CLINICAL STUDY PROTOCOL

Phase 1 Dose Escalation Trial of Intra-Tumoral Injection of NIS Measles Virus (Edmonston Strain) in Combination with Atezolizumab in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC)

Protocol Number: VYR-MV1-101

Study Drug:	NIS Measles Virus (MV-NIS)
Sponsor:	Vyriad 221 1st Ave SW, Suite 102 Rochester, MN 55902
Medical Monitor:	Alice S Bexon, MD, Chief Medical Officer Vyriad
Date of Protocol:	3 January 2017
Protocol Version:	**3.0**
Previous Version:	**2.0**

1. PROCEDURES IN CASE OF EMERGENCY

Serious Adverse Events

All serious adverse events (SAEs)* occurring in patients while on-study or within 30 days of receiving the last dose of study drug regardless of relationship, must be promptly reported (within 24 hours) by telephone, email, or telefax to the sponsor (or designee).

Emergency Contact Information

For SAE/SUSAR reporting:	**For any other questions or to contact the Medical Monitor:**
Alice S Bexon, MD Cell#: 617 417 7300 Email: pv-vyriad-mv1@bexonclinical.com	Alice S Bexon, MD Cell#: 617 417 7300 Email: alice.bexon@bexonclinical.com

SAE AND SUSAR CRITERIA

* A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section **11.3** Serious Adverse Events for additional information):

- Death
- Life-threatening adverse drug event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability / incapacity
- A congenital anomaly/birth defect
- An important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Some serious events will not be reported as SAEs, including:

- Disease progression
- Death due to disease progression occurring more than 30 days after the last dose of study drugs
- Medical or surgical procedures when the condition that leads to the procedure is an adverse event
- Pre-existing diseases, or conditions or laboratory abnormalities present or detected prior to the screening visit, that do not worsen
- Situations for which an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions)

** A suspected unexpected serious adverse reaction (SUSAR) is any untoward and unintended responses to an investigational product related to any dose administered, of which the nature, or severity, is not consistent with the applicable product information (see also Section **11.4.2** of this document; Suspected Unexpected Serious Adverse Reactions). All suspected adverse reactions related to an investigational medicinal product which occur in the concerned trial and that are both unexpected and serious are patient to expedited reporting.

2. SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Alice S Bexon, MD, CMO	3 January 2017 Date of Signature

3. INVESTIGATOR SIGNATURE

I have read this protocol, including all appendices, and I agree to conduct the study in compliance with all applicable regulations (including 21 CFR Part 312). I will also make a reasonable effort to complete the study within the time designated. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Vyriad. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

I am aware that, prior to the commencement of this study, the Institutional Review Board must approve this protocol and the informed consent document associated with the clinical facility where the study will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol. I agree to provide all patients with a signed and dated copy of their informed consent document, as required by FDA and ICH regulations. I further agree to report to Vyriad any adverse events in accordance with the terms of this protocol and FDA regulation 21 CFR 312.64.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature	Date of Signature (DD MM YYYY)
Name of Investigator (please print)	

4. SYNOPSIS

Study title	Phase 1 Dose Escalation Trial of Intra-Tumoral Injection of NIS Measles Virus (Edmonston Strain) in Combination with Atezolizumab in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC)
Clinical phase	Phase 1
Trial centers	1-3 centers; lead center: Mayo Clinic Cancer Center, Rochester, MN 55905
Study rationale	Vyriad is developing the investigational medicinal product MV-NIS, which is an oncolytic measles virus (MV). The MV is a spherical, enveloped, negative-strand RNA virus that is antigenically monotypic with only one serotype, and is being developed for the treatment of oncological conditions. MV-NIS is a recombinant, replicating, measles virus strain derived from the highly attenuated Edmonston strain of measles vaccine, MVEdmtag (Dingli 2004). The MVEdmtag strain incorporates two acquired mutations in the viral P gene encoding the V-protein, which prevents the MV mediated inhibition of the target cell type I interferon response (Dingli 2004; Ohno 2004). Among the surface proteins, the H-protein is critical to facilitate attachment of the measles virus to the receptors, CD46, SLAM and nectin-4 (Dorig 1993; Tatsuo 2000; Nielsen 2001; Noyce 2011). The other membrane protein, F-protein allows not only for cell fusion once MV attaches to the cell but also fusion with uninfected neighboring cells. The NIS gene encodes for the human thyroid sodium iodine symporter and was cloned into the MVEdmtag strain to improve non-invasive monitoring of the location and proportion of infected cells (Dai 1996; Dingli 2004). The NIS gene was cloned downstream of the hemagglutinin (H) gene (Dingli 2004). Expressed NIS actively imports iodide into cells, with sodium gradients driving cellular uptake. Expression of the NIS gene can be used as an imaging transgene to monitor viral infection. This allows use of gamma camera, single photon emission computed tomography (SPECT), or positron emission tomography–CT (PET-CT) for *in vivo* monitoring of viral replication following administration of ^{123}I or ^{99m}Tc isotopes. The therapeutic efficacy of engineered vaccine strain-MV has been demonstrated using both *in vitro* and *in vivo* models of various solid tumors and hematologic malignancies. Pre-clinical data is available for hematologic and solid malignancies including, but not limited to, ovarian cancer (Peng 2002; Hasegawa 2006), glioblastoma multiforme (Phuong 2003), breast cancer (McDonald 2006), multiple myeloma (Peng 2001; Dingli 2004), lymphoma (Grote 2001), hepatocellular carcinoma (Blechacz 2006), prostate cancer (Msaouel 2009b), and mesothelioma (Li 2010). Programmed cell death-1 (PD-1) and programmed death ligand-1 (PD-L1) are two of the many immunologic checkpoints that regulate the immune response with clinically available mAbs for the treatment of advanced cancers, including NSCLC. Currently, two anti-PD-1 antibodies, nivolumab and pembrolizumab, and one anti-PD-L1 antibody, atezolizumab, are FDA approved in advanced or metastatic NSCLC. Checkpoint blockade with PD-(L)1 inhibitors is one of the most promising forms of cancer immunotherapy that improves the capacity of the immune system to acknowledge and delete tumors. While a subset of advanced NSCLC patients benefits from PD-(L)1 blockade, unfortunately a majority of patients do not respond to single agent checkpoint inhibition.

	Therefore, new therapeutic approaches that expand the available endogenous anti-tumor T cell repertoire or increase the tumor cell antigenicity for T cell recognition are rational therapeutic agents to be combined with checkpoint inhibition. Available clinical trial data shows that oncolytic therapy with MV-NIS is well tolerated, and several patients have experienced a disease response or stabilization. Preliminary studies of immune responses in patients receiving MV-NIS therapy suggest some patients develop improved T cell responses to measles antigens and known tumor antigens. In conclusion, our preclinical data utilizing NSCLC cell lines, multiple published preclinical reports on the successful combination of oncolytic viral therapy and PD-1/PD-L1 axis blockade, acceptable safety and toxicity data from available clinical trials, and preliminary immune response data from patients receiving MV- NIS, support the combination of intra-tumoral (IT) MV-NIS with PD-(L)1 blockade in a clinical trial setting for patients with advanced NSCLC. Study VYR-MV1-101 is a Phase 1 study designed to determine the maximum tolerated dose (MTD) and toxicity of attenuated MV-NIS virus combined with atezolizumab in patients with recurrent and metastatic NSCLC. The study will further evaluate safety, clinical and immune responses in an expansion cohort of 18 additional patients with NSCLC.
Study objectives	<u>Primary objective:</u> • To determine the maximum tolerated dose (MTD) of the intra-tumoral administration of an Edmonston strain MV genetically engineered to produce NIS (MV-NIS), in combination with the PD-L1 inhibitor atezolizumab in patients with recurrent and metastatic NSCLC. <u>Secondary objectives:</u> • To describe the safety and toxicity of the intra-tumoral administration of MV-NIS with atezolizumab. • To assess preliminary antitumor efficacy by following: – radiographic objective response rate (ORR) – duration of response (DOR) – progression-free survival (PFS) …in the injected lesion, non-injected lesions and overall, per RECIST 1.1. <u>Exploratory objectives:</u> • To determine the time-course of viral infection, dissemination, and elimination through the measurement of NIS gene expression using SPECT/CT imaging. • To assess viremia, viral replication, and viral shedding/persistence following intra- tumoral administration of MV-NIS and immunotherapy. • To obtain preliminary data regarding the antitumor efficacy by serial measurements of radioiodine uptake by SPECT/CT, radiological ORR, DOR and PFS and to correlate with PD-L1 expression and other immune biomarkers. • To characterize the peripheral blood immune phenotype, presence and peripheral blood repertoire representation of neoantigen-specific T cells, and cell-free DNA of patients at potential immunologic transition points including study enrollment, therapy initiation, during therapy, and at follow-up.

<table>
<tr><td></td><td>

To evaluate if therapy with MV-NIS, atezolizumab, or both alters the peripheral blood immune phenotype, presence and peripheral blood repertoire representation of neoantigen-specific T cells, or cell-free DNA.
To characterize the tumor microenvironment by immunohistochemistry (IHC) for PD-L1 and other immune markers of interest on tissue prior to and at the completion of MV-NIS injection and following atzolizumab treatment.
To evaluate if MV-NIS alter the pretreatment tumor microenvironment levels of PD-L1 or immune markers after therapy in the lesion injected with MV-NIS.
To determine if lesions not injected with MV-NIS express comparable levels of PD-L1 or contain an immune marker milieu within the tumor microenvironment similar to the lesion injected with MV-NIS after treatment with MV-NIS and atezolizumab.
To assess if changes to the circulating or tumor microenvironment immune biomarkers associate with clinical response.
To evaluate the tumor genomic mutational burden by whole exome sequencing, level of neoantigen expression and signal transduction pathways by RNAseq prior to and after therapy with MV-NIS and atezolizumab.
To determine if changes to the tumor genomic mutational burden, level of neoantigen expression or alterations in signal transduction pathways are associated with clinical response.
To assess the secondary efficacy parameters (ORR, DOR and PFS) using irRECIST in addition to classical RECIST 1.1.
To compare PFS of the combination of MV-NIS and atezolizumab in patients with recurrent and metastatic NSCLC versus historical controls.
To evaluate if the combination of intra-tumoral MV-NIS and atezolizumab results in improved ORR and DOR when compared to historical controls of patients treated with atezolizumab as a single agent.

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<tr><td>Dosage and administration</td><td>
<u>Dose escalation:</u>

MV-NIS will be administered once intra-tumorally with a 21-gauge, Quadrafuse® or other suitable needle using ultrasound or CT guidance on day 1 of treatment in 3 escalating dose cohorts, starting at dose level 1. If dose level 1 is not tolerated, a single de-escalation may be performed as follows:
<table>
<tr><th>Dose Level</th><th>Number of viruses</th></tr>
<tr><td>-1</td><td>3×10^7</td></tr>
<tr><td>1</td><td>1×10^8</td></tr>
<tr><td>2</td><td>3×10^8</td></tr>
<tr><td>3</td><td>1×10^9</td></tr>
</table>
Atezolizumab will be given per the US prescribing information (Tecentriq® USPI 2016) at 1200 mg IV on day 15 and then once every 3 weeks thereafter until progression of disease, discontinuation due to toxicity, or withdrawal of consent.

<u>Expansion cohort:</u>
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	Once the MTD is established, an expansion cohort will further evaluate safety, clinical and immune responses at the MTD of MV-NIS in combination with standard-dose atezolizumab: • MV-NIS at the established MTD given by intra-tumoral injection on day 1 followed by atezolizumab at 1200 mg IV on day 15 and subsequently every 3 weeks. Should a patient develop measles during the study, treatment with immune globulin will be administered 400 mg/kg/d for 3-5 days. Aerosolized Ribavirin (6 grams/day over 12-18 hours/day for 3 days, up to 7 days in length) can also be considered at the discretion of the treating physician for patients not responding to immune globulin.
Study design	This is a phase 1, dose escalation study of the combination of intra-tumoral MV-NIS and systemic atezolizumab in patients with recurrent and metastatic NSCLC. After the dose escalation phase of the trial, a dose expansion cohort will further investigate safety, clinical and immune responses at the MTD. Figure 1 shows the study design. A standard 3+3 design will be used for the dose escalation part of the study. Starting at dose level 1, three patients will be treated per dose level. The first three patients treated at dose level 1 will be enrolled at least 24 hours apart. All patients will be observed for a dose-limiting toxicity (DLT) period of 36 days after MV-NIS administration (which is 3 weeks after atezolizumab) and the last patient in each cohort must have completed the DLT period prior to each dose escalation decision. Resolution of viremia in all patients at a dose level is required prior to dose escalation being allowed. The decision to dose escalate will be made jointly by the safety committee. Dose Escalation Teleconferences (DETs) will occur prior to dose escalation for subsequent cohorts. The cumulative safety experience, which includes data from the current and previous dose cohorts, will be discussed by the Sponsor and the Investigators. If a DLT is observed, 3 additional patients will be enrolled at that dose level. If 1/6 patients experiences DLT, escalation may proceed; if ≥2/6 patients experience DLT, the MV-NIS dose will be de-escalated and 3 further patients added at the previous dose level. Dose level -1 will only be explored if dose level 1 is not tolerated. Doses will not be escalated in any individual patient. Any patient who experiences a DLT will be taken off study drugs, but will be followed up for response and PFS. If no DLTs are seen at any of the dose levels, then the MTD will be the maximum delivered dose (1×10^9). MTD will be defined as the highest safely administered dose at which no more than one out of six or 0/3 patients experience DLT. The first 6 patients of the expansion cohort will be enrolled and observed for 36 days after the 6^{th} patient has received treatment, prior to any additional patients being treated. If ≤1/6 DLTs is observed then the remaining patients will be enrolled and treated sequentially, with no waiting period or limitation on simultaneous enrolment. If ≥2/6 patients in the expanded cohort experience a DLT, then the entire expansion cohort will be re-enrolled at the next lower dose level. If a patient fails to complete the initial course of therapy (defined as study drug administration and four weeks of observation) for reasons other than adverse events or disease progression based on the day 36 CT-scan, then the patient will be regarded as non-evaluable for DLT and an additional patient will be treated at the current dose level. However, all AE information from patients who received any study treatment will be utilized in the analysis.

	In both the escalation and expansion cohorts, the *in vivo* distribution of MV-NIS infected cells and the kinetics of virus spread and elimination will be monitored by SPECT/CT imaging. ^{99m}Tc SPECT/CT imaging will be performed prior to registration, 5-7 days after MV-NIS administration and 15 days after MV-NIS administration if previous scan is positive.
Number of patients	The study will involve 9-24 patients in the escalation phase and 15-18 in the expansion cohort, to provide a total cohort of 21 patients for efficacy evaluation at the MTD.
Main criteria for inclusion	Note: all eligibility criteria must be verified and submitted to the medical monitor to permit study registration. Day 1 may only occur after registration (at least 1 day and up to 7 days later). **Inclusion criteria:** 1. Age ≥ 18 years. 2. Diagnosis of metastatic lung cancer, with: a. histologic confirmation of the primary NSCLC histology; b. at least one lesion amenable for intra-tumoral injection of MV-NIS. 3. Patient meets the FDA-approved indication for atezolizumab treatment in NSCLC (Tecentriq® USPI 2016). 4. Patient may have more than one site of recurrence/metastatic disease but only one lesion will be injected that is ≥ 1 cm in size (if in the lung, the lesion must be ≥2 cm and adjacent to the pleura). 5. Measurable disease per RECIST 1.1. 6. ECOG Performance Status (PS) 0 or 1. 7. Ability to provide informed consent. 8. Willingness to comply with all required protocol procedures including providing biologic specimens, participating in the SPECT/CT imaging and returning to the clinical study site for follow up visits. 9. Life expectancy of more than 12 weeks (in the opinion of the enrolling investigator). 10. The following laboratory values obtained ≤ 14 days prior to registration. a. ANC ≥1500/mm^3 b. Platelets ≥100,000/mm^3 c. HgB >9.0 g/dL d. Total bilirubin ≤ institutional upper limit of normal (ULN) e. SGOT (AST) ≤2.5 x ULN f. Creatinine ≤1.5 x ULN 11. Must be willing to implement contraception throughout study and for the 8 weeks following last study drug administration. **Exclusion criteria:** 1. Patients with any other prior malignancy are not allowed except for the following: a. Adequately treated basal cell or squamous cell skin cancer b. In situ cervical cancer c. Adequately treated Stage I or II cancer from which the patient is currently in complete remission or other cancer from which the patient has been disease-free for 2 years.

	2. Uncontrolled CNS metastases or treatment by neurosurgical resection, radiation or brain biopsy within 4 weeks prior to Day 1. 3. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways. 4. Any of the following prior therapies: a. Chemotherapy ≤ 3 weeks prior to registration; b. Biologic therapy ≤ 4 weeks prior to registration; c. Radiation therapy ≤ 3 weeks prior to registration; d. Investigational therapy ≤ 4 weeks prior to registration. 5. Failure to fully recover from acute, reversible effects defined as ≤ grade 1 CTCAE v.4.03 of prior systemic therapy regardless of interval since last treatment. 6. Other concurrent investigational therapy (utilized for a non-FDA-approved indication and in the context of a research investigation). 7. Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects: a. Pregnant women b. Nursing women c. Men or women of childbearing potential who are unwilling to employ adequate contraception during treatment and 8 weeks following the completion of study drug treatment. 8. Patients with active, known or suspected autoimmune disease. Exceptions are vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger. 9. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immuno-suppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. 10. History of organ transplantation. 11. Receiving therapeutic anticoagulation (warfarin, low molecular weight heparin, or other novel oral anticoagulants). 12. Requiring blood product support. 13. Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA), or human immunodeficiency virus (HIV1 or 2) indicating acute or chronic infection. 14. Active infection (any grade) ≤5 days prior to registration. 15. History of tuberculosis or history of Mantoux PPD positivity. 16. Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

<table>
<tr><td></td><td>17. Current exposure to household contacts ≤15 months old or household contact with known immunodeficiency.
18. Unwillingness to avoid household contacts ≤15 months old or household contact with known immunodeficiency 1 week after treatment.
19. Allergy to measles vaccine or history of severe reaction to prior measles vaccination.
20. Allergy to iodine. Note: This does not include reactions to intravenous contrast materials.</td></tr>
<tr><td>Duration of study participation</td><td>Duration of screening: up to 21 days.

Duration of treatment: Treatment with MV-NIS once only on day 1 and treatment with atezolizumab until progression, intolerability or withdrawal of consent. See Table 1 for the schedule of visits and assessments. All treatment decisions regarding continuation of therapy will be made based on modified irRECIST V 1.1 criteria and irRC.

Duration of follow-up: 30 days' safety follow up after stopping study drugs for progressive disease (PD) or until PD if study drugs are discontinued for safety reasons.</td></tr>
<tr><td>Safety assessments</td><td>The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03) will be used for grading toxicities. Safety assessments will include adverse events (AEs), serious adverse events (SAEs), physical examinations (PEs), vital sign measurements, clinical safety laboratory evaluations per Table 2 (hematology, serum chemistry, coagulation and urinalysis), measles virus immunity, assessment of viral shedding and assessments of viremia. Diagnosis of measles in this trial is based on the CDC definition of clinical measles. Patients who develop a clinical measles infection will be removed from the trial and followed up until resolution of all symptoms.

