visible injected tumor(s) and non-injected tumors and of any remaining visible local reactions in or around the injected lesion(s) for exploratory analysis.

10.12 PHARMACOKINETICS AND IMMUNOGENICITY

Blood samples will be collected from all enrolled patients for the determination of serum mRNA-2416 concentrations at the time points indicated in Table 6. Blood samples will also be collected to assess the potential for immunogenicity in each treatment cycle in the peripheral circulation at the time points indicated in Table 6. Immunogenicity to the study treatment will be assessed by monitoring the formation of anti-PEG and anti-OX40L antibodies. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment.

10.12.1 DURVALUMAB PHARMACOKINETICS

Blood samples will be collected at the time points indicated in Table 6 and may be used to assess durvalumab serum concentration.

If emerging data from this study are consistent with the existing data from other durvalumab clinical trials, durvalumab PK sampling may be reduced or discontinued.

10.13 BIOMARKERS

In this study, biomarker samples will be collected per Tables 6, 7,8 and 9. The biomarker analysis will be used to investigate the effect of mRNA-2416, as well as to determine how the markers are associated with clinical outcome. Immune responses will be studied in the peripheral circulation and in tumor biopsy specimens. Tumor biopsies will be examined using methods such as immunohistochemistry, quantitative immunofluorescence, RNA sequencing and/or electrochemiluminescence (ECL) assays to evaluate changes in key immune pathway axes, such as PD-L1/PD-1 and OX40L/OX40, as well as characterization (eg, phenotype, distribution, and activation) of tumor infiltrating lymphocyte and myeloid populations. Cytokines may also be examined in both tumor and blood tissues using methods such as RNA sequencing and enzyme-linked immunosorbent assay (ELISA)/ ECL assays, respectively.

The goal of the biomarker assessments is to provide supportive data for the clinical study; however, there may be circumstances when a decision is made to stop a collection or not perform or discontinue an assessment (eg, inadequate sample number, sample quality or assay issues that preclude analysis, or impossibility to perform correlative analyses). Therefore, sample collection and/or assessment may be omitted at the discretion of the Sponsor.

The sample collection information must be entered on the appropriate sample collection log eCRF page(s). Sample details including volume and instructions for the collection, handling, and shipment of samples are outlined in the laboratory manual for the study.

Table 6: Sampling schedule for Pharmacokinetics, Immunogenicity, and Cytokine Profiling

Cycle	Day	Scheduled Time (Sampling Window)	Purpose[a]
1	1	Pre-dose of Cycle 1 Day 1	PK, Cytokines, IG
1	1	3 h from start of injection (± 10 min)	PK, Cytokines
1	1	6 h from start of injection (± 30 min)	PK, Cytokines
1	2	24 h from start of injection (± 60 min)	PK, Cytokines
1	8	168 h from start of injection (± 24 h)	PK, Cytokines
1	15	Pre-dose of Cycle 1 Day 15	IG
2	1	Pre-dose of Cycle 2 Day 1	PK, Cytokines, IG, mAb PK
3	1	Pre-dose of Cycle 3 Day 1	IG
3	15	Pre-dose of Cycle 3 Day 15	IG
4	1	Pre-dose of Cycle 4 Day 1	IG
5	1	Pre-dose of Cycle 5 Day 1	IG
6	1	Pre-dose of Cycle 6 Day 1	IG
6	15	Pre-dose of C1D15	IG
EOT		Anytime	IG
Unscheduled		Anytime when needed	PK, Cytokines, IG, mAb PK

Abbreviations: EOT, end of treatment; FU, follow-up; IG, immunoglobulin; PEG, polyethylene glycol, mAb, monoclonal antibody (durvalumab).

a. IG analyte is anti- PEG and -OX40L anti-drug antibody

10.13.1 TUMOR BIOPSIES

Patients enrolled in the Biopsy Cohort Enrichment (Section 8.2.2) and all patients in the Dose Expansion period must consent to pre-treatment and on-treatment tumor biopsies. For all patients, every attempt to biopsy the same lesion pre- and post-dose should be made to minimize inter-lesion variability. If, for any reason, a lesion that has been biopsied pre-dose is not amenable to intratumoral injection with study drug, a different lesion or lesions may be injected, providing that the lesion can be biopsied post-dose.

For all biopsies of tumors that have received intratumoral injections, the biopsy site should be the same as, or as close as possible to, the site of injection of mRNA-2416.

Biopsies of superficial lesions may be performed by punch biopsy or by excision biopsy, at the discretion of the investigator. For visceral lesions, a core biopsy may be obtained under imaging guidance preferably using an 18-gauge biopsy needle. For optimal results, 4 to 6 passes are requested, if feasible. Fine needle

aspiration of cells from tumors will not be suitable for analysis. Institutional standard operating procedures and safety procedures should be used for each biopsy procedure. Biopsied tissue samples should be placed immediately into formalin fixative, and labeled, processed, and shipped as outlined in the mRNA-2416-P101 Laboratory Manual.

10.13.2 DOSE ESCALATION BIOPSY COLLECTION PLAN

For patients in the dose escalation biopsy cohorts, collection of newly obtained tumor samples during screening and at 1 of the time points as specified below is required unless not medically feasible and agreed by the Sponsor. Up to 9 patients may be enrolled into the Biopsy Cohort Enrichment at each dose level, 3 patients in Group A, 3 in Group B and 3 in Group C.

Escalation Biopsy Group A:

Patients will undergo a baseline biopsy of a lesion distinct from the planned site of intratumoral injection up to 14 days pre-dose Cycle 1 Day 1 and a biopsy within Cycle 1 Day 22 - 28. The primary analysis of the biopsies from biopsy Group A will focus on infiltration of immune effector cells into tumor lesions distal from the tumor lesion(s) that are injected with mRNA-2416 (eg, an abscopal anti-tumor effect).

Escalation Biopsy Group B:

Patients will undergo a baseline tumor biopsy of a lesion that is planned for intratumoral injection up to 14 days pre-dose Cycle 1 Day 1 and a biopsy of the injected tumor lesion 24 to 48 hours post-dose Cycle 1 Day 1. The biopsy site should be the same as, or as close as possible to, the site of injection of mRNA-2416.

Escalation Biopsy Group C:

Patients will undergo a baseline tumor biopsy of a lesion that is planned for intratumoral injection up to 14 days pre-dose Cycle 1 Day 1 and a biopsy of the injected tumor lesion 24 to 48 hours post-dose Cycle 2 Day 1. The biopsy site should be the same as, or as close as possible to, the site of injection of mRNA-2416.

The primary analysis of the biopsies from biopsy Groups B and C will focus on expression of OX40L protein immediately after injection of mRNA.

