Statistical Analysis Plan

BRACHY-CHOR-001

SAP for BN-Brachyury Chordoma Radiation Trial

A Phase 2 Trial of BN-Brachyury and Radiation Therapy in Patients with Advanced Chordoma

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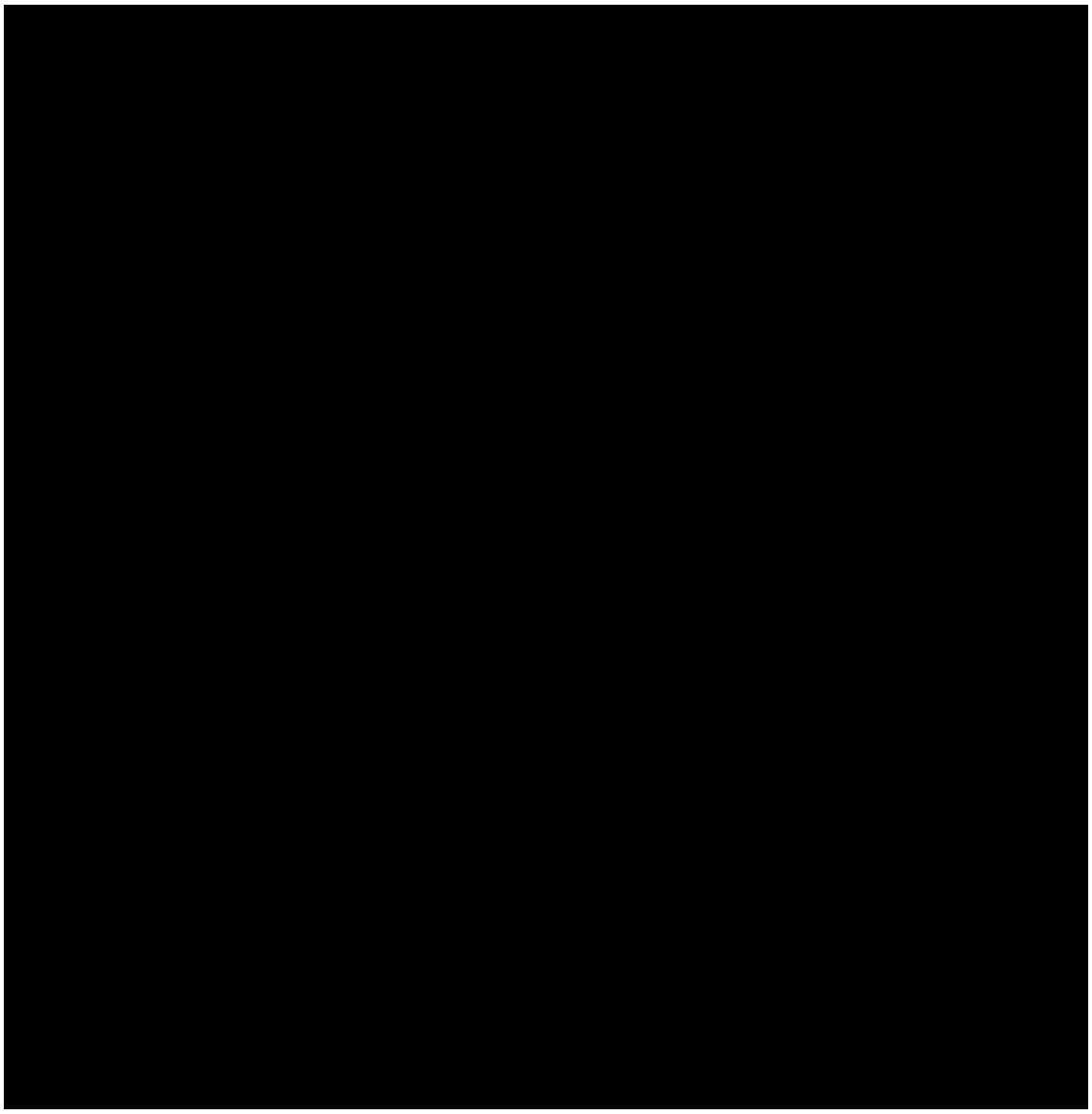


Contents

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANA	Anti-nuclear Antibodies
AST	Aspartate Aminotransferase
ATC	Anatomic-Therapeutic-Chemical
BMI	Body Mass Index
BN	Bavarian Nordic
BPI-SF	Brief Pain Inventory-Short Form
BUN	Blood Urea Nitrogen
CR	Complete Response
CSR	Clinical Study Report
CTC	Circulating Tumor Cells
CT	Computed Tomography
DL	Detection Limit
DSMB	Data and Safety Monitoring Board
EAS	Evaluable Analysis Set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISPOT	Enzyme-Linked ImmunoSpot
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FPV	Fowlpox Virus
HIV	Human Immunodeficiency Virus
IMRT	Intensity-Modulated Radiation Therapy
Inf.U	Infectious Units
irRC	Immune-Related Response Criteria
MedDRA	Medical Dictionary for Regulatory Affairs
MVA	Modified Vaccinia Ankara
MRI	Magnetic Resonance Imaging
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OR	Objective Response
ORR	Objective Response Rate
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PFS	Progression-Free Survival
PR	Partial Response

Abbreviation	Definition
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneously
SOC	System Organ Class
SRS	Stereotactic Radiosurgery
TAA	Tumor-Associated Antigen
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

Introduction

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing trial data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the trial protocol.