DLT will be defined as an AE that is not pre-existing due to malignancy, attributed (definitely, probably, or possibly) to the MV-NIS, occurring within 36 days of MV-NIS administration and meeting the following criteria:
<table>
<tr><td>Hematologic:</td><td>≥ grade 3 as per NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03 except grade 3 ANC lasting <72 hours.</td></tr>
<tr><td>Renal:</td><td>Serum creatinine ≥2 times baseline.</td></tr>
<tr><td>Viremia:</td><td>Lasting for ≥ 4 weeks after intratumoral injection.</td></tr>
<tr><td>Clinical measles:</td><td>Any grade per CDC definition (http://www.cdc.gov/measles/hcp/index.html)</td></tr>
<tr><td>Other non-hematologic, including:
• Allergic reactions
• Autoimmune toxicity
• Organ toxicity</td><td>≥ grade 3 AE as per NCI CTCAE v4.03.</td></tr>
</table>
AEs meeting these definitions but related only to atezolizumab will not be considered a DLT.</td></tr>
</table>

	The AE reporting period for a patient enrolled in the study begins when the patient provides informed consent and is continued through 30 days after the last dose of study drug (MV-NIS or atezolizumab). All AEs that occur in enrolled patients during screening and study drug treatment must be recorded in the case report forms (CRFs), regardless of the relationship of the AE to study drug. All SAEs occurring between informed consent and through the 30-day follow-up period after last study drug administration should be reported to Vyriad regardless of relationship to study drug. All related AEs ongoing at discontinuation of study drug should be reported until resolution or stabilization. Any known untoward event that occurs beyond the AE reporting period that the investigator assesses as possibly related to MV-NIS should also be reported to Vyriad. Vital sign measurements, including sitting blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study.
PK evaluation	The *in vivo* distribution of MV-NIS infected cells and the kinetics of virus spread and elimination will be monitored by SPECT/CT imaging. SPECT/CT imaging will be performed prior to registration, 7 days after MV-NIS administration and 15 days after MV-NIS administration if previous scan is positive.
PD evaluation	Tissue analysis for MV-NIS: Tumor biopsy is to be performed by radiologist post virus injection according to Table 1. Samples will be stored in: a. RNAlater® for quantitative RT-PCR for MV-NIS RNA to determine copy numbers of virus/µg cellular RNA and RNASeq® b. frozen sections for exome analysis c. formalin-fixed paraffin embedded (FFPE) for pathology analysis (H&E and immune marker IHC). Tissue analysis for tumor microenvironment: Tumor biopsy FFPE slides will be stained for immune markers including but not limited to CD3, CD4, CD8, CD14, CD20, and PD-L1. Assessment of neoantigens and tumor-specific immune response: whole exome sequencing and RNA sequencing will be performed from normal tissue (PBMCs) and tumor biopsy samples obtained before and ~2 weeks after MV-NIS injection. Detailed bioinformatics analysis will be undertaken to determine mutational/antigen profiles. Identification of candidate 9-10 amino acid peptides containing mutations predicted to bind with high affinity to patients' MHC Class I molecules will be done by using the Immune Epitope Database prediction algorithm. Chosen peptides will be synthesized and used to prepare MHC fluorescent tetramers for their use for flow cytometry of patient peripheral T cells and/or TILs to determine frequency of tumor specific T cells pre and post therapy. In addition, functional assays of T cells will be performed by IFN-gamma release assays.
Efficacy	RECIST v1.1 will be used to assess anti-tumor efficacy for the secondary efficacy endpoint. An exploratory analysis using irRECIST will also be performed. irRECIST will be used for defining progressive disease (PD) on study as follows to account for the possibility of pseudoprogression or tumor flare. Patients should be reevaluated for disease response every 9 weeks after cycle 1 (i.e. at end of cycles 4, 7, 10, etc). For clinically stable patients, if imaging shows PD, treatment may be continued and tumor assessment should be repeated ≥ 9 weeks later to confirm or refute PD. Clinically stable is defined by the following criteria:

	• Absence of signs and symptoms indicating disease progression • No decline in ECOG performance status • Absence of rapid progression of disease • Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention. In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions. Patients who are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the patient will be discontinued from study treatment as specified in the protocol, and the first radiographic evidence of PD should be the date of progression. If radiologic progression is not confirmed, then the patient should resume/continue study treatment and have their next scan according to the protocol-specified schedule. If progression is not confirmed and the patient continues on treatment, the next scan that documents disease progression (and is confirmed by a second scan at least 4 weeks later), will be considered the date of disease progression. If a patient with confirmed radiographic progression (i.e., 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the sponsor. Clinically stable patients should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non- worsening PD) to continue study treatment. Imaging during the follow-up period is to be repeated every 12 weeks (± 7 days) for patients who discontinue study treatment for reasons other than disease progression until the end of the study.
Statistical methods	Statistics and sample size calculation This study will employ the standard "3+3" design for phase 1 clinical trials (Storer 1989; Simon 1997) and as such no formal statistical analysis is planned for the escalation part of the study. For the expansion cohort, the sample size calculation is based on a method proposed by Cancer Research UK for small oncology studies (Khan 2012). Based on data with atezolizumab in the unselected metastatic NSCLC population, the null hypothesis is set at an ORR of 20%, with the target ORR for the combination of 45%. With an α=0.043 and 80.29% power, at least 8 responses in 21 patients are needed to show success. Analysis populations Safety Population: The safety population consists of all patients who receive at least one dose of the study medication. All safety and tolerability evaluations will be based on this analysis set. PK/PD Population: The PK/PD population includes all patients without protocol deviations affecting interpretability of PK and/or PD. Efficacy Population: primary efficacy analyses will utilize the treated population at the MTD, meaning all patients who receive at least 1 dose of study drug at the MTD; an additional analysis will include all treated patients, which is identical to the Safety Population. Interim analysis One interim analysis is planned at the end of the escalation phase.

	General statistical considerations The data will be presented in table formats listing the mean, standard deviation, median, range and number of patients per dose level for continuous data, or listing count and percentages for categorical data as appropriate. Primary objective: determine MTD based on proportion of patents with DLTs The number and proportion (with 95% exact CI) of patients with DLTs is presented by dose for the escalation phase, the expansion phase and overall. DLT will be categorized per the headings in the DLT section (Hematologic, Renal, Viremia, Clinical Measles and other non-hematologic) and number and proportion (with 95% exact CI) of patients for each component is presented by dose for the escalation phase. Overall safety analysis The overall analysis of safety will be a comprehensive evaluation of AEs and/or toxicity, presented by dose and tumor type cohort and overall, based on: • DLTs • Recording of AEs by CTCAE V4.03 • Results of monitoring vital signs • Results of clinical chemistry, hematology, coagulation, and urine analysis tests • Changes in physical examination • Occurrence of late or cumulative AEs • Occurrence of autoimmune AEs • Need for concomitant medications. Results will be presented using descriptive statistics to display maximum toxicity grade for a given AE per patient by dose cohort, expansion cohort and overall. Non-hematologic toxicities will be evaluated via the ordinal CTCAE standard toxicity grading only. Hematologic toxicity and other safety lab value changes will be assessed using continuous variables as the outcome measures (primarily nadir/peak and percent change from baseline values) as well as categorization via CTCAE standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level and patient will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of the analysis of these variables. Secondary outcome measure/analyses Efficacy: ORR and DOR will be calculated for the expansion cohort and overall using both RECIST 1.1 and irRECIST 1.1. Both efficacy endpoints will be summarized by descriptive statistics including confidence intervals. The distribution of ORR and DOR will be displayed graphically. PFS is defined as the time from first dose of study drug until PD or death, whichever occurs first. PFS will be calculated for the expansion cohort and overall, using both RECIST and irRECIST, as above. Simple summary statistics will be supplemented by Kaplan-Meier survival estimates and

	related confidence intervals. Patients lost to follow-up or starting a new therapy without PD will be censored for time to event analyses at their most recent disease assessment. Pharmacokinetic and Pharmacodynamic analysis Pharmacokinetic evaluation: Results of SPECT/CT imaging to determine infected cells and kinetics of virus spread and elimination will be summarized by dose and time by descriptive statistics and displayed graphically. Pharmacodynamic evaluation: tissue analysis for MV-NIS, tissue analysis for tumor micro environment and assessment of neoantigens and tumor specific immune response will be summarized by dose and time by descriptive statistics and displayed graphically. Exploratory outcome measure/analyses (analysis will be detailed in the SAP) Data will be gathered for a number of laboratory correlative variables for each patient. Descriptive statistics and simple scatter plots will form the basis of presentation of these data. Correlations between these laboratory values and other outcome measures will be carried out by standard parametric and nonparametric correlation procedures (Pearson's and Spearman's coefficients). Prerequisite normality testing of these data will be carried out via standard Shapiro-Wilk testing (Shapiro and Wilk 1965). Where patterns of correlation are indicated, ordinary and partial correlation coefficients (controlling for dose levels) will be calculated. Inferential testing for significant shifts in the correlative laboratory data results across dose levels will be carried out only as a hypothesis- generating exercise. The small cell size will mean, for example, that only a shift of 1.5 standard deviations in the sample means can be detected via a one-sided Wilcoxon procedure with a 5% type I error rate. In all such situations, confidence intervals will be presented as the primary method of analysis. Hence, such hypothesis testing will only be used as exploratory for directing further research. Ancillary timed endpoints/analysis: exploratory analysis may be carried out on time-related variables MV-NIS cohorts including time until any treatment related toxicity, time until treatment related grade 3+ toxicity and time until hematologic nadirs (WBC, ANC, platelets). Simple summary statistics will be supplemented by Kaplan-Meier survival estimates and related confidence intervals (Pepe and Fleming 1991; Lee 1992). The effect of dose and ancillary dichotomized covariates such as age will be explored using log rank testing involving one covariate at a time. Again, the small sample size restricts the generalizability of such testing, but the results will provide preliminary indication for future research in subsequent phase 2 trials.

Table 1: Study Assessments - MV-NIS then Atezolizumab – Dose Escalation and Expansion Cohorts

Tests and Procedures	≤21 days prior to regist-ration	≤14 days prior to regist-ration	Day 1	Day 3 ± 1 day	Day 8 ± 1 day	Day 15 +1 or -3 days[9]	Day 36 ± 1 day (Cycle 2/ Day 1)	Day 1 of Each Subsequent 21 Day Cycle	Follow-up 30 days after last dose of atezolizumab
Informed Consent	X								
Inclusion/Exclusion criteria	X								
Demographics	X								
Height	X								
History and exam[1], weight, PS, vital signs	X				X	X	X	X	X
Hematology (see Table 2)		X			X		X	X	X
Coagulation (see Table 2)		X							X
Serum chemistry (see Table 2)		X			X		X	X	X
Urinalysis (dipstick) (see Table 2)		X			X		X	X	X
Pregnancy Test (see Table 2)[2]	X[2]								
Virology screen (HIV, HBV, HCV see Table 2)	X								
Measles virus immunity (serum anti-measles IgG)	X*						X		
Tumor Measurement per RECIST 1.1[3]	X						X	X[10]	X[11]
SPECT/CT	X*				X				
Treatment (MV-NIS intratumoral injection)			X						
Treatment (Atezolizumab IV infusion)[4]						X	X	X[4]	
Concomitant medications	X→	X→	X→	X→	X	X→	X→	X	X→
AE assessment	X→	X→	X→	X→	X	X→	X→	X	X→
Tumor biopsy[5]	X*					X	X		
Viral shedding: mouth swab/ urine collection[6]	X*					X			
Blood: Paxgene Viremia[7]	X*			X		X	X		
Blood for exploratory analysis [8]	X*					X	X		

* To be performed after registration but prior to study agent being given on Day 1.

1. Targeted physical exam only after baseline/screening.
2. For women of childbearing potential only. Must be done ≤ 7 days prior to registration.
3. Tumor assessments should be performed per RECIST 1.1, including confirmation of response at least 4 weeks later. irRECIST should be used for continuation of treatment decision in case of clinical stability with potential pseudoprogression/flare.
4. Atezolizumab will be administered every 3 weeks according to the approved US PI (Tecentriq 2016).
5. Biopsies to be obtained by radiologist under CT guidance. Pre-treatment biopsy will be of lesion planned for MV-NIS injection. Biopsy 12-15 days post-MV-NIS injection will be after SPECT/CT imaging but before atezolizumab administration and include 6 core biopsies of the MV-NIS-injected lesion and 6 core biopsies of an uninjected lesion (if feasible). See lab manual for further details and prioritization of processing in the case of insufficient material. Biopsies of injected lesion and an uninjected lesion may be repeated at day 36 (+/- 5 days) if feasible. Biopsies for a) paraffin sections, b) exome and RNA sequencing, c) infectious virus recovery,
   d) qRT-PCR for viral RNA. Exome sequencing only at baseline. See lab manual for details on processing and collection.
6. Mouth swab and urine collection for shedding studies by infectious virus recovery. See lab manual for details on processing and collection.
7. Assessment of viremia: Collect 2.5 ml blood into PAXgene tube (2 tubes). Perform at day 3, 15 and 36 (if day 15 is positive). If at day 36, there is 10-fold increase in MV-NIS/mcg of RNA, repeat tests will be performed within 2 days to confirm the result. Weekly testing will be done thereafter until resolution to baseline. See lab manual for details.
8. Research blood for a) immune phenotyping by flow cytometry, b) PBMC for exome and RNA sequencing, c) T cell analysis for neoantigen and tetramer assays. Exome sequencing done only at baseline. See lab manual for processing and collection.
9. Day 15 visit may be split into 2 visits to permit flexibility in biopsy timing and recovery prior to atezolizumab treatment as follows: Day 12-15 SPECT/CT, viral shedding, viremia, research blood for flow cytometry, PBMCs for sequencing and T cell assay must be performed PRIOR to tumor biopsy; Day 15-16 physical exam, history, vitals, PS and atezolizumab administration.
10. After Cycle 1, tumor measurements per RECIST 1.1 will be conducted every 3 cycles (i.e. cycles 4, 7, 10 etc.) until PD. For patients whose disease progresses, immune-related response criteria may be used by the investigator to continue therapy in the presence of potential pseudoprogression or tumor flare with clinical stability as appropriate until PD is confirmed.
11. Patients who discontinue atezolizumab for reasons other than disease progression will continue to have tumor evaluations every 12 weeks per standard of care until PD.

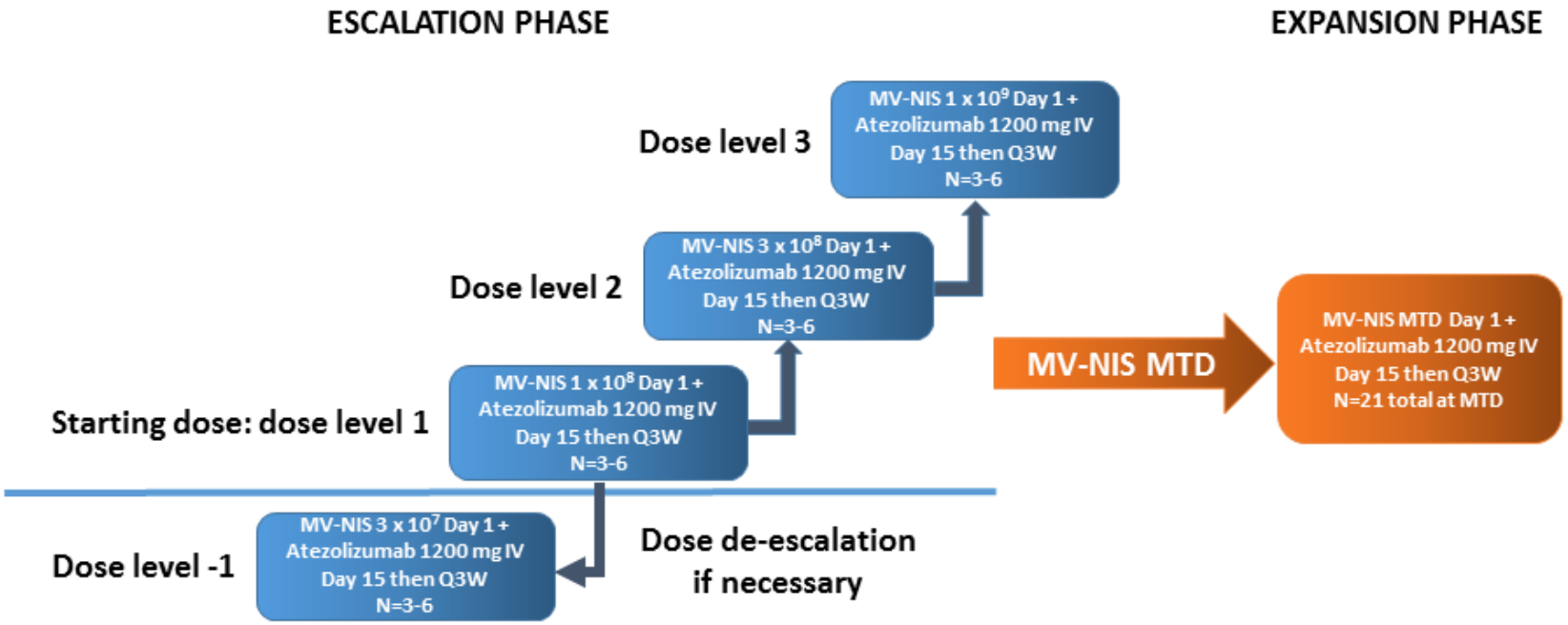
Table 2: Clinical Safety Laboratory Panels[1]

Hematology	Serum Chemistry	Urinalysis (dipstick)
• WBC with differential (including neutrophils, basophils, eosinophils, lymphocytes, monocytes) • hemoglobin • hematocrit • platelet count • MCV	• albumin • amylase • alkaline phosphatase • ALT • AST • bicarbonate • BUN • calcium • chloride • creatinine • GGT • glucose (random) • magnesium • phosphorous • potassium • sodium • total bilirubin • total protein • TSH	• appearance • color • pH • specific gravity • ketones • leukocytes • protein • glucose • bilirubin • urobilinogen • occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Coagulation		
• PT • INR • APTT		
Serum pregnancy test (women of childbearing potential)		**Virology screen**
• βHCG		• HIV 1 and 2 antigen/antibody combination immunoassay • HBV surface antigen • HCV RNA testing

WBC = white blood cell count; PT = prothrombin time; INR = international normalized ratio; APTT = activated partial thromboplastin time; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; MCV = mean corpuscular volume; TSH = thyroid stimulating hormone; βHCG= β human chorionic gonadotropin; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus

1. In the case of grade 3-4 laboratory abnormalities, and any clinically significant lab findings which potentially meet the definition of DLT, repeat tests must be performed every 1-2 days in order to verify duration accurately and observe recovery.