Table 7: Dose Escalation Tumor Biopsy Analyses by Group

Group	Biopsy Timing	Biopsy Site	Analyses	
			OX40/OX40L Expression	Additional Tumor Microenvironment Characterization by IHC/ QIF and/or RNAseq
A	First biopsy: Within 14 days pre-study (C1D1)	Any lesion NOT planned for injection of study drug	X	X
	Second biopsy: Between Cycle 1 Day 22-28	Lesion that has NOT been injected with study drug (same lesion as baseline)	X	X
B	First biopsy: Within 14 days pre-study (C1D1)	Any lesion planned for injection of study drug	X	X
	Second biopsy: 24-48 hrs after C1D1 injection	Lesion injected with study drug *biopsy should be at the injection site if possible (same lesion as baseline)	X	X

Group	Biopsy Timing	Biopsy Site	Analyses	
			OX40/OX40L Expression	Additional Tumor Microenvironment Characterization by IHC/ QIF and/or RNAseq
C	First biopsy: Within 14 days pre-study (C1D1)	Any lesion planned for injection of study drug	X	X
	Second biopsy: 24-48 hrs after C2D1 injection	Lesion injected with study drug *biopsy should be at the injection site if possible (same lesion as baseline)	X	X

OX40L=OX40 ligand; QIF= quantitative immunofluorescence; RNAseq= RNA sequencing

10.13.3 DOSE EXPANSION BIOPSY COLLECTION PLAN

For all patients in dose expansion, collection of newly obtained tumor samples during screening and at 1 of the time points as specified below is required unless not medically feasible and agreed by the Sponsor. An additional optional biopsy at the time of treatment response or disease progression is also requested if medically feasible.

For all patients in dose expansion, biopsies at screening should be performed on a lesion which is planned for injection of study treatment, as well as a distal non-visceral lesion which is not planned for injection of study treatment if medically feasible. Similarly, the on-treatment biopsies should be performed on a lesion which has been injected with study treatment, as well as on a distal non-visceral lesion which has not been injected with study treatment if medically feasible. Every attempt should be made to biopsy the same injected and distal lesions at all time points.

Patients in dose expansion will be assigned to biopsy groups which each have a different timepoint for the on-treatment biopsies, as specified below.

Arm A Expansion Biopsy Group D:

Within 14 days pre-dose Cycle 1 Day 1: A baseline tumor biopsy of a lesion that is planned for intratumoral injection, as well as a distal non-visceral lesion which is not planned for injection if medically feasible.

24 to 48 hours post-dose Cycle 1 Day 1: Tumor biopsy of the injected tumor lesion, as well as a distal non-visceral lesion which has not been injected with study treatment if medically feasible. The biopsy of the injected lesion should include or be as close as possible to the injection site.

Arm A Expansion Biopsy Group E:

Within 14 days pre-dose Cycle 1 Day 1: A baseline tumor biopsy of a lesion that is planned for intratumoral injection, as well as a distal non-visceral lesion which is not planned for injection if medically feasible

Pre-dose Cycle 2 Day 1: Tumor biopsy of the injected tumor lesion, as well as a distal non-visceral lesion which has not been injected with study treatment if medically feasible The biopsy of the injected lesion should include or be as close as possible to the injection site.

Arm B Expansion Biopsy Group F:

Within 14 days pre-dose Cycle 1 Day 1: A baseline tumor biopsy of a lesion that is planned for intratumoral injection, as well as a distal non-visceral lesion which is not planned for injection if medically feasible.

24 to 48 hours post-dose Cycle 1 Day 1: Tumor biopsy of the injected tumor lesion, as well as a distal non-visceral lesion which has not been injected with study treatment if medically feasible. The biopsy of the injected lesion should include or be as close as possible to the injection site.

Arm B Expansion Biopsy Group G:

Within 14 days pre-dose Cycle 1 Day 1: A baseline tumor biopsy of a lesion that is planned for intratumoral injection, as well as a distal non-visceral lesion which is not planned for injection if medically feasible

Pre-dose C1D15: Tumor biopsy of the injected tumor lesion, as well as a distal non-visceral lesion which has not been injected with study treatment if medically feasible. The biopsy of the injected lesion should include or be as close as possible to the injection site.

Arm B Expansion Biopsy Group H:

Within 14 days pre-dose Cycle 1 Day 1: A baseline tumor biopsy of a lesion that is planned for intratumoral injection, as well as a distal non-visceral lesion which is not planned for injection if medically feasible

Pre-dose Cycle 2 Day 1: Tumor biopsy of the injected tumor lesion, as well as a distal non-visceral lesion which has not been injected with study treatment if medically feasible. The biopsy of the injected lesion should include or be as close as possible to the injection site.

Table 8: Arm A Dose Expansion Tumor Biopsy Analyses by Group

Group	Biopsy Timing	Biopsy Sites	Analyses	
			OX40/OX40L Expression	Additional Tumor Microenvironment Characterization by IHC/ QIF and/or RNAseq
D	First biopsies: Within 14 days pre-study (C1D1)	1) Lesion planned for injection of study drug 2) Lesion NOT planned for injection of study drug	X	X
	Second biopsies: 24-48 hrs after C1D1 injection	1) Lesion injected with study drug 2) Lesion NOT injected with study drug	X	X
E	First biopsies: Within 14 days pre-study (C1D1)	1) Lesion planned for injection of study drug 2) Lesion NOT planned for injection of study drug	X	X
	Second biopsies: Pre-dose C2D1 injection	1) Lesion injected with study drug 2) Lesion NOT injected with study drug	X	X

OX40L=OX40 ligand; QIF= quantitative immunofluorescence; RNAseq= RNA sequencing

Table 9: Arm B Dose Expansion Tumor Biopsy Analyses by Group

Group	Biopsy Timing	Biopsy Sites	Analyses	
			OX40/OX40L Expression	Additional Tumor Microenvironment Characterization by IHC/ QIF and/or RNAseq
F	First biopsies: Within 14 days pre-study (C1D1)	1) Lesion planned for injection of study drug 2) Lesion NOT planned for injection of study drug	X	X
	Second biopsies: 24-48 hrs after C1D1 injection	1) Lesion injected with study drug 2) Lesion NOT injected with study drug	X	X
G	First biopsies: Within 14 days pre-study (C1D1)	1) Lesion planned for injection of study drug 2) Lesion NOT planned for injection of study drug	X	X
	Second biopsies: Pre-dose C1D15 injection	1) Lesion injected with study drug 2) Lesion NOT injected with study drug	X	X
H	First biopsies: Within 14 days pre-study (C1D1)	1) Any lesion planned for injection of study drug 2) Any lesion NOT planned for injection of study drug	X	X
	Second biopsies: Pre-dose C2D1 injection	1) Lesion injected with study drug (same lesion as baseline) 2) Lesion NOT injected with study drug (same lesion as baseline)	X	X

OX40L=OX40 ligand; QIF= quantitative immunofluorescence; RNAseq= RNA sequencing

10.13.4 ADDITIONAL BIOMARKER ASSESSMENTS

During the trial, in addition to the biomarkers outlined in the study endpoints, exploratory biomarker analysis may be conducted on any remaining tumor and/or blood samples (including PK samples). These studies would extend the search for other potential relevant biomarkers to investigate the effect of mRNA-2416 as well as to determine how changes in the markers may relate to exposure and clinical outcomes. In addition, other methodologies for assessing biomarkers of immunologic response, such as (DNA sequencing or quantitation) or other methods may be employed. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

After the study is completed, with patient consent, any remaining biological samples may be stored for up to 15 years to address further scientific questions related to mRNA-2416 or cancer. A decision to perform such exploratory research may arise from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

10.14 PREGNANCY CONSIDERATIONS

There is no information on the effects of the study medication on fetal development in humans. Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

10.14.1 INSTRUCTIONS FOR MALE PATIENTS

Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of study treatment). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 5).

