CV301-BLD-001

Statistical Analysis Plan

A Phase 2, Multicenter, Single-Arm Trial of CV301 in Combination with PD-1/L1 Blockade in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer

Revision Chronology

Edition	Date	Version
Final v1.0	17JUL2019	New Document

Signature Page

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Table of Contents

Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADR	Adverse Drug Reaction
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic-Therapeutic-Chemical
β-HCG	Beta-Human Chorionic Gonadotropin
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events, version 5.0
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EE	Efficacy Evaluable
EOT	End of Treatment
FAS	Full Analysis Set
FPV	Fowlpox Virus
FU	Follow Up
ICF	Informed Consent Form
ICH	International Conference on Harmonisation (now International Council for Harmonisation)
IMAE	Immune Mediated Adverse Event
LTFU	Long Term Follow Up
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Erythrocyte Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Mismatch Repair
MSI	Microsatellite Instability
MVA-BN	Modified Vaccinia Ankara – Bavarian Nordic
NCI	National Cancer Institute
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
RBC	Red Blood Cell/Erythrocyte
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable Disease

Abbreviation	Definition
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TPS	Tumor Proportion Score
UC	Urothelial Cancer
WBC	White Blood Cell/Leukocyte
WHO DDE	World Health Organization Drug Dictionary Enhanced

General Definitions

Vaccination

A vaccination in this trial means receiving subcutaneous (SC) injection(s) with either MVA-BN-CV301 or FPV-CV301.

Trial Treatment

Trial treatment refers to dosing with any of the following trial products:

- Prime with MVA-BN-CV301 given SC on Days 1 and 22.
- Boost with FPV-CV301, given SC every 21 days for 4 doses, followed by boosts every 6 weeks until 6 months on trial, then every 12 weeks until completion of 2 years.
- Atezolizumab fixed dose of 1200 mg intravenous on Day 1 of each 21-day cycle.

Trial Medication

Trial medication refers to dosing with atezolizumab.

Treated Subjects

A subject is considered treated once they have received the first dose of trial product.

Trial Day (Study Day)

The day of trial is defined from the day of first vaccination. The day of first vaccination is defined as Day 1, the day after first vaccination is Day 2, and so on. Similarly, the day before first vaccination in the screening period is defined as Day -1, and so on. Note, no reference is made to the time of the vaccination in the calculation of the trial day, i.e., at midnight a new trial day begins regardless of the time of first vaccination. Note, to maintain conformance with Clinical Data Interchange Standards Consortium (CDISC) data standards, in datasets “trial day” will be referred to as “study day.”

Baseline

If not otherwise specified, “baseline” refers to the last measurement prior to first treatment with vaccine, including re-screening or pre-treatment unscheduled visit values. Note for determination of baseline values, data that are collected on the day of first vaccination but prior to the first vaccination, per protocol, will be considered pre-treatment data and will be eligible to be used as baseline values. Baseline data will be summarized without specification as to which visit the data were originally reported.

In cases where no pre-treatment values exist for a baseline parameter within a subject, the subject will be considered as having no baseline, and post-baseline changes and percent changes will not be able to be calculated.

Screening Phase

All data collected from the initial screening visit (within 28 days prior to first dose) until first dose of trial vaccine. This may include any unscheduled or re-screening visit results up to the first trial vaccination.

Active Trial Phase

All data collected at the visit of first vaccination (Visit 1) through Visit 14 plus 30 days, including unscheduled visits, will be considered part of the active trial phase. For safety analyses, data will be collected until 30 days (Visit 14 for completers) after the last treatment. For subjects who discontinue treatment early, the 30 days will start at the most recently received trial product.

Long Term Follow-up (LTFU) Period

All data collected after the Active Trial Phase until the final trial visit or contact (if actual visits are not performed during follow-up). Note that for subjects who do not return for LTFU visits or do not agree to follow-up by phone, no LTFU phase data may be available for reporting. The LTFU period may be extended up to 2 years or until all subjects achieve the OS endpoint.

Early Treatment Discontinuation

Subjects may discontinue from treatment at any time, however subjects discontinuing prior to the End of Treatment visit (EOT; Visit 14) will be considered early treatment discontinuations.

Early Trial Discontinuation

Subjects are followed up until death or trial closure, regardless of treatment completion status. Subjects who withdraw from trial survival follow up will be considered early trial discontinuations. A subject who discontinues treatment early still may be a trial completer if all follow-up survival data are collected.

Medical History

Diseases, treatments, and surgical interventions occurring before, and up to, signing of informed consent form (ICF) will be considered medical history. Similar events occurring between informed consent and first vaccination will be considered pre-treatment adverse events (AEs), and captured on the AE page. Note events reflecting previous cancer diagnoses and treatments will be collected as part of prior bladder cancer history and therapy and not included with general medical history events.

Adverse Event

AEs are defined as any untoward occurrence of a medical event in a clinical trial subject temporally associated with the administration of a trial product or medicinal product which does not necessarily have a causal relationship with the trial product. Clinically significant abnormal laboratory values are also considered AEs. Collection of AEs begins at the time the subject signs the ICF and continues for 30 days following administration of the last dose of trial product for non-serious AEs and unrelated SAEs/AESIs; and for 100 days for related SAEs/AESIs.

Treatment Emergent Adverse Event (TEAE)

A TEAE is an AE with an onset on or after initiation of trial product, or an AE present at initiation of trial product that worsens. This includes all AEs occurring from first dose of trial product through 30 days after of last dose of trial product, if unrelated to trial product or non-serious. All trial product-related SAEs and AESIs through 100 days after the last dose of trial product will be counted as TEAEs.

Related TEAEs

A TEAE is determined to be related to trial product for the purpose of CSR reporting if assessed by the investigator as possible, probable, or definitely related to trial product. If a relationship is missing and the TEAE started after the initiation of an individual trial product, then the TEAE will be analyzed as being related to that individual trial product. Relationship will be collected separately for MVA-BN-CV301, FPV-CV301, and atezolizumab.

Serious Adverse Events

AEs that meet the seriousness criteria as described in Section 8.1.4 of the trial protocol are considered serious adverse events (SAEs). Collection of SAEs begins at the signing of the ICF and continues for 30 days after the last treatment with trial product for unrelated events, and for 100 days after the last dose for treatment-related events.

Severe Adverse Events

AEs are graded for severity using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Levels include 1: Mild, 2: Moderate, 3: Severe, 4: Life Threatening, and 5: Death. For analysis, severe AEs will include AEs ≥ Grade 3.

Adverse Events of Special Interest

AEs of special interest (AESIs) include Immune-mediated AEs (IMAEs) and cardiac events but may also include other events based on the opinion of the investigator. Autoimmune diseases and immune-mediated clinical syndromes, occurring after first treatment with trial

product, will be reported as potential IMAEs. In addition, cardiac events are considered AESIs. A Cardiac AESI is defined as:

- Any cardiac sign or symptom (attributed by the investigator to be cardiac related) developed since the first vaccination
- ECG abnormalities determined to be clinically significant developed since the first vaccination

Additionally, for atezolizumab AESIs will be reported based on the manufacturer's requirements (See trial protocol section 8.1.3 for further details).