Figure 1: Overview of Study Design



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LIST OF ABBREVIATIONS

AE	adverse event(s)
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CMO	chief medical officer
CNS	central nervous system
CR	complete response
CRA	clinical research associate (monitor)
CRF	case report form
CRO	clinical research organization
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DET	dose escalation teleconference
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	good clinical practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HgB	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
^{123}I	iodine-123
ICF	informed consent form
ICH	International Conference on Harmonization
IFN	interferon
INR	International Normalized Ratio
IRB	Institutional Review Board
irRC	immune-related response criteria
irRECIST	adaptation of RECIST for immune oncology
IT	intra-tumoral
IV	intravenous
mAbs	monoclonal antibody(ies)
MHC	major histocompatibility complex
MTD	maximum tolerated dose

MV	measles virus
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NIS	human thyroidal sodium iodide symporter
NSCLC	non-small cell lung cancer
ORR	objective response rate
PD	progressive disease; pharmacodynamic(s)
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PE	physical exam
PET-CT	positron emission tomography
PFS	progression free survival
PI	principal investigator
PK	pharmacokinetic(s)
PPD	purified protein derivative
PS	performance status
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SOP	standard operating procedure
SPECT-CT	single photon emission computed tomography
SUSAR	suspected unexpected serious adverse reaction
^{99m}Tc	technetium-99m
$TCID_{50}$	median tissue culture infective dose
TIL	tumor-infiltrating lymphocyte
ULN	upper limit of normal
USPI	United States prescribing information

5. BACKGROUND AND RATIONALE

5.1. MV-NIS

Vyriad is developing the investigational medicinal product MV-NIS, which is an oncolytic measles virus (MV). The MV is a spherical, enveloped, negative-strand RNA virus that is antigenically monotypic with only one serotype, and is being developed for the treatment of oncological conditions.

MV-NIS is a recombinant, replicating, measles virus strain derived from the highly attenuated Edmonston strain of measles vaccine, MVEdmtag (Dingli 2004). The MVEdmtag strain incorporates two acquired mutations in the viral P gene encoding the V-protein, which prevents the MV mediated inhibition of the target cell type I interferon response (Dingli 2004; Ohno 2004). Among the surface proteins, the H-protein is critical to facilitate attachment of the measles virus to the receptors, CD46, SLAM and nectin-4 (Dorig 1993; Tatsuo 2000; Nielsen 2001; Noyce 2011). The other membrane protein, F-protein allows not only for cell fusion once MV attaches to the cell but also fusion with uninfected neighboring cells. The NIS gene encodes for the human thyroid sodium iodine symporter and was cloned into the MVEdmtag strain to improve non-invasive monitoring of the location and proportion of infected cells (Dai 1996; Dingli 2004). The NIS gene was cloned downstream of the hemagglutinin (H) gene (Dingli 2004). Expressed NIS actively imports iodide into cells, with sodium gradients driving cellular uptake. Expression of the NIS gene can be used as an imaging transgene to monitor viral infection. This allows use of gamma camera, single photon emission computed tomography (SPECT), or positron emission tomography–CT (PET-CT) for *in vivo* monitoring of viral replication following administration of ^{123}I or ^{99m}Tc isotopes.

5.1.1. MV-NIS Nonclinical Toxicology

MV-NIS nonclinical toxicology has been characterized in multiple species using a variety of dosing regimens. Details are provided in the current version of the Investigator's Brochure.

5.1.2. Clinical Experience with MV-NIS

The safety of MV-NIS as a monotherapy has been demonstrated in numerous clinical trials. Moreover, several patients have experienced a disease response or stabilization. Preliminary studies of immune responses in patients receiving MV-NIS therapy suggest some patients develop T cell responses to measles antigens and known tumor antigens suggesting that in addition to the tumor cell death elicited by viral mediated oncolysis, MV-NIS promotes the generation of systemic antitumoral immune responses. Details are provided in the current version of the Investigator's Brochure.

5.2. Safety Profile of MV-NIS

To date, 16 patients have received intraperitoneal MV-NIS at doses of 10^8 or 10^9 $TCID_{50}$ and 45 patients have received IV MV-NIS at doses of 10^6 to 10^{11} $TCID_{50}$. Twelve patients have received MV-NIS intrapleurally at doses from 10^8 to $9x10^9$ $TCID_{50}$. The highest dose levels in all three routes of administration were recommended for further study. Six patients have received MV-NIS 10^8 $TCID_{50}$ intratumorally with one DLT.

The most common related AEs (>1 patient) with intraperitoneal administration were all grade 1 and 2, in order of descending frequency: abdominal pain (50%), fatigue (37.5%), fever, neutropenia, leukopenia and flatulence (all at 19%), nausea, diarrhea and abdominal distension (all at 12.5%). There were no DLTs.

In the IV study, related grade 1-2 AEs seen in at least 5 patients were: nausea (n=10); chills and leukopenia (each n=8); fever (n=6); and diarrhea and neutropenia, (each n=5). Grade 3-4 AEs deemed at least possibly related to protocol therapy were: neutropenia (n=10); thrombocytopenia (n=5); anemia (n=2); and lymphopenia (n=1). One patient treated with cyclophosphamide and $TCID_{50}$ 9x107 had a grade 3 left ventricular failure possibly related to therapy. One grade 4 neutropenia was considered a DLT at the highest dose level (10^{11} $TCID_{50}$).

With intratumoral administration the only toxicities observed in more than one patient were anorexia, fatigue (both 33%) and lymphopenia (50%). There was 1/6 DLTs (grade 3 oral cavity fistula in non-injected tumor).

With intrapleural administration the most frequent toxicities were hematological including anemia, thrombocytopenia, leukopenia and neutropenia. There were no DLTs reported.

The Investigator's Brochure contains a summary of all MV-NIS-related AEs reported to date across the clinical trials, irrespective of route of administration.

5.3. Rationale

5.3.1. Study Rationale

The therapeutic efficacy of transgenic, vaccine strain-MV has been demonstrated using both *in vitro* and *in vivo* models of various solid tumors and hematologic malignancies. Pre-clinical data is available for hematologic and solid malignancies including, but not limited to, ovarian cancer (Peng 2002; Hasegawa 2006), glioblastoma multiforme (Phuong 2003), breast cancer (McDonald 2006), multiple myeloma (Peng 2001; Dingli 2004), lymphoma (Grote 2001), hepatocellular carcinoma (Blechacz 2006), prostate cancer (Msaouel 2009b), and mesothelioma (Li 2010).

Programmed cell death-1 (PD-1) and programmed death ligand-1 (PD-L1) are two of the many immunologic checkpoints that regulate the immune response with clinically available mAbs for the treatment of advanced cancers, including non-small cell lung cancer (NSCLC). Currently, two anti-PD-1 antibodies, nivolumab and pembrolizumab, and one anti-PD-L1 antibody, atezolizumab, are FDA approved in advanced or metastatic NSCLC. Checkpoint blockade with PD-(L)1 inhibitors is one of the most promising forms of cancer immunotherapy that improves the capacity of the immune system to acknowledge and delete tumors. While a subset of advanced NSCLC patients benefits from PD-(L)1 blockade, unfortunately a majority of patients do not respond to single agent checkpoint inhibition. Therefore, new therapeutic approaches that expand the available endogenous anti- tumor T cell repertoire or increase the tumor cell antigenicity for T cell recognition are rational therapeutic agents to be combined with checkpoint inhibition. Available clinical trial data shows that oncolytic therapy with MV-NIS is well tolerated, and several patients have experienced a disease response or stabilization. Preliminary studies of immune responses in patients receiving MV-NIS therapy suggest some patients develop improved T cell responses to measles antigens and known tumor antigens. In conclusion, our preclinical data utilizing NSCLC cell lines, multiple published preclinical reports on the

successful combination of oncolytic viral therapy and PD-1/PD-L1 axis blockade, acceptable safety and toxicity data from available clinical trials, and preliminary immune response data from patients receiving MV- NIS, support the combination of intra-tumoral MV-NIS with PD-L1 blockade in a clinical trial setting for patients with advanced NSCLC.

Study VYR-MV1-101 is a Phase 1 study designed to determine the maximum tolerated dose (MTD) and toxicity of attenuated MV-NIS virus combined with atezolizumab in patients with recurrent and metastatic NSCLC. The study will further evaluate safety, clinical and immune responses in an expansion cohort of 18 additional patients with NSCLC.

5.3.2. Rationale for Dosage Selection

Routes of administration relevant for this protocol in terms of determining an appropriate starting dose include intratumoral, intraperitoneal and intrapleural routes. Studies have been conducted at pleural doses up to $9x10^9$, peritoneal doses up to 10^{11} and IT doses up to 10^8 $TCID_{50}$ with no MTD reached to date.

Taking a conservative approach, the lowest of these doses already used in the clinic is proposed as the starting dose for this study.

6. STUDY OBJECTIVES

6.1. Primary Objectives

- To determine the MTD of the intra-tumoral administration of an Edmonston strain MV genetically engineered to produce NIS, in combination with the PD-L1 inhibitor atezolizumab in patients with recurrent and metastatic NSCLC.

6.2. Secondary Objectives

- To describe the safety and toxicity of the intra-tumoral administration of MV-NIS with atezolizumab.
- To assess preliminary antitumor efficacy by following:
  - radiographic objective response rate (ORR)
  - duration of response (DOR)
  - progression-free survival (PFS)

  … in the injected lesion, non-injected lesions and overall, per RECIST 1.1.

6.3. Exploratory objectives

- To determine the time-course of viral infection, dissemination, and elimination through the measurement of NIS gene expression using SPECT/CT imaging.
- To assess viremia, viral replication, and viral shedding/persistence following intra-tumoral administration of MV-NIS and immunotherapy.
- To obtain preliminary data regarding the antitumor efficacy by serial measurements of radioiodine uptake by SPECT/CT, radiological ORR, DOR and PFS and to correlate with PD-L1 expression and other immune biomarkers.
- To characterize the peripheral blood immune phenotype, presence and peripheral blood repertoire representation of neoantigen-specific T cells, and cell-free DNA of patients at potential immunologic transition points including study enrollment, therapy initiation, during therapy, and at follow-up.
- To evaluate if therapy with MV-NIS, atezolizumab, or both alters the peripheral blood immune phenotype, presence and peripheral blood repertoire representation of neoantigen-specific T cells, or cell-free DNA.
- To characterize the tumor microenvironment by immunohistochemistry (IHC) for PD-L1 and other immune markers of interest on tissue prior to and at the completion of MV-NIS injection and following atezolizumab treatment.
- To evaluate if MV-NIS alter the pretreatment tumor microenvironment levels of PD-L1 or immune markers after therapy in the lesion injected with MV-NIS.
- To determine if lesions not injected with MV-NIS express comparable levels of PD-L1 or contain an immune marker milieu within the tumor microenvironment similar to the lesion injected with MV-NIS after treatment with MV-NIS and atezolizumab.

- To assess if changes to the circulating or tumor microenvironment immune biomarkers associate with clinical response.
- To evaluate the tumor genomic mutational burden by whole exome sequencing, level of neoantigen expression and signal transduction pathways by RNAseq prior to and after therapy with MV-NIS and atezolizumab.
- To determine if changes to the tumor genomic mutational burden, level of neoantigen expression or alterations in signal transduction pathways are associated with clinical response
- To assess the secondary efficacy parameters (ORR, DOR and PFS) using irRECIST in addition to classical RECIST 1.1.
- To compare PFS of the combination of MV-NIS and atezolizumab in patients with recurrent and metastatic NSCLC versus historical controls
- To evaluate if the combination of intra-tumoral MV-NIS and atezolizumab results in improved ORR and DOR when compared to historical controls of patients treated with atezolizumab as a single agent.

7. INVESTIGATIONAL PLAN

7.1. Overview of Study Design

This is a phase 1, dose escalation study of the combination of intra-tumoral MV-NIS and systemic atezolizumab in patients with recurrent and metastatic NSCLC. After the dose escalation phase of the trial, a dose expansion cohort will further investigate safety, clinical and immune responses at the MTD. Figure 1 shows the study design. The study will involve 9-24 patients in the escalation phase and 15-18 in the expansion cohort, to provide a total cohort of 21 patients for efficacy evaluation at the MTD.

7.1.1. Dose escalation

MV-NIS will be administered once intra-tumorally, to a single tumor, with a 21-gauge needle, Quadrafuse®, or other suitable needle using ultrasound or CT guidance on day 1 of treatment in 3 escalating dose cohorts, starting at dose level 1 (Table 3).

Table 3: MV-NIS Dose Levels

Dose Level	Number of viruses
-1	3×10^7
1	1×10^8
2	3×10^8
3	1×10^9

Atezolizumab will be given per the US prescribing information (Tecentriq® USPI 2016) at 1200 mg IV on day 15 and then every 3 weeks thereafter until progression of disease, discontinuation due to toxicity, or withdrawal of consent.

7.1.1.1. DLT definition

DLT will be defined as an AE that is not pre-existing due to malignancy, attributed (definitely, probably, or possibly) to the MV-NIS, occurring within 36 days of MV-NIS administration and meeting the following criteria:

Hematologic:	≥ grade 3 as per NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03 except grade 3 ANC lasting < 72 hours.
Renal:	Serum creatinine ≥2 times baseline.
Viremia:	Lasting for ≥ 4 weeks after intratumoral injection.
Clinical measles:	Any grade per CDC definition (http://www.cdc.gov/measles/hcp/index.html)
Other non-hematologic, including: • Allergic reactions • Autoimmune toxicity • Organ toxicity	≥ grade 3 AE as per NCI CTCAE v4.03.

Note: in the case of grade 3-4 laboratory abnormalities, and any other clinically significant lab findings which potentially meet the definition of DLT, repeat tests must be performed every 1-2 days in order to verify duration accurately and observe recovery.

AEs meeting these definitions but related only to atezolizumab will not be considered a DLT.

7.1.2. Conduct of escalation cohorts

A standard 3+3 design will be used for the dose escalation part of the study. Starting at dose level 1 (refer to Table 3), three patients will be treated per dose level. The first three patients treated at dose level 1 will be enrolled at least 24 hours apart. All patients will be observed for a DLT period of 36 days after MV-NIS administration (which is 3 weeks after atezolizumab) and the last patient in each cohort must have completed the DLT period prior to each dose escalation decision. Resolution of viremia in all patients at a dose level is required prior to dose escalation being allowed.

If a DLT is observed, 3 additional patients will be enrolled at that dose level. If 1/6 patients experiences DLT, escalation may proceed; if ≥2/6 patients experience DLT, the MV-NIS dose will be de-escalated and 3 further patients added at the previous dose level. Dose level -1 will only be explored if dose level 1 is not tolerated. Doses will not be escalated in any individual patient. Any patient who experiences a DLT will be taken off study drugs, but will be followed up for response and PFS.

If no DLTs are seen at any of the dose levels, then the MTD will be the maximum delivered dose (1×10^9). MTD will be defined as the highest safely administered dose at which no more than one out of six or 0/3 patients experience DLT.

The first 6 patients of the expansion cohort will be enrolled and observed for 36 days after the 6^{th} patient has received treatment prior to any additional patients being treated. If ≤1/6 DLT is observed then the remaining patients will be enrolled and treated sequentially, with no waiting period or limitation on simultaneous enrolment. If ≥2/6 patients in the expanded cohort experience a DLT, then the entire expansion cohort will be re-enrolled at the next lower dose level.

If a patient fails to complete the initial course of therapy (defined as study drug administration and four weeks of observation) for reasons other than adverse events or disease progression based on the day 36 CT-scan, then the patient will be regarded as non-evaluable for DLT and an additional patient will be treated at the current dose level. However, all AE information from patients who received any study treatment will be utilized in the analysis.

7.1.3. Expansion cohort

Once the MTD is established, an expansion cohort will further evaluate safety, clinical and immune responses, to give a total of 21 patients at the MTD of MV-NIS in combination with standard-dose atezolizumab: MV-NIS at the established MTD given by intra-tumoral injection on day 1 followed by atezolizumab at 1200 mg IV on day 15 and subsequently every 3 weeks.

7.1.4. Viral and safety monitoring

In both the escalation and expansion cohorts, the *in vivo* distribution of MV-NIS infected cells and the kinetics of virus spread and elimination will be monitored by SPECT/CT imaging.

Technetium-99m (^{99m}Tc) SPECT/CT imaging will be performed prior to registration, 7 days after MV- NIS administration and 15 days after MV-NIS administration if previous scan is positive.

A safety committee will be established to monitor and evaluate the safety of patients and to maintain oversight of study data and monitoring process. The board will consist of the Vyriad study team, the investigators and any other person the investigators consider necessary to assist with study decisions. The board will meet according to the Safety Committee Charter established at the beginning of the trial. The safety committee will also meet at unscheduled times according to clinical necessity. All SAEs will be reported to the safety committee within 3 working days after learning of the event.

If a suspected DLT occurs, a safety committee meeting will be held as rapidly as possible. In the meantime, dosing of the ongoing patients in that cohort will continue unless there is reason to suspect there is an unacceptable safety risk based on the nature and/or severity of the observed DLT.

The decision to dose escalate will be made collectively by the safety committee. Dose Escalation Teleconferences (DETs) will occur prior to dose escalation for subsequent cohorts. The cumulative safety experience, which includes data from the current and previous dose cohorts, will be discussed by the Sponsor and the Investigators.

Based on the data presented and ensuing discussion during the teleconference, decisions such as implementation of additional monitoring, continuation of enrollment, or dose adjustments will be made by those present. Minutes from each meeting will be taken and formal notification of recommendations and decisions will be communicated to all study sites by the Sponsor or designee after the meeting.

Should a patient develop measles, treatment with immune globulin will be administered 400 mg/kg/d for 3-5 days. Aerosolized Ribavirin (6 grams/day over 12-18 hours/day for 3 days, up to 7 days in length) can also be considered at the discretion of the treating physician for patients not responding to immune globulin.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03) will be used for grading toxicities. Safety assessments will include adverse events (AEs), serious adverse events (SAEs), vital sign measurements, ECOG status, clinical safety laboratory evaluations (hematology, serum chemistry, coagulation and urinalysis). In the case of grade 3-4 laboratory abnormalities, and any other clinically significant lab findings which potentially meet the definition of DLT, repeat tests must be performed every 1-2 days in order to verify duration accurately and observe recovery.

7.1.5. Efficacy and pharmacodynamics

Patients will be evaluated for efficacy (tumor response) according to RECIST 1.1 and irRECIST criteria.

PD assessments will include RT-PCR of MV-NIS. Mouth swabs and urine samples will also be collected for evaluation of viremia. Correlative blood sampling for biomarkers of immune response will be collected at key time points during the study. Pre and post (if feasible) treatment tumor tissue biopsies will be used for correlative research. Blood sampling for flow cytometry or functional immune cell analysis will be used to analyze peripheral blood immunocyte populations and to collect information on free DNA to measure change in tumor

levels in the blood.

7.2. Discussion of Study Design

An open-label single ascending dose escalation design is the standard design to define the safety, tolerability, and MTD of MV-NIS.