This statistical plan will be followed completely for the analysis of data derived from the clinical trial. If any additional analyses are included in the clinical study report (CSR), they will be clearly described as additional, unplanned analyses.

The analyses described within are based on the final clinical trial protocol: *A Phase 2 Trial of BN-Brachyury and Radiation Therapy in Patients with Advanced Chordoma, Version 4.0* dated 22-Aug-2019. The current SAP includes all analyses that will be performed for the final CSR.

The SAP is archived with other pertinent trial documentation as noted in Bavarian Nordic (BN) SOP BN0003973.

General Definitions

Trial Day: The trial day is defined from the date of first vaccination. Per the trial protocol, the day of first vaccination is defined as Day 0, and the day prior to the first vaccination is Day -1. In order to align with trial data submission standards per CDISC, purpose of the analyses and in the datasets, date of first vaccination is referred to as Day 1. 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. Trial day will be calculated as Date of event - Date of first vaccination + 1 if event is on or after the date of first vaccination. For pre-vaccination events, trial day will be calculated as Date of event - Date of first vaccination. Note this will result in trial day being 1 day greater than the visit label.

Baseline: If not otherwise specified, baseline refers to the last non-missing measurement before first vaccination with trial product. Measurements taken on the day of first vaccination that were scheduled to occur prior to the first vaccination, based on the protocol schedule of events, will be considered baseline values, even if no specific time is associated with the measurement. If times are associated with a measurement, the measurements taken just prior to the first vaccination will be considered baseline.

Screening Period: The time from the signing of informed consent form (ICF) until first dose of trial vaccination. Data collected during the Screening Period will be summarized separately from post-treatment data. This will include any data collected during unscheduled visits occurring between screening and the first vaccination of trial product.

Overall Treatment Period: All data collected from the first vaccination of trial treatment through the last trial visit (regardless of completion status) will be considered part of the overall treatment period. A final visit is planned for approximately 30 days after the last treatment visit. Specifically, the overall treatment period will consist of the pre-radiation vaccination period, radiation therapy period, post-radiation vaccination period 1 and post-radiation vaccination period 2, which are defined below.

Pre-Radiation Vaccination Period: The time from the date of first vaccination of MVA-BN-Brachyury to the day prior to the start of radiation therapy. Subjects should have received 2 doses of MVA-BN-Brachyury and 1 dose of fowlpox (FPV)-Brachyury during this period.

BN-Brachyury: Term that refers to both MVA-BN-Brachyury and FPV-Brachyury trial vaccines when used together in a prime-boost regimen.

Radiation Therapy Period: from the start date of radiation therapy to the day prior to resuming FPV-Brachyury injections.

Post-Radiation Vaccination Period 1: The time from the date of restart of FPV-Brachyury injections after radiation therapy to the day prior to the scheduled FPV-Brachyury injection at the End Radiation + 26 weeks visit. FPV-Brachyury will be administered every 4 weeks during this period.

Post-Radiation Vaccination Period 2: The time from the date of the FPV-Brachyury injection at the End Radiation + 26 weeks visit to the last scheduled trial visit (i.e., last injection of FPV-Brachyury + approximately 30 days). FPV-Brachyury will be administered every 12 weeks during this period.

Treatment Emergent Adverse Events: An AE with an onset on or after initiation of trial treatment, or an AE present at initiation of trial treatment that worsens (*i.e.*, increase in severity: On-Trial Grade > Baseline Grade) as determined by the investigator will be considered a treatment-emergent adverse event (TEAE). TEAEs are collected through the last scheduled visit (approximately 30 days after the last dose of trial product).

Serious Adverse Events (SAEs) and AEs of Special Interest (AESIs): SAEs and AESIs that occur on or after initiation of trial treatment through 30 days after the last dose of trial product are considered as TEAEs. SAEs and AESIs will be followed until resolution.

Modified Response Evaluation Criteria in Solid Tumors (mRECIST): Standard Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 to be used only for radiographic assessment of the irradiated tumor(s) (target lesions). Non-irradiated tumors (non-target lesions) will not be part of the mRECIST assessment. Refer to Section 3.5.3.2 for additional details.

Response: Response for the primary analysis will be determined using mRECIST or Immune-Related Response Criteria (irRC), in which only target tumors receiving adequate radiotherapy will be considered for RECIST assessment and primary endpoint analysis. Progression of non-

target lesions will be assessed as exploratory analyses based on standard RECIST 1.1 for this trial. Refer to Section 3.5.3.2 for additional details.

Progressive Disease (PD): Advancement of disease as defined by target tumor enlargement from nadir using mRECIST or irRC. Progression of non-target lesions will not be considered as disease progression for the primary endpoint analysis of this trial.

Target Lesions: Only tumors that are measurable and have received adequate radiotherapy will be considered target lesions for determination of response. All other tumors will be considered non-target lesions.

Objective Response (OR): A subject achieving Complete Response (CR) or Partial Response (PR) per mRECIST or irRC.

Objective Response Rate (ORR): The proportion of subjects meeting the criteria for OR.

Duration of Response: From the time that criteria are first met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented. The smallest target-tumor measurements on trial (i.e., nadir tumor load) will be used as reference for progressive disease.

Progression Free Survival (PFS): The time interval from the date of first trial vaccination to objective tumor progression, or death from any cause occurring prior to tumor progression. The rate of PFS at a fixed time point is defined as the proportion of subjects who have not experienced objective progression or death from the date of first trial vaccination to the fixed time point of interest.