1 Introduction

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing trial data and outlines the key statistical programming specifications. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the trial protocol. The SAP is written based on recommendations from *ICH E3: Structure and Content of Clinical Study Reports* (ICH, 1996), and *ICH E9: Statistical Principles for Clinical Trials* (ICH, 1998). Table, figure and listing shells are described in a separate document.

The included analyses described are based on the final clinical trial protocol "A Phase 2, Multicenter, Single-Arm Trial of CV301 in Combination with PD-1/L1 Blockade in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer version 2.0." This SAP will be followed completely for the analysis of data derived from the clinical trial. If any unforeseen additional analyses are included in the clinical study report (CSR) they will be clearly described as additional, unplanned analyses.

2 Trial Overview

2.1 Trial Description

This is a Phase 2, single-arm, multi-institutional clinical trial designed to study the combination of CV301 with atezolizumab in the first-line treatment of urothelial cancer (UC) not eligible for cisplatin-containing chemotherapy (Cohort 1), as well as in the second-line treatment of UC previously treated with standard first-line cisplatin-based chemotherapy (Cohort 2). The trial will be performed using an optimal two-stage design within each cohort (Simon, 1989). For the purpose of this trial, subjects are considered enrolled once they have received their first dose of trial product.

Stage 1, Cohort 1: Enroll 14 subjects. If objective response is not achieved in at least four subjects, the cohort will be stopped for futility. If objective response is achieved in at least four subjects, the cohort will proceed to Stage 2.

Stage 1, Cohort 2: Enroll 13 subjects. If objective response is not achieved in at least three subjects, the cohort will be stopped for futility. If objective response is achieved in at least three subjects, the cohort will proceed to Stage 2.

Stage 2, Cohort 1: Enroll an additional 19 subjects. If any subject is not evaluable for the primary endpoint, the subject may be replaced until a total of 33 subjects are evaluable for the primary endpoint of objective response rate (ORR).

Stage 2, Cohort 2: Enroll an additional 22 subjects. If any subject is not evaluable for the primary endpoint, the subject may be replaced until a total of 35 subjects are evaluable for the primary endpoint of ORR.

2.2 Design Techniques to Avoid Bias

This trial is single arm, so no blinding or randomization will occur. To maintain overall type-1 error and stop the trial early if no signs of efficacy are seen, a Simon 2-stage design will be employed within each cohort.

2.2.1 Methods of Assigning Subjects to Treatment Groups

This is a single arm trial, in which all subjects in both cohorts will receive CV301 in combination with atezolizumab.

2.2.2 Blinding

This is a single arm, open-label trial. No blinding will be used.

2.3 Objectives

2.3.1 Primary Objective

ORR (Rate of subjects achieving a best response of either Complete Response [CR] or Partial Response [PR]) as per investigator assessed Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

2.3.2 Secondary Objectives

The secondary objectives of the trial are:

- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Duration of Response
- Safety of the treatment combination of CV301 with atezolizumab

2.3.3 Exploratory Objectives

Analysis of biopsy tissue for differences between pre- and post-treatment samples correlation to subject survival e.g.:

- T cell receptor (TCR) clonality
- Tumor-Infiltrating-Lymphocytes (TILs)
- Protein expression for e.g. Programmed Death Ligand 1 (PD-L1) and other biomarkers
- Gene expression profiling for molecular subtyping

Analysis of tumor DNA for tumor mutational burden; DNA damage response gene mutations, microsatellite instability (MSI) status, and mismatch repair (MMR) deficiency status

Analysis of peripheral blood mononuclear cells (PBMCs) / serum for differences between pre- and post-treatment samples correlation to subject survival e.g.:

- Antigen-specific immune responses to carcinoembryonic antigen (CEA) and mucin-1 (MUC-1) as well as to other tumor-associated antigens (TAAs) to assess antigen cascade
- Immunophenotyping of immune cell subsets by flow cytometry
- Soluble biomarkers (e.g., cytokines and classical tumor markers)
- TCR clonality
- PD-1/L1 staining

2.4 Trial Population

The trial will enroll subjects who are at least 18 years of age, are willing and able to sign informed consent, have documented locally advanced or metastatic urothelial cancer. Subjects must have a life expectancy of at least 12 weeks, adequate organ function, and measurable disease assessable by RECIST v1.1.

2.5 Inclusion Exclusion Criteria

A list of inclusion and exclusion criteria is provided in the trial protocol. Subjects are required to meet all of the inclusion criteria and none of the exclusion criteria to enter the trial.

2.6 Endpoints

2.6.1 Primary Endpoint

ORR, defined as the proportion of subjects with a confirmed objective response (CR+PR) per investigator assessment according to RECIST v1.1.

2.6.2 Secondary Efficacy Endpoints

- OS, defined as the time from start of treatment to the time of death from any cause.
- Duration of response, defined as the time from the initial occurrence of documented OR until documented disease progression or death due to any cause on trial, whichever occurs first.
- PFS defined as the time from start of treatment to the first event of death or progressive disease (PD) per RECIST v1.1.
- Percentage of subjects with OS and PFS at 6 (PFS only), 9 (PFS only), 12, 18 and 24 months.
- Immune-related Response Criteria assessment of response rate per iRECIST, delayed responses (pseudo-progressions), duration of response and PFS.

2.6.3 Secondary Safety Endpoints

Safety of the combined treatment based on the following:

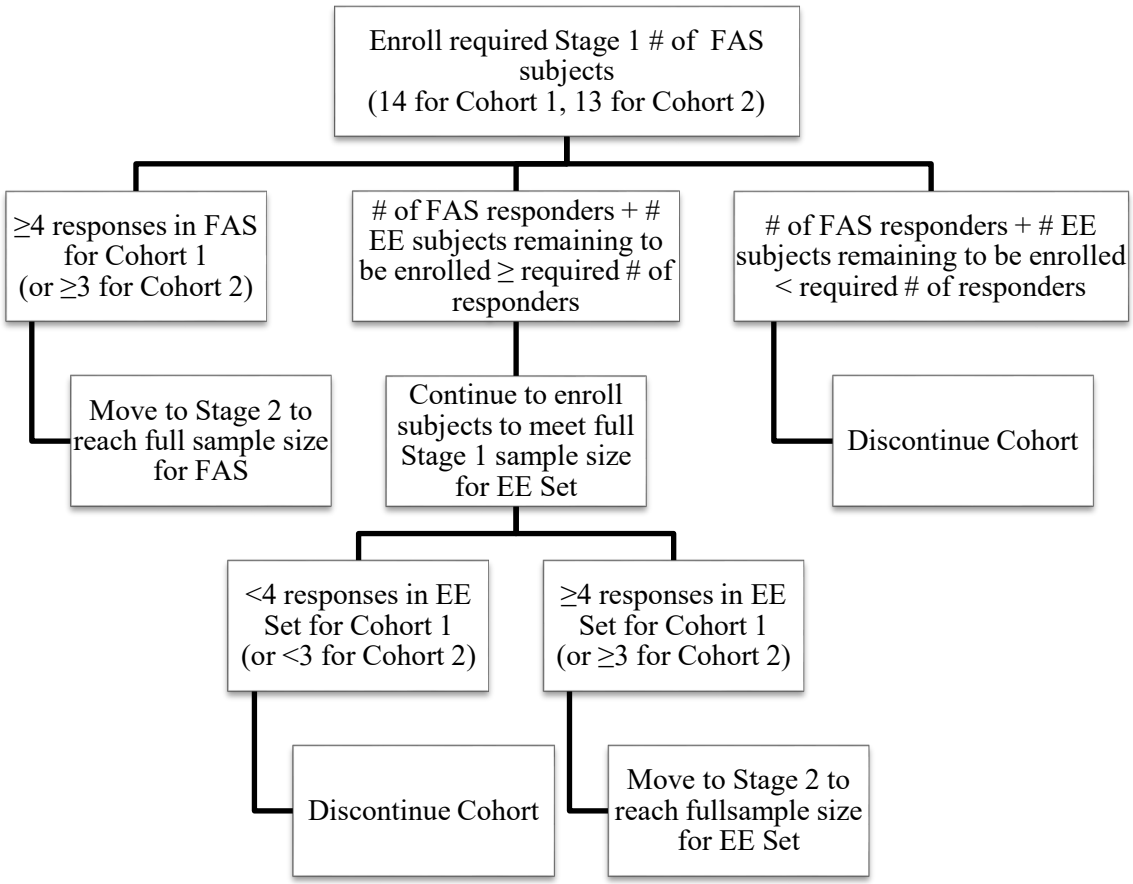
- AEs (incidence, severity, and seriousness of TEAEs)
- Safety Laboratory Measurements (summaries and shifts from baseline)
- Vital Sign Measurements (summaries)