7.3. Conditions for Terminating the Study

Vyriad has the right to terminate the study at any time. In terminating the study, Vyriad and the investigator will ensure that adequate consideration is given to the protection of the patients' interests. Reasons for study discontinuation may include, but are not limited to the following:

- The incidence or severity of AEs in this or other studies evaluating MV-NIS indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Drug supply issues.
- Data recording is inaccurate or incomplete.
- Excessive patient self-withdrawal.
- Significant protocol deviations (e.g., violation of eligibility criteria, dosing errors, missing data for study endpoint analysis).

The following data and materials are required by Vyriad before a study can be considered to be complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study, including the follow-up period for all enrolled patients.
- Case Report Forms/Records. Electronic case report forms (eCRFs) will be used in this study. Records (including correction forms) for all enrolled patients will be properly completed by appropriate study personnel, and signed and dated by the principal investigator, as required.
- Principal investigator sign-off of all required CRF forms.
- Completed Drug Accountability Records, Drug Inventory Log, and Inventory of Returned Drug forms or documentation of destruction, as appropriate.
- Return of all unused study drug to Vyriad unless an alternate disposition method is agreed upon at study initiation by Vyriad and investigational site(s).
- Copies of protocol amendments and other documents, and IRB approval/notification, as applicable.
- A summary of the study prepared by the principal investigator (IRB summary closure letter is an acceptable equivalent).

8. STUDY POPULATION

8.1. Target Population

This study will be conducted in up to 24 patients with metastatic lung cancer, with histologic confirmation of the primary NSCLC histology and with at least one lesion amenable for intra-tumoral injection with MV-NIS.

Note: all eligibility criteria must be verified and submitted to the medical monitor to permit study registration. Day 1 may only occur after registration (at least 1 day and up to 7 days later).

8.2. Inclusion Criteria

Patients will be included if they meet the following criteria:

1. Age ≥ 18 years.
2. Diagnosis of metastatic lung cancer, with:
   a. Histologic confirmation of the primary NSCLC histology
   b. At least one lesion amenable for intra-tumoral injection of MV-NIS.
3. Patient meets the FDA-approved indication for atezolizumab treatment in NSCLC (Tecentriq® USPI 2016).
4. Patient may have more than one site of recurrence/metastatic disease but only one lesion will be injected that is ≥ 1 cm in size (if in the lung, the lesion must be ≥2 cm and adjacent to the pleura).
5. Measurable disease per RECIST 1.1.
6. ECOG Performance Status (PS) 0 or 1.
7. Ability to provide informed consent.
8. Willingness to comply with all required protocol procedures including providing biologic specimens, participating in the SPECT/CT imaging and returning to the clinical study site for follow up visits.
9. Life expectancy of more than 12 weeks (in the opinion of the enrolling investigator).
10. The following laboratory values obtained ≤ 14 days prior to registration.
    a. ANC ≥1500/mm^3
    b. Platelets ≥100,000/mm^3
    c. HgB >9.0 g/dL
    d. Total bilirubin ≤ institutional upper limit of normal (ULN)
    e. SGOT (AST) ≤2.5 x ULN
    f. Creatinine ≤1.5 x ULN
11. Must be willing to implement contraception throughout study and for the 8 weeks following last study drug administration.

8.3. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Patients with any other prior malignancy are not allowed except for the following:
    a. Adequately treated basal cell or squamous cell skin cancer
    b. In situ cervical cancer
    c. Adequately treated Stage I or II cancer from which the patient is currently in complete remission or other cancer from which the patient has been disease-free for 2 years.
2. Uncontrolled CNS metastases or treatment by neurosurgical resection, radiation or brain biopsy within 4 weeks prior to Day 1.
3. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
4. Any of the following prior therapies:
    a. Chemotherapy ≤ 3 weeks prior to registration;
    b. Biologic therapy ≤ 4 weeks prior to registration;
    c. Radiation therapy ≤ 3 weeks prior to registration;
    d. Investigational therapy ≤ 4 weeks prior to registration.
5. Failure to fully recover from acute, reversible effects defined as ≤ grade 1 CTCAE v.4.03 of prior systemic therapy regardless of interval since last treatment.
6. Other concurrent investigational therapy (utilized for a non-FDA-approved indication and in the context of a research investigation).
7. Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:
    a. Pregnant women
    b. Nursing women
    c. Men or women of childbearing potential who are unwilling to employ adequate contraception during treatment and 8 weeks following the completion of study drug treatment.
8. Patients with active, known or suspected autoimmune disease. Exceptions are vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
9. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immuno-suppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
10. History of organ transplantation.

11. Receiving therapeutic anticoagulation (warfarin, low molecular weight heparin, or other novel oral anticoagulants).
12. Requiring blood product support.
13. Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA), or human immunodeficiency virus (HIV1 or 2) indicating acute or chronic infection.
14. Active infection (any grade) ≤5 days prior to registration.
15. History of tuberculosis or history of Mantoux PPD positivity.
16. Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
17. Current exposure to household contacts ≤15 months old or household contact with known immunodeficiency.
18. Unwillingness to avoid household contacts ≤15 months old or household contact with known immunodeficiency 1 week after treatment.
19. Allergy to measles vaccine or history of severe reaction to prior measles vaccination.
20. Allergy to iodine. **Note:** This does not include reactions to intravenous contrast materials

8.4. Removal of Patients from Study

Withdrawal of a patient from the study means that no further study visits or procedures are performed and no further data are collected. Every reasonable effort will be made to keep the patient in the study; however, in the event that a patient is withdrawn from the study, every effort will be made by the investigator to complete and report the reasons for withdrawal as thoroughly as possible. The reason for termination must be clearly documented on the appropriate page of the CRF. Study withdrawal should include the final assessments, as required by the protocol and every effort should be made to perform the study follow-up procedures (e.g., laboratory tests, physical examination including an evaluation of toxicity/adverse events).

A termination CRF must be completed for all enrolled patients.

The patient may be withdrawn from the study for any of the following reasons.

- Voluntary withdrawal by patient
- Patient lost to follow-up
- Termination of the study by sponsor
- Patient death

If a patient dies, Vyriad will actively seek to determine the date and cause of death.

If there is an ongoing toxicity associated with MV-NIS, patients must be followed with appropriate medical management until resolution or stabilization.

A reasonable effort should be made to contact any patient who is lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. If a patient is unreachable by telephone after three (3) attempts, the minimum of a registered letter should be sent requesting that the patient make contact with the investigator.

8.5. Replacement of Patients in Study

A patient who discontinues from the trial during the active treatment for reasons other than AE/SAE, or disease progression can be replaced.

9. STUDY DRUG

9.1. MV-NIS

MV-NIS is a live, tissue culture adapted measles virus engineered to express the human thyroidal sodium iodide symporter (NIS). The virus was constructed by inserting the NIS gene (cDNA) into a full-length infectious molecular clone of an attenuated Edmonston lineage measles virus (MV-tag). This virus is not a vaccine. MV-NIS propagates on Vero cells with kinetics equivalent to the parental strain of virus. It propagates selectively in human cancer cells that it infects by binding preferentially to CD46, a membrane protein that is overexpressed in tumor cell lines.

The virus is directly cytopathic to tumor cells leading to the formation of multinucleated syncytia that die by apoptosis. MV-NIS infected tumor cells express NIS, a membrane ion channel that actively transports iodide into cells. Radioiodine uptake by cells expressing NIS provides the basis for in vivo radioiodine imaging that can reveal the profile of MV-NIS gene expression and the location of MV-NIS infected cells during virus spread and elimination.

9.1.1. Preparation and Storage

MV-NIS will be prepared at the Viral Vector Production Laboratory of the Department of Molecular Medicine and stored at ≤-65° C. The virus will be thawed and mixed with NS immediately prior to administration.

MV-NIS will be stored in an alarmed, temperature-monitored, secure freezer with restricted access. It will be required that the freezer be on a circuit equipped with a backup generator. MV-NIS will be stored in clearly-labeled vials within secondary packaging at or below -65° C with appropriate bio-hazard labeling (indicating the nature of the agent) on the freezer door and the door of the room.

The MV-NIS will be prepared under biosafety level 1 guidelines in pharmacy under the direction of an appropriately trained pharmacist. All surfaces must be cleaned with 70% isopropyl alcohol before and after use. All equipment not dedicated for the study use will be sterilized or cleaned using 10% bleach solution, followed by 70% isopropyl alcohol before subsequent use. Sterile normal saline will be used to dilute the investigational product. See study specific Pharmacy Manual for details.

9.1.2. Handling and Thawing

BSL-1 infection control policies should be utilized for preparation, transport, and disposal of the investigational product. Appropriate gowns, gloves, safety glasses with side shields or face shields should be worn at all times during handling.

Thawing should occur at room temperature with the vial(s) upright. Hot water baths should not be used. Thaw time at room temperature is approximately 10 minutes. After MV-NIS is thawed it must be stored on ice or refrigerated (2-8º C) until virus preparation begins. Injection should not occur until the virus is fully thawed. Injection should also not be performed if the virus formulation has been thawed for more than 2.5 hours. The study Pharmacy Manual contains detailed instructions on proper handling, thawing and preparation of MV-NIS for clinical administration.

9.1.3. Spills or Environmental Contamination

In the event of a spill, people in the immediate area will be alerted and other institutional personnel will be notified as required by institutional policies. The spill area will be contained by limiting non-essential traffic in the area and using barriers to prevent the flow of material beyond the local area. Personnel that are involved in the cleanup of the spill will wear gloves, gown, surgical/procedure mask and safety glasses with side shields. Aerosols will be allowed to settle before paper towels or lab diapers are placed carefully over the spill. Spills must be absorbed.

For best results, cover the spill area with paper towels and apply a 10% bleach solution (1:10 dilution of commercial chlorine bleach, e.g. Clorox). Start application from the outer perimeter and work inwards. Allow contact with bleach for 20-30 minutes. Fresh paper towels soaked in 10% bleach solution will then be used to wipe the spill area. Area should then be wiped down with paper towels soaked in a 70% ethanol solution to remove bleach that can corrode surfaces if not removed. All waste items will be disposed per institutional policies. Refer to local institutional guidelines for BSL-1 agents.

9.1.4. Randomization and Blinding

This is an open-label, non-randomized study.

9.1.5. MV-NIS Administration

Trial treatment with MV-NIS will be given by appropriately trained surgical and interventional radiology sub-investigators. The tumor will be injected with a 21-gauge needle for tumors 2 cm or smaller; or for larger tumors, the Quadrafuse® multiprong needle may be used to better distribute the virus, or needle type can be per the radiologist's discretion.

The assigned dose of MV-NIS will be diluted in 0.9% normal saline. Injected fluid volume will be based on Table 4 below. Intra-tumoral injection will be performed under ultrasound guidance if the tumor can be easily seen and accessed with ultrasound or else CT guided injection will be performed for the deeper, non-US visualized lesions. It will be up to the radiologist to determine if the lesion is safe to inject and biopsy.

Administration into sites including skin, soft tissue, nodal, or lung lesions are permitted. Criteria for administration are as follows (Table 4):

Table 4: Injection Site Size and Image Guidance Criteria

Injection site	Size criteria for injection[1]	Image guidance required
Skin	≥ 1 cm	Photographs pre-injection[2]
Soft tissue (not penetrating skin surface and not nodal)	≥ 1 cm	Ultrasound or CT
Nodal	≥ 1.5 cm[3]	Ultrasound or CT
Lung	≥ 2 cm	CT

1 – Measured in the longest dimension
2 – Photograph should include measuring tape documenting longest measurable dimension
3 -- Nodal measured 1.5 cm in the shortest dimension

Once the MV-NIS dose for the participant has been assigned, the virus will be thawed and diluted in normal saline immediately prior to administration (up to 30 minutes). The final volume is dependent on the dose level assigned.

The volume delivered to the tumor will be dependent on the size of the tumor nodule(s) and will be determined according to the following algorithm:

- Up to 0.5 mL for tumors of 1.0 to 1.5 cm longest dimension.
- Up to 1.0 mL for tumors of 1.5 to 2.5 cm longest dimension.
- Up to 2.0 mL for tumors of 2.5 to 5 cm longest dimension.
- Up to 4.0 mL for tumors >5 cm longest diameter

Once the trial treatment is thawed and diluted, administration will occur as follows (these are general guidelines, a more detailed description of the procedure will be provided to the study center):

1. The injection site will be cleaned with the use of an appropriate agent, such as chlorhexadine or betadine.
2. The area will be draped in a sterile fashion.
3. If felt to be necessary by the administering sub-investigator, the study participant will be given minimal sedation per routine standard of care.
4. Local anesthetic using 1% lidocaine may be used at the injection site if deemed necessary by the administering sub-investigator per routine standard of care. However, this should not be injected directly into the lesion. Adequate analgesia should be accomplished if the local anesthetic is injected around the lesion.
5. Using appropriate image guidance as outlined in Table 4, the administering sub-investigator will administer the MV-NIS via a 21-gauge needle or a Quadrafuse® needle (or per radiologist's discretion) into the pre-identified tumor site.
6. For visible lesions, the injection site may be pre-treated with a topical anesthetic agent. MV-NIS should be injected along multiple different, evenly spaced, tracks within the lesion in order to obtain as wide a dispersion as possible.
7. Injection of the viral product should occur slowly. If the tumor site is >2 cm in diameter, this may require multiple injections due to the amount of dissolved viral product. If multiple injections are required, these should be administered approximately 2 cm apart from the prior injection. Total time for the procedure is anticipated to take 30-60 minutes.
8. Post-procedure dressings should be applied per standard practice. The injection site will be swabbed with alcohol and covered with a dry occlusive dressing (an absorbent pad and an occlusive cover – e.g. Tegaderm® or Tegaderm® with absorbent pad).
9. Monitoring post-procedure should occur in the treating department or in the Post Anesthesia Care Unit (PACU) for about 2 hours after the procedure with vital signs checked per institutional standards.

9.1.6. Atezolizumab Administration

Atezolizumab will be given at 1200 mg IV every 3 weeks per Tecentriq® US Package Insert and will be continued until the progression of disease, discontinuation due to toxicity, or withdrawal of consent.

9.1.7. Dose Modifications and Delays for Toxicity Related to Study Drug

Since there is only one dose of MV-NIS administered per patient, there are no dose modifications or delays in this study for MV-NIS. If the patient experiences an acute injection or procedure related reaction the procedure should be abandoned and supportive care provided. If study drug administration is abandoned due to technical reasons not associated with an AE, the procedure may be reattempted at another time at the investigators discretion. Consult the medical monitor regarding reassessment of eligibility in such cases.

Dose modifications and delays for atezolizumab should be based on the approved Tecentriq® US Package Insert.

9.1.7.1. Study Drug Discontinuation

Discontinuation of a patient from study means that no further MV-NIS or atezolizumab will be administered but the remaining study visits or procedures are performed and follow-up data are collected.

A patient may be discontinued for any of the following reasons:

- Progression of disease (see Section 10)
- An AE requires permanent discontinuation of study drug
- Voluntary withdrawal by patient
- Protocol deviation
- Patient lost to follow-up
- Patient death
- Termination of study by sponsor.

Patients whose study drug is discontinued due to toxicity are to be followed until there is either:

- Resolution or stabilization to baseline or Grade 1
- The patient is lost to follow-up
- The event is otherwise explained.

9.1.8. Management of Adverse Events

9.1.8.1. Ancillary Treatment/Supportive Care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheal, analgesics,

and anti-emetics received from the first administration of study drugs until 30 days after the final study drug dose are to be recorded in the medical record.

Specific guidelines on AEs include the following: MV infection, acute injection reactions, nausea and fever.

9.1.8.2. MV Infection

Diagnosis of measles in any MV-NIS trial is based on the CDC definition of clinical measles and includes:

- a generalized rash lasting ≥3 days, and
- temperature ≥ 38.3°C (≥ 101°F), and
- cough, coryza, and conjunctivitis.

Should a patient develop measles, treatment with immune globulin will be administered 400 mg/kg/d for 3-5 days. Aerosolized Ribavirin (6 grams/day over 12-18 hours/day for 3 days, up to 7 days in length) can also be considered at the discretion of the treating physician for patients not responding to immune globulin.

Patients who develop measles must be removed from the trial and followed up to 15 years for evidence of persistent toxicity.

9.1.8.3. Acute Injection Reactions

It is anticipated that participants will experience a viral mediated injection reaction following the administration of the study treatment. This may include fevers, chills/rigors, and even anaphylactic type reactions. Treatment of these toxicities is dependent on the discretion of the principal investigator and sub investigators. Guidelines for treatment of each symptom are below in Table 5.

If observed in >1 patients, prophylactic measures will be implemented per institutional guidelines.

Table 5: Supportive Medications for Acute Injection Reactions

Drug/Agent	Dose	Route	Toxicity
Acetaminophen	650 mg	PO/PR	Febrile Reaction
Ibuprofen	400-600 mg	PO	Febrile Reaction
Diphenhydramine	25-50 mg	PO/IV	Allergic Reaction
Meperidine	50 mg	IV	Rigors
Methylprednisone	1 mg/kg	IV	Allergic reaction or anaphylaxis
Normal Saline	Determined by Investigator	IV	Anaphylaxis
Epinephrine	1 mg	SQ	Anaphylaxis

9.1.8.4. Antiemetics

Prophylactic administration of antiemetics prior to treatment will not be allowed at the start of the study; however, it is allowed after treatment should a patient develop nausea/vomiting associated with the treatment. Prophylactic antiemetics may be permitted by the safety committee at any time during the study if a significant proportion of patients experience nausea and vomiting.

Acceptable treatment options for nausea/vomiting include:

- Ondansetron 4-8 mg po q 8 hours as needed or 4 mg IV q 8 hours as needed;
- Granisetron 1 mg po q 12 hours as needed or 10 mcg/kg q 12 hours as needed;
- Prochlorperazine 5-10 mg po q 6-8 hours as needed, 25 mg rectally bid as needed, or 2.5-5 mg IV by slow infusion (5 mg/min) q 6 hours as needed;
- Lorazepam 0.5-2 mg po q 4-6 hours needed.
- Corticosteroids as antiemetics are not allowed.

9.1.8.5. Antipyretics

Acceptable treatment options for fever include acetaminophen 500 mg 1-2 tabs q 4-6 hours as needed up to 4 grams a day and NSAIDs, such as ibuprofen 400 mg q 4-6 hours as needed or naproxen 250-500 mg bid as needed.

9.2. Study Drug Accountability and Patient Treatment Compliance

The principal investigator is responsible for ensuring adequate accountability of all used and unused study drug. While the principal investigator may delegate components of drug accountability tasks to documented designee(s) (e.g., pharmacist), the ultimate responsibility for drug control and accountability resides with the investigator. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition) and the maintenance of patient dispensing records and returned study product documentation. Dispensing records will document quantities received from Vyriad and quantities dispensed to patients, including lot number, date dispensed, patient identification number, patient initials, and the initials of the person dispensing study drug. Reasons for deviation from the expected dispensing regimen also must be recorded.

Refer to the Pharmacy Manual for instructions on drug accountability, return and destruction.

9.3. Concomitant Medication and Treatment

Concomitant therapy includes any medication (e.g., prescription drugs, over–the–counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient 4 weeks prior to starting study treatment until End of Study visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). All therapy and/or medication administered to manage adverse events should be recorded on the adverse event eCRF.

