STATISTICAL ANALYSIS PLAN

Phase Ib Study of Avelumab Plus Bacille Calmette-Guerin (BCG) in Patients with Non-muscle Invasive Bladder Cancer (ABC Trial)

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Test Products:	Avelumab Intravesical BCG

Abbreviations

BCG	Bacille Calmette-Guérin
CFS	Cystectomy-free survival
cOR	Clinical response
CR	Complete response
EOS	End of study
NMIBC	Non-muscle Invasive Bladder Cancer
OS	Overall survival
pCR	Pathological complete response
PFS	Progression free survival
PR	Partial response
RFS	Recurrence free survival
SAP	Statistical analysis plan

Contents

1. **Objectives**
    a. **Primary Objectives**
        i. To evaluate the safety and tolerability of combination induction therapy with BCG + avelumab as defined as the ability to complete a full induction course (at least 5 of 6 treatments of BCG + avelumab within eight weeks of starting treatment).

    b. **Major Secondary Objectives**
        i. To evaluate the feasibility and tolerability of combination therapy with BCG + avelumab as measured by the endpoint of 6 month treatment completion rate based on patients completion of at least 2 of 3 treatments within a 5 week period at the 6 Month maintenance treatment.
        ii. To evaluate 3-month complete response (CR) rate, 6-month CR rate, recurrence free survival (RFS), cystectomy-free survival (CFS), and overall survival.

    c. **Patient-reported Outcome Objectives**
        i. To evaluate the impact of combination therapy with BCG + avelumab on quality of life in patients with NMIBC.

    d. **Exploratory Research Objectives**
        i. To identify potential biomarkers that would associate with tumor response from the combination of avelumab and intravesical BCG.
2. **Endpoints**
    a. **Primary Endpoint**
        i. Completion of induction therapy with combined BCG + avelumab as defined as freedom from dose-limiting toxicity (DLT) (Section 5.2.1) preventing completion of at least 5 of 6 treatments of BCG + avelumab within 8 weeks.
    b. **Secondary Endpoint**
        i. 6 Month maintenance treatment completion as defined as completion of at least 2 of 3 maintenance treatments within a 5 week period without DLT or disease progression. Disease status will be evaluated based on cystoscopy and urine cytology prior to maintenance therapy. Patients with persistent or recurrent high-grade disease at 6 Month cystoscopy will be taken off treatment. Low-grade recurrence will be tolerated without treatment interruption.
        ii. 3-month and 6-month complete response (CR) based on negative cystoscopy and urine cytology.
        iii. Recurrence free survival (RFS) at 6 and 12 months, defined as proportion of patients who are alive and free of persistent or recurrent NMIBC based on cystoscopy, cytology and/or biopsy.
        iv. Progression-free survival (PFS) at 6 and 12 months, as defined by time from day of first treatment to first progression to higher grade or stage, including muscle-invasive disease or death from any cause
        v. Cystectomy-free survival (CFS), defined as time from study initiation to cystectomy or death
        vi. Overall survival, defined as time from day of first treatment to death from any cause
    c. **Exploratory Endpoint**

i. To obtain preliminary data of potential biomarkers that would associate with tumor response from the combination of avelumab and intravesical BCG.
ii. Avelumab combined with intravesical BCG will improve quality of life in patients with NMIBC.

3. Design information

a. General statistical considerations

i. This is a single arm, phase Ib study. A total of 18 evaluable patients will be enrolled at the Stephenson Cancer Center. More than 40 patients with bladder cancer initiate intravesical BCG treatment in our Urologic Oncology clinic each year, including approximately 40% patients with BCG-treated but unresponsive NMIBC (persistent or recurrent) who are hopefully eligible for the proposed study. Based on our prior experience with a similar patient population, we anticipate enrollment of 1 patient per month.

ii. An interim safety analysis will be conducted when 3-6 patients have received ≥ 5 doses of BCG treatment in dose level 1. If the combination therapy in dose level 1 is not tolerated (2 or more patients experience a DLT), dose level -1 will be evaluated in additional 3-6 eligible patients.

iii. The planned sample size is 18 evaluable patients for dose expansion cohort. Conservatively allowing for up to 10% dropout, we will enroll up to 27 patients for an evaluable 18. Thus the maximal study period will be 54 months (30 months accrual plus 12 months study treatment plus 12 months survival followup). It is assumed this is sufficient to observe the minimum number completed cycles and to assess the time-to-event variables, including recurrence free survival and OS.