Brief Pain Inventory-Short Form (BPI-SF): A questionnaire to evaluate the severity of a subject's pain and the impact of this pain on the subject's daily functioning.

1 Trial Overview

1.1 Trial Description

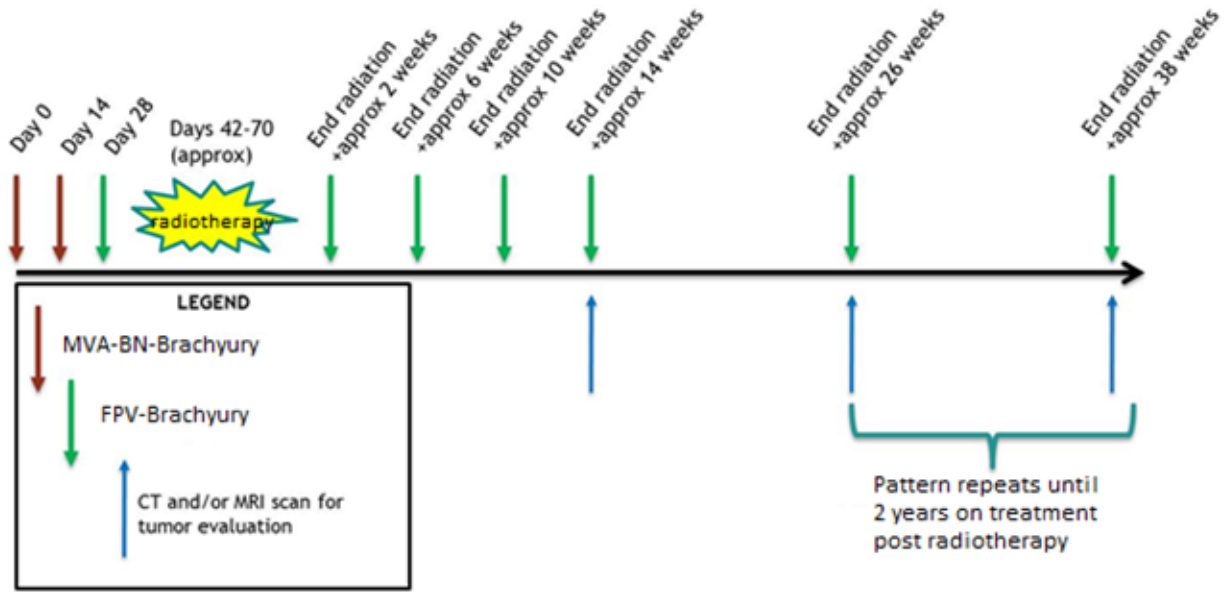
This is a single-arm phase 2 clinical trial using a Simon two-stage optimal design (Simon, 1989). The goal is to demonstrate that BN-Brachyury plus radiation therapy can induce objective radiographic responses in subjects. In stage 1, a minimum threshold of activity will be needed to proceed to stage 2.

Stage 1: Enroll 10 subjects. If objective response (OR) is not achieved in any subjects, the trial will be stopped for lack of activity. If OR is achieved in ≥1 subject, the trial will proceed to stage 2. If any subject is not evaluable for the primary endpoint, the subject may be replaced.

Stage 2: Enroll an additional 19 subjects for a total of 29 subjects. If any subject is not evaluable for the primary endpoint, replacement subjects may be enrolled until a total of 29 subjects are evaluable for the primary endpoint.

Subjects will be treated with two priming doses of MVA-BN-Brachyury (Doses 1 and 2) and one dose of FPV-Brachyury (Dose 3) prior to initiation of radiotherapy. Radiotherapy will begin at least 2 weeks and not more than 4 weeks after first administration of FPV-Brachyury (Dose 3). At least 2 weeks following completion of radiotherapy (or upon resolution of any reversible AEs related to radiotherapy), the subject will resume vaccination with FPV-Brachyury and proceed to ongoing booster doses with FPV-Brachyury through approximately 2 years beyond completion of radiotherapy. A final visit will occur 30 days after the last treatment visit. Refer to Figure 1 for a summary of the trial vaccine schedule.

Figure 1 Trial Vaccination Schedule



1.2 Objectives

1.2.1 Primary Objective:

To determine if the combination of BN-Brachyury administered with radiotherapy will result in a clinically meaningful ORR when compared with historical control.

1.2.2 Secondary Objectives:

- To confirm the safety profile of BN-Brachyury plus radiation therapy
- PFS by mRECIST 1.1 criterion
- Improvement in clinical symptoms as measured by the Brief Pain Inventory-Short Form (BPI-SF) pain assessment

1.2.3 Exploratory Objectives:

- To evaluate the differences in clinical outcome measures by location of primary tumor (Sacral vs. Mobile Spine vs. Clival)
- To measure AE profile by location of primary tumor
- To evaluate other clinical endpoints that might be indicative of clinical benefit:
  - ORR by standard RECIST 1.1

  - PFS by other criteria, including Choi, volumetric, and standard RECIST 1.1

- To evaluate changes in immune and tumor related biomarkers of pre- versus post-baseline samples
  - Peripheral blood mononuclear cells (PBMC)
    - Brachyury and other tumor-associated antigen (TAA) specific T-cell activation
    - Immune cell subset quantification and characterization
  - Serum
    - Analysis for soluble factors associated to immune response, e.g., antibodies or cytokines

1.3 Trial Population

The population proposed for inclusion in this trial are male and female subjects at least 12 years old with advanced chordoma who are planning to be treated with radiotherapy to at least one lesion. In an effort to demonstrate clinical activity in the population most likely to be eligible for this treatment, adolescents have been included.