2.6.4 Interim Analyses

The trial is designed using Simon's 2-stage design in 2 cohorts, number of subjects with objective responses will be continuously monitored with pre-specified efficacy-based stopping rules for each cohort. Although the primary efficacy analysis will be performed on the FAS, if it is unclear within the first 14 FAS subjects in Cohort 1 (or 13 in Cohort 2) that the criteria are met for futility for Stage 1, enrollment will continue in the cohort until the full Stage 1 sample size is reached for the EE Set. If, even with enrolling additional subjects for the EE Set and those subjects all being responders, the cohort would not be able to reach the required number of responders to move to Stage 2, the cohort will be discontinued without reaching the full size of the EE Set in Stage 1.

The decision rules are described in Figure 1.

Figure 1. Interim Analysis Decision Tree



Any decisions made regarding continuation of the trial will happen for each cohort, individually.

2.6.4.1 Primary Interim Analysis

The first post-treatment objective radiographic response assessment by the investigator will occur approximately 10 weeks after first treatment, with the second occurring 12 weeks later at the Week 22 visit. When the first 14 subjects in the FAS in Cohort 1, or the first 13 subjects in the FAS in Cohort 2 have completed at least 2 post-baseline CT scans (or MRIs if applicable), analysis for the FAS will be performed. If the number of responders meets the Stage 1 continuation criterion (> 3 responses for Cohort 1 or > 2 responses for Cohort 2), enrollment for the cohort will continue until the FAS has a total 33 subjects in Cohort 1, or 35 subjects in Cohort 2. Subjects who are enrolled to the EE set for the Stage 1 sensitivity analyses will be included as part of the total number of subjects in the FAS.

For subjects who have completed multiple scans, the best objective response will be used. Since the number of responders is continuously monitored, if the continuation criterion is met in either cohort in the FAS before the first 14 subjects in Cohort 1 and the first 13

subjects in Cohort 2 have completed at least 2 post-baseline tumor assessments, enrollment for the cohort will resume as described above.

If the number of responders does not meet the continuation criterion when the first 14 subjects in the FAS in Cohort 1, or the first 13 subjects in the FAS in Cohort 2, have completed at least 2 post-baseline tumor assessments, progress prior to having 2 post-baseline tumor assessments, or discontinue early from the trial, the combination treatment for the cohort will not be considered promising.

2.6.4.2 Sensitivity Interim Analysis

If the success criterion can be met in the EE set, the cohort will continue until the number of subjects in the EE set reaches the Stage 1 sample size, and a sensitivity analysis will be performed when all subjects in the EE set have completed at least 2 post-baseline tumor assessments, progress prior to having 2 post-baseline tumor assessments, or discontinue early from the trial.

- If the number of responders in the EE set does not meet the Stage 1 continuation criterion, the cohort will be discontinued. If the number of subjects completing 2 post-baseline tumor assessment in the EE set exceeds the planned Stage 1 sample size at time of the interim analysis, the Stage 1 stopping rule will be based on a revised criterion ε_1, where ε_1 is the largest integer for which the power would remain above 70% for each cohort by assuming the planned n is the final total number of EE subjects. The probability of rejecting the treatment is

  $$B(\varepsilon_1; p, m_1) + \sum_{x=\varepsilon_1+1}^{\min(m_1,r)} b(x; p, m_1)\, B(r-x; p, n-m_1), \qquad [1]$$

  where $B(\varepsilon_1; p, m_1)$ and $b(x; p, m_1)$ are the binomial distribution and density function; m_1 is the Stage 1 sample size, and r is the design rejection criterion at the end of the trial when the sample size is n (Simon, 1989). When p equals the alternative hypothesis, [1] represents the type II error, β, and thus the power equals 1- β.

- If the number of responders in the EE set meets the Stage 1 continuation criterion ($>\varepsilon_1$), a further decision will be made whether to continue to Stage 2 to enroll a total of 33 evaluable subjects in Cohort 1 or 35 evaluable subjects in Cohort 2 for sensitivity analyses. If a strong signal in the EE set is not observed, the cohort will be discontinued. If there is a high probability (>50%) that the alternative hypothesis (43% in Cohort 1 and 33% in Cohort 2) is true based on data obtained from Stage 1, the cohort will continue to Stage 2 based on the EE set. The posterior probability will be calculated based on a non-informative prior, p ~ Beta (1,1).

3 Trial Design

Trial Procedure	Screening Phase Day -28 to Day 1	Week (3 wk interval +/- 4 days)						Week (6 wk interval +/- 1 wk)		Week (12 wk interval +/- 2 wks)						Long Term FU
		1	4	7	10	13	16	22	28	40	52	64	76	88	100 EOT[12]	3-month interval +/- 2 wks
		Day														
		1	22	43	64	85	106	148	190	274	358	442	526	610	694 EOT	
		Visit														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Trial Procedures																
Informed Consent[1]	X															
Demographics	X															
Medical History	X															
Physical Exam incl. vital signs[2]	X															
Targeted PE incl. vital signs[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[3]	X															
Eligibility Criteria	X															
Concomitant Medications	X	collected at all clinic visits (including atezolizumab dosing visits)														
Adverse Events[4]	X	collected at all clinic visits (including atezolizumab dosing visits)														X[4]
Survival Status and Auto-immune/ IM clinical manifestation																X
Tumor Biopsy	X[5]			X[6]												
Radiology Assessments																
CT scan: Thorax, Abdomen and Pelvis[7]	X				X			X	X	X	X	X	X	X	X	

Trial Procedure	Screening Phase Day -28 to Day 1	Week (3 wk interval +/- 4 days)						Week (6 wk interval +/- 1 wk)		Week (12 wk interval +/- 2 wks)						Long Term FU
		1	4	7	10	13	16	22	28	40	52	64	76	88	100 EOT[12]	3-month interval +/- 2 wks
		Day														
		1	22	43	64	85	106	148	190	274	358	442	526	610	694 EOT	
		Visit														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Laboratory Assessments																
Hematology[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV, HbsAg, HCV	X															
INR, PT, aPTT	X															
Thyroid function test	X	X		X		X	every 6 weeks									
Biomarker Analyses[9]	X		X		X			X			X					
Urinalysis	X		X		X		X	X	X	X	X	X	X	X	X	
Pregnancy Test[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing																
Prime Vaccine: MVA-BN-CV301[11]		X	X													
Boost Vaccine: FPV-CV301[11]				X	X	X	X	X	X	X	X	X	X	X	X	
Atezolizumab		X	X	X	X	X	X	every 3 weeks[8,10]								

EOT = End of Treatment, PE = Physical Examination, AE = Adverse Event, SAE = Serious Adverse Event, AESI = Adverse Event of Special Interest, WOCBP = Women of Childbearing Potential

[1] ICF can be obtained prior to Screening visit

[2] Blood pressure and pulse rate should be obtained after the subject has been seated in an upright position for at least 5 minutes.