b. Sample Size and Power

i. The primary objective is to ensure patients can tolerate a complete induction course of combination therapy as defined by the ability to receive at least 5 of 6 treatments of BCG + avelumab within eight weeks of starting treatment. By using a modified 3+3 design for DLT observation, we expect to enroll 3-6 patients for dose level 1. If dose level 1 is not tolerated, then an additional 3-6 patients will be enrolled in dose level -1.

ii. The most important secondary objective is to evaluate the feasibility of remaining on combination treatment to complete Month 6 maintenance therapy without dose-limiting toxicity. Therefore, an additional 12-15 patients will be enrolled and will receive the final dose. The proportion of patients completing Month 6 maintenance will be calculated and a 95% confidence interval constructed for the completion rate. The expected completion rate is about 60%. However, the final sample size was obtained from feasibility and not formal power analysis. With 18 patients at the final dose and an expected completion rate of 60%, the lower bound of the two-sided Wilson Score 95% confidence interval (CI) would be 37.6%. Although this lower limit was not clinically meaningful, it is provided to show the width of the CI given a desired 60% completion rate and the small sample size.

iii. In order to enroll 18 evaluable patients for dose expansion cohort, we may need to screen up to 27 patients if dose level -1 will be evaluated as the final dose level since we expect a percentage of these patients to be screen failures or withdrawals.

4. Study Populations

Inclusion and exclusion criteria are sometimes modified during the duration of the protocol. Before beginning analysis, the statistical team will review the criteria in the SAP to confirm it is up to date with the current criteria.

Target population: Male or female patients must be 18 years of age or older before the screening visit to be enrolled in the study. Patients must have histologic or cytological diagnosis of Non-muscle Invasive Bladder Cancer (NMIBC), and the cancer is BCG-treated but unresponsive (recurrent or persistent). Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate clinical laboratory values.

a. Inclusion Criteria

i. Histologically or cytologically documented Non-muscle Invasive Bladder Cancer (NMIBC).
ii. Patient with BCG-treated but unresponsive NMIBC (persistent or recurrent defined as tumor lesion present after prior response).
iii. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 2.
iv. Patients who are able to understand and sign the informed consent form.
v. Age ≥ 18 years old.
vi. Ability to comply with protocol.
vii. Life expectancy >/=12 weeks.
viii. Adequate hematologic and end-organ function.
    1. ANC ≥ 1500/µL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first dose of study treatment).
    2. Platelet count ≥ 100,000/µL (without transfusion within 2 weeks prior to the first dose of study treatment)
    3. Hemoglobin ≥ 9.0 g/dL; Patients may be transfused or receive erythropoietic treatment, at least 7 days prior to the first dose of study treatment, to meet this criterion.
    4. AST and ALT ≤ 2.5 × ULN.
    5. Serum bilirubin ≤ 1.5 × ULN; Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
    6. INR and aPTT ≤ 1.5 × ULN; this applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
    7. Creatinine clearance >/=30 milliliters per minute (mL/min) (calculated using the Cockcroft-Gault formula).
ix. For women of childbearing potential: Negative serum or urine pregnancy test at screening.
x. For both male and female subjects: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 30 days after the last dose of study drug.

xi.

b. Exclusion Criteria

i. Evidence of locally advanced or metastatic bladder cancer (including disease involving renal pelvis, ureter, or prostatic urethra).
ii. Evidence of muscle-invasive bladder cancer.
iii. Evidence of extravesical bladder cancer.
iv. Active central nervous system (CNS) metastases.
v. Prior treatment with PD-L1 inhibitor.
vi. Prior radiation to the bladder.
vii. Patient has a known additional malignancy that required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin.
viii. Patient is considered a poor medical risk that would interfere with cooperation with the requirements of the study.
ix. Patient has a condition or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment.
x. Patient has not recovered (i.e, to ≤Grade 1 or to baseline) from previous intravesical BCG or other anti-cancer therapy induced AEs.
    1. alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable 11.
xi. Treatment with any approved anti-cancer therapy, including chemotherapy (systemic or intravesical), radiation therapy, or hormonal therapy within 3 weeks prior to the first dose of study treatment.
    1. Use of hormone-replacement therapy and oral contraceptives is permitted.
xii. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 4 weeks prior to the first dose of study treatment.
xiii. Pregnant or lactating, or intending to become pregnant during the study.
    1. Women who are not postmenopausal (≥ 12 months of non−therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to the first dose of study treatment.
xiv. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
xv. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.
xvi. Allergy or hypersensitivity to components of the avelumab formulation.
xvii. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
    1. Patients with medically controlled endocrinopathy (e.g., hypothyroidism, adrenal insufficiency), diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.
xviii. Prior allogeneic stem cell or solid organ transplantation.
xix. Current use of immunosuppressive medication, EXCEPT for the following:

1. Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection).
2. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent.
3. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

xx. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
    1. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

xxi. Positive test for HIV.

xxii. Active hepatitis B (positive hepatitis B surface antigen [HBsAg] test at screening);
    1. Patients with past or resolved hepatitis B (HBV) infection (positive anti-hepatitis B core antigen [anti-HBc] antibody test) are eligible. HBV DNA must be obtained in these patients prior to the first dose of study treatment.

xxiii. Active hepatitis C.
    1. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction assay is negative for HCV RNA.

xxiv. Active infection requiring systemic therapy.

xxv. Severe infections within 4 weeks prior to the first dose of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

xxvi. Significant cardiovascular disease, such as cerebral vascular accident/stroke (< 6 months prior to enrollment), New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina.

xxvii. Administration of a live/attenuated vaccine within 4 weeks prior to the first dose of study treatment, within 5 months following the administration of the last dose of study drug, or anticipation that such a live/attenuated vaccine will be required during the study.

xxviii. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

5. Analysis Populations

The analysis populations are defined as below.

a. **Safety population:** All patients who receive at least one dose of combination avelumab and BCG will be included in the analyses of compliance and safety.
b. **Biomarker population:** For biomarker analysis, the biomarker population will comprise all evaluable patients who have sufficient baseline and on-study biomarker measurements.
c. **Evaluable population:** Evaluable patients will be defined as patients who receive at least 5 doses of intravesical BCG and avelumab IV weekly during induction treatment and complete the first post-treatment cystoscopy and/or urine cytology for tumor assessment. Patients

who discontinued study treatment due to toxicity incurred by previous therapy will be evaluated for safety analysis, but will be replaced by additional patients for the efficacy analysis.

Patients removed from study for early withdrawal or hypersensitivity reactions will be replaced if they have received less than 5 doses of study treatment during induction treatment, but will be included in the safety analysis.

Patients who do not receive at least 5 doses of intravesical BCG and avelumab IV during induction treatment will be considered unevaluable for efficacy analysis and will be replaced unless the missed doses were due to development of grade 3-4 adverse events related to study treatment.

Evaluable population will be used for the analysis of EORTC QOQ-C30 (Section 6) and antitumor measures (Section 8).

6. Patient Population Summary

a. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) functional scales, symptom scales, and global health and quality of life scale will be summarized.

7. DLT Analysis

a. Completion of induction therapy with combined BCG + avelumab as defined as freedom from dose-limiting toxicity (DLT) preventing completion of at least 5 of 6 treatments of BCG + avelumab within 8 weeks. Dose limiting toxicity will be based on the first 6 weeks of proposed study treatment. If 0/3 patients experience a DLT, dose expansion cohort will be activated for additional 15 patients. If 1/3 patients experiences a DLT, the dose level 1 will be expanded to 3 more patients. If 1/6 patients experiences a DLT, the dose expansion cohort will be activated for additional 12 patients. If 2 or more of the 6 patients experience a DLT, the dose level -1 will be evaluated. If the combination therapy in Cohort -1 is not tolerated (2 or more patients experience a DLT), the study will be suspended for reassessment.

i. Definition of Dose limiting toxicity

1. During safety lead-in phase, Dose limiting toxicity (DLT) will be monitored during the first 6 weeks of the combination avelumab and intravesical BCG. DLTs will be defined as any and all adverse events at least possibly related to study drug which occur in the DLT evaluation period and meet the criteria below, as evaluated by the NCI-CTCAE version 5.0.
2. Note: DLTs and other toxicities will be discussed between the Principal Investigator, and the Data Safety Monitoring Committee (DSMC). The discussions are the basis for the decisions regarding dose expansion (or de-escalation) according to the rules of the protocol.
3. DLT will be classified as either hematologic or non-hematologic toxicity (assessed in accordance with the CTCAE Version 5.0 criteria).
4. The following are DLTs:
    a. Toxicity causing greater than 2 weeks of dose delay. For example, if a subject has dose delay greater than 2 weeks due to an AE, such AE is a DLT.

b. Grade 4 neutropenia greater than 5 days.
c. ALT/AST > 3x ULN with bilirubin > 2x ULN without another explanation (e.g., cholestasis).
d. Any Grade 3 hypersensitivity reaction is a DLT.
e. Grade 4 thrombocytopenia of any duration.
f. Grade 3 thrombocytopenia with significant hemorrhage of any duration.
g. Febrile neutropenia
h. Any non-hematological Grade ≥ 3 toxicities will be a DLT.