No standard preventative medications will be given for supportive care. Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. If the

patient must use a concomitant medication during the study, it is the responsibility of the principal investigator to ensure that details regarding the medication are recorded on the CRF.

9.3.1. Prohibited therapy

Prohibited treatments include the following:

- Other investigational drugs
- Concurrent anti-cancer therapies such as chemotherapy, gene therapy, biologics, radiation therapy, or immunotherapy

If any of these therapies are needed, the patient will be considered to have evidence of progressive disease. This will lead to the patient's discontinuation from the study.

9.3.2. Additional Anti-Cancer Treatment and Radiotherapy

Patients should not receive additional therapeutic anti-cancer treatment until after PD has been documented on study and follow-up study assessments have been completed. If a patient requires additional anti-cancer treatment without radiological evidence of PD, the date of new treatment start will be considered the date of PD. If a patient stops study drug (atezolizumab) without evidence of PD, the patient will enter the Follow-up Period and followed every 3 months until PD.

9.3.3. Interaction of MV-NIS with Other Medications

Drug-drug interaction studies have not been conducted on MV-NIS.

10. EFFICACY ASSESSMENTS

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be utilized as per RECIST 1.1, CT is the preferred imaging technique in this study.

Tumor measurements for efficacy evaluation will be done 5 weeks (36 day visit) after IT injection of the study drug and then every 3 cycles (i.e. cycles 4, 7, 10 etc.) until PD thereafter. A radiological assessment of CR or PR requires confirmatory imaging at least 4 weeks after the initial assessment of response was observed.

If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment.

For patients whose disease progresses, immune-related response criteria per irRECIST may be used by the investigator to continue therapy in the presence of potential pseudoprogression or tumor flare with clinical stability as appropriate until PD is confirmed.

For clinically stable patients, if imaging shows PD, treatment may be continued at the discretion of the investigator and tumor assessment should be repeated ≥ 9 weeks later to confirm or refute PD.

Clinically stable is defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions. Patients who are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the patient will be discontinued from study treatment as specified in the protocol, and the first radiographic evidence of PD should be the date of progression. If radiologic progression is not confirmed, then the patient should resume/continue study treatment and have their next scan according to the protocol-specified schedule. If progression is not confirmed and the patient continues on treatment, the next scan that documents disease progression (and is confirmed by a second scan at least 4 weeks later), will be considered the date of disease progression.

If a patient with confirmed radiographic progression (i.e., 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the sponsor. Clinically stable patients should also have at the confirmatory scan no further increase in the target lesions, no

unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) to continue study treatment.

Imaging during the follow-up period is to be repeated every 12 weeks (± 7 days) for patients who discontinue study treatment for reasons other than disease progression until the end of the study.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, and lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and, in addition, should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm. All target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in

	the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	All other lesions (or sites of disease) are identified as non-target lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. Lymph nodes with short axis $\geq$ 10mm but < 15mm should be considered non-target lesions. Nodes that have a short axis < 10mm are considered non-pathological and are not recorded or followed.

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm. Tumor marker results must have normalized.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).
Stable Disease (SD):	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the patient also has measurable disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Table 6: Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall response	
CR	CR	No	CR	**CR:** disappearance of all target and non-target lesions, normalization of tumor marker level, and reduction in pathological lymph nodes short axis to <10 mm. **PR:** 30% decrease in the sum of diameters of the target lesions. **PD:** 20% increase in the sum of diameters of the target lesions.
CR	Non-CR / non-PD	No	PR	
CR	NE	No	PR	
PR	Non-PD or NE	No	PR	
SD	Non-PD or NE	No	SD	
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

If there is suspicion of disease progression based on clinical or laboratory findings before the scheduled assessment, an unscheduled assessment should be performed. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment.

11. SAFETY

11.1. Safety Parameters

The NCI-CTCAE; Version 4.03 will be used for grading toxicities unless otherwise specified. Patients will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data. Safety parameters to be measured/assessed include vital sign measurements, physical examinations, concomitant medications, hematology, serum chemistries, urinalysis, pregnancy testing, and ECOG performance status.

11.2. Adverse Event Definition

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs include:

- Suspected adverse drug reactions (abbreviated as either SADR or SAR). This may be serious or not serious.
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity.
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, ECG results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug.
- Other medical events, regardless of their relationship to the study drug, such as injury, surgery, accidents, extensions of symptoms, or apparently unrelated illnesses.

Findings existing prior to signing informed consent will be recorded as medical history. For the purpose of data collection, all untoward events that occur after informed consent through 30 days after last dose of study treatment are to be recorded on CRFs by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); when the condition that leads to the procedure is an AE.
- Pre-existing diseases, or conditions or laboratory abnormalities present or detected prior to the screening visit, those do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social, and/or convenience admissions).
- Overdose of the study drug or a concomitant medication without any signs or symptoms, unless the patient is hospitalized for observation.

11.3. Adverse Event/Serious Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record. Adverse events will then be reported on the Adverse Event eCRF as follows:

- After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). Any other adverse event should not be reported.
- After initiation of study drug, all adverse events/serious adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug.
- After a period of 30 days from the last dose of study drug, Investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug.

11.4. Evaluating Adverse Events

The investigator will determine the seriousness, intensity, and causality of an AE associated with the use of the study drug (i.e., events where there is a reasonable possibility that the event may have been caused by the study drug) based on the definitions that follow.

The adverse event severity grading scale for the NCI CTCAE (v4.03) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7: Severity Grading for non-CTCAE Listed Adverse Events

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living.[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living.[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

NCI CTCAE-National Cancer Institute Common Terminology Criteria for Adverse Events. Note: Based on the NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event per the definition of serious adverse event.

[d] Grade 4 and 5 events must be reported as serious adverse events per the definition of serious adverse event.

11.4.1. Serious Adverse Events

(Notify sponsor or designee within 24 hours of first awareness)

The SAE definition and reporting requirements are in accordance with the ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2A, with Title 21 Part CFR 312.32, and the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies.

SAE: An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- **Death:** This includes any death that occurs while the patient is "on study" as well as any death that occurs within 30 days after last dose of study drug administration.

  Note: Death is an outcome of an AE, and not an AE in itself. The event(s) that caused death (e.g., illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- **Life-threatening adverse event:** An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death).

- **Inpatient hospitalization or prolongation of existing hospitalization:** In the absence of an AE, the investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

  – Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol

  – Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center

  – Hospitalization for survey visits or annual physicals

In addition, a hospitalization planned before the start of the study for a pre-existing condition which has not worsened does not count as an SAE.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical event: An event that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Some serious events will not be reported as SAEs, including:

- Disease progression
- Death due to disease progression occurring more than 30 days after the last dose of study drugs

- Medical or surgical procedures when the condition that leads to the procedure is an AE
- Pre-existing diseases, or conditions or laboratory abnormalities present or detected prior to the screening visit, that do not worsen
- Situations for which an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

11.4.2. Suspected Unexpected Serious Adverse Reactions (SUSAR)

(Notify sponsor or designee within 24 hours of first awareness)

A suspected unexpected serious adverse reaction is any adverse drug event, the specificity or severity of which is not consistent with those noted in the current protocol and/or Investigator's Brochure (IB). This refers to any AE that has not been previously observed (e.g., included in the IB), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

11.4.3. Unexpected Adverse Events

An AE is considered "unexpected" if it is not listed in the Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application. Also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.4.4. Non-Serious Adverse Events

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

11.4.5. Protocol-Related Adverse Events

AEs that are not test drug related may nevertheless be considered by the investigator or the Medical Monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an event that occurs during a washout period or that is related to a procedure required by the protocol.

11.4.6. Relationships/Causality to Study Drug

The investigator will attempt to assess the relationship of the event to study drug using a 5- point scale (not related, unlikely-related, possibly related, probably related, or definitely related).

11.4.7. Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the patient's eCRF. The date of onset as well as the duration of the event also should be recorded. In addition, the method used to treat the AE and the outcome of the AE also will be noted. The investigator will assess the relationship of the event to study drug (not related, unlikely-related, possibly related, probably related, or definitely related).

11.4.8. Adverse Event Monitoring and Follow-up

The investigator will follow all patients who experience adverse events until there is a return to the patient's baseline condition, Grade 1 severity or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. Where a diagnosis is possible, it is preferable to report this diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis.

11.4.9. Laboratory Abnormalities

For the purposes of grading creatinine, the upper limit of normal – not the patient's baseline value - will be used to determine grade.

Non-Clinically Significant (NCS) Laboratory Abnormalities

All laboratory results must be filed in the patient's medical record and be monitored. The investigator must review laboratory results in a timely manner demonstrated by signature/date and assignment of clinical significance assessment. Non-clinically-significant laboratory abnormalities, i.e., minor deviations from the normal range, are expected and it is likely that no medical intervention will be required. Such results will not be considered to be AEs.

Clinically Significant (CS) Laboratory Abnormalities

Any grade 3-4 laboratory abnormality and any other lab abnormality that is considered to be clinically significant by the investigator will be recorded on the AE eCRF. A clinically significant abnormal test result will be considered an AE if:

- It is not associated with an already reported AE, diagnosis or pre-existing condition
- There is a change in concomitant medication or intervention as needed, in direct response to the laboratory result
- The investigator exercises his/her discretion to make significance determinations for any patient laboratory result or result that requires intervention

All such lab abnormalities will be repeated and assessed by the investigator as soon as possible for "seriousness" and if they meet the regulatory definition of "serious", they will be reported as SAEs following regulatory and protocol requirements. Repeat laboratory tests may be run in order to monitor the result. In the case of grade 3-4 laboratory abnormalities, and any other clinically significant lab findings which potentially meet the definition of DLT, repeat tests must be performed every 1-2 days in order to verify duration accurately and observe recovery.

Serious Laboratory Abnormalities

Any lab abnormality meeting the regulatory definition of "serious" must be recorded on both the AE eCRF/record and the SAE Form. If a patient experiences a serious toxicity or dies, the FDA will be notified within 24 hours, as required.

11.4.10. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the Medical History eCRF. A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it

is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”)

11.4.11. Lack of Efficacy or Worsening of NSCLC

Cancer events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

11.4.12. Pregnancy and Nursing Mothers

If a patient inadvertently becomes pregnant while on treatment with MV-NIS, the patient will immediately be removed from the treatment phase of the study. The site will contact the patient at least monthly and document the patient’s status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the study PI and/or study Project Manager within 24 hours. If the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) the study site will report the event within 2 working days to Vyriad. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported and followed as described above.

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them), including the pregnancy of a male patient's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients and female partners of male patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the study center and within 2 working days to Vyriad.

It is unknown whether MV-NIS is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

11.4.13. Serious Adverse Event Reporting

11.4.13.1. Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US Food and Drug Administration (FDA) as well as all other participating investigators of the event.

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies, the sponsor is required to submit written documentation, in the form of an IND safety report, detailing:

- Any event associated with the use of the drug, that is both serious and unexpected, or
- Any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug.

Written submission must be made by the sponsor to the FDA and the IRBs as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. Any unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor shall also inform all investigators.

11.4.13.2. Time-Frame for Reporting

Any death, pregnancy, or SAE experienced by a patient from the time of informed consent until 30 days after receiving the last dose of study drug, regardless of relationship to study drug, or any death that occurs more than 30 days after receiving study drug, and is believed to be study drug-related, must be promptly reported (within 24 hours of the investigator becoming aware of the event) by e-mail to the sponsor (or designee).

Email: pv-vyriad-mv1@bexonclinical.com.

In the event of an issue with the email, notify the sponsor via telephone at the number below. The investigator will be able to contact the safety Medical Monitor at all times:

Alice S Bexon, MD,
Chief Medical Officer
Tel: 617-417-7300

11.4.13.3. Information to be Provided by the Investigator

SAEs must be recorded on the SAE CRF page. This requirement includes all SAEs that occur after informed consent and through 30 days after last dose of study treatment, and in addition, any SAE that are assessed as possibly related to study treatment by the investigator, even if the SAE occurs more than 30 days after the last dose of study treatment.

The minimum information required for SAE reporting includes identity of investigator, site number, patient number, an event description, SAE term(s), onset date, the reason why the event is considered to be serious (i.e., the seriousness criteria) and the investigator's assessment of the relationship of the event to study treatment (not related, unlikely-related, possibly related,

probably related, or definitely related). Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded on the SAE form. Forms for reporting SAEs will be provided to the study sites.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by the Vyriad Drug Safety personnel or designee.

When reporting SAEs, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For example, dyspnea should not be used as an SAE term if the diagnosis which caused the dyspnea is known to be malignant pleural effusion. There is no requirement that the chosen SAE term be listed in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
  - Elective or previously scheduled surgery, e.g. a previously scheduled ventral hernia repair
  - Procedures for pre-existing conditions that have not worsened after initiation of treatment
  - Pre-specified study hospitalizations for observation
  - Events that result in hospital stays of less than 24 hours and that do not require admission, e.g. an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

11.4.14. Regulatory Reporting

Vyriad (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Vyriad will make a determination as to whether the criteria for expedited reporting have been met.

Vyriad (or designee) will submit SAEs that meet the criteria for expedited reporting to the Regulatory Authorities in accordance with local regulations governing safety reporting.

Reporting of SAEs by the investigator to his or her IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

11.4.15. Follow-up Information on a Serious Adverse Event

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has returned to baseline or is otherwise explained by the investigator.

Follow-up data concerning the SAE (e.g., diagnostic test reports, physician's summaries, etc.) also must be submitted to Vyriad, as they become available, by telefax or email transmission, until resolution of the SAE.

11.5. Other Safety Considerations

11.5.1. Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the Medical Monitor.

11.5.2. Follow-Up of Serious Adverse Events

Any SAE that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 30 days after last dose of study treatment must be followed until either resolution of the event or determination by the investigator that the event has returned to baseline/resolved, Grade 1 or has become stable. This follow-up guidance also applies to SAEs that occur *more than 30 days after last dose* of study treatment.

11.6. Safety Monitoring

Patients will be closely monitored for adverse events of interest through standard safety reporting as well as regular medical review of safety data outputs from both the clinical and pharmacovigilance databases. SAEs, including deaths, and withdrawals due to adverse events will also be closely monitored.

12. STUDY ASSESSMENTS AND PROCEDURES

Once Vyriad has confirmed a cohort slot availability, an informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. Screening assessments should be performed within 21 days before the IT dose of study drug is administered on Day 1. Study eligibility will be based on satisfying all of the study inclusion and exclusion criteria for each cohort.

Study Day 1 is defined as the date the study drug is administered via IT injection, with subsequent study days numbered sequentially thereafter.

If significant changes from baseline are noted during the course of the study, additional unscheduled clinic visits may be undertaken by the investigator, or requested by the sponsor, in order to determine both the relevance of the finding(s) and the duration of the event(s).

12.1. Procedures to be Performed

12.1.1. Informed Consent

The Investigator must obtain documented consent and HIPAA waiver from each potential patient prior to participating in a clinical trial. Adequate time must be allowed for the patient to ask questions and make a voluntary decision. Consent must be documented by the patient's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the patient before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB/ERC's approval/favorable opinion in advance of use. The patient should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sanford Research requirements.

No protocol-specific procedures, including screening procedures that are not standard of care procedures, are to be performed until the patient has signed and dated an IRB/IEC-approved ICF.

12.1.2. Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the patient qualifies for the trial. An enrollment form will be completed by the investigator and sent to Vyriad for review prior to enrollment being permitted.

12.1.3. Demographics and Height

Demographic data will include age, sex, and self-reported race/ethnicity. Height will be recorded at screening.

12.1.4. Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

12.1.5. Complete and Abbreviated Physical Examinations

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history.

For cycles that do not require a full physical exam per the Schedule of Assessments, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

Weight will be taken with each physical exam (complete or abbreviated).

12.1.6. Vital Sign Measurements

The investigator or qualified designee will take vital signs at screening, prior to the administration of the dose of trial treatment and at other specified time points per the Schedule of Assessments, after the patient has been sitting for 5 minutes. Vital signs should include temperature (Celsius/Fahrenheit), pulse (beats per minute), respiratory rate (breaths per minute), weight and blood pressure (mm Hg).

Please note that blood pressure measurements are to be performed using appropriate technique (per guidelines of the American Heart Association). Specifically, patients should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized. Record cuff size, arm used, and patient's position (if not seated).

12.1.7. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

The investigator or qualified designee will assess the patient's ECOG performance status (see Appendix 1) as specified in the Schedule of Assessments.

12.1.8. Hematology, Serum Chemistries, Coagulation and Urinalysis

Samples for laboratory assessments (hematology, serum chemistries, coagulation and urinalysis) are to be collected (see Table 2). Laboratory tests for screening should be performed within 14 days prior to treatment initiation. Blood samples for hematology, serum chemistry, coagulation and urinalysis will be prepared using standard procedures. Urinalysis will only be conducted as clinically indicated (see Table 2).

Abnormalities in clinical laboratory tests that lead to a change in patient management are considered clinically significant for the purposes of this study, and will be recorded on the AE CRF page. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated lab values) must be reported as an SAE (see Section 11.3). Furthermore, at screening, a blood sample will be analyzed for HIV and hepatitis B and C serology.

12.1.9. Pregnancy Test

Serum pregnancy tests are to be performed for females of childbearing potential within 7 days of study treatment.

12.1.10. Virology Screening

HIV, HPV and HCV virology will be performed at screening to ensure eligibility.

12.1.11. Assessment of Peripheral Immune Response to Viral Administration

Measles virus specific immunity will be measured by means of measuring anti-measles virus specific antibodies (IgG).

Assessments will be performed at screening and at the day 36 assessment.

12.1.12. Disease and Response Assessments

12.1.12.1. Baseline Tumor Imaging

Initial tumor imaging (diagnostic CT scan) must be performed within the 21-day screening period prior to enrollment to confirm measurable disease. Patient must have 2 identified target lesions, one for injecting and one as a control. Baseline imaging must be performed per RECIST 1.1. The baseline imaging scan should be reviewed by each individual site prior to enrollment to confirm measurable disease.

12.1.12.2. Tumor Imaging During Trial

Tumor imaging will occur on day 36 after MV-NIS injection. After Cycle 1, tumor measurements per RECIST 1.1 will be conducted every 3 cycles (i.e. cycles 4, 7, 10 etc.) until PD. For patients whose disease progresses, immune-related response criteria may be used by the investigator to continue therapy in the presence of potential pseudoprogression or tumor flare with clinical stability as appropriate until PD is confirmed.

12.1.13. Viral Bio-distribution Imaging (SPECT/CT)

Single-photon emission computerized tomography (SPECT/CT) is the scan that will be utilized to assess viral bio-distribution and elimination. SPECT/CT imaging will be performed after IV ^{99m}Tc administration (2 hours after 20 mCi) at baseline and day 8. If there is uptake in organs other than the thyroid, stomach, or salivary glands on day 8, an additional SPECT/CT imaging study will be performed on day 15 to document elimination of the virus and infected cells. If the SPECT/CT is positive on day 15 then follow up imaging will be performed on day 36 if the day 15 scan is positive.