1.4 Inclusion/Exclusion Criteria

The full list of inclusion and exclusion criteria for the trial can be found in the synopsis of the trial protocol.

1.5 Endpoints

Primary endpoints:

- ORR anytime within 12 months post-completion of radiation on target lesion(s) based on mRECIST 1.1 or irRC. Refer to Section 3.5.3.2 for the modified response criteria.

Secondary efficacy endpoints:

- PFS by mRECIST 1.1 or irRC on target lesion(s)
- Improvement in clinical symptoms measured by the BPI-SF

Safety endpoints:

- Injection site reactions
- Other AEs
- Clinically significant shifts in chemistry and hematology laboratory values

Exploratory endpoints:

- ORR anytime post completion of radiation on all lesions by standard RECIST 1.1
- ORR anytime within 12 months post completion of radiation on target lesion(s) based on Choi criteria (Choi et al., 2007) and volumetric criteria (Fenerty et al., 2016)
- PFS based on all lesions by standard RECIST 1.1
- PFS based on target lesion(s) by other criteria:
  - Choi criteria (Choi et al., 2007)
  - Volumetric (Fenerty et al., 2016)
- PBMC samples: T-cell response to BN-Brachyury

2 Trial Design

The schedules of events can be found in the Appendices.

3 Statistical Methods

3.1 Planned Sample Size

The null hypothesis that the true ORR anytime within 12 months after completion of radiation is 5% will be tested based on a one-sided alternative. In the first stage, 10 subjects will be accrued. If there are 0 responders in these 10 subjects, the trial will be terminated. If there is at least 1 responder in these 10 subjects, 19 additional subjects will be accrued for a total of 29 subjects. The null hypothesis will be rejected if 4 or more responses are observed in 29 subjects. This design retains a one-sided type I error rate of ≤ 0.05 and achieves 80% power when the true response rate is 20%.

The optimal design minimizes the expected sample size under the null hypothesis while satisfying the type I error and power constraint. With the above design, the probability of early termination is 60% and the expected sample size is 17.6 when the true response rate is 5% (under the null hypothesis).

3.2 Analysis Sets

For the statistical analysis, there are two analysis sets: the Evaluable Analysis Set (EAS) and the Full Analysis Set (FAS).

The EAS consists of all subjects who have completed the following:

- Two prime doses of MVA-BN-Brachyury, and
- One booster dose of FPV-Brachyury prior to radiation, and

- Completed radiation therapy, and
- At least 3 out of 4 booster doses of FPV-Brachyury in 14 weeks after radiation, and
- Have both baseline (defined as measurement prior to first prime dose of MVA-BN-Brachyury), and at least one post-baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan for objective tumor evaluation.

The primary analysis population for ORR anytime within 12 months after completion of radiation and secondary efficacy endpoints is the EAS. Subjects who failed to meet the evaluable criteria will be replaced to retain the statistical power unless four or more responses have been observed or the number of responders will still be less than four even if all replacement subjects would be responders. If there are more than 10 evaluable subjects at the end of stage 1 analysis or more than 29 evaluable subjects at the end of stage 2 analysis, primary evaluation will be based on the first 10 accrued or first 29 accrued evaluable subjects. Sensitivity analyses will include all evaluable subjects if applicable.

The FAS consists of all subjects who have enrolled and received any dose of MVA-BN-Brachyury or FPV-Brachyury. This is the primary analysis set for safety and immune response, and the secondary analysis set for efficacy.

3.3 Subgroups

Location of primary tumor: Sacral, Mobile Spine, or Clival

Histologic subtype: Classic, Chondroid

3.4 Data Conventions and Handling of Missing Data

3.4.1 Missing or Partial Dates

All data will be listed as captured in the electronic case report form (eCRF); however, 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	Imputation Flag
Day	First of Month	Last of Month	D
Month	01 January	31 December	M
Year	First Treatment Date	Date of Data Cutoff/Lock	Y

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.

3.4.2 Data Handling Conventions for Efficacy 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 that no progression has occurred.

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 and will be considered to have progression for the by-time-point PFS analyses.

3.4.3 Assignment of AEs to a Trial Period and Vaccination Period

Each AE will be assigned to a trial period or a vaccination period using the date of first vaccination and the date of onset of the AE.

- All AEs with onset before the date of the first trial vaccination will be classified as a baseline sign or symptom and belong to the Screening period.
- All AEs starting on or after the date of first trial vaccination will be assigned to the Treatment period and be considered TEAEs.

TEAEs will also be assigned to the following vaccination periods (See General Definitions for definitions of periods):

- Pre-radiation Vaccination Period
- Radiation Therapy Period
- Post-Radiation Vaccination Period 1
- Post-Radiation Vaccination Period 2

Per the missing data rules, missing start dates will be set to the date of first vaccination and will be considered both TEAEs and part of the Treatment period.

3.4.4 General Considerations for AEs

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 (or higher) will be used to code verbatim AE terms and baseline signs and symptoms for summarization into system organ classes (SOCs) and preferred terms (PTs).