[3] Troponin I will only be measured if clinically indicated.

[4] The reporting period for non-serious AEs and unrelated SAEs/AESIs ends 30 days after last administration of the trial product. The reporting period for related SAEs/AESIs ends 100 days after last administration of the trial product. A phone follow-up will be performed 100 days after the last administration of trial product to collect this information and schedule a follow-up visit, if clinically indicated.

[5] Patients who do not have archived tissue specimens meeting eligibility requirements must undergo a biopsy sample collection during the screening period. Acceptable samples included core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsy samples for cutaneous, subcutaneous, or mucosal lesions.

[6] Optional at any of the following visits: Visit 3-6.

[7] If there is a medical reason, subject may have MRI instead of CT scan upon approval from BN.

[8] Hematology and Serum Chemistry will be performed prior to every atezolizumab infusion. Hematology will include hemoglobin, hematocrit, red blood cell count, total white blood cell count with differential, platelet count, mean cell volume, mean corpuscular hemoglobin, and red blood cell distribution width. Serum chemistry will include: total protein, albumin, alkaline phosphatase, total bilirubin, ALT, AST, lactate dehydrogenase, creatinine, blood urea nitrogen, uric acid, glucose, calcium, phosphorus, bicarbonate, chloride, potassium, sodium, lipase and amylase.

[9] Sample collection (peripheral blood for PBMC, serum) must occur prior to vaccine dosing. Sample collection for Biomarker analyses should be repeated if subject comes off trial due to PD or AE or if the subject has an objective response.

[10] For WOCBP, a pregnancy test is required prior to every atezolizumab infusion. Urine or serum pregnancy test is acceptable at any given visit depending on investigator and/or patient preference.

[11] The trial subject must be kept under close observation at the clinical trial site for at least 30 minutes following vaccinations.

[12] EOT visit should take place within 28 days of withdrawal.

4 Statistical Methods

4.1 Planned Sample Size

A Simon's two-stage Minimax design (Simon, 1989) was used to calculate sample size for Cohort 1. Cohort 1 will have a minimum of 14 subjects and a maximum of 33 subjects, with the maximum occurring if and only if at least 4 subjects have an objective response in the first stage of the trial. The alternative admissible 2-stage design (Jung et al., 2004) was used to calculate sample size for Cohort 2. Cohort 2 will have a minimum of 13 subjects and a maximum of 35 subjects, with the maximum occurring if and only if at least 3 subjects have an objective response in the first stage of the trial. The total minimum sample size for the trial is 27, with a maximum of 68 subjects.

The design for Cohort 1, platinum ineligible subjects, is based on a prior published ORR of 23% for atezolizumab monotherapy (Balar et al., 2017). The null hypothesis that the true ORR is 0.23 will be tested against a one-sided alternative. The null hypothesis will be rejected if 13 or more responses are observed in 33 subjects. This design yields an actual 1-sided type I error rate of 0.0244 and power of 0.7027 when the true ORR is 0.43 for the combination.

The design for Cohort 2, platinum refractory subjects who are anti-PD-L1 naïve, is based on a prior published ORR of 15% for atezolizumab monotherapy (Rosenberg et al., 2016). The null hypothesis that the true ORR is 0.15 will be tested against a one-sided alternative. The null hypothesis will be rejected if 10 or more responses are observed in 35 subjects. This design yields an actual 1-sided type I error rate of 0.0249 and power of 0.7092 when the true ORR is 0.33 for the combination.

Based on simulations with the two-stage, two-cohort design, the overall type-1 error rate will be approximately 4.7%, and the power for the trial, indicating at least one of the two cohorts will be positive given the alternative hypotheses are true, is approximately 91%.

4.2 Analysis Populations

For the purpose of statistical analysis, there will be 2 analysis populations: Full Analysis Set (FAS) and the Efficacy Evaluable (EE) Set.

The FAS consists of all subjects taking any amount of trial vaccine, whether MVA-BN-CV301 or FPV-CV301. The FAS will be the primary population for all analyses.

The EE Set consists of all subjects from the FAS who meet the following criteria:

- Received 2 prime doses of MVA-BN-CV301 (Weeks 1 and 4)
- Have a baseline CT/MRI scan assessable per RECIST v1.1

The EE set will be used for sensitivity analyses of the primary and secondary efficacy endpoints.

Although the primary efficacy analysis is on the FAS population, enrollment may continue for Stage 1 until the EE set reaches the full sample size of 14 for Cohort 1, or 13 for Cohort 2 (Section 2.6.4).

4.3 Data Handling Conventions

4.3.1 Visit Windowing

For analysis purposes, all by-visit data will be mapped to a visit window to maintain consistency of therapeutic duration among summaries at each time point. The visit that occurs out of window may be analyzed along with data from an earlier or later visit if the trial day falls into a different visit window category. In addition, unscheduled visits that fall into the window for a scheduled visit may be counted along with that visit, such that no data are excluded from potential summaries. In the case of multiple visit results within a visit window, descriptive statistics will be based on non-missing data from a visit closest to the scheduled visit day. Categorical summary will be based on the worst non-missing results. For the current trial, visits will be mapped by trial day as follows:

Table 1 Windowing Schema for Screening and the Treatment Period

Visit Number	Visit	Planned Trial Day	Protocol Allowed Visit Window (days)	Trial Day Window for Analysis (days)
1	Screening	Within 28 days of first treatment	-28 to -1	<1
2	Week 1	1	1	1-11
3	Week 4	22	18-26	12-32
4	Week 7	43	39-47	33-53
5	Week 10	64	60-68	54-74
6	Week 13	85	81-89	75-95
7	Week 16	106	102-110	96-127
8	Week 22	148	144-152	128-169
9	Week 28	190	183-197	170-232
10	Week 40	274	267-281	233-316
11	Week 52	358	351-365	317-396
12	Week 64	442	428-456	397-484
13	Week 76	526	512-540	485-568
14	Week 88	610	596-624	569-652
15	Week 100	694	680-708	> 652

As long-term FU visits only collect concomitant medication and vital status data, no windowing will be needed for this trial phase.

4.3.2 Missing or Partial Dates

All data will be listed and summarized as captured in the electronic Case Report Form (eCRF) or transferred from external sources (e.g., lab, ECG). It may be necessary to impute incomplete dates to correctly assign events to a period or to calculate durations.