5. The following may be considered as exceptions to DLTs: 1.
    a. Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours.
    b. Grade 3 fatigue lasting < 5 days.
    c. Grade 3 hypertension that can be controlled with medical therapy.
    d. An increase of indirect (unconjugated) bilirubin indicative of Gilbert's syndrome.
    e. Serum lipase and/or serum amylase CTCAE Grade 3 ≤ 7 consecutive days without clinical signs or symptoms of pancreatitis.

ii. Definition of DLT Evaluable Population

1. Patients enrolled in safety lead-in cohort who receive at least 4 doses and complete the DLT observation period (the first 42 days of induction treatment), unless the patient discontinued the study treatment due to a DLT.

8. Antitumor Evaluation

a. The proportion of patients receiving a complete induction course (at least 5 of 6 treatments of BCG + avelumab within eight weeks of starting treatment) at 3 months and at 6 months will be calculated and a 95% Wilson score confidence interval constructed for the completion rate.
b. The 3-month and/or 6-month complete response (CR) rates will be summarized as the proportion (and 95% CI) of patients with complete tumor response at month 3 or 6 of study treatment. Patients who remain CR at end of study (EOS) are censored at their last cystoscopy date.
c. The duration of response will be calculated as time from the date of first response (complete response (CR), partial response (PR), pathological complete response (pCR)) to the first date of non-response. Duration of response will be summarized using the Kaplan-Meier method. Median duration of response with 95% CI will be computed. Results will be presented in tabular and graphic form, as appropriate.
d. Progression-Free Survival (PFS) at six month and twelve months is defined as the time in months from the first dose of the drug to the date of death or the first documented date of progression, whichever comes first. For patients who did not die and did not have progression, the PFS is censored at the last documented tumor assessment. Survival curve for PFS will be generated using the Kaplan-Meier method. Median PFS with 95% CI will be computed. Those without an event are censored at their last valid tumor assessment, or at the last tumor assessment before patient start of the new therapy if a patient has started new anti-cancer therapy.

e. Overall survival (OS) is defined as time in months from first dose of the drug to the date of death. Patients who are still alive at EOS are censored on the date they were last known to be alive. Survival curve for OS will be generated using the Kaplan-Meier method. Median OS with 95% CI will be computed. If overall survival cannot by calculated due to no patient deaths, it will not be reported.
f. Recurrence free survival (RFS) at 6 and 12 months, defined as proportion of patients who are alive and free of persistent or recurrent NMIBC based on cystoscopy, cytology and/or biopsy. Survival curve for RFS will be generated using the Kaplan-Meier method. Median PFS with 95% CI will be computed. Patients without a recurrence will be censored at their last cystoscopy date.
g. Cystectomy-free survival (CFS), defined as time from study initiation to cystectomy or death. Survival curve for CFS will be generated using the Kaplan-Meier method. Median PFS with 95% CI will be computed. If CFS cannot be calculated due to not enough patients undergoing cystectomy, it will not be reported.

9. Safety Analyses

a. Adverse Events

i. Severity of AEs will be graded according to the CTCAE Version 5.0. Adverse events not included in the CTCAE, Version 5.0 must be graded as follows: Mild, Moderate, Severe, Life-threatening, and Fatal according to the following definitions:
    1. Mild: The AE is noticeable to the patient but does not interfere with routine activity.
    2. Moderate: The AE interferes with routine activity but responds to symptomatic therapy or rest.
    3. Severe: The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
    4. Life-threatening: The AE places the patient at risk of death at the time of the event.
    5. Fatal: The AE results in the death of the patient.
ii. Frequency and severity of adverse events will be tabulated by body system, type and maximum grade. Serious adverse events will be listed.

b. Laboratory Abnormalities

i. An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:
    1. an action on the study drug is made as a result of the abnormality
    2. intervention for management of the abnormality is required
    3. at the discretion of the investigator should the abnormality be deemed clinically significant

10. Handling of Missing Data

Every effort will be made to collect information at all defined visits including at early withdrawal or dropout. Reasons for missing data will be summarized. However, there will be no imputation of missing data.