10.14.2 INSTRUCTIONS FOR FEMALE PATIENTS

Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table 5) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use a male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

Please note, females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

- Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 10. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 10 Highly effective methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] This is also considered a hormonal method

10.14.3 PREGNANCY REPORTING

Pregnancy is considered an immediately reportable event (but not an AE), and the investigator will record information concerning the pregnancy on the appropriate form and submit it to the Medical Monitor, Moderna pharmacovigilance at drugsafety@modernatx.com, and contract research organization (CRO) within 24 hours of learning of a patient's pregnancy. Study drug administration will be stopped in any female patient who becomes pregnant while participating in the study, and the patient will be followed to determine the outcome of the pregnancy.

10.14.3.1 FOLLOW-UP IN THE EVENT OF A PREGNANCY

The IRB and the Sponsor will be informed of all pregnancies in study patients.

The patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriages and congenital abnormalities will be reported as SAEs. Information on the status of the mother and child will be forwarded to the Medical Monitor or designee. Generally, follow-up will be in accordance with regulatory guidance and at least 6 to 8 weeks after the estimated delivery date. Any premature termination of the pregnancy will be reported.

10.15 OVERDOSE MANAGEMENT

For this study, any dose of mRNA-2416 or durvalumab greater than the patient's assigned dose level will be considered an overdose. No specific information is available regarding treatment for overdose of mRNA-2416 or durvalumab.

In the event of a suspected overdose, the investigator must do the following:

1. Contact the Medical Monitor and PPD pharmacovigilance/ SAE hotline immediately.

2. Closely monitor the patient for AEs/SAEs and laboratory abnormalities until last safety follow-up visit.
3. Report any signs or symptoms associated with the overdose as an AE and record details in the relevant AE/SAE sections in the electronic case report form (eCRF).
4. Document the quantity of the excess dose in the eCRF.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 QUALITY CONTROL

11.1.1 MONITORING

The Sponsor, or designee(s), will monitor the study for compliance to the protocol, applicable laws and regulations, and GCP. The monitor(s) will verify data on the eCRF versus source data. The monitor is also responsible for ensuring that the proper records are maintained. Monitoring reports will be issued for each monitoring visit.

11.2 QUALITY ASSURANCE

Quality assurance personnel may audit the clinical trial sites and/or study-related materials at any time during the study.

12 ASSESSMENT OF SAFETY

Safety will be assessed through AEs, laboratory data (eg, hematology, chemistry, and liver function tests), ECGs, physical examinations, vital signs, weight, concomitant medications and procedures, and ECOG performance status.

The PI and designated study staff are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

All SAEs/SUSARs will be reported to Health Authorities and investigators per 21 CFR 312.32.

12.1 DEFINITIONS

12.1.1 ADVERSE EVENT

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 ICF through the patient's last Safety follow-up visit or study discontinuation, whichever is later). This would include any side effect, injury, toxicity, sensitivity reaction, intercurrent illness, or sudden death. A pre-existing condition is one that is present at study entry and is reported as part of the patient's medical history. It should be reported as an AE if the frequency, intensity, or character of the condition worsens during study drug treatment.

The development of new or progression of existing metastasis from the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study unless they meet serious criteria as defined in Section 12.1.3.

Patients should be instructed to report all AEs to the investigator or study staff. AEs must be appropriately documented in the patient's original source documents and entered into the eCRF. Investigators should report syndromes rather than list symptoms. The severity of each AE will be categorized using NCI CTCAE Version 4.03.

12.1.2 ADVERSE DRUG REACTION

An adverse drug reaction (ADR) is any untoward and unintended response in a patient to an investigational medicinal product, which is related to any dose administered to that patient.

12.1.3 SERIOUS ADVERSE EVENT

An SAE is any AE (undesirable experience associated with the use of a medical product in a patient) where the patient outcome is:

- Death
  - Report if suspected that the death was an outcome of the adverse event and include the date if known.
- Life-threatening
  - Report if suspected that the patient was at substantial risk of dying at the time of the adverse event or use or continued use of the device or other medical product might have resulted in the death of the patient.
- Hospitalization (initial or prolonged)
  - Report if admission to the hospital or prolongation of hospitalization was as a result of the adverse event.
  - Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (eg, life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Disability or Permanent Damage
  - Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, that is, the adverse event resulted in a significant, persistent, or permanent change or impairment, damage, or disruption in the patient's body function/structure, physical activities, and/or quality of life.
- Congenital Anomaly/Birth Defect
  - Report if suspected that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
- Other Serious (Important Medical Events)
  - Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders), or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Clarification should be made between the terms "serious" and "severe" because the terms are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

12.1.4 UNEXPECTED ADVERSE REACTIONS

For expedited reporting purposes, expectedness of AEs will be assessed against the investigational treatment regimen the patient is receiving at the time of the event. AE terms not listed as an expected event in the Investigator's Brochure(s) for mRNA-2416 alone (Arm A) or mRNA-2416 and/or durvalumab, (Arm B) will be considered as unexpected.

12.1.5 DURVALUMAB ADVERSE EVENTS OF SPECIAL INTEREST

An AE of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP and may require close monitoring and rapid communication by the investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the investigator has any questions with regards to an event being an imAE, the investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include the following:

- Diarrhea/colitis and intestinal perforation
- Pneumonitis/ILD
- hepatitis/transaminase increases
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash/dermatitis
- Nephritis/blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis/polymyositis
- Neuropathy/neuromuscular toxicity (eg, Guillain-Barré syndrome, and myasthenia gravis)

- Other inflammatory responses that are rare and/or less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological, and rheumatological events.

In addition, infusion-related reactions, and hypersensitivity and/or anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.
Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix E). These guidelines have been prepared by the Sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug and/or study regimen by the reporting investigator.

12.2 AE COLLECTING AND REPORTING

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF starting from the time of ICF signing through the patient's last safety follow-up visit or study discontinuation, whichever is later (ie, the "AE reporting period"). From the time of ICF signing to first dose of mRNA-2146, only AEs related to study procedures will be collected. Also, once a patient has ended study treatment and has initiated any new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected.

Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs that occur during the AE reporting period, as defined by the protocol, must be reported by the investigator to the contract research organization (CRO), as the designee of the Sponsor, within 24 hours of the investigator becoming aware of the SAE. All SAEs and deaths that occur during the AE reporting period, whether or not considered causally related to the study drug, will be reported to the FDA per 21 CFR 312.32. After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (eg, SAEs related to invasive procedures such as biopsies or medication washout). The information collected will include a minimum of the following: patient number, a narrative description of the event, and an assessment by the investigator as to the intensity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by the Sponsor or its representative CRO. Detailed instructions for the collecting and reporting of SAEs will be provided in the Investigator Site File.

If there are serious, unexpected ADRs associated with the use of the study drug, the Sponsor or its designated CRO will notify the appropriate regulatory agency(ies) and all participating investigators on an expedited basis (7 days for fatal or life-threatening, serious, unexpected ADRs; 15 days for all other serious, unexpected ADRs). The Sponsor has delegated the responsibility to promptly notify the IRB/IEC of all unexpected serious ADRs involving risk to human patients in accordance with the rules and regulations of the IRB/IEC to the PI.

An unexpected event is one that is not reported in the IB.

REPORTING OF SAES AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

All SAEs must be reported to the designated CRO within 24 hours of the investigational site's knowledge of the occurrence. Each investigational site will submit the SAE information to the CRO.

The SAE information transmitted to the CRO will include the following (as available):

- Patient ID, investigator name, and site number
- SAE information: event term, onset date, severity, and causal relationship
- Basic demographic information (eg, age, sex, weight, etc)
- The outcomes attributable to the event (eg, death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, other important medical event[s])
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study drug administration
- A statement whether study drug was discontinued or study drug administration schedule was modified
- A statement whether event recurred after reintroduction of study drug if administration had been discontinued or withheld
- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding or observation notes, discharge summaries, autopsy reports, and death certificates.

The SAE information should be transmitted within 24 hours with as much of the above information as available at the time. Supplemental information may be transmitted and should not delay the initial transmission. The Sponsor or CRO may contact the investigational site to solicit additional information or follow-up on the event. Investigational sites will be provided with detailed instructions on the procedures for transmitting SAEs to the CRO.

For regulatory purposes, initial reports of serious ADRs should be transmitted within the prescribed time frame as long as the following minimum information is available: patient identification, suspect study drug, reporting source, and an event or outcome that can be identified as being both serious and unexpected for which, in the investigator's opinion, there is a suspected causal relationship.

A suspected unexpected serious adverse reaction (SUSAR) that is fatal or life-threatening must be reported to the competent authority and ethics committee immediately (within 7 days) after the Sponsor becomes aware of the event. Any additional information must be reported within 8 days of sending the first report.

A SUSAR that is not fatal or life-threatening must be reported to the competent authority and ethics committee as soon as possible (within 15 days) after the Sponsor becomes aware of the event.

12.3 RELATIONSHIP TO STUDY DRUG

For each reported AE, the investigator must make an assessment of the relationship of the event to each study drug using the following scale:

- Not Related: An event that is not associated with study drug administration and is judged clearly due to causes other than the study drug.
- Related: An event that is or may be associated with study drug administration.

- The terms Possibly Related and Probably Related will not be used. Any event that is possibly or probably related to study drug should be recorded as Related by the Investigator.

In the event of death, the cause of death should be recorded as the AE and the relationship to study drug assessed as above. “Death” is an outcome and is NOT the AE. The only exception is “sudden death” when the cause is unknown.

12.4 LABORATORY TEST ABNORMALITIES

Clinically significant abnormal laboratory findings that are detected during the study or are present at baseline and significantly worsen will be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Clinical significance is at the discretion of the investigator and may be defined as those findings which:

- Are directly responsible for discontinuation from the study,
- Require treatment or other therapeutic intervention,
- Require further monitoring, or
- Require further diagnostic evaluation (other than repeat of the same test to confirm the abnormality).

All abnormal laboratory values considered to be clinically significant will be recorded on the AE page of the eCRF. Significant abnormal laboratory values occurring during the clinical study should be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

12.5 FOLLOW-UP OF AES

All AEs must be reported in detail on the appropriate page in the eCRF and followed to resolution or stabilization. During the post-treatment follow-up period, all SAEs and related non-serious AEs should be followed until resolution or stabilization, which is defined as grade 1 or less. Patients will be referred to their primary care doctor for further follow-up as needed post-study.

The severity of ongoing AEs at last visit will be recorded. Any additional clinical sequelae emerging from the AE should be recorded as a separate AE.

13 STATISTICAL METHODS

A detailed Statistical Analysis Plan (SAP) will be used to guide the analysis and reporting of data collected in this study.

13.1 DATA COLLECTION AND PROCESSING

Creation and validation of the clinical database, data entry, data management, and transfer of central laboratory data will be conducted in accordance with 21 Code of Federal Regulations (CFR) Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials.

eCRFs will be completed for all enrolled patients. Please refer to the case report form (CRF) Completion Guidelines for instructions on which eCRFs will be completed for patients who are enrolled but not treated.

13.2 SAMPLE SIZE CONSIDERATIONS

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 is 0.05 will be tested, and this design with 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 overall response rate is 0.20. If there is 1 or more response observed from the 13 subjects 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. If four or more responses are observed in the 27 evaluable patients, mRNA-2416 will be considered active in ovarian cancer patients, and may warrant further development.

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 overall response rate is 0.1 will be tested, and this design with 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 overall response rate is 0.25. If there is 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. If eight or more responses are observed in the 41 evaluable patients, mRNA-2416 in combination with durvalumab will be considered active in ovarian cancer patients, and may warrant further development.

13.3 HANDLING OF MISSING DATA

Details of the handling of missing data will be provided in the SAP.

13.4 STATISTICAL METHODOLOGY

All data collected in this study will be presented in data listings and, where indicated, tabulated in summary tables. Data will be presented and summarized using the SAS System (SAS Institute Inc, Cary, NC).

Continuous variables will be summarized with the number of observations, mean, standard deviation, median, minimum, and maximum.

Categorical variables will be summarized with frequencies and percentages. Percentages will be based on non-missing data unless specified otherwise.

Except where indicated in the SAP, "baseline" is defined as the closest value prior to the start of treatment with study drug.

13.4.1 ANALYSIS POPULATIONS

The following definitions will be used in assigning patients into analysis populations:

- Intent-to-Treat Population – All patients who are enrolled (ie, assigned a patient number).
- Safety Population – All enrolled patients who received any amount of study drug.
- Activity Evaluable Population – All enrolled patient who received any amount of study drug and have at least 1 tumor response evaluation.

13.4.2 SAFETY ANALYSES

All safety analyses will be conducted in the Safety Population.

Verbatim descriptions of AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Summary tables will be provided for all TEAEs. A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. The number and percentage of patients reporting a TEAE in each dose cohort will be tabulated by system organ class and preferred term, severity, and relationship to study drug. The number and percentage of patients reporting a SAE and reporting a TEAE leading to premature discontinuation of study drug in dose cohort will be summarized by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same patient more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to study drug. Clinically relevant abnormal physical examination results are recorded as AEs; thus, physical examination data will not be summarized in a table.