For prior and concomitant medications, AEs, and cancer history dates the following rules will apply:

Missing	Rule for start date	Rule for end date	Flag for imputation
Day	First of month	Last of month*	D
Month†	1 January	31 December*	M
Year†	First Treatment Date	Date of Data Cutoff/Lock	Y

* Unless the imputed start date is before first visit date, in which case first visit date is used; or the imputed stop date is after last visit date in which case last visit date available is used.

† It is assumed that a missing Month implies a missing Day as well, and that a missing Year implies a missing Month and Day.

If the imputation of an AE start date leads to a date prior to the date of first vaccination, and it is possible that the AE start date can be on or after date of first vaccination based on partial date information (e.g., occurred on the same month), it will be set to the date of first vaccination to be conservative. In the event the imputation of an end date leads to a date after the death date of a subject, the death date will replace the imputed date.

4.3.3 Data Handling Conventions for Efficacy Analyses

Subjects who have no record of CR/PR and withdraw early from the trial or are lost to follow up will be considered as non-responders for the ORR analyses.

For PFS, if a subject has no date of death and has not progressed by the time of the analysis, the subject will be censored at the last radiologic assessment showing no progression has occurred. For sensitivity analyses on the FAS, if a subject has no post-baseline radiologic assessment, they will be censored on Day 1.

4.3.4 Assignment of AEs to Treatment Period

Each AE will be assigned to a treatment period using date of vaccination (or infusion if this is the final treatment) and date of onset of AE:

- All AEs beginning before the first treatment with trial product will be classified as pre-treatment AEs belonging to the Screening Phase.
- All AEs starting on the day of first MVA-BN-CV301 vaccination until the day prior to the first FPV-CV301, or until early treatment termination, will be assigned to the MVA Vaccination Period.

- All AEs starting after the first FPV-CV301 vaccination through 30 days post-last trial product, or until early termination, will be assigned the FPV Vaccination Period.
- All AEs starting after the first dose of trial product through 30 days post last trial product (CV301 or atezolizumab, whichever is latest) will be included in the Overall Treatment Period.
- Related SAEs and AESIs starting after 30 days but prior to 100 days after the last trial product dose will be assigned to the FU phase of the trial. Other AEs (i.e., not serious or unrelated) occurring during the same time period will be assigned to the FU phase but excluded from tables, if collected, as they are not considered treatment emergent.

If an AE coincides with the date of a vaccination, the AE will be assigned to the treatment period corresponding to the vaccination on this date to be conservative.

4.3.5 General Consideration for AEs

MedDRA version 21.0 will be used to code AEs, medical history events, and baseline signs and symptoms.

Duration of an AE is calculated as follows:

end date of AE – start date of AE + 1

- In case of missing start date or missing end date, duration will be missing.
- In case of ongoing end date, the duration will not be calculated.

Time interval between vaccination and onset of AE are calculated as follows:

Relative day of onset of AE is calculated as follows:

onset date of AE – most recent vaccination date + 1

- In case of missing start date, no calculation will be performed.

4.4 Analysis and Presentation Methods

4.4.1 General Presentation Methods

All individual data entered in the eCRF and applicable derived data will be listed in subject-level data listings. Listings will be sorted by subject, visit, and parameter, based on the domain presented. Tables will be sorted by parameter and scheduled visit, as applicable.

All tables will be presented by cohort as follows:

- Cohort 1

- Cohort 2
- Overall (Excluding efficacy displays)

With the exception of titer data, continuous measurements will be summarized using the number of observations (n), mean, standard deviation, minimum, median, and maximum (Max). Categorical data will be summarized using frequencies and percentages, unless otherwise stated. Titer data, as well as any data that are log-normally distributed, will be summarized using geometric means and 95% confidence intervals (CIs).

All statistical summaries and analyses will be performed using SAS® version 9.3 or higher (SAS Institute, Cary, NC, USA) for Windows.

In the case of repeated assessments at individual time points, all reported values will be presented in subject-level listings based on the CRF visit. For tabular summaries, an individual analysis value will be chosen or created from the multiple values at the time point and flagged at the analysis dataset level per the visiting window in Section 4.3.1. The value used for analysis in the tables will be flagged in the listings.

4.4.2 Considerations for Multicenter Studies

CV301-BLD-001 will be performed in approximately 12 trial sites with a possible range of 27-68 subjects split into 2 cohorts. As the maximum number of subjects per cohort per site is fewer than 10, no by-center analyses will be performed.

4.4.3 Adjustments for Covariates

Due to the baseline differences in the two cohorts, all efficacy analyses will be performed within cohort. Additionally, small sample size prevents further subgroup analyses from being possible.

4.4.4 Adjustments for Multiple Comparisons

Due to the two-cohort, two-stage design of this Phase 2 trial, the primary endpoint of ORR will be tested multiple times. To account for this, the sample size for each cohort was based on a one-sided nominal alpha of 0.025 and 70% power. As each cohort represents an independent test, the overall trial wide type I error rate would remain at or below 0.05 (one-sided). Based on simulations with the two-stage, two-cohort design, the overall type-1 error rate will be approximately 4.7%, and the power for the trial indicating at least one of the two cohorts will be positive given the alternative hypotheses are true, is approximately 91%.

4.4.5 Efficacy Analyses

4.4.5.1 Primary Endpoint

The primary efficacy endpoint for the trial is the ORR, defined as the proportion of subjects achieving CR or PR, whichever occurs first, based on investigator-assessed RECIST v1.1 evaluations. Due to the Simon's 2-stage design, hypothesis testing will occur at the end of Stage 1 (interim analysis), and if successful, at the end of Stage 2 within each cohort.

The success criteria are based on the point estimate of the FAS within each cohort. For Cohort 1, at least 4 responses are required in the first 14 subjects to move to Stage 2. For the final Cohort 1 analysis, the null hypothesis that ORR is no more than 0.23 will be rejected if 13 or more responses are observed in the 33 subjects of the FAS. For Cohort 2, at least 3 responses are required in the first 13 subjects to move to Stage 2. For the final Cohort 2 analysis, the null hypothesis that the ORR is no more than 0.15 will be rejected if 10 or more responses are observed in the 35 subjects of the FAS.

In case the number of subjects in the analysis set(s) exceeds the planned sample size, the success criteria will be chosen to preserve the design type I error rate of 0.025 (one-sided) using the exact 2-stage binomial calculation (replacing p with p_0 in formula [1], Section 2.6.4.2). Type I error equals 1 minus the result from formula [1] when $p = p_0$.

For the final trial analysis, the number and percentage of subjects in each RECIST v1.1 response category, as well as those with a best objective response of CR or PR, will be summarized based on the FAS. The two-sided 90% exact binomial confidence interval for the ORR will be calculated using the Clopper-Pearson method.

Sensitivity analyses will be explored at the end of the trial based on a repeated analysis for any potential immune-related responses observed, as well as a repeat of the analysis on the EE set. For immune-related response cases, ORR analyses using iRECIST criteria will also be provided. For iRECIST, complete or partial responses are still able to be achieved after an initial unconfirmed progression, whereas with RECIST v1.1 once any evidence of progression is recorded, no further responses can be evaluated. For subjects who are not evaluated by iRECIST criteria, their tumor response based on RECIST v1.1 response guidelines will be used.