3.4.4.1 AE Severity

Adverse events will be categorized and graded by the Investigator using standard terminology for grading the severity (intensity) of the AE. This trial will use the NCI-CTCAE version 4.03 (or higher) five-point scale (Grades 1 to 5) with unique clinical descriptions of severity for each referenced AE. Missing severities will not be imputed.

3.4.4.2 AE Causality

The relationship between the occurrence of an AE and the trial treatment will be assessed using the categories “none,” “unlikely,” “possible,” “probable,” and “definite.” This assessment is applied to each trial product (MVA-BN-Brachyury, FPV-Brachyury, and Radiation) individually. For assessing related AEs in analyses, if the relationship of any of the products is considered possible, probable, or definite, the AE will be considered related to trial treatment. In the event of a missing causality, the AE will be classified as related.

3.4.4.3 Serious Adverse Events (SAEs)

Refer to trial protocol Section 8.1.4 for the definition of SAEs in this trial.

3.4.4.4 AEs of Special Interest (AESIs)

Refer to trial protocol Section 8.1.5 for the definition of AESIs in this trial.

3.5 Analysis and Presentation Methods

3.5.1 General Presentation Methods

Categorical variables will be summarized using frequencies and percentage of subjects within each category, unless otherwise stated. Continuous variables will be summarized using the following statistics: mean, standard deviation, median, minimum, and maximum. Variables that are log normally distributed will be presented using geometric means and confidence intervals. Percentages will be presented to one decimal place. If a frequency is 0, the percentage will not be presented to draw attention to the non-zero cells of the tables.

For continuous statistics, precision will be based on the precision of the original data points. Means and medians will be presented to the original precision plus one decimal place. Standard deviations will be presented to the original precision plus two decimal places. The minimum and

maximum will be presented to the precision of the original data. In the event these precision rules result in a precision with more than four decimal places, only 4 decimal places will be presented.

All individual data entered in the eCRF and derived data will be listed as measured in subject--level listings. Tables will be sorted by scheduled visit, as appropriate. Listings will be sorted by subject and visit, as appropriate.

3.5.2 Software

All statistical summaries and analyses of safety and efficacy data will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA).

3.5.3 Efficacy Analyses

3.5.3.1 Efficacy Variables

Refer to efficacy and exploratory endpoints in Section 1.5. Other detailed tumor response information such as measurements of lesion size will be provided in subject-level listings only.

3.5.3.2 Response Criteria

Primary and Secondary Endpoints

mRECIST criteria will be used for radiographic assessment of the irradiated tumor(s) (target lesions) only. Non-irradiated tumors (non-target lesions) will not be assessed for the primary endpoint by mRECIST, but clinical decisions based on tumor growth may be made on investigator discretion. Additionally, at investigator discretion, irRC principles can be used for target lesion(s). If a subject has enlargement of their target lesion(s) at the first restaging scan after completion of radiotherapy, they may remain on trial until confirmation of progression on a subsequent scan (at least 4 weeks later). Similarly, any response must also be confirmed with a repeat scan at least 4 weeks later. Progression of a non-target lesion does not result in disease progression by the mRECIST evaluation to be used in this trial. The purpose of the trial is to determine if radiation plus vaccine can shrink the irradiated tumor. In these cases, local interventions may be considered to other non-target lesions (surgery, radiation, or ablation) at the investigator's discretion. Progression of any non-target lesion that requires systemic treatment will result in the subject being taken off trial. If a subject must come off trial due to progression of any non-target lesion prior to meeting the evaluable definition, they may be replaced with another subject to ensure statistical power is maintained for the primary analysis.

In some cases, if more than one lesion can be irradiated, multiple target lesions may be selected. Only those that receive adequate radiotherapy (as defined by radiation requirements for enrollment in the trial protocol) will be considered target lesions for RECIST assessments and primary endpoint analysis.

All subjects in this trial must be assessed for response to treatment, even if there are major treatment deviations. If a subject has not completed adequate treatment to be evaluated for response to treatment, they should still be assessed, but may be replaced to maintain statistical power. The primary endpoint assessment of ORR anytime within 12 months following completion of radiation will be based on the response to adequate treatment, which will require vaccination and completion of adequate radiotherapy. Progression prior to that point will not be considered treatment failure for purposes of primary endpoint analysis.

Exploratory Endpoints

Standard RECIST 1.1 evaluations based on all available non-irradiated lesion data, and Choi and Volumetric evaluations based on irradiated target lesion data, were to be performed by external radiological reviewers, and the results were to be included in exploratory analyses per the protocol. However, due to constraints with the independent reader evaluations, only a limited number of scans were read, and these analyses will not be performed for the purpose of the final CSR. Further details are in Section 3.5.3.5.

3.5.3.3 Primary Efficacy Analysis

The primary efficacy endpoint, ORR (defined as the proportion of subjects with CR or PR) based on best post-treatment tumor assessment of target lesion(s) anytime within 12 months after completion of radiation, will be summarized, and the 90% confidence interval will be computed. Due to the discrete and conservative property of the exact (Clopper-Pearson) confidence limit, the Wilson score confidence limits will be used. The Wilson interval has been shown to have better performance than the Clopper-Pearson interval (Brown, 2001).

The success criteria are based on the point estimate of the EAS. At least one responder must be observed in the first 10 subjects to continue to stage 2. For the final analysis, the null hypothesis that ORR is no more than 5% will be rejected if 4 or more responses are observed in all subjects who are included in the EAS (Section 3.2).