12.1.14. MV-NIS Administration

Trial treatment with MV-NIS will be given by appropriately trained surgical and interventional radiology sub-investigators. MV-NIS will be administered IT in one single tumor location as agreed upon by the principal investigator and administering sub-investigator using a 21- or 22-gauge needle or Quadrafuse® needle (or per radiologist's discretion) on day 1. Refer to Section 9.1.5.

12.1.15. Atezolizumab IV Infusion

Atezolizumab will be administered starting on day 15 and then every 3 weeks thereafter.

12.1.16. Prior and Concomitant Medications

All concomitant medications will be recorded 4 weeks prior to signs the informed consent form through the 30 day follow-up period.

12.1.17. Adverse Event Assessments

Information regarding the occurrence of AEs and SAEs will be collected from the time the patient signs the informed consent form throughout their participation in the study, including the 30 days after the patient's last dose of study drug, unless a new treatment has been started. Any known untoward event that occurs beyond the AE reporting period that the investigator assesses as possibly related to study drug also should be reported to Vyriad.

Note: AEs resulting in a patient's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the sponsor.

12.1.18. Tumor Samples

All patients will have a mandatory core or excisional biopsy of lesion planned for MV-NIS injection (fine needle aspirate is not adequate) sent to a central lab for correlative research, performed retrospectively. This must be obtained within 21-day screening period before enrollment.

Post-treatment biopsy (12-15 days post-MV-NIS injection) will be after SPECT/CT imaging but before atezolizumab administration and include 6 core biopsies of the MV-NIS-injected lesion and 6 core biopsies of an uninjected lesion (if feasible). See the Lab Manual for further details and prioritization of processing in the case of insufficient material. Biopsies of injected lesion and an uninjected lesion may be repeated at day 36 (+/- 5 days) if feasible.

The Day 15 visit on the schedule of assessments (Table 1) may be split into 2 visits to permit flexibility in biopsy timing and recovery prior to atezolizumab treatment as follows: Day 12-15 the investigator may perform the biopsy, preceded by SPECT/CT, viral shedding, viremia, blood for flow cytometry, PBMCs for exosome and T cell tetramer assay; Day 15-16 perform the physical exam, history, vitals, PS and atezolizumab administration. Concomitant medications and AEs will be recorded at both time-points, as necessary.

12.1.19. Viral Shedding: Mouth Swab and Urine Specimens

Mouth swabs should be collected as described in the Lab Manual.

Patients will collect a mid-stream urine sample of 100 cc. Specimens will be collected at screening and on day 15.

If a patient is found to be shedding the virus in urine or mouth swab specimens(s), family members who do not have documentation of immunity, will be offered testing to assess anti-measles virus immunity by Enzyme Immunoassay (Diamedix, see section 3.18) and testing of mouth swab specimens(s) for the presence of MV-NIS. Measles vaccination will be offered to seronegative individuals, as per standard clinical practice.

12.1.20. Assessment of Viremia

Patient's peripheral blood will be monitored for evidence of measles virus viremia. This will be performed by quantitative RT-PCR.

Assessment of measles viremia will be performed at screening, day 3, 15 and 36 (if day 15 is positive). If at day 36, there is 10-fold increase in MV-NIS/mcg of RNA, repeat tests will be performed within 2 days to confirm the result. Weekly testing will be done thereafter until resolution to baseline.

12.1.21. Blood for Exploratory Analysis

The peripheral blood immune phenotype will be assayed by whole blood flow cytometry.

Whole blood collected will be separated by magnetic bead cell separation in CD4, CD8, CD20 and CD14 fractions. Leukocyte fractions will be stored at -≤68ºC for future epigenetic analysis. Additional whole blood collection and PBMC separation will be done for whole exome sequencing and RNA sequencing.

Blood will also be used for T-cell analysis for neoantigen and tetramer assays. Details of sample collection procedures are outlined in the Laboratory manual.

12.1.22. 30-Day Follow-up

The final mandatory 30-Day Follow-Up Visit should be conducted at approximately day 30 after the last dose of study drug with the CT imaging visit or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Follow-Up Visit should be recorded. Patients with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

Patients who discontinue trial procedures for a reason other than disease progression will move into survival follow up. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or end of study.

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

12.1.23. Unscheduled Visits

If additional visits are needed (e.g., for resolution of an adverse event), the following procedures and evaluations may be performed as needed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination, including weight
- Hematology, serum chemistry and urinalysis
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Tumor assessment
- AE assessment
- Concomitant medications

13. STATISTICAL CONSIDERATIONS

13.1. General Design

This study will employ the standard "3+3" design for phase 1 clinical trials (Storer 1989; Simon 1997) and as such no formal statistical analysis is planned for the escalation part of the study.

For the expansion cohort, the sample size calculation is based on a method proposed by Cancer Research UK for small oncology studies (Khan 2012). Based on data with atezolizumab in the unselected metastatic NSCLC population, the null hypothesis is set at an ORR of 20%, with the target ORR for the combination of 45%. With an α=0.043 and 80.29% power, at least 8 responses in 21 patients are needed to show success.

13.1.1. Analysis populations

Safety Population: The safety population consists of all patients who receive at least one dose of the study medication. All safety and tolerability evaluations will be based on this analysis set.

PK/PD Population: The PK/PD population includes all patients without protocol deviations affecting interpretability of PK and/or PD.

Efficacy Population: primary efficacy analyses will utilize the treated population at the MTD, meaning all patients who receive at least 1 dose of study drug at the MTD; an additional analysis will include all treated patients, which is identical to the Safety Population.

13.1.2. Interim analysis

One interim analysis is planned at the end of the escalation phase.

13.1.3. General statistical considerations

The data will be presented in table formats listing the mean, standard deviation, median, range and number of patients per dose level for continuous data, or listing count and percentages for categorical data as appropriate.

13.1.4. Primary objective: determine MTD based on proportion of patients with DLTs

The number and proportion (with 95% exact CI) of patients with DLTs is presented by dose for the escalation phase, the expansion phase and overall.

DLT will be categorized per the headings in the DLT section (hematologic, renal, viremia, clinical measles and other non-hematologic) and number and proportion (with 95% exact CI) of patients for each category is presented by dose for the escalation phase.

13.1.5. Overall safety analysis

The overall analysis of safety will be a comprehensive evaluation of AEs and/or toxicity, presented by dose and tumor type cohort and overall, based on:

- DLTs
- Recording of AEs by CTCAE V4.03
- Results of monitoring vital signs
- Results of clinical chemistry, hematology, coagulation, and urine analysis tests
- Changes in physical examination
- Occurrence of late or cumulative AEs
- Occurrence of autoimmune AEs
- Need for concomitant medications.

Results will be presented using descriptive statistics to display maximum toxicity grade for a given AE per patient by dose cohort, expansion cohort and overall.

Non-hematologic toxicities will be evaluated via the ordinal CTCAE standard toxicity grading only. Hematologic toxicity and other safety lab value changes will be assessed using continuous variables as the outcome measures (primarily nadir/peak and percent change from baseline values) as well as categorization via CTCAE standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level and patient will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of the analysis of these variables.

13.1.6. Secondary outcome measure/analyses

Efficacy: ORR and DOR will be calculated for the expansion cohort and overall using both RECIST 1.1 and irRECIST 1.1. Both efficacy endpoints will be summarized by descriptive statistics including confidence intervals. The distribution of ORR and DOR will be displayed graphically.

PFS is defined as the time from first dose of study drug until PD or death, whichever occurs first. PFS will be calculated for the expansion cohort and overall, using both RECIST and irRECIST, as above. Simple summary statistics will be supplemented by Kaplan-Meier survival estimates and related confidence intervals. Patients lost to follow-up or starting a new therapy without PD will be censored for time to event analyses at their most recent disease assessment.

13.1.7. Pharmacokinetic and Pharmacodynamic analysis

Pharmacokinetic evaluation: results of SPECT/CT imaging to determine infected cells and kinetics of virus spread and elimination will be summarized by dose and time by descriptive statistics and displayed graphically.

Pharmacodynamic evaluation: tissue analysis for MV-NIS, tissue analysis for tumor micro environment and assessment of neoantigens and tumor specific immune response will be summarized by dose and time by descriptive statistics and displayed graphically.

13.1.8. Exploratory outcome measure/analyses (analysis will be detailed in the SAP)

Data will be gathered for a number of laboratory correlative variables for each patient. Descriptive statistics and simple scatter plots will form the basis of presentation of these data. Correlations between these laboratory values and other outcome measures will be carried out by standard parametric and nonparametric correlation procedures (Pearson's and Spearman's coefficients). Prerequisite normality testing of these data will be carried out via standard Shapiro-Wilk testing (Shapiro and Wilk 1965).

Where patterns of correlation are indicated, ordinary and partial correlation coefficients (controlling for dose levels) will be calculated. Inferential testing for significant shifts in the correlative laboratory data results across dose levels will be carried out only as a hypothesis-generating exercise. The small cell size will mean, for example, that only a shift of 1.5 standard deviations in the sample means can be detected via a one-sided Wilcoxon procedure with a 5% type I error rate. In all such situations, confidence intervals will be presented as the primary method of analysis. Hence, such hypothesis testing will only be used as exploratory for directing further research.

Ancillary timed endpoints/analysis: exploratory analysis may be carried out on time-related variables MV-NIS cohorts including time until any treatment related toxicity, time until treatment related grade 3+ toxicity and time until hematologic nadirs (WBC, ANC, platelets). Simple summary statistics will be supplemented by Kaplan-Meier survival estimates and related confidence intervals (Pepe and Fleming 1991; Lee 1992). The effect of dose and ancillary dichotomized covariates such as age will be explored using log rank testing involving one covariate at a time. Again, the small sample size restricts the generalizability of such testing, but the results will provide preliminary indication for future research in subsequent phase 2 trials.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Monitoring the Study

All aspects of the study will be carefully monitored by Vyriad or authorized representatives according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations.

It is understood that the responsible Vyriad study monitor (or designee) will contact and visit the investigator regularly and will be allowed on request to inspect the various records of the trial (eCRFs and other pertinent data) provided that patient confidentiality is maintained in accordance with local requirements. The principal investigator and key trial personnel must be available to assist the monitor during these visits. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on patient profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the course of the study, a study monitor (CRA) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. In the course of the clinical study, access will be available to Vyriad or designee (e.g., CRO) to view the eCRFs after completion of the individual sections of the study.

Electronic CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross checking with source documents is required to monitor the progress of the study.

The monitor will visit the sites at regular intervals throughout the study according to the monitoring plan, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them and clarifying any data queries. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The completed and corrected eCRFs/CRFs for completed visits will either be collected by the monitor at the end of the study or obtained electronically for data processing. The investigator is responsible for the timely completion of eCRFs by assigned study staff. The eCRFs should be completed within seven (7) days of the patient's visit. A copy of the eCRFs will be retained by the investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the Investigator's Brochure, and any protocol amendments.

Upon completion of the study, the monitor will make a final assessment of the conduct of the study and inventory all clinical supplies to be returned to Vyriad.

14.2. Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Vyriad Quality Assurance Unit (or designee), or to health authority inspectors after appropriate notification.

Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality. Each investigator will have assured Vyriad of full access to complete source data for study participants and associated necessary support at all times.

In addition to routine monitoring procedures, audits of clinical research activities in accordance with SOPs may be performed to evaluate compliance with the protocol, the principles of GCP and any applicable regulatory requirements. A regulatory authority or IRB may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority or IRB requests an inspection, the investigator must immediately inform Vyriad that this request has been made.

Study conduct may be assessed during the course of the study by a Clinical Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol. This designee, as well as the CRA, will be permitted to inspect the study documents (study protocol, eCRFs, investigational product accountability, original study-relevant medical records).

All patient data will be treated confidentially. Furthermore, the study protocol, each step of the data-recording procedure and the handling of the data as well as the study report may be patient to independent review by a Quality Assurance representative. Clinical site and study audits will be conducted as necessary to assure the validity of the study data.

Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. ETHICAL ASPECTS

15.1. Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the most recent version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of

21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Patients", and Part 56, "Institutional Review Boards". In addition, the investigator agrees to adhere to the protocol and to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved.

The appropriate Institutional Review Boards (IRBs) must approve the protocol and any amendments and the patient informed consent form (ICF) prior to implementation.

Voluntary written informed consent must be obtained from every patient prior to participation in this clinical study. The rights, safety, and well-being of participating patients are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked based upon scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

15.2. Good Clinical Practice

The principal investigator will ensure that the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50 (1998) and 21 CFR, part 56, (1998) are followed. Since this is a covered clinical trial, the principal investigator is adhered to 21 CFR, part 54, (1998). A covered clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition patient to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Vyriad or proprietary interests in the drug being studied. This documentation must be provided prior to the participation of the principal investigator and any sub-investigator. The principal investigator and sub-investigator agree to notify Vyriad of any change in reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol-defined activities.

15.3. Informed Consent

A properly executed, written informed consent document, in compliance with 21 CFR, Part 50 and the International Conference on Harmonization (ICH) guidelines, will be obtained from each patient before the patient is entered into the study and before any study screening procedure is performed that involves risk. Attention will be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human

Patients (21 CFR 50.25[a]) and (21 CFR 50.25[b]), as necessary. Sample ICFs will be supplied to each site. Vyriad or its designee must review any proposed deviations from the sample ICF. The final IRB-approved document must be provided to Vyriad for regulatory purposes.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each patient (or the patient's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the patient or to the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. The site will retain the original signed/dated consent form and any associated HIPAA authorization for all consented patient candidates.

The eCRF for this study contains a section for documenting informed patient consent, and this must be completed appropriately. Signed ICFs must remain in each patient's study file and must be available for verification by study monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All patients (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their written consent to continue in the study.

15.4. Institutional Review Board

This study is being conducted in compliance with the protocol, the ICH GCP Guidelines, and the applicable regulatory requirements under a United States IND application. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB. This board must operate in accordance with the current federal or local regulations. The investigator will send a letter or certificate of IRB approval to Vyriad (or designee) before patient enrollment and whenever subsequent modifications to the protocol are made.

15.5. Future Use of Patient Samples

Not all of the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Following the conclusion of the study, the samples may be used for additional research. These samples will be held for a maximum of 5 years. This research will help to understand disease subtypes, drug response and toxicity, and possibly identify new drug targets or biomarkers that predict patient response to treatment. The use of the samples for internal research will be done according to the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 25 2006) and the EMEA Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (EMEA/CHMP/PGxWP/201914/2006). If a patient requests destruction of their tissue and blood samples and the samples have not yet been de-identified, Vyriad will destroy the samples as described in this FDA guidance. Vyriad will notify the investigator in writing that the samples have been destroyed.

16. PROTOCOL AMENDMENTS

Protocol modifications to ongoing studies must be made only after consultation between a Vyriad representative and the investigator. Protocol modifications will be prepared, reviewed, and approved by Vyriad representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study patients, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change of telephone number) or to eliminate an immediate hazard to study patients. In these circumstances, immediate approval of the chairman of the IRB must be sought, and the investigator should inform Vyriad, and the full IRB within 5 business days after the emergency occurs.

17. STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

17.1. Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) investigator's study file and (2) patient clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, eCRFs, query forms, IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, email communication and patient screening and enrollment logs. The investigator must keep these two categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the investigation is discontinued and the FDA is notified. After that period of time, the documents may be destroyed patient to local regulations with prior written permission from Vyriad. If the investigator wants to assign the study records to another party or move them to another location, Vyriad must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Vyriad to store these in a sealed container outside of the study site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the study site.

17.2. Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each patient are based. They are separate and distinct from the eCRFs.

These records include detailed notes on:

- Medical history
- Date and time of informed consent with HIPAA authorization either contained in the ICF or presented to the patient candidate as a standalone document
- Description of the complete consenting process
- The basic identifying information that linked the patient's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the patient
- The medical condition of the patient during their involvement in the study

- All AEs
- The patient's exposure to the study medication
- The patient's exposure to any concomitant therapy
- All relevant observations and data on the condition of the patient throughout the trial
- Justification for all entries in the patient's eCRF
- Radiology images (hard copy and digital), and reports if required
- Death information and any available autopsy data

A patient log of all potentially eligible patients considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain patients' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented patients will be logged, regardless of whether they ultimately enroll.

Upon request, the investigator will supply Vyriad with any required background data from the study documentation or clinic records. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

17.3. Electronic Case Report Forms

Clinical trial data for this study will be captured on electronic case report forms (eCRF) designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11. Corrections to data will be made according to 21 CFR Part 11, Electronic Records; Electronic Signatures. There will also be an electronic audit trail. The investigator agrees to provide all information requested on the eCRF in an accurate manner according to instructions provided. The investigator should ensure the accuracy, completeness, and timeliness of the data reported to Vyriad in the eCRF and in all required reports.

An eCRF is required to be submitted for every patient who receives any amount of study drug. This includes submission of retrievable data on patients who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where indicated by the principal investigator or authorized delegate from the study staff. If a patient stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

17.4. Confidentiality of Trial Documents and Patient Records

The investigator must ensure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to Vyriad and the IRB, patients should be identified by an identification code and/or initials and not by their names. The investigator should keep a patient enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to Vyriad (e.g. patients' written consent forms) in strict confidence.

Authorized regulatory officials and Vyriad personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drug, patient bodily fluids and tissue, and/or

other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Vyriad.

The principal investigator also agrees that all information received from Vyriad, including but not limited to the Investigator's Brochure, this protocol, CRFs, the investigational new drug, and any other study information remain the sole and exclusive property of Vyriad during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The principal investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

18. PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to Vyriad for review at least 30 days before submission. This allows Vyriad to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In the event that Vyriad coordinates a publication or presentation of study results from all study sites, the participation of investigator or other representatives of study site as a named author shall be determined in accordance with Vyriad policy and generally accepted standards for authorship.

This study will be posted to clinicaltrials.gov to permit publication in appropriate peer reviewed journals.

19. REFERENCES

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TECENTRIQ (atezolizumab) Prescribing Information, Genentech 2016.

APPENDIX 1. ECOG PERFORMANCE STATUS CRITERIA

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton,J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

APPENDIX 2. TECENTRIQ® US PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TECENTRIQ safely and effectively. See full prescribing information for TECENTRIQ.

TECENTRIQ® (atezolizumab) injection, for intravenous use
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Indications and Usage (1.2)	10/2016
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6)	10/2016

INDICATIONS AND USAGE

TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy. (1.1)
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.1)

  This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1)
- Metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ. (1.2)

DOSAGE AND ADMINISTRATION

- Administer 1200 mg as an intravenous infusion over 60 minutes every 3 weeks. (2.1)
- Dilute prior to intravenous infusion. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Related Pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-Related Hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.2)
- Immune-Related Colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.3)
- Immune-Related Endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis.
  - Thyroid Disorders: Monitor for changes in thyroid function. Withhold for symptomatic thyroid disease.
  - Adrenal Insufficiency: Withhold for symptomatic adrenal insufficiency.
  - Type 1 Diabetes Mellitus: Withhold for ≥ Grade 3 hyperglycemia.
- Immune-Related Myasthenic Syndrome/Myasthenia Gravis, Guillain-Barré or Meningoencephalitis: Permanently discontinue for any grade. (5.5)
- Ocular Inflammatory Toxicity: Withhold for moderate and permanently discontinue for severe ocular inflammatory toxicity. (5.5)
- Immune-Related Pancreatitis: Withhold for moderate or severe, and permanently discontinue for life-threatening pancreatitis, or any grade of recurring pancreatitis. (5.5)
- Infection: Withhold for severe or life-threatening infection. (5.6)
- Infusion Reaction: Interrupt or slow the rate of infusion for mild or moderate infusion reactions and discontinue for severe or life-threatening infusion reactions. (5.7)
- Embryo-Fetal Toxicity: TECENTRIQ can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 20%) in patients with locally advanced or metastatic urothelial carcinoma were fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation. (6.1)

Most common adverse reactions (≥ 20%) in patients with metastatic non-small cell lung cancer were fatigue, decreased appetite, dyspnea, cough, nausea, musculoskeletal pain, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Locally Advanced or Metastatic Urothelial Carcinoma

TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials *[see Clinical Studies (14.1)]*.