4.4.5.2 Secondary Endpoints

4.4.5.2.1 Progression-Free Survival

PFS is defined as the time interval from first treatment to objective tumor progression or death. Accordingly, the precise definition of progression and the timing of CT scans to document progression are very important. Every effort must be made to assure that timeframes for post-treatment CT scans are achieved, so that both treatment groups can be usefully compared.

Assessments must be adequate to evaluate target lesions, non-target lesions, and to search for new lesions.

The secondary endpoint of PFS will be based on the investigator's assessment using RECIST v1.1 response guidelines. PFS will be defined as the time from the day of first treatment to the start of disease progression or death (any cause), whichever occurs first. Subjects who do not have disease progression or have not died will be censored at the date when the last tumor assessment determines a lack of progression. If a subject begins a new anti-cancer therapy or has radiotherapy or surgery at a lesion site prior to documented progression (or death), the subject will be censored at the last assessment where the subject was documented as progression free prior to the intervention.

The Kaplan-Meier curve for PFS and the median PFS will be presented for the FAS.

Additionally, an investigator assessed PFS analysis that includes both investigator-judged PD according to RECIST v1.1 and symptomatic deterioration will be provided.

A binary endpoint for PFS will also be analyzed at milestone time points. The number and percentage of subjects who are progression free based on the above definition at 6, 9, 12, 18, and 24 months will be summarized within the FAS. The two-sided 90% exact binomial confidence interval for the PFS at each time point will be calculated using the Clopper-Pearson method.

A recently published meta-analysis concluded that in checkpoint inhibitor trials 6-month PFS rate is recommended as an endpoint because it is the best predictor of 12-month OS rate. In the absence of prospective validation, the decision adopted is to retain 6-month PFS rate as a secondary endpoint with the aim of complement the primary endpoint ORR in the interpretation of trial results as a whole.

In case some additional immune-related responders are observed, PFS analysis using iRECIST criteria will be performed. The iRECIST modification requires a confirmation of PD at least 4 weeks later with imaging; once confirmed, the date of progression is defined as the first date that the total tumor burden was shown to have increased by at least 20% compared with the nadir. For subjects who are not evaluated by iRECIST criteria, their disease progression based on RECIST v1.1 response guidelines will be used.

4.4.5.2.2 Overall Survival

OS is defined as the time between the date of first treatment and the date of death due to any cause. Subjects who are alive or have the competing events of "definite" loss to follow-up or withdrawal of consent will be right censored at the date of last contact.

OS = Date of death/competing event/censoring - date of first treatment + 1.

Imputation of missing date parts will follow the rules previously specified. Competing events for death are "definite" lost to follow-up and withdrawal of consent for continued vital status assessments. Both competing events are subject to revision for an individual subject with the passage of time. Subjects will be censored for competing events as well as survival by using their last contact date in the clinical database.

The 12-month OS rate and the product-limit estimate of median survival, as well as their 90% confidence intervals will be summarized. A Kaplan-Meier curve will summarize OS graphically. The 18-month and 24-month survival rates will also be provided along with their 90% CIs.

4.4.5.2.3 Duration of Response

Duration of response is defined as the time from response (CR or PR, whichever occurs first) to investigator assessed progression using RECIST v1.1 or death, and will be summarized based on the number of subjects with response in the FAS. Subjects who do not have disease progression or have not died will be censored at the date when the last tumor assessment determines a lack of progression.

Duration of response will be summarized using the product-limit estimate of median survival along with its 90% confidence interval. The Kaplan-Meier curve will summarize duration of response graphically.

In case some additional immune-related responders are observed, duration of response analyses using iRECIST criteria will be provided. For subjects who are not evaluated by iRECIST criteria, their tumor response based on RECIST v1.1 response guidelines will be used.

4.4.6 Exploratory Endpoint Analysis

4.4.6.1 Tissue Biopsy Variables

Pre-treatment tumor tissue samples are required for inclusion in the trial, and will be collected at screening if an archived tumor sample is not available. Optional tumor biopsies will be collected at any of the following visits: Visit 3 through 6, but are not required.

- Number and localization (immunoscore) of Tumor-Infiltrating Lymphocytes
- Number and localization (immunoscore) of PD-L1 positive tumor cells (TPS) and immune cells.
- Presence and strength of gene expression signatures correlated to immune status and response (signatures ranked from low to high)

The following analyses will optionally be performed based on BN review of previous results:

- Diversity of T-cell receptor clonality – (higher number of specific clones is a better outcome)

- Degree of tumor mutational burden (burden ranked from low to high)
- Presence and degree of DNA damage response gene mutations (MSI status [positive/negative], MMR deficiency status [mutated/not mutated])

4.4.6.2 Peripheral Blood Mononuclear Cells and Serum

PBMC and serum samples will be taken at Screening, as well as visits 2, 4, 7, and 10.

PBMC Variables

- Number of specific spot forming units and/or antigen specific cells per 10^6 PBMC in stimulations with peptide pools of CEA, Mucin-1 or other Tumor-associated antigens
- Percentage of defined immune cell populations
- T-cell receptor clonality (see above)

Serum Variables

- Amount of soluble biomarkers including cytokines and classical tumor markers

4.4.6.3 Exploratory Endpoint Analysis

In general, analyses of exploratory endpoints will be based on the FAS with available data for the exploratory analyses. Missing data will not be imputed. Analyses will focus on comparing the post-baseline values with the baseline values for changes in the measured parameters of immune response.

Correlation between objective tumor response or clinical parameters and measured parameters of immune responses will be explored.

Continuous data will be summarized via mean (and 95% CI), standard deviation, median, minimum, and maximum by visit where samples are collected per trial schedule. In case of log-normal data, log transformations may be performed and summarized with the geometric means in place of the arithmetic means and 95% CIs.

Detailed analyses for the exploratory immune response measures will be added to a SAP amendment when preliminary results are available.

4.4.7 Disposition and Trial Population Information

4.4.7.1 Disposition

All subjects screened will be accounted for in a disposition table and CONSORT diagram (Schulz et al., 2010). A summary table will be presented specifying the number of subjects screened, treated, completing the active treatment phase, included in each analysis set,

withdrawing from active treatment phase, entering follow up, and the number withdrawing from follow up. For subjects withdrawing from treatment or follow up, the frequency of primary reasons for withdrawal will also be summarized. A separate summary for screening failures and reason for screening failure will also be presented.

A listing will present all screened subjects, date of completion or discontinuation, date of last dose of trial product, reason for discontinuation from treatment, and reason for withdrawal from follow up.

4.4.7.2 Analysis Populations

Frequencies and percentages of each trial population will be presented along with disposition. Reasons for exclusion from any population group will be included in the screening failure or protocol deviations summaries.

4.4.7.3 Protocol Deviations

Protocol deviations are collected on both a site and subject-level basis. Subject level deviations will be databased and listed, including deviation term, deviation category, and affected visits or dates. Categorized deviations will be summarized using frequencies and percentages in a table for the FAS.

4.4.7.4 Demographics and Baseline Characteristics

Variables

- Age at Screening (years)
- Age Group 1 (< 45, ≥ 45 – < 55, ≥ 55 – < 65, ≥ 65 – < 75, ≥ 75)
- Age Group 2 (< median, ≥ median)
- Sex (Male, Female)
- Childbearing Status (Yes, No: Post-Menopausal, No: Surgically Sterile, N/A)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height [cm]
- Body weight [kg]
- BMI [kg/m^2]
- Tobacco Use (Current Smoker, Previous Smoker, Never Smoked)

Analyses

Subject-level listings will be presented for all data in the database. Tables of descriptive statistics for demographics will be produced for the FAS. Descriptive statistics will be presented for the continuous demographic variables by cohort and overall. Frequencies and percentage of subjects will be tabulated for all categorical variables by cohort and overall. Percentages will be based on the total number of subjects in the FAS for demographics and baseline disease characteristics within each cohort.