3.5.3.3.1 Additional Analyses of the Primary Efficacy Endpoint

Baseline tumor measurements will be taken during the screening period. Objective tumor responses will be assessed every 3 months starting approximately 14 weeks after radiation therapy. Besides ORR based on the best post-treatment tumor assessment within 12 months after radiation therapy and during the trial, ORR will also be summarized for the EAS by visits with scheduled tumor assessments.

Best post-treatment tumor responses within 12 months after radiation therapy and during the trial by mRECIST will also be summarized for the EAS by location of primary tumor and histologic subtype (refer to subgroups summarized in Section 3.3), and for the FAS as a sensitivity analysis. For sensitivity analyses based on the FAS, subjects without post-treatment tumor assessments will be analyzed as non-responders (regardless of survival status) for OR endpoints.

The 90% Wilson score confidence intervals will be calculated. The duration of response and tumor measurements will only be provided in subject-level listings.

Percent change from Baseline in target lesion by visits will be plotted for the EAS by different subgroups: best OR, current radiation dose group categories (≤ median current radiation dose in Gray and > median current radiation dose in Gray), baseline disease location, and therapy type (proton therapy and other therapy).

3.5.3.4 Secondary Efficacy Analyses

3.5.3.4.1 PFS Based on Target Lesion(s)

PFS is defined as the time interval from first vaccination to objective tumor progression based on the mRECIST criteria or death, 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 target tumor progression. The product-limit Kaplan-Meier curve will summarize PFS graphically. Median survival and 95% confidence intervals will be computed based on the product limit method (Greenwood's formula for the standard error estimate) overall and by subgroups defined in Section 3.3. Progression-free survival rates will be summarized by visit where scheduled tumor assessment is performed, along with their Wilson score confidence intervals.

Primary analyses of PFS will be based on the EAS. PFS rates will also be summarized for the FAS where subjects without post-treatment tumor assessment will be considered to have progressed. Median survival and 95% confidence interval will not be analyzed for the FAS, as these estimates will not differ from those for the EAS because censoring at time 0 is equivalent to excluding these subjects.

Additionally, PFS from current treatment versus PFS from previous treatment will be explored. The ratio of current treatment PFS in days / previous treatment PFS in days for each subject will be calculated. Summary statistics will be presented for EAS. It will also be summarized for EAS by current radiation treatment dose categories: <= median current radiation dose in Gray and > median current radiation dose in Gray. Highest dose of radiation treatment for each subject is used as defining the current radiation treatment dose categories. Subject's most recent previous treatment will be used for the derivation and calculation of PFS from previous treatment. Figures will also be generated to present the ratio by overall and by current treatment radiation dose categories.

3.5.3.4.2 BPI-SF

The following pain intensity and pain interference scores (Cleeland, 2009) will be summarized and listed:

- From the eCRF, pain intensity recorded as "Worst", "Least", and "Average" in the last week and pain intensity recorded as "Right now".
- Composite pain severity score (a mean severity score of the above four pain items)

- Composite pain interference score (a mean of the seven interference items). This will be calculated if at least four of the seven interference items have been completed on a given administration. Otherwise, the pain interference score will be considered missing.

For each subject, the worst observed score and the best observed score during the following periods will be summarized:

- Pre-Radiation Vaccination Period
- Radiation Therapy Period
- Post-Radiation Vaccination Period 1
- Post-Radiation Vaccination Period 2
- Overall Treatment Period

A score of 10 is the worst pain imaginable and a score of 0 is no pain. The worst score in each period is defined as the highest value within the period. The best score in each period is defined as the lowest value within the period.

Pain score category is defined for the “Worst” pain endpoint as 0 as no pain, 1-4 as mild pain, 5-6 as moderate pain and 7-10 as severe pain (Serlin, 1995).

For summary tables, the primary analysis will be performed on the EAS with additional analyses performed on the FAS. Continuous summary statistics will be provided for the worst observed score and the best observed score within each period for “Worst”, “Least”, “Average”, and “Right Now” pain intensities as well as composite pain severity and composite pain interference scores. Individual pain interference items will be included in subject-level listings and will be plotted.

To explore if there is a correlation between tumor response and pain score, continuous summary statistics will be provided for the worst score within each period for "Worst", "Least", "Average", and "Right now" pain intensities as well as composite pain severity and composite pain interference scores by best overall tumor response per mRECIST. Similarly, a summary table will be provided for the best score within each period by best overall tumor response. Mean score and 95% CI will also be plotted over time by visit and by best overall tumor response for each BPI-SF item.

Additionally, a separate table will be presented for the number of subjects with improvement in “Worst” pain item and continuous summary statistics of the duration of improvement by best overall tumor response. Improvement in ”Worst” pain item score is defined as a subject that has a reduction in pain score of 2 points from baseline and remains a reduction in pain score for at least 1 timepoint after the initial timepoint with pain reduction post-baseline (Cleeland, 2013). The duration of improvement is defined as the difference in weeks between the first timepoint of reduction in pain score of 2 points from baseline to the timepoint before an increase in pain of at least 2 points from the nadir value during the improvement time period. A Kaplan Meier figure will be provided for duration of improvement in the subset of subjects who experience pain improvement. The plot will be stratified by best overall response.