1.2 Metastatic Non-Small Cell Lung Cancer

TECENTRIQ is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of TECENTRIQ is 1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer TECENTRIQ as an intravenous push or bolus.

2.2 Dose Modifications

No dose reductions of TECENTRIQ are recommended.

Withhold TECENTRIQ for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN *[see Warnings and Precautions (5.2)]*
- Grade 2 or 3 diarrhea or colitis *[see Warnings and Precautions (5.3)]*
- Symptomatic hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, or Grade 3 or 4 hyperglycemia *[see Warnings and Precautions (5.4)]*
- Grade 2 ocular inflammatory toxicity *[see Warnings and Precautions (5.5)]*
- Grade 2 or 3 pancreatitis, or Grade 3 or 4 increases in amylase or lipase levels (greater than 2.0 times ULN) *[see Warnings and Precautions (5.5)]*
- Grade 3 or 4 infection *[see Warnings and Precautions (5.6)]*
- Grade 2 infusion-related reactions *[see Warnings and Precautions (5.7)]*
- Grade 3 rash

TECENTRIQ may be resumed in patients whose adverse reactions recover to Grade 0–1.

Permanently discontinue TECENTRIQ for any of the following:

- Grade 3 or 4 pneumonitis *[see Warnings and Precautions (5.1)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN *[see Warnings and Precautions (5.2)]*
- Grade 4 diarrhea or colitis *[see Warnings and Precautions (5.3)]*
- Grade 4 hypophysitis *[see Warnings and Precautions (5.4)]*
- Myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis (all grades) *[see Warnings and Precautions (5.5)]*
- Grade 3 or 4 ocular inflammatory toxicity *[see Warnings and Precautions (5.5)]*
- Grade 4 or any grade of recurrent pancreatitis *[see Warnings and Precautions (5.5)]*
- Grade 3 or 4 infusion-related reactions *[see Warnings and Precautions (5.7)]*
- Grade 4 rash

2.3 Preparation and Administration

Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration whenever solution and container permit. TECENTRIQ is a colorless to slightly yellow solution. Discard the vial if the solution is cloudy, discolored, or visible particles are observed. Do not shake the vial.

Prepare the solution for infusion as follows:

- Withdraw 20 mL of TECENTRIQ from the vial.
- Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with 0.9% Sodium Chloride Injection only.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard used or empty vials of TECENTRIQ.

Storage of Infusion Solution

This product does not contain a preservative.

Administer immediately once prepared. If diluted TECENTRIQ infusion solution is not used immediately, it can be stored either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration for infusion.
- Under refrigeration at 2°C–8°C (36°F–46°F) for no more than 24 hours.

Do not freeze.

Do not shake.

Administration

Administer the initial infusion over 60 minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

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

3 DOSAGE FORMS AND STRENGTHS

Injection: 1200 mg/20 mL (60 mg/mL) colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Related Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer steroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Withhold TECENTRIQ until resolution for Grade 2 pneumonitis. Permanently discontinue TECENTRIQ for Grade 3 or 4 pneumonitis *[see Dosage and Administration (2.2)]*.

Across clinical trials, 2.6% (51/1978) of patients developed pneumonitis. Fatal pneumonitis occurred in two patients.

Urothelial Carcinoma

In 523 patients with urothelial carcinoma who received TECENTRIQ, pneumonitis occurred in six (1.1%) patients. Of these patients, there was one patient with fatal pneumonitis, one patient with Grade 3, three patients with Grade 2, and one patient with Grade 1 pneumonitis. TECENTRIQ was held in all cases and five patients were treated with corticosteroids. Pneumonitis resolved in three patients. The median time to onset was 2.6 months (range: 15 days to 4.2 months). The median duration was 15 days (range: 6 days to 3.1+ months).

NSCLC

In 1027 patients with NSCLC who received TECENTRIQ, pneumonitis occurred in 38 (3.7%) patients. Of these patients, there was one patient with fatal pneumonitis, two patients with Grade 4, thirteen patients with Grade 3, eleven patients with Grade 2, and eleven patients with Grade 1 pneumonitis. TECENTRIQ was held in 24 patients and 21 patients were treated with corticosteroids. Pneumonitis resolved in 26 of the 38 patients. The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median duration was 1.4 months (range: 0 days to 12.6+ months).

5.2 Immune-Related Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ treatment. Liver test abnormalities occurred in patients who received TECENTRIQ. Monitor patients for signs and symptoms of hepatitis. Monitor AST, ALT, and bilirubin prior to and periodically during treatment with TECENTRIQ. Administer corticosteroids at a dose of 1–2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin, followed by corticosteroid taper. Withhold TECENTRIQ for Grade 2 and permanently discontinue TECENTRIQ for Grade 3 or 4 immune-mediated hepatitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Across clinical trials (n=1978), Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.3%), and total bilirubin (1.6%).

Urothelial Carcinoma

In patients with urothelial carcinoma (n=523), Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.5%), and total bilirubin (2.1%). Immune-mediated hepatitis occurred in 1.3% of patients. Of these cases, one patient died from hepatitis, five patients had Grade 3, and one

patient had Grade 2 hepatitis. The median time to onset was 1.1 months (range: 0.4 to 7.7 months). TECENTRIQ was temporarily interrupted in four patients; none of these patients developed recurrence of hepatitis after resuming TECENTRIQ.

NSCLC

In patients with NSCLC, Grade 3 or 4 elevation occurred in ALT (1.4%), AST (1.3%), and total bilirubin (0.6%). Immune-mediated hepatitis occurred in 0.9% (9/1027) of patients. Of these nine patients, one patient had Grade 4, four patients had Grade 3, three patients had Grade 2, and one patient had Grade 1 immune-mediated hepatitis. The median time to onset was 28 days (range: 15 days to 4.2 months). TECENTRIQ was temporarily interrupted in seven patients; none of these patients developed recurrence of hepatitis after resuming TECENTRIQ.

5.3 Immune-Related Colitis

Immune-mediated colitis or diarrhea, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ. Monitor patients for signs and symptoms of diarrhea or colitis. Withhold treatment with TECENTRIQ for Grade 2 diarrhea or colitis. If symptoms persist for longer than 5 days or recur, administer 1–2 mg/kg prednisone or equivalent per day. Withhold treatment with TECENTRIQ for Grade 3 diarrhea or colitis. Treat with IV methylprednisolone 1–2 mg/kg per day and convert to oral steroids once the patient has improved. For both Grade 2 and Grade 3 diarrhea or colitis, when symptoms improve to Grade 0 or Grade 1, taper steroids over ≥ 1 month. Resume treatment with TECENTRIQ if the event improves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day. Permanently discontinue TECENTRIQ for Grade 4 diarrhea or colitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Across clinical trials, colitis or diarrhea occurred in 19.7% (389/1978) of all patients.

Urothelial Carcinoma

In 523 patients with urothelial carcinoma who received TECENTRIQ, colitis or diarrhea occurred in 98 (18.7%) patients. Ten patients (1.9%) developed Grade 3 or 4 diarrhea. Four patients (0.8%) had immune-mediated colitis or diarrhea with a median time to onset of 1.7 months (range: 1.1 to 3.1 months). Immune-mediated colitis resolved with corticosteroid administration in three of these patients, while the other patient died without resolution of colitis in the setting of diarrhea-associated renal failure.

NSCLC

In 1027 patients with NSCLC who received TECENTRIQ, colitis or diarrhea occurred in 198 (19.3%) patients. Twelve patients (1.2%) developed Grade 3 colitis or diarrhea. Five patients (0.5%) had immune-mediated colitis or diarrhea with a median time to onset of 21 days (range: 12 days to 3.4 months). Of these patients, one had Grade 3, two had Grade 2, and two had Grade 1 immune-mediated colitis or diarrhea. Immune-mediated colitis or diarrhea resolved with corticosteroid administration in four of these patients, while the fifth patient died due to disease progression prior to resolution of colitis.

5.4 Immune-Related Endocrinopathies

Immune-related thyroid disorders, adrenal insufficiency, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred in patients receiving TECENTRIQ. Monitor patients for clinical signs and symptoms of endocrinopathies.

Hypophysitis

Hypophysitis occurred in 0.2% (1/523) of patients with urothelial cancer receiving TECENTRIQ. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids and hormone replacement as clinically indicated. Withhold TECENTRIQ for Grade 2 or Grade 3

and permanently discontinue for Grade 4 hypophysitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Thyroid Disorders

Thyroid function was assessed routinely only at baseline and the end of the study. Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. Asymptomatic patients with abnormal thyroid function tests can receive TECENTRIQ. For symptomatic hypothyroidism, withhold TECENTRIQ and initiate thyroid hormone replacement as needed. Manage isolated hypothyroidism with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, withhold TECENTRIQ and initiate an anti-thyroid drug as needed. Resume treatment with TECENTRIQ when symptoms of hypothyroidism or hyperthyroidism are controlled and thyroid function is improving *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Across clinical trials, hypothyroidism and hyperthyroidism occurred in 3.9% (77/1978) and 1.0% (20/1978) of patients, respectively.

Urothelial Carcinoma

In 523 patients with urothelial carcinoma who received TECENTRIQ, hypothyroidism occurred in 2.5% (13/523). One patient had Grade 3 and twelve patients had Grade 1–2 hypothyroidism. The median time to first onset was 5.4 months (range: 21 days to 11.3 months). Thyroid stimulating hormone (TSH) was elevated and above the patient's baseline in 16% (21/131) of patients with a follow-up measurement.

Hyperthyroidism occurred in 0.6% (3/523) of patients with urothelial carcinoma. Of the three urothelial carcinoma patients, one patient had Grade 2 and two patients had Grade 1 hyperthyroidism. The median time to onset was 3.2 months (range: 1.4 to 5.8 months). TSH was decreased and below the patient's baseline in 3.8% (5/131) of patients with a follow-up measurement.

NSCLC

In 1027 patients with NSCLC who received TECENTRIQ, hypothyroidism occurred in 4.2% (43/1027). Three patients had Grade 3 and forty patients had Grade 1–2 hypothyroidism. The median time to onset was 4.8 months (range 15 days to 31 months.) TSH was elevated and above the patient's baseline in 17% (54/315) of patients with follow-up measurement.

Hyperthyroidism occurred in 1.1% (11/1027) of patients with NSCLC. Eight patients had Grade 2 and three patients had Grade 1 hyperthyroidism. The median time to onset was 4.9 months (range: 21 days to 31 months). TSH was decreased and below the patient's baseline in 7.6% (24/315) of patients with a follow-up measurement.

Adrenal Insufficiency

Adrenal insufficiency occurred in 0.4% (7/1978) of patients across clinical trials, including two patients with Grade 3, four patients with Grade 2, and one patient with Grade 1. Adrenal insufficiency resolved in two patients.

For symptomatic adrenal insufficiency, withhold TECENTRIQ and administer methylprednisolone 1–2 mg/kg per day IV followed by oral prednisone 1–2 mg/kg per day or equivalent once symptoms improve. Start steroid taper when symptoms improve to ≤ Grade 1 and taper steroids over ≥ 1 month. Resume treatment with TECENTRIQ if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day and the patient is stable on replacement therapy, if required *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Diabetes Mellitus

New onset diabetes with ketoacidosis has occurred in patients receiving TECENTRIQ. Diabetes mellitus without an alternative etiology occurred in one (0.2%) patient with urothelial carcinoma and three (0.3%) patients with NSCLC.

Initiate treatment with insulin for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycemia (fasting glucose >250–500 mg/dL), withhold TECENTRIQ. Resume treatment with TECENTRIQ when metabolic control is achieved on insulin replacement therapy *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.5 Other Immune-Related Adverse Reactions

Other immune-related adverse reactions including meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré, ocular inflammatory toxicity, and pancreatitis, including increases in serum amylase and lipase levels, have occurred in ≤ 1.0% of patients treated with TECENTRIQ.

Meningitis / Encephalitis

Monitor patients for clinical signs and symptoms of meningitis or encephalitis. Permanently discontinue TECENTRIQ for any grade of meningitis or encephalitis. Treat with IV steroids (1–2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) once the patient has improved. When symptoms improve to ≤ Grade 1, taper steroids over ≥ 1 month *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Motor and Sensory Neuropathy

Monitor patients for symptoms of motor and sensory neuropathy. Permanently discontinue TECENTRIQ for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Institute medical intervention as appropriate. Consider initiation of systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Pancreatitis

Symptomatic pancreatitis without an alternative etiology occurred in 0.1% (2/1978) of patients across clinical trials. Monitor patients for signs and symptoms of acute pancreatitis. Withhold TECENTRIQ for ≥ Grade 3 serum amylase or lipase levels (> 2.0 ULN), or Grade 2 or 3 pancreatitis. Treat with 1–2 mg/kg IV methylprednisolone or equivalent per day. Once symptoms improve, follow with 1–2 mg/kg of oral prednisone or equivalent per day. Resume treatment with TECENTRIQ when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Permanently discontinue TECENTRIQ for Grade 4 or any grade of recurrent pancreatitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.6 Infection

Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage occurred in patients receiving TECENTRIQ. Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold TECENTRIQ for ≥ Grade 3 infection *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Across clinical trials, infections occurred in 38.4% (759/1978) of patients.

Urothelial Carcinoma

In 523 patients with urothelial carcinoma who received TECENTRIQ, infection occurred in 197 (37.7%) patients. Grade 3 or 4 infection occurred in sixty (11.5%) patients, while three patients died due to infections. Urinary tract infections were the most common cause of Grade 3 or higher infection, occurring in 37 (7.1%) patients.

NSCLC

In Study 3, a randomized trial in patients with NSCLC, infections were more common in patients treated with TECENTRIQ (43%) compared with those treated with docetaxel (34%). Grade 3 or 4 infections occurred in 9.2% of patients treated with TECENTRIQ compared with 2.2% in patients treated with docetaxel. Two patients (1.4%) treated with TECENTRIQ and three patients (2.2%) treated with docetaxel died due to infection. Pneumonia was the most common cause of Grade 3 or higher infection, occurring in 7.7% of patients treated with TECENTRIQ.

5.7 Infusion-Related Reactions

Severe infusion reactions have occurred in patients in clinical trials of TECENTRIQ. Infusion-related reactions occurred in 1.3% (25/1978) of patients across clinical trials, 1.7% (9/523) of patients with urothelial carcinoma, and 1.6% (16/1027) of patients with NSCLC. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion reactions *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Immune-Related Pneumonitis *[see Warnings and Precautions (5.1)]*
- Immune-Related Hepatitis *[see Warnings and Precautions (5.2)]*
- Immune-Related Colitis *[see Warnings and Precautions (5.3)]*
- Immune-Related Endocrinopathies *[see Warnings and Precautions (5.4)]*
- Other Immune-Related Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Infection *[see Warnings and Precautions (5.6)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Urothelial Carcinoma

The data described in Table 1 reflects exposure to TECENTRIQ in Cohort 2 of Study 1. This cohort enrolled 310 patients in a single arm trial with locally advanced or metastatic urothelial

carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen *[see Clinical Studies (14.1)]*. Patients received 1200 mg of TECENTRIQ intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (range: 0.1, 46 weeks).

The most common adverse reactions (≥ 20%) were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). The most common Grade 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.

Three patients (0.9%) who were treated with TECENTRIQ experienced either sepsis, pneumonitis, or intestinal obstruction which led to death. TECENTRIQ was discontinued for adverse reactions in 3.2% (10/310) of the 310 patients. Sepsis led to discontinuation in 0.6% (2/310) of patients. Adverse reactions leading to interruption of TECENTRIQ occurred in 27% of patients; the most common (> 1%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (> 2%) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state.

Table 1 summarizes the adverse reactions that occurred in ≥ 10% of patients while Table 2 summarizes Grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in Cohort 2 of Study 1.

Table 1: All Grade Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in Study 1

	TECENTRIQ N = 310	
Adverse Reaction	All Grades (%)	Grades 3 – 4 (%)
All Adverse Reactions	96	50
Gastrointestinal Disorders		
Nausea	25	2
Constipation	21	0.3
Diarrhea	18	1
Abdominal pain	17	4
Vomiting	17	1
General Disorders and Administration		
Fatigue	52	6
Pyrexia	21	1
Peripheral edema	18	1
Infections and Infestations		
Urinary tract infection	22	9
Metabolism and Nutrition Disorders		
Decreased appetite	26	1
Musculoskeletal and Connective Tissue Disorders		
Back/Neck pain	15	2
Arthralgia	14	1
Renal and urinary disorders		
Hematuria	14	3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	16	4
Cough	14	0.3
Skin and Subcutaneous Tissue Disorders		
Rash	15	0.3
Pruritus	13	0.3

Table 2: Grade 3–4 Laboratory Abnormalities in Patients with Urothelial Carcinoma in Study 1 in ≥ 1% of Patients

Laboratory Test	Grades 3–4 (%)
Lymphopenia	10
Hyponatremia	10
Anemia	8
Hyperglycemia	5
Increased Alkaline phosphatase	4
Increased Creatinine	3
Increased ALT	2
Increased AST	2
Hypoalbuminemia	1

NSCLC

The safety of TECENTRIQ was evaluated in Study 3, a multi-center, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression *[see Clinical Studies (14.2)]*. Patients received 1200 mg of TECENTRIQ (n=142) administered intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression or docetaxel (n=135) administered intravenously at 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. The median duration of exposure was 3.7 months (range: 0–19 months) in TECENTRIQ-treated patients and 2.1 months (range: 0–17 months) in docetaxel-treated patients.

The most common adverse reactions (≥ 20%) in patients receiving TECENTRIQ were fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%). The most common Grade 3-4 adverse reactions (≥2%) were dyspnea, pneumonia, hypoxia, hyponatremia, fatigue, anemia, musculoskeletal pain, AST increase, ALT increase, dysphagia, and arthralgia.

Nine patients (6.3%) who were treated with TECENTRIQ experienced either pulmonary embolism (2), pneumonia (2), pneumothorax, ulcer hemorrhage, cachexia secondary to dysphagia, myocardial infarction, or large intestinal perforation which led to death. TECENTRIQ was discontinued due to adverse reactions in 4% (6/142) of patients. Adverse reactions leading to interruption of TECENTRIQ occurred in 24% of patients; the most common (>1%) were pneumonia, liver function test abnormality, upper respiratory tract infection, pneumonitis, acute kidney injury, hypoxia, hypothyroidism, dyspnea, anemia, and fatigue. Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (> 2%) were pneumonia, dyspnea, pleural effusion, pyrexia, and venous thromboembolism.