The following formula will be used to calculate BMI:

BMI = Weight (kg)/[Height (m)]^2

4.4.7.5 Bladder Cancer History and Baseline Disease Characteristics

Variables

- Eastern Cooperative Oncology Group (ECOG) Performance Status (0, 1, ≥ 2)
- Time from Initial Diagnosis to First Treatment (years)
- Duration of Primary Curative Intervention (months)
- Disease Free Interval (months)
- Time from Recurrence after a Disease-Free Interval to First Treatment (years)
- Primary Tumor Site (Renal Pelvis, Ureter, Urethra, Urinary Bladder, Other)
- Stage at Diagnosis (I, II, III, IV)
- T Category (T_x, T_0, T_a, T_{is}, T_1, T_{2a}, T_{2b}, T_{3a}, T_{3b}, T_{4a}, T_{4b})
- N Category (N_x, N_0, N_1, N_2, N_3)
- M Category (M_0, M_1)
- PD-L1 tumor proportion score (TPS; < 1%, ≥ 1% - 10%, ≥ 10%)
- Current Metastatic Disease Sites (Yes, No)
    - Sites of Current Metastatic Disease: Adrenals, Bone, Bone Marrow, Chest Wall, Central Nervous System/Brain, Fallopian Tubes, Kidney, Large Intestine, Liver, Lung, Lymph Nodes, Pancreas, Peritoneum, Pleura, Rectum, Small Intestine, Spleen, Stomach, Uterus, Other

Analyses

Missing dates for cancer history will be imputed per Section 4.3.2. Frequencies and percentage of subjects will be tabulated for categorical variables by cohort and overall. Percentages will be

based on the total number of subjects in the FAS within each cohort. The following formulas will be used to calculate the above time-specific variables:

Time from Initial Diagnosis to First Treatment = (Date of First Treatment – Date of Initial Diagnosis + 1)/365.25

The following will be included only in subject-level listings:

Duration of primary curative intervention in months = (End Date of Primary Curative Intervention – Start Date of Primary Curative Intervention + 1)/30.4375

Disease-free interval in months = (Date of Recurrence – End Date of Primary Curative Intervention + 1)/30.4375

Time from Recurrence after a Disease-Free Interval to First Treatment in months = (Date of First Treatment – Date of Recurrence + 1)/30.4375

4.4.7.6 General Medical History and Baseline Signs and Symptoms

Medical history data are collected at screening and coded to MedDRA version 21.0 preferred terms (PTs) and system organ classes (SOCs). Summaries of medical history events will be created by PT and SOC for the FAS. SOCs will be sorted by descending incidence, and within each SOC, PTs will be sorted by descending incidence in the overall column.

Baseline signs and symptoms are defined as AEs that occur between the signing of informed consent and the first treatment with trial product. These events are to be reported along with the TEAEs in the CRF, but will be summarized separately as events prior to the initiation of treatment with trial product. Like medical history events, they will be coded to MedDRA PTs and SOCs. Baseline signs and symptoms will also be listed by SOC and PT along with the AE data. Relative day of onset will be calculated as described in Section 4.3.5.

4.4.7.7 Prior and Concomitant Medication and Procedures

All prior and concomitant medication will be coded to WHO DDE (B3 version 2018 Mar) Anatomic-Therapeutic-Chemical (ATC) classes and preferred names. Displays of **prior** medications include medications where end date is before date of first administration of trial product. Displays of **concomitant** medications include all medications started prior to first treatment and are ongoing, medications with missing end dates, or medications with start dates after the first administration of trial product. Tables by ATC class and preferred name, ordered in descending incidence of ATC class and preferred name within ATC class, will be presented for the FAS. Subject level listings will be created based on the original CRF data along with the WHO Drug coding results.

4.4.7.8 Non-drug Therapies and Procedures

All non-drug therapies and procedures will be coded to SOCs and PTs using the MedDRA dictionary version 21.0. Tables by SOC and PT for the FAS, with SOCs being sorted by decreasing incidence in the overall column, and PTs sorted similarly within SOCs. Subject level listings will be created based on the original CRF data.

4.4.7.9 Post-Treatment Cancer Therapies

Post-treatment cancer therapies are medications or combinations of medications that are captured after the subject has withdrawn from the active treatment period. Each new therapy (single or combination of medications) will be classified by type (hormonal, immunotherapy, chemotherapy, etc.) and counted as a new line of therapy for the purpose of analysis. Analyses based on the number of post-treatment lines of therapy and categories of post-treatment lines of therapy will be performed along with efficacy endpoints.

4.4.7.10 Exposure

Exposure Variables

- Number of CV301 (MVA-BN and FPV) vaccinations received
- Number of atezolizumab treatments received
- Duration of exposure to trial product

Exposure Analyses

Exposure to trial products will be summarized by the number of doses received for each trial product (categorical and continuous summaries) as well as the total duration in days the subject was treated. Duration is calculated as follows:

Date of Last Dose of Trial product – Date of First Dose of Trial product + 1.

Summaries of exposure will be performed by cohort and overall based on the subjects in the FAS. Exposure data will also be listed by subject.

Note, as trial products are given at office visits, treatment compliance is not expected to be an issue. Therefore, no compliance calculations will be performed for the trial.

4.4.8 Safety Variables and Analyses

4.4.8.1 Adverse Events

Variables

- Baseline Signs and Symptoms (pre-treatment AEs)

  Any AE recorded between ICF signing and first treatment with trial product, regardless of seriousness.

- TEAEs
- SAEs
- AESIs

  AESIs include IMAEs and Cardiac events. IMAEs will be collected from the "Potential IMAE" CRF page where the question "Does this event have an immune-mediated etiology or an immune-mediated component?" on the IMAE page is marked as "Yes." Cardiac AESIs will be identified where "AESI?" is marked as Yes on the AE CRF page. As events coded as "Cardiac disorders" per MedDRA SOC and ECGs with clinically significant abnormalities are considered AESIs, cross checking will be performed to ensure all clinically significant ECG results have a corresponding AE in the database prior to database lock. In addition, Troponin I laboratory testing will also be cross checked versus the AE page in the CRF if results are deemed clinically significant by the investigator.

- Relationship to trial product (MVA-BN-CV301, FPV-CV301, atezolizumab)

  Relationship is collected as unrelated, unlikely, possibly, probably, or definitely related on the AE CRF page. AEs reported as possibly, probably, or definitely related, along with any missing relationship values, will be summarized as related to the treatment of interest. For overall trial product relationship summaries, if any of the three individual trial products are considered related to the AE, the overall relationship will be defined as related to trial product.

- Severity of AEs (per CTCAE v5.0 grade)

  TEAEs will be categorized as 1: Mild, 2: Moderate, 3: Severe, 4: Life Threatening, or 5: Death on the AE CRF page. For summaries, severe AE displays will include all AEs ≥ Grade 3

- TEAEs leading to Treatment Discontinuation

  Treatment discontinuation will be identified as an AE with an action taken of "Drug Withdrawn" for any of the three trial products.