A separate table to summarize time to worsening in BPI-SF "Worst" pain item by best overall response will also be presented. A worsening in "Worst" pain item is defined as an increase in post-baseline pain score of at least 2 points and worsening in pain category among subjects who had no or mild pain at baseline and moderate or severe pain post-baseline or moderate pain at baseline and severe pain post-baseline. Time to worsening is defined the number of weeks in subjects who had at least a 2 point increase in pain and with no or mild pain at baseline to moderate or severe pain post-baseline or with moderate pain at baseline to moderate or severe pain post-baseline (Cleeland, 2013). A Kaplan Meier figure will be provided for the time to worsening in the subset of subjects who experience pain worsening and the figure will be plotted by best overall response.

To further explore the correlation between pain score and tumor response, worst observed BPI-SF scores by period and best observed BPI-SF scores will be summarized for subjects with any shrinkage in irradiated target lesions throughout the trial. Shrinkage in irradiated target lesions is defined as measurable lesions irradiated as part of trial treatment which decreased in length after baseline. Subjects are counted in the "Any shrinkage" category based on a decrease in the sum of the longest diameter of the irradiated target lesions of least a 5 mm . If there is no change, a decrease of less than 5 mm in the sum of the longest diameter of the irradiated target lesions or an increase in the sum of the longest diameter of the irradiated target lesions, subjects are counted in the "No shrinkage" category.

Shift tables of BPI-SF scores from baseline to worst observed values within each post-baseline periods and worst observed values in overall treatment period , and from baseline to best observed values within each post-baseline periods and best observed values in overall treatment period will also be presented by pain score categories for each BPI-SF item.

3.5.3.5 Exploratory Analyses

Analyses of exploratory endpoints will be based on the FAS where at least one baseline and one post-baseline assessment are available. Missing data will not be imputed. Analyses will focus on comparing the post-baseline values with the baseline value.

Exploratory Endpoints

Exploratory analyses based on standard RECIST 1.1, Choi Criteria, and Volumetric Criteria will not be performed. Due to specific radiographic image requirements for an evaluation and comparison by the independent radiological reviewer, the number of scans collected in the trial meeting these requirements are limited and will not be able to provide a meaningful comparison with the trial's primary and secondary efficacy endpoints.

Biomarkers

Samples for PBMC and serum will be collected at Screening/Baseline, Day 28, 2 weeks from end of radiation, and 6 weeks from end of radiation. Measurements from samples taken prior to first trial vaccination are referred to as baseline values.

Results from two ELISPOT tests will be analyzed: single peptide Brachyury-specific T cells and peptide pool Brachyury-specific T cells. Summary tables will be generated for the results for each test by visit and will also be listed. Along with observed results, ratio to baseline results will also be presented in the summary table for post-baseline visits. Geometric mean will be calculated by taking the antilogarithm of the mean of the $\log_{10}$ transformations. The detection limit (DL) is defined as 10. Results below the DL will be given a value of ½ of DL for the purpose of calculations. Descriptive statistics will be derived for all visits including number of observations, geometric mean, with 95% CI (derived based on the antilogarithm of the 95% CI of the $\log_{10}$ transformations constructed using the t-distribution), median, minimum and maximum. Geometric mean with 95% CI by visit will also be presented in a figure.

Additionally, ELISPOT results for each test will be summarized by best overall tumor response per mRECIST by visit to explore the correlation between tumor response and immune response. Descriptive statistics will be derived for all visits including number of observations, geometric mean, with 95% CI (derived based on the antilogarithm of the 95% CI of the $\log_{10}$ transformations constructed using the t-distribution).

3.5.4 Subject Disposition

All subjects screened and having signed informed consent will be accounted for. A summary table specifying the number and percentage of subjects ineligible following screening (and reasons), meeting all eligibility criteria, treated, completing the treatment period (pre-radiation vaccination period, radiation therapy period, post-radiation vaccination periods), discontinuing trial treatment early (and reasons), and not completing the post-treatment follow-up visit (and reasons) will be generated.

A listing will present all enrolled subjects, flag for analysis sets, date of completion or discontinuation, reason for discontinuation, last trial day (weeks), and last post-radiation therapy day (weeks). All subjects not eligible for the trial will be listed, including the reason why they were not eligible.

Subjects who are excluded from the EAS, flag for analysis sets (FAS and EAS) and reasons for exclusion will be listed. Other protocol deviations will also be provided in a subject level listing.

3.5.5 Demographics and Baseline Characteristics

3.5.5.1 Demographics and Baseline Characteristics Variables

<u>Demographics</u>

- Age

- Age Group (12 to <18, 18+)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, Native American or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Race Group (White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Baseline Characteristics

- Height (cm)
- Weight (kg)
- Body Mass Index (BMI; kg/m^2)
- HIV antibody (positive, negative)
- Hepatitis B surface antigen (positive, negative)
- Hepatitis C virus (positive, negative)

Baseline Disease Characteristics

- Eastern Cooperative Oncology Group (ECOG) Status (0, 1, 2)
- Disease duration at screening (years; date of diagnosis to date of informed consent)
- Original diagnosis
- Histological classification (classical, chondroid)
- Primary tumor site (clival, mobile spine, sacral)
- Disease status at diagnosis (localized, locally advanced, metastatic)
- Current disease status (localized, locally advanced, metastatic)
- Curative intervention (yes, no), duration of primary curative intervention, disease-free intervals, and time from recurrence after a disease-free interval, if applicable.
- Site of metastasis, if applicable

12-Lead Electrocardiogram (ECG) at Screening

- Investigator's overall interpretation (normal, abnormal)
- Investigator rated clinical significance (clinically significant, not clinically significant)

3.5.5.2 Demographics and Baseline Characteristics Analyses

Demographics and baseline characteristics will be summarized based on the FAS. An additional summary table will be generated based on the EAS.