Descriptive statistics for hematology, chemistry, and coagulation data will be summarized by dose cohort and time point and for the overall worst value post-baseline. Toxicity grades will be determined based on the CTCAE criteria version 4.03, and shift tables will be presented. The number and percentage of patients with at least a 2-grade increase from baseline will be summarized by dose cohort.

Descriptive statistics of the change from baseline for vital signs will be summarized by dose cohort and time point. Abnormal values, identified by threshold values defined in the SAP, will be summarized.

Descriptive statistics for ECG parameters at baseline and at the Post-treatment Safety Assessment visit and the change from baseline will be presented by dose cohort.

13.4.3 EFFICACY ANALYSES

The Activity Evaluable Population will be used for the analyses of efficacy data based on the dose of mRNA-2416 received.

Best response will be determined for each patient in accordance with RECIST 1.1, and Cheson guidelines and the objective response rate presented for each dose cohort. The overall objective response rate based on irRC or LYRIC will also be determined. The disease control rate based on RECIST 1.1 will also be

determined for Phase II patients. Progression-free survival and durability of response will be determined using Kaplan-Meier methodology. Please refer to Appendix C and D for a description of "Immune-related Response Criteria," and RECIST 1.1 criteria.

The details of Simon's two-stage study design and analysis used for Arm A and Arm B Phase II will be included in the Statistical Analysis Plan (SAP).

13.4.4 PK AND PHARMACODYNAMIC ANALYSES

mRNA-2416 and durvalumab PK parameters to be determined will include, but are not limited to, Cmax, time to maximum observed concentration, elimination half-life, and AUC. Where possible, descriptive statistics of the PK parameters will be provided; individual patient mRNA-2416 concentrations, actual sampling times, and PK parameters will be listed.

This study will assess the immunological effects of each treatment cycle on the cellular and humoral immune responses in the peripheral circulation and in tumor biopsy specimens. Humoral immune responses (potential antibody production) to the study drug will be compared to baseline in serum samples.

Tumor biopsies will be examined using immunohistochemistry, qualitative immunofluorescence and/or an orthogonal approach (i.e. ELISA) for changes in OX40L/OX40 and PD-L1/PD-1 expression levels, as well as characterization of tumor infiltrating lymphocyte populations (eg, phenotype, distribution, and activation). Plasma may be evaluated for changes in cytokine levels.

13.4.5 INTERIM ANALYSIS

No interim analysis is planned for this study.

14 STUDY DRUG MATERIALS

Details of the study drugs, dispensing, dosing, and accountability are summarized in the sections below. For detailed information, please refer to the Pharmacy Manual.

14.1 INVESTIGATIONAL PRODUCT

The investigational product, mRNA-2416 injection, is a novel mRNA encoding human OX40L encapsulated in a lipid nanoparticle. For additional information on the investigational product, please refer to the IB.

The investigational product, durvalumab, is a human monoclonal antibody (mAb) of the IgG 1, kappa subclass, that blocks the interaction of PD-L1 with programmed cell death protein 1 (PD-1) on T-cells. For additional information on the investigational product, please refer to the IB.

14.2 STUDY DRUG PREPARATION

mRNA-2416 is formulated in 20 mM trometamol (Tris) buffer, 140 mM sodium chloride, 5% sucrose solution for intratumoral injection. The study drug will be administered undiluted and the administration volume will vary depending on the target dose of mRNA. The total volume of mRNA-2416 injected will not exceed 4 mL, or 8 mg mRNA. Instructions for preparation of mRNA-2416 for this clinical study will be detailed separately in the Pharmacy Manual.

Durvalumab is formulated in 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0,02% weight/volume (w/v) polysorbate 80. It has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10,0 ml. Instruction for preparation of durvalumab (MEDI4736) for this clinical study will be detailed separately in the Pharmacy Manual.

14.3 STUDY DRUG STORAGE

mRNA-2416 must be stored at -20ºC ± 5ºC in a restricted access area. For further details, please consult the Pharmacy Manual.

Durvalumab must be stored at 2˚C - 8˚C in a restricted access area. Product must not be frozen. For further details, please consult the Pharmacy Manual.

14.4 STUDY DRUG PACKAGING AND LABELING

mRNA-2416 will be supplied in 2 mL glass vials containing 2 mg/mL of mRNA. Each vial contains a 1.4 mL fill volume (2.8 mg mRNA).

Durvalumab will be supplied as a 500mg vial solution for infusion after dilution (50 mg/ml).

The study medication will be labeled according to the requirements of local law and legislation as well as current Good Manufacturing Practice and GCP guidelines. Proof labels, detailing actual label text, will be available in the study files of all participating countries.

14.5 STUDY DRUG ACCOUNTABILITY

The investigational materials are to be prescribed only by the PI or the sub-investigators named on the Form FDA 1572 and may only be dispensed by authorized personnel at the institution(s) listed therein. Under no circumstances will the PI allow investigational product to be used other than as directed by the protocol.

It is the responsibility of the investigator, or designee, to ensure that a current record of inventory or drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and are open to inspection by the FDA or other regulatory authorities at any time. For further details, please consult the Pharmacy Manual.

14.6 STUDY DRUG HANDLING AND DISPOSAL

Upon the completion or termination of the study, and upon written authorization from the Sponsor or its representative, all unused and/or partially used study drug must be destroyed at the investigative site or returned to a central drug depot, as instructed by the Sponsor or its representative. It is the investigator's responsibility to ensure that the Sponsor or its representative has provided written authorization for study drug destruction, that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained.

15 INVESTIGATOR REQUIREMENTS

15.1 AE COLLECTION AND REPORTING

The investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment
- Determine the seriousness, relationship, and severity of each event
- Determine the onset and resolution dates of each event
- Monitor and record all pregnancies and follow up on the outcome of the pregnancy
- Transmit SAE information to the designated CRO within 24 hours of the study site staff becoming aware of new information
- Ensure all AE and SAE information are supported by documentation in the patients' medical records
- Report SAEs to local ethics committees, as required.

15.2 PROTOCOL ADHERENCE

Each investigator must adhere to the protocol as detailed in this document and agree that any changes to the protocol must be approved by the Sponsor prior to seeking approval from the IRB/IEC. Each investigator will be responsible for enrolling only those patients who have met the protocol inclusion and exclusion criteria. The Sponsor and/or its representative reserves the right to close sites when appropriate (eg, in instances where the protocol is not being followed, untimely input of data into eCRFs, under-enrollment, etc.).

15.3 CASE REPORT FORMS

eCRFs will be supplied by the Sponsor, or its representative, for the recording of all study data as specified in this protocol. eCRFs should be handled in accordance with instructions from the Sponsor or its representative. eCRFs must be completed by the designated study personnel. It is the responsibility of the PI to ensure that accurate eCRFs are completed in a timely manner.