- TEAEs leading to Death

TEAEs with either an outcome of "Fatal" or a severity of "5: Death" will be considered TEAEs leading to death.

Analyses

Summary tables will be presented by treatment period (MVA Vaccination Period, FPV Vaccination Period, and Overall Treatment Period), cohort, and overall including frequency and incidence of AEs, and ordered by descending incidence of SOCs and PTs for the following categories:

- Any TEAEs
- Non-Serious TEAEs occurring in ≥ 5% of either cohort or overall
- Related TEAEs, including the following subcategories:
  - TEAEs related to MVA-BN-CV301
  - TEAEs related to FPV-CV301
  - TEAEs related to atezolizumab
  - TEAEs related to trial product
- TEAEs ≥ Grade 3
- Related TEAEs ≥ Grade 3
- SAEs
- Related SAEs
- AESIs, including IMAEs and Cardiac Events
- Related AESIs
- TEAEs leading to discontinuation of treatment

In addition to the above summary categories, listings will also include the following:

- Baseline Signs and Symptoms
- TEAEs leading to death
- Post-treatment period SAEs and AESIs

A summary table of TEAEs will be created for the following categories: TEAEs, SAEs, AESIs, Related TEAEs, Severe TEAEs, Severe and Related TEAEs, Serious and Related TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death. Event counts and subject incidences will be presented within each category and cohort, as well as overall, for the FAS.

The incidence for the above categories will be calculated as the number of subjects developing the specified AE type, divided by the number of subjects in the cohort. The incidence of AEs will also be calculated within each treatment period.

TEAEs will be summarized by SOC and PT and ordered by descending incidence of SOC, as well as descending incidence of PT within SOC. For TEAEs and related TEAEs, summaries will also be provided by

All AEs will be listed by subject, SOC, and PT. Per protocol, no new AEs should be reported during the LTFU phase, with the exception of related SAEs and related AESIs through 100 days post-last treatment. Any other AEs are reported during the LTFU phase will be listed and flagged as non-treatment emergent, but will not be included in the tables.

For summaries by relationship, CRF relationship categories will be dichotomized as related or unrelated per the above definition. Subjects experiencing more than one TEAE within an SOC or PT will be reported for the highest relationship category for the event of interest.

For summaries by severity, the CTCAE v5.0 grade will be used to summarize severe AEs including AEs ≥ Grade 3. Again, if a subject has multiple AEs within an SOC or PT the most severe AE will be counted for the event of interest.

A bar chart of TEAEs occurring in ≥ 5% of the either cohort or the overall trial population will be created, with a bar for Cohort 1, Cohort 2, and Overall within PT, and different colors within the bars for related vs. unrelated incidences. Bars will be presented in descending order of PT incidence in the overall cohort.

4.4.8.2 Clinical Laboratory Assessments

Variables

Hematology	Serum Chemistry	Urinalysis
• hemoglobin • hematocrit • red blood cell count • mean cell volume • mean corpuscular hemoglobin • RBC distribution width • total white blood cell count • 5-part differential including neutrophils, lymphocytes, monocytes, eosinophils, and basophils • platelet count	• total protein • albumin • alkaline phosphatase • total bilirubin • ALT • AST • lactate dehydrogenase • creatinine • blood urea nitrogen • uric acid • glucose • calcium • phosphorus • bicarbonate • chloride • potassium • sodium • lipase • amylase Thyroid Function Test Panel: • T3 • T4 • thyroid stimulating hormone (TSH)	• specific gravity • protein • glucose • blood • microscopy **Coagulation and Serology** • INR • PT • aPTT • HIV • HBsAg • HCV (performed at screening only)

Safety laboratory tests (hematology and serum chemistry) will be determined at the Screening Visit and at Visits 1-14, while urinalysis will be performed at the Screening and Visits 2, 4, 6-14 for all subjects. Thyroid function tests (TSH, free T3, and free T4) will be performed at Screening and every 6 weeks through to Visit 14.

Analyses

For the purpose of analysis, laboratory data will be converted to standard SI units during creation of the SDTM datasets. The original laboratory values and units will also be stored in the SDTM datasets. Only the SI units will be used in tables and listings. SI units and conversions will be included in the SDTM documentation.

Chemistry and hematology laboratory values and changes from baseline will be summarized at each scheduled visit using continuous descriptive statistics separately for each laboratory category and parameter.

For chemistry and hematology laboratory parameters with corresponding CTCAE grading scales, "shift tables" will be used to evaluate categorical changes from Screening to post-treatment visits with respect to a dichotomized CTCAE grading value (≤ Grade 2, ≥ Grade 3). Parameters with both a high and low CTCAE category (e.g., glucose as hypoglycemia vs. hyperglycemia) will be presented in both directions in the shift table.

For chemistry and hematology laboratory parameters without CTCAE grading scales, shift tables will be produced based on changes from screening to post-treatment visit values based on normal ranges (Low, Normal, High).

Summaries of subjects with investigator-assessed clinically significant results will be produced by laboratory category (hematology, chemistry, and urinalysis), parameter, and visit. An additional summary will be added to this for any clinically significant result during each treatment period, and for any time during the active treatment phase.

For subject-level listings, out of range laboratory values will be flagged as either "L" for below normal range, "H" for above normal range, or "A" for abnormal results in which ranges do not apply. Clinically significant abnormal laboratory values will be listed separately as part of the ICH reporting recommendations (ICH E3 section 14.3.4). Any laboratory parameters which are not included in the protocol but reported by the central or local laboratories (e.g., in order to define an AE) will be listed but not tabulated, including laboratory results which are take only for screening purposes (INR, PT, aPTT, HIV, HBsAg, HCV).

Pregnancy tests

Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test or urine β-HCG pregnancy test prior to each atezolizumab infusion for women of childbearing potential. Information on all pregnancy tests will be listed by subject and visit.

4.4.8.3 Vital Signs and ECG

Vital Signs Variables

- Heart rate [beats per minute]
- Systolic and diastolic blood pressure [mmHg]
- Body temperature [°C]
- Respiratory Rate (breaths per minute)

12-lead ECG Variables

ECGs are scheduled to be performed at Screening only. Additional ECGs will be performed and reported if clinically indicated.

- Investigator's interpretation (normal, abnormal not clinically significant, abnormal clinically significant, incomplete analysis, un-interpretable)
- Investigator-rated clinical significance
- Heart Rate (beats/min)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)

Vital Sign and ECG Analyses

Measured vital signs values and changes from baseline will be summarized at each time point using descriptive statistics. All measured values will be listed.

The investigator's overall interpretation of the ECG results as well as the measured values listed above will be presented in subject-level listings. As no post-treatment ECGs are planned, no summaries will be produced.

4.4.8.4 Physical examination

Complete physical examinations will be performed at Screening, and targeted physical examination at all other visits. Physical examination performance will be listed along with the date of examination will be listed along with vital signs assessments. Physical examination findings occurring after the signing of informed consent will be entered into the AEs CRF page. Findings occurring prior to first vaccination will be considered baseline signs and symptoms, with those occurring afterward as TEAEs.

4.5 Alterations to the Clinical Trial Protocol

No alterations to the protocol specified analyses have been made in this plan.

5 References

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