Table 3 summarizes adverse reactions that occurred in at least 10% of TECENTRIQ-treated patients and at a higher incidence than in the docetaxel arm. Table 4 summarizes selected laboratory abnormalities worsening from baseline that occurred in ≥10% of TECENTRIQ-treated patients and at a higher incidence than in the docetaxel arm.

Table 3: Adverse Reactions Occurring in ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3–4]) (Study 3)

	TECENTRIQ (n=142)		Docetaxel (n=135)	
Adverse Reaction	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**
	Percentage (%) of Patients			
General Disorders and Administration Site Conditions				
Pyrexia	18	0	13	0
Infections and infestations				
Pneumonia	18	6	4	2
Metabolism and nutrition disorders				
Decreased appetite	35	1	22	0
Musculosketal and connective tissue disorders				
Arthralgia	16	2	9	2
Back pain	14	1	9	1
Psychiatric Disorders				
Insomnia	14	0	8	2
Respiratory, thoracic and mediastinal disorders				
Dyspnea	32	7	24	2
Cough	30	1	25	0

Table 4: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3–4]) (Study 3)

	Percentage of Patients with Worsening Laboratory Test from Baseline			
	TECENTRIQ		Docetaxel	
Test	All grades %	Grade 3–4 %	All grades %	Grade 3–4 %
Hyponatremia	48	13	28	8
Hypoalbuminemia	48	5	49	1
Alkaline Phosphatase increased	42	2	24	1
Aspartate aminotransferase increased	33	2	15	0
Alanine aminotransferase increased	31	2	9	1
Creatinine increased	19	1	14	2
Hypokalemia	18	2	11	4
Hypercalcemia	13	0	5	0
Total Bilirubin increased	11	0	5	1

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Among 275 patients in Study 1, 114 patients (41.5%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. Among 135 patients in Study 3, 73 patients (54.1%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. In Study 1 and Study 3, the presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy.

Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of ATAs to TECENTRIQ with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death *[see Data]*. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise a lactating woman not to breastfeed during treatment and for at least 5 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

Infertility

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of TECENTRIQ have not been established in pediatric patients.

8.5 Geriatric Use

Of the 310 patients with urothelial carcinoma treated with TECENTRIQ in Study 1, 59% were 65 years or older. Of the 142 patients with NSCLC treated with TECENTRIQ in Study 3, 39% were 65 years or older. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

8.6 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with mild hepatic impairment. TECENTRIQ has not been studied in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no information on overdose with TECENTRIQ.

11 DESCRIPTION

Atezolizumab is an Fc-engineered, humanized, monoclonal antibody that binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors. Atezolizumab is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

TECENTRIQ injection for intravenous infusion is a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each mL of TECENTRIQ contains 60 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), sucrose (821.6 mg), polysorbate 20 (8 mg), pH 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PD-L1 may be expressed on tumor cells and/or tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

Patients' exposures to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose 1200 mg administered every 3 weeks. Based on a population analysis that included 472 patients in the dose range, the typical population clearance was 0.20 L/day, volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. The population PK analysis suggests steady state is obtained after 6 to 9 weeks (2 to 3

cycles) of repeated dosing. The systemic accumulation in area under the curve (AUC), maximum concentration (Cmax) and trough concentration (Cmin) was 1.91, 1.46 and 2.75-fold, respectively. In a posthoc analysis, atezolizumab clearance was found to decrease over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline value of approximately 17.1% (40.6%). However, the decrease in CL was not considered clinically relevant.

Specific Populations: Age (21–89 years), body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumor burden, region or race, mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m^2), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin < 1.0 to 1.5 × ULN and any AST), level of PD-L1 expression, or ECOG status had no clinically significant effect on the systemic exposure of atezolizumab.

The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or moderate or severe hepatic impairment (bilirubin > ULN and AST > ULN or bilirubin ≥ 1.0 to 1.5 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

Drug Interaction Studies

The drug interaction potential of atezolizumab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of atezolizumab for carcinogenicity or genotoxicity.

Animal fertility studies have not been conducted with atezolizumab; however, an assessment of the male and female reproductive organs was included in a 26-week, repeat-dose toxicity study in cynomolgus monkeys. Weekly administration of atezolizumab to female monkeys at the highest dose tested caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries. This effect occurred at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible. There was no effect on the male monkey reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Urothelial Carcinoma

TECENTRIQ was investigated in Study 1, a multicenter, open-label, two-cohort trial that included patients with locally advanced or metastatic urothelial carcinoma. In Cohort 2 of Study 1, 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with TECENTRIQ. This study excluded patients who had: a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents or systemic immunosuppressive medications. Patients received an intravenous infusion of 1200 mg of TECENTRIQ every 3 weeks until unacceptable

toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed objective response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

In this cohort, the median age was 66 years, 78% were male, 91% of patients were Caucasian. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had visceral metastases. Sixty-two percent of patients had an ECOG score of 1 and 35% of patients had a baseline creatinine clearance of < 60 mL/min. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty-one percent of patients had received ≥ 2 prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area). The remaining, 68% of patients, were classified as having PD-L1 expression of <5% (PD-L1 stained tumor-infiltrating IC covering < 5% of the tumor area).

Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 5. The median follow-up time for this cohort was 14.4 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

Table 5: Summary of Efficacy from Cohort 2 of Study 1

	All Patients	**PD-L1 Expression Subgroups**	
	N=310	**PD-L1 Expression of < 5% in IC[1] (N=210)**	**PD-L1 Expression of ≥ 5% in IC[1] (N=100)**
Number of IRF-assessed Confirmed Responders	46	20	26
ORR % (95% CI)	**14.8% (11.1, 19.3)**	**9.5% (5.9, 14.3)**	**26.0% (17.7, 35.7)**
Complete Response (CR) (%)	5.5%	2.4%	12.0%
Partial Response (PR) (%)	9.4%	7.1%	14.0%
Median DOR, months (range)	NR (2.1+, 13.8+)	12.7 (2.1+, 12.7)	NR (4.2, 13.8+)

NR = Not reached

\+ Denotes a censored value

[1] PD-L1 expression in tumor-infiltrating immune cells (IC)

14.2 Metastatic Non-Small Cell Lung Cancer

Previously Treated Metastatic NSCLC

The efficacy of TECENTRIQ was investigated in two multi-center, international, randomized, open-label trials in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen. Study 2 was a trial in 1225 patients with the primary analysis population consisting of the first 850 randomized patients and Study 3 was a trial in 287 patients. In both studies, eligible patients were stratified by PD-L1 expression status in tumor-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Patients

were randomized (1:1) to receive either TECENTRIQ administered intravenously at 1200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical progression or docetaxel administered intravenously at 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. These studies excluded patients who had: a history of autoimmune disease, had active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumor assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. In Study 2, tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and IC using the VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for the analyses described below.

In Study 2, among patients in the primary analysis population, the median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-fourths of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy five percent of patients received only one prior platinum-based therapeutic regimen. In Study 3, the median age was 62 years (range: 36 to 84), and 59% of patients were male. The majority of patients were white (79%). Approximately two-thirds of patients had non-squamous disease (66%), 7% had known EGFR mutation, 1% had ALK rearrangements, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (33%) or 1 (67%). Approximately two-thirds of patients received only one prior platinum-based therapeutic regimen.

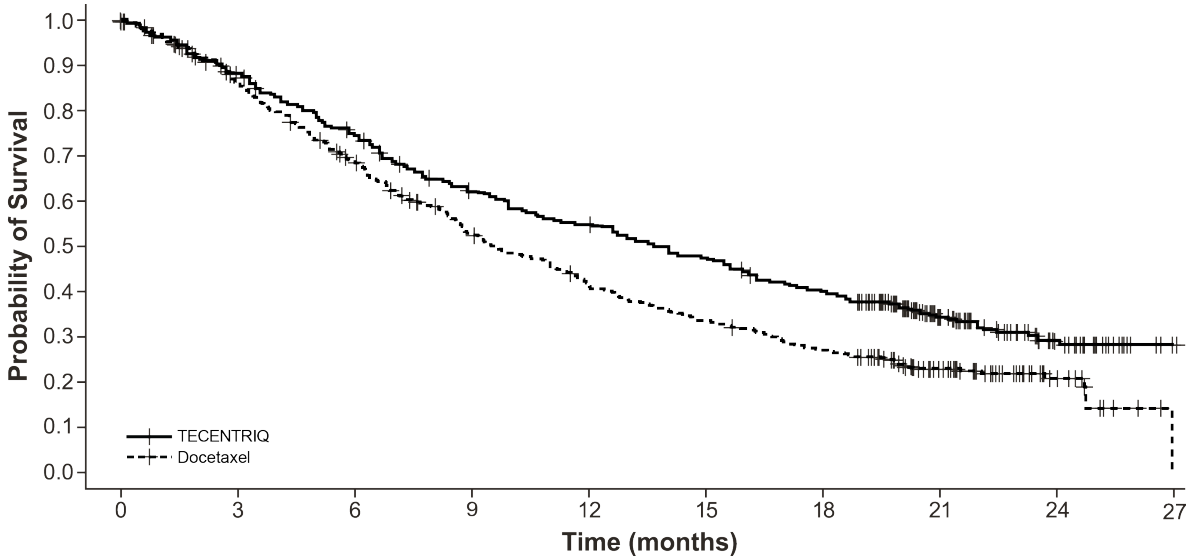
The major efficacy outcome measure of Study 2 was overall survival (OS) in the primary analysis population (first 850 randomized patients). The major efficacy outcome measure of Study 3 was overall survival (OS). Other efficacy outcome measures for Study 3 included investigator-assessed objective response rates and duration of response per RECIST v1.1. The results of Study 2 with a median follow up of 21 months are presented in Table 6 and Figure 1.

Table 6: Efficacy Results in the Primary Analysis Population from Study 2

	TECENTRIQ (n=425)		Docetaxel (n=425)
Overall Survival			
Deaths (%)	271 (64%)		298 (70%)
Median, months	13.8		9.6
(95% CI)	(11.8, 15.7)		(8.6, 11.2)
Hazard ratio[1] (95% CI)		0.74 (0.63, 0.87)	
p-value[2]		0.0004	

[1] Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] Based on the stratified log-rank test
CI=confidence interval

Figure 1: Kaplan-Meier Plot of Overall Survival in the Primary Analysis Population in Study 2



No. Patients at Risk

TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3	

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

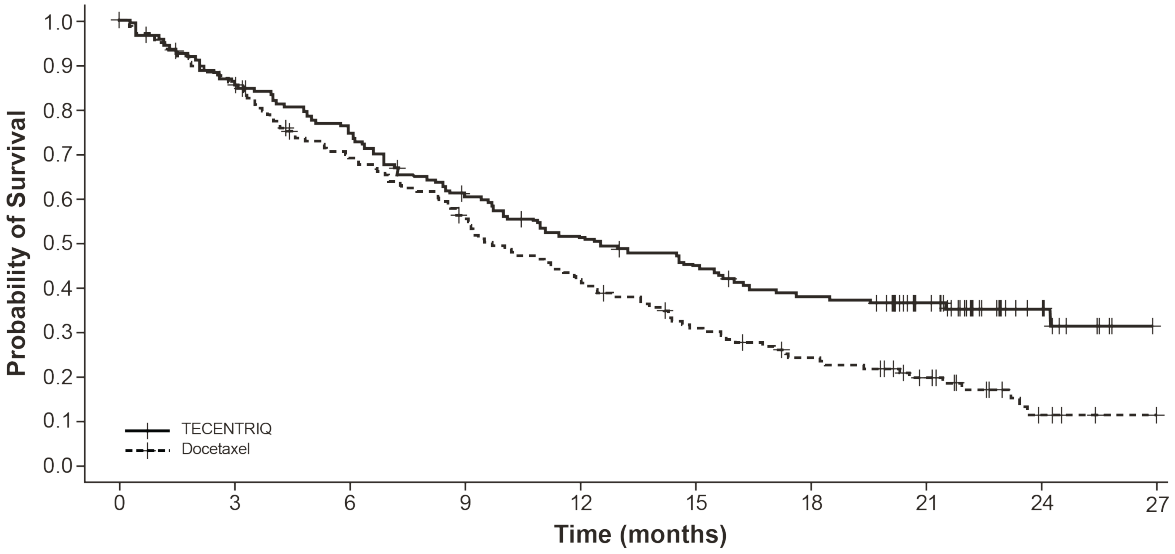
Results of an updated survival analysis in Study 3 with a median follow-up of 22 months are provided for all randomized patients (Table 7 and Figure 2).

Table 7: Efficacy Results from Study 3

	TECENTRIQ (n=144)	Docetaxel (n=143)
Overall Survival		
Deaths (%)	90 (63%)	110 (77%)
Median, months	12.6	9.7
(95% CI)	(9.7, 16.0)	(8.6, 12.0)
Hazard ratio[1] (95% CI)	0.69 (0.52, 0.92)	
Objective Response Rate[2] n (%)	22 (15%)	21 (15%)
(95% CI)	(10%, 22%)	(9%, 22%)
Complete response	1 (0.7%)	0
Partial response	21 (15%)	21 (15%)
Duration of Response[2]	n=22	n=21
Median (months)	18.6	7.2
(95% CI)	(11.6, NE)	(5.6, 12.5)

[1] Stratified by PD-L1 expression in tumor-infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
CI=confidence interval; NE=not estimable

Figure 2: Kaplan-Meier Plot of updated Overall Survival in Study 3



No. of Patients at Risk

TECENTRIQ	144	139	131	123	117	110	106	95	90	84	78	73	70	67	64	60	54	52	50	49	46	34	24	14	11	5	1
Docetaxel	143	130	123	118	106	97	92	87	82	73	65	61	55	49	46	39	36	33	29	27	24	18	12	9	5	2	1

16 HOW SUPPLIED/STORAGE AND HANDLING

TECENTRIQ injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion supplied as a carton containing one 1200 mg/20 mL single-dose vial (NDC 50242-917-01).

Storage: Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-related adverse reactions that may require corticosteroid treatment and interruption or discontinuation of TECENTRIQ, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.2)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.3)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis *[see Warnings and Precautions (5.4)]*
- Meningoencephalitis, myasthenic syndrome/myasthenia gravis, and Guillain-Barré syndrome: Advise patients to contact their healthcare provider immediately for signs or symptoms of meningitis, myasthenic syndrome/myasthenia gravis, or Guillain-Barré syndrome *[see Warnings and Precautions (5.5)]*.
- Ocular Inflammatory Toxicity: Advise patients to contact their healthcare provider immediately for signs or symptoms of ocular inflammatory toxicity *[see Warnings and Precautions (5.5)]*.
- Pancreatitis: Advise patients to contact their healthcare provider immediately for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.5)]*.
- Infection: Advise patients to contact their healthcare provider immediately for signs or symptoms of infection *[see Warnings and Precautions (5.6)]*.
- Infusion-Related Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*.
- Rash: Advise patients to contact their healthcare provider immediately for signs or symptoms of rash *[see Dosage and Administration (2.2)]*.

Embryo-Fetal Toxicity

Advise female patients that TECENTRIQ can cause fetal harm. Instruct females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

TECENTRIQ® [atezolizumab]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
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South San Francisco, CA 94080-4990

U.S. License No. 1048

MEDICATION GUIDE
TECENTRIQ® (te-SEN-trik)
(atezolizumab)
injection

What is the most important information I should know about TECENTRIQ?

TECENTRIQ is a medicine that may treat your bladder cancer or lung cancer by working with your immune system. TECENTRIQ can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

Call or see your healthcare provider right away if you get any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

Intestinal problems (colitis). Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach area (abdomen) pain or tenderness

Hormone gland problems (especially the pituitary, thyroid, adrenal glands, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- feeling more hungry or thirsty than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- urinating more often than usual
- nausea or vomiting
- stomach area (abdomen) pain
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Nervous system problems (neuropathy, meningitis, encephalitis). Signs and symptoms of nervous system problems may include:

- severe muscle weakness
- numbness or tingling in hands or feet
- fever
- confusion
- changes in mood or behavior
- extreme sensitivity to light
- neck stiffness

Inflammation of the eyes. Signs and symptoms may include:

- blurry vision, double vision, or other vision problems
- eye pain or redness

Severe infections. Signs and symptoms of infection may include:

- fever
- cough
- frequent urination
- flu-like symptoms
- pain when urinating

Severe infusion reactions. Signs and symptoms of infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- swelling of your face or lips
- dizziness
- fever
- feeling like passing out
- back or neck pain

Getting medical treatment right away may help keep these problems from becoming more serious.
Your healthcare provider will check you for these problems during your treatment with TECENTRIQ. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or completely stop treatment with TECENTRIQ if you have severe side effects.

What is TECENTRIQ?

TECENTRIQ is a prescription medicine used to treat:

- **a type of bladder cancer called urothelial carcinoma**

TECENTRIQ may be used when your bladder cancer:

- has spread or cannot be removed by surgery (advanced urothelial carcinoma), **and**
- you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

- a type of lung cancer called non-small cell lung cancer (NSCLC)

TECENTRIQ may be used when your lung cancer:

- has spread or grown, **and**
- you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, and it did not work or is no longer working.

It is not known if TECENTRIQ is safe and effective in children.

Before you receive TECENTRIQ, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are being treated for an infection
- are pregnant or plan to become pregnant. TECENTRIQ can harm your unborn baby. If you are able to become pregnant, you should use an effective method of birth control during your treatment and for at least 5 months after the last dose of TECENTRIQ.
- are breastfeeding or plan to breastfeed. It is not known if TECENTRIQ passes into your breastmilk. Do not breastfeed during treatment and for at least 5 months after the last dose of TECENTRIQ.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive TECENTRIQ?

- Your healthcare provider will give you TECENTRIQ into your vein through an intravenous (IV) line over 30 to 60 minutes.
- TECENTRIQ is usually given every 3 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will test your blood to check you for certain side effects.

If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of TECENTRIQ?

TECENTRIQ can cause serious side effects, including:

- **See "What is the most important information I should know about TECENTRIQ?"**

The most common side effects of TECENTRIQ in people with urothelial carcinoma include:

- feeling tired
- decreased appetite
- nausea
- urinary tract infection
- fever
- constipation

The most common side effects of TECENTRIQ in people with non-small cell lung cancer include:

- feeling tired
- decreased appetite
- shortness of breath
- cough
- nausea
- constipation

TECENTRIQ may cause fertility problems in females, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of TECENTRIQ. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TECENTRIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about TECENTRIQ, talk with your healthcare provider. You can ask your healthcare provider for information about TECENTRIQ that is written for health professionals.

What are the ingredients in TECENTRIQ?

Active ingredient: atezolizumab

Inactive ingredients: glacial acetic acid, L-histidine, sucrose, polysorbate 20

Manufactured by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990 USA
U.S. License No. 1048 TECENTRIQ is a registered trademark of Genentech, Inc.
For more information, call 1-*844-832-3687* or go to www.TECENTRIQ.com.
This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 10/2016