15.4 SOURCE DOCUMENT MAINTENANCE

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, email correspondences, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the investigator(s) and made available for inspection by Sponsor representatives and/or regulatory authorities. The original signed informed consent form for each participating patient shall be filed with records kept by the investigator(s) and a copy given to the patient.

15.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by the Sponsor or authorized Sponsor representatives to inspect study data, patient's medical records, and CRFs in accordance with International Council for Harmonisation (ICH) guidelines, GCPs, and the respective United States (US) or foreign regulations and guidelines, as applicable.

The investigator will permit representatives of the Sponsor and/or regulatory authorities the ability to inspect facilities and records relevant to the study.

15.6 STUDY COMPLETION

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

1. Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
1. eCRFs properly completed by appropriate study personnel and signed and dated by the investigator
2. Complete Drug Accountability records (drug inventory log and an inventory of returned or destroyed clinical material)
3. Copies of protocol amendments and IRB/IEC approval or notification, if appropriate.

16 PROTECTION OF HUMAN PATIENTS AND GENERAL STUDY ADMINISTRATION

This study will be conducted in compliance with the ICH E6 GCP (consolidated guidelines and the ethical principles of the Declaration of Helsinki) and any additional national or IRB/IEC-required procedures.

16.1 INFORMED CONSENT

This study will be conducted in compliance with ICH E6 GCP (consolidated guidelines pertaining to informed consent). At the first visit, prior to initiation of any study-related procedures, patients will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation conditions, and risks and benefits. Clinical assessments and local laboratory results performed as part of the patient's standard of care may be used to establish eligibility.

A copy of the signed consent document or a second original must be given to the patient. The original signed consent document will be retained by the investigator. In case of significant changes to safety, the patient will be re-consented. This procedure must have prior agreement from the IEC/IRB. If applicable, the informed consent will be provided in a certified translation for non-English speaking patients. Signed consent forms must remain in the patient's study file and be available for verification by Sponsor personnel or regulatory agency at any time.

16.2 IRB APPROVAL

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB for approval. IRB approval of the protocol, informed consent document, and any advertisement used to recruit study patients must be obtained before the study may be initiated.

16.3 PATIENT DATA PROTECTION

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (eg, Protected Health Information authorization in North America).

The patient will not be identified by name in the eCRF or in any study reports, and these reports will be used for research purposes only. The Sponsor and designee(s) and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

17 DATA MANAGEMENT AND MONITORING

Training sessions, regular monitoring of investigators by Sponsor-designated personnel, instruction manuals, data verification, cross-checking, and data audits will be performed to ensure quality of all study data. Investigator meetings will be performed to prepare investigators and other study personnel for appropriate collection of study data.

The Sponsor will perform internal and/or external audits of study data.

It will be the responsibility of the investigator(s) to assure that essential laboratory and pharmacy manuals are available at the investigator/institutional site. Any or all of these documents may be subject to, and should be available for, audit by the Sponsor's auditor and/or inspection by regulatory authorities.

17.1 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of investigators, their addresses, qualifications, and extent of involvement. It is understood that the investigator is required to provide the Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by any regulatory authorities, by the Sponsor, and the IRB/IEC, as appropriate. At a patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Patient medical information obtained during the course of this study is confidential, and disclosure to third parties other than those noted above is prohibited.

17.2 RETENTION OF RECORDS

US Investigational New Drug (IND) exemption regulations require that records and documents pertaining to the conduct of this study and the distribution of investigational products, including CRFs, consent forms, laboratory test results, and medication inventory records, must be kept on file by the PI for a minimum of 2 years after notification by the Sponsor that a marketing application has been approved for the study drug being test (CFR Title 21, Part 312, Section 62[c]). If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the US FDA and applicable foreign authorities have been notified. The Sponsor will notify the investigator of these events. No study records should be destroyed without prior authorization from the Sponsor. This study will be conducted under a US IND; for study sites outside the US, the investigator must comply with US FDA IND regulations and with those of the relevant national and local regulatory authorities.

18 FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement and must comply with all local and national rules and regulations.

19 PUBLICATION POLICY

The publication policy is outlined in the Clinical Trial Agreement. The data generated in this clinical trial are the exclusive property of ModernaTX, Inc. and are confidential. Written approval from Moderna is required prior to disclosing any information related to this clinical trial. The Sponsor will meet with the PIs to determine the Publication Plan.

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APPENDIX A: ECOG PERFORMANCE STATUS

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.	

APPENDIX B: SAFETY LABORATORY TESTS AND HEPATITIS SEROLOGY

Hematology	
Hemoglobin	Monocytes
Hematocrit	Eosinophils
Leukocyte count (white blood cell [WBC])	Basophils
Neutrophils	Platelets
Lymphocytes	Bands (if available)
Coagulation (Screening Only)	
Prothrombin time	Fibrinogen
Partial thromboplastin time	
Urinalysis	
Appearance	Blood
pH	Specific gravity
Protein/Albumin	Ketones
Glucose	Bilirubin
Leukocyte esterase	Nitrates
Urine microscopy (red blood cell, WBC, crystals, and casts) – *if clinically indicated*	
Clinical Chemistry	
Magnesium	Lactic dehydrogenase (LDH)
Bicarbonate	Total bilirubin
Sodium	Glucose
Potassium	Total protein
Phosphorus	Albumin
Chloride	Creatinine
Calcium (corrected)	Blood urea nitrogen (BUN)
Alkaline phosphatase	Uric acid
Alanine aminotransferase (ALT/GPT)	Lipase
Aspartate aminotransferase (AST/GOT)	Amylase
	Thyroid-stimulating hormone
Hepatitis Serology	
Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs)
Hepatitis B core antibody (anti-HBc)	Hepatitis C (HCV) antibody

APPENDIX C: SUMMARY OF TUMOR ASSESSMENT CRITERIA

Table 1a: Comparison between RECIST 1.1 and irRC

Criteria	CR	PR	PD
RECIST 1.1	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm Note: the appearance of one or more new lesions is also considered progression.
irRC	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart	≥50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart (as measured bi-dimensionally)	≥25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart, where Tumor Burden = SPD index lesions + SPD new, measurable lesions

Table 1b: Comparison between Cheson Criteria and LYRIC

Criteria	CR	PR	PD
Cheson (Lugano)	PET-CT, score 1, 2, or 3* with or without a residual mass on 5PS† OR on CT, target nodes/nodal masses must regress to ≤1.5 cm in LDi	PET-CT score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. OR On CT ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. OR On CT, an individual node/lesion must be abnormal with: LDi >1.5 cm and increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm
			In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by ≥2 cm from baseline. New or recurrent splenomegaly
			New or clear progression of preexisting nonmeasured lesions
			Regrowth of previously resolved lesions
			A new node >1.5 cm in any axis or a new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
			Assessable disease of any size unequivocally attributable to lymphoma
			AND/OR new or recurrent involvement of the bone marrow
LYRIC	Same as Cheson	Same as Cheson	As with Lugano with the following exceptions:
			IR
			IR(1): ≥50% increase in SPD in first 12 weeks
			IR(2): <50% increase in SPD with
			a. New lesion(s), or
			b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment
			IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

Reference: Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. J Clin Oncol. 2014; 32(27):3059-68

Table 2: Derivation of irRC overall responses

Measurable response	Nonmeasureable response		Overall response
Index and new, measureable lesions (tumor burden),[a] %	**Non-index lesions**	**New, nonmeasurable lesions**	**Using irRC**
↓100	Absent	Absent	irCR[b]
↓100	Stable	Absent	irPR[b]
↓100	Unequivocal progression	Absent	irPR[b]
↓≥50	Absent/Stable	Absent	irPR[b]
↓≥50	Unequivocal progression	Absent	irPR[b]
↓<50 to <25↑	Absent/Stable	Absent	irSD
↓<50 to <25↑	Unequivocal progression	Absent	irSD
≥25?	Any	Absent	irPD[b]

irCR=immune-related complete response; irPD=immune-related progressive disease; irRC=immune-related response criteria; irSD=immune-related stable disease

[a] Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).

[b] Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Reference:

Wolchok JD, Hoos A, O'Day S et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

Summary of Cheson Criteria

Revised Criteria for Response Assessment

Response and site	PET-CT-based response	CT-based response
Complete response	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS No extralymphatic sites of disease	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial response	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

Response and site	PET-CT-based response	CT-based response
No response/Stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses,	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	LDi >1.5 cm and increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS=5-point scale; CT=computed tomography; FDG=fluorodeoxyglucose; IHC=immunohistochemistry; LDi=longest transverse diameter of a lesion; MRI=magnetic resonance imaging; PET=positron emission tomography; PPD=cross product of the LDi and perpendicular diameter; SDi=shortest axis perpendicular to the LDi; SPD=sum of the product of the perpendicular diameters for multiple lesions.

Reference:

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):3059-3068.

APPENDIX D: SUMMARY OF RECIST 1.1 CRITERIA

A summary of RECIST 1.1 criteria is presented below. For a full description of RECIST 1.1, refer to Eisenhauer et al 2009. For a full description of Cheson criteria for lymphomas, refer to Cheson et al 2014.

RECIST 1.1	
Minimum size measureable lesions	CT: 10 mm Clinical: 10 mm (must be measurable with calipers) Chest x-ray: 20 mm Lymph node: • CT • ≥15 mm short axis for target • ≥10 - <15 mm for non-target • <10 mm is non-pathological
Overall tumor burden	5 lesions (2 per organ)
Response criteria target disease	
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression.
SD:	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
Response criteria non-target disease	
CR	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
PD	Unequivocal progression of existing non-target lesions. Appearance of one or more new lesions is also considered progression.

References:

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.

APPENDIX E: DOSE MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-MEDIATED, INFUSION RELATED, AND NON IMMUNE-MEDIATED REACTIONS

Table 10: Dose modification and toxicity management guidelines for immune-mediated, infusion related, and non-immune-mediated reactions

General considerations	
Dose modifications	**Toxicity management**
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: − It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. − Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. − Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.

General considerations

Dose modifications	Toxicity management
If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤ 1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤ 10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For Grade ≥ 3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study	− For persistent (> 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − Some events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the Study Physician, and promptly pursue specialist consultation. − If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (> 28 days of taper). − More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP,

General considerations

Dose modifications	Toxicity management
drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade < 1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (ie, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. − Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any grade**	**General guidance**	**For any grade:** − Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1. • If toxicity worsens, then treat as Grade 3 or Grade 4.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		• If toxicity improves to Grade ≤ 1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	− If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started − If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] − Consider pulmonary and infectious disease consult. − Consider, as necessary, discussing with Study Physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):**

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])		− Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with Study Physician. − Hospitalize the patient. − Supportive care (eg, oxygen). − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any grade**	**General guidance**	**For any grade:**

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			− Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. − Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. − Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of < 4 over baseline per day) (Colitis: asymptomatic; clinical or	No dose modifications.	**For Grade 1:** − Monitor closely for worsening symptoms. − Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	diagnostic observations only)		
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤ 1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤ 1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** − Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. − Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. − If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks [a]. **Caution:** it is important to rule out

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			bowel perforation and refer to infliximab label for general guidance before using infliximab. − Consider, as necessary, discussing with Study Physician if no resolution to Grade ≤ 1 in 3 to 4 days. − Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥ 7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated,	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤ 1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 3 or 4:** − Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. − Monitor stool frequency and volume and maintain hydration. − Urgent GI consult and imaging and/or colonoscopy as appropriate. − If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg, infliximab at 5 mg/kg once every 2 weeks). **Caution**:

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	**Grade 4** Permanently discontinue study drug/study regimen.	Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs)	**Any grade**	**General guidance**	**For any grade:** − Monitor and evaluate liver function test: AST, ALT, ALP, and TB. − Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT > ULN and ≤ 3.0 × ULN and/or TB > ULN and ≤ 1.5 × ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** − Continue LFT monitoring per protocol.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTs)" in HCC patients**	**Grade 2** (AST or ALT > 3.0 × ULN and ≤ 5.0 × ULN and/or TB > 1.5 × ULN and ≤ 3.0 × ULN)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤ 1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤ 1 in 1 to 2 days, consider, as necessary, discussing with Study Physician. – If event is persistent (> 3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (ie, mycophenolate mofetil).[a] Discuss with Study Physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT > 5.0 × ULN and ≤ 20.0 × ULN and/or TB > 3.0× ULN and ≤ 10.0 × ULN) (Grade 4: AST or ALT > 20 × ULN and/or TB > 10 × ULN)	**For Grade 3:** For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤ 1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤ 1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study	**For Grade 3 or 4:** − Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. − If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (ie, mycophenolate mofetil). Discuss with Study Physician if mycophenolate is not available. **Infliximab should NOT be used.** − Perform hepatology consult, abdominal workup, and imaging as appropriate. − Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		drug/study regimen if the elevations do not downgrade to Grade ≤ 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT > 3 × ULN + bilirubin > 2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause. [b] **For Grade 4:**	

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of**	**Any grade**	**General guidance**	**For Any grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [eg, portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load > 2000 IU/mL – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
DILI/liver decompensation			antiviral HCV medications if HCV viral load increased by ≥ 2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT > ULN and ≤ 5.0 × ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin**	

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		or signs of DILI/liver decompensation	
	Grade 2 (Isolated AST or ALT > 5.0 × ULN and ≤ 8.0 × ULN, if normal at baseline) (Isolated AST or ALT > 2.0 × baseline and ≤ 12.5 × ULN, if elevated > ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤ 1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** − Regular and frequent checking of LFTs (eg, every 1 to 3 days) until elevations of these are improving or resolved. − Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. − Consider, as necessary, discussing with Study Physician. − If event is persistent (> 3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. − If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			additional abdominal workup (including liver biopsy) and imaging (ie, liver ultrasound), and consider starting immunosuppressives (ie, mycophenolate mofetil).[a] Discuss with Study Physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Grade 3 (Isolated AST or ALT > 8.0 × ULN and ≤ 20.0 × ULN, if normal at baseline) (Isolated AST or ALT > 12.5 × ULN and ≤ 20.0 × ULN, if elevated > ULN at baseline)	• Hold study drug/study regimen dose until resolution to Grade ≤ 1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤ 1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do	**For Grade 3:** − Regular and frequent checking of LFTs (eg, every 1-2 days) until elevations of these are improving or resolved. − Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. − Consider, as necessary, discussing with Study Physician. − If Investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. − If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		not downgrade to Grade ≤ 1 or baseline within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause. [b]	promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with Study Physician if mycophenolate is not available. **Infliximab should NOT be used.** − Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 4 (Isolated AST or ALT > 20 × ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4: Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥ 1.5 × ULN, if normal at baseline; or 2 × baseline, if > ULN at baseline) or signs of DILI/liver decompensation (eg, fever, elevated INR):			

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
- **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** - **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** - **Grade 3-4: Permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any grade**	**General guidance**	**For any grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** − Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. − Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine > 1.5 to 3.0 × baseline; > 1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤ 1 or	**For Grade 2:** − Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. − Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		baseline, then resume study drug/study regimen after completion of steroid taper.	− Consult nephrologist and consider renal biopsy if clinically indicated. − If event is persistent (> 3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. − Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] − When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine > 3.0 × baseline;	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Carefully monitor serum creatinine on daily basis.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	> 3 .0 to 6.0 × ULN; Grade 4: serum creatinine > 6.0 × ULN)		− Consult nephrologist and consider renal biopsy if clinically indicated. − Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General guidance**	**For any grade:** − Monitor for signs and symptoms of dermatitis (rash and pruritus). − IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	Grade 1	No dose modifications.	**For Grade 1:** − Consider symptomatic treatment, including oral anti-pruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (> 1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤ 1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤ 1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** − Obtain dermatology consult. − Consider symptomatic treatment, including oral anti-pruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). − Consider moderate-strength topical steroid. − If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with Study Physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. − Consider skin biopsy if the event is persistent for > 1 to 2 weeks or recurs.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤ 1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Consult dermatology. − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Consider hospitalization. − Monitor extent of rash [Rule of Nines]. − Consider skin biopsy (preferably more than 1) as clinically feasible. − Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] − Consider, as necessary, discussing with Study Physician.
Endocrinopathy	**Any grade**	**General guidance**	**For any grade:**

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
(eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	(depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)		− Consider consulting an endocrinologist for endocrine events. − Consider, as necessary, discussing with Study Physician. − Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). − Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3, and free T4 and other relevant endocrine and related labs (eg, blood glucose and ketone levels, HgA1c). − For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. − If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis,

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). − If TSH < 0.5 × LLN, or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes	**For Grade 2 (including those with symptomatic endocrinopathy):**

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled.	− Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. − For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, hydrocortisone, sex hormones). − Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. − Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤ 10 mg/day or equivalent.	treatment of cancer-related infections [Category 2B recommendation]).[a] − For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid	**For Grade 3 or 4:** − Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. − For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (eg, hydrocortisone, sex hormones).

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		replacement (eg, adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤ 10 mg/day or equivalent.	− For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. − Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia	**Any grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining	**General guidance**	**For any grade:** − Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications).

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Gravis and Guillain-Barre)	the CTC grade/severity)		− Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). − Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). − Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** − See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤ 1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose	**For Grade 2:** − Consider, as necessary, discussing with the Study Physician. − Obtain neurology consult. − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine).

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		until resolution to Grade ≤ 1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤ 1 and after completion of steroid taper.	− Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤ 1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days.	**For Grade 3 or 4:** − Consider, as necessary, discussing with Study Physician. − Obtain neurology consult. − Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		For Grade 4: Permanently discontinue study drug/study regimen.	promptly treat with additional immunosuppressants (eg, IV IG). − Once stable, gradually taper steroids over ≥ 28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any grade**	**General guidance**	**For any grade:** − The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. − Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. − Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. − It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** − Consider, as necessary, discussing with the Study Physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤ 1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** − Consider, as necessary, discussing with the Study Physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤ 1.	**For Grade 3 or 4 (severe or life-threatening events):** − Consider, as necessary, discussing with Study Physician. − Recommend hospitalization.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	− Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Myocarditis	**Any grade**	**General guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For any grade:** − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. − Consider, as necessary, discussing with the Study Physician. − Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (eg, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			ECHO to assess wall motion abnormalities when needed. − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (eg, BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion)	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate	**For Grade 2-4:** − Monitor symptoms daily, hospitalize. − Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	(Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support)	study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	determined whether and when to complete diagnostic procedures including a cardiac biopsy. − Supportive care (eg, oxygen). − If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Myositis/Polymyositis ("Poly/myositis")	**Any grade**	**General guidance**	**For any grade:** − Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. − If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. − Consider, as necessary, discussing with the Study Physician.

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			− Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (ie, consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** − Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. − Consider Neurology consult.

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			− Consider, as necessary, discussing with the Study Physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤ 1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** − Monitor symptoms daily and consider hospitalization. − Obtain Neurology consult, and initiate evaluation. − Consider, as necessary, discussing with the Study Physician. − If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant − If clinical course is *not* rapidly progressive, start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day − If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as

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Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤ 1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 3 or 4 (severe or life-threatening events):** − Monitor symptoms closely; recommend hospitalization. − Obtain Neurology consult, and complete full evaluation. − Consider, as necessary, discussing with the Study Physician. − Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. − If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as

Specific immune-mediated reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		For Grade 4: - Permanently discontinue study drug/study regimen.	TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Consider whether patient may require IV IG, plasmapheresis. − Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Abbreviations: AChE, acetylcholine esterase; ADL, activities of daily living; AE, adverse event; ALP, alkaline phosphatase test; ALT, alanine aminotransferase; ASTc, aspartate aminotransferase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DM, diabetes mellitus; DILI, drug-induced liver injury; ECG, electrocardiogram; ECHO, echocardiogram; GI, gastrointestinal; HBcAB, hepatitis B core antibody; HBeAg, hepatitis B viral protein; HbsAg, surface antigen of the hepatitis B virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HgA1c, hemoglobin A1c; ILD, interstitial lung disease; imAE, immune-mediated adverse event; IG, immunoglobulin; IV, intravenous; LFT, liver function tests; LLN, lower limit of normal; MRI, magnetic resonance imaging; NCI, National Cancer Institute; NCCN, National Comprehensive Cancer Network; PJP, *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO, By mouth; T3, triiodothyronine; T4, thyroxine; TB, total bilirubin; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

[a] ASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” by Michael Postow MD.

[b] US Food and Drug Administration Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

Abbreviations:

Infusion-related reactions

Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Any grade	General guidance	**For any grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).

Infusion-related reactions

Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤ 2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; IM, intramuscular; IV, intravenous; NCI, National Cancer Institute.

Non–immune-mediated reactions

Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Any grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.

Non–immune-mediated reactions

Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."