Age is recorded at the time of screening and will be presented using continuous statistics.

BMI will be calculated as:

$$BMI = weight\ (kg) / [height\ (m)]^2$$

Baseline disease characteristics will be summarized using continuous statistics or percentages and frequencies, as appropriate.

Disease duration at baseline in years will be calculated as:

(Date of Informed Consent - Date of Initial Diagnosis + 1) / 365.25

If applicable, time from recurrence after a disease-free interval to first trial treatment in years will be calculated as

(Date of First Treatment - Date of Recurrence + 1) / 365.25

Note if either the initial diagnosis date or recurrence date are partial, they will be imputed based on the missing date rules in Section 3.4.1.

If dates are complete, duration of curative intervention and disease-free intervals will be calculated and will be included in subject-level listings only. Missing or partial dates will not be imputed.

Duration of curative intervention in months will be calculated as:

(End Date of Primary Curative Intervention - Start Date of Primary Curative Intervention + 1) / 30.4

Disease-free interval in months will be calculated as:

(Date of Recurrence - End Date of Primary Curative Intervention + 1) / 30.4

In addition, sites of metastasis will be included only in subject-level listings. Screening ECGs will also be listed.

3.5.5.3 Medical History

Relevant medical history will be summarized for the purpose of characterizing the trial population based on the FAS. Medical history terms will be coded by SOC and PT to the MedDRA version 21.0 or higher.

For medical histories, summaries by SOC and PT will count a subject once for each SOC, and once for each PT within an SOC. SOCs will be displayed in the order of descending frequency, and PTs will be displayed by descending frequency within SOC. Non-drug therapies performed prior to treatment will also be included in the summary table as an additional class “non-drug therapies/surgical procedures”. These therapies or procedures may not be coded by MedDRA and will be footnoted as such.

Ongoing medical diagnosis or surgical procedures will be flagged in the medical history subject-level listing.

3.5.6 Prior and Concomitant Therapies and Medications

3.5.6.1 Prior Cancer Treatments

All prior cancer treatments will be captured regardless of time relative to being screened for the trial.

The following detailed prior chordoma therapy information will be collected:

- Any prior systemic cancer therapy (yes, no)
- Number of regimens
- Reason for administration
- Therapeutic agent
- Duration of therapy
- Best response to therapy
- Reason for discontinuation
- Field of radiation, total dose of radiation if applicable

If applicable, therapeutic agents will be coded using the World Health Organization (WHO) Drug Dictionary B3 Global version March 2018 (or higher). Frequencies of subjects who received prior cancer treatment will be summarized by Anatomic-Therapeutic-Chemical (ATC) drug class and preferred drug name. Other detailed prior chordoma therapy information will be provided in subject-level listings.

3.5.6.2 Prior and Concomitant Medication

In this trial, all non-cancer treatment prior and concomitant medications taken in the 90 days prior to the screening visit will be captured. Prior medications are defined as those medications started prior to the date of first vaccination with trial product. Concomitant medications include those that are started prior to first vaccination and are ongoing at the time of first vaccination, or those that start after first vaccination. Medications can be classified as both prior and concomitant.

Other cancer therapies started after trial treatment (if allowed per protocol) will be captured on the concomitant medications page.

All prior and concomitant medications will be coded using the WHO Drug Dictionary B3 Global version March 2018 (or higher).

The incidence of prior and concomitant medication usage will be summarized separately by ATC drug class and preferred drug name, sorted by descending incidence of drug class and descending incidence of preferred drug names within drug class. A separate table will summarize prior and concomitant medication separately by preferred drug name sorted by descending frequency.

3.5.6.3 Non-Drug Therapies

Non-drug therapies taking place after the start of treatment will be coded to MedDRA version 21.0 or higher SOCs and PTs. These will be summarized separately from the medications and will be sorted by descending frequency of SOC, and then PT within SOC.

3.5.7 Treatment Exposure and Compliance

MVA-BN-Brachyury will be given subcutaneously (SC) for one dose each on Day 0 and Day 14. One dose = four 0.5 mL injections for a total dose of at least 5 x 10^7 Inf.U.

FPV-Brachyury will be given SC on Day 28 visit, then every 4 weeks for 4 doses (End of Radiation + 2, 6, 10, and 14 weeks), then given every 12 weeks (End of Radiation +26, 38, 50, 62, 74, 86, 98, and 110 weeks). One dose = one 0.5 mL injection with a nominal titer of 1 x 10^9 Inf.U per 0.5 mL.

All summaries of treatment exposure will be based on the FAS. The total number of MVA-BN-Brachyury injections will be summarized categorically as 0 - < 4, 4 - < 8, 8, and > 8. The total number of FPV-Brachyury doses will be summarized numerically and categorically as 0 - < 4, 4 - < 8, 8-12, and > 12. Total duration of exposure in weeks is defined as (date of last trial vaccination - date of first trial vaccination + 1) / 7. Duration of exposure will be summarized descriptively.

For radiation therapy, the percentage of subjects with different numbers of target lesions treated and non-target lesions treated (e.g., 1, 2, 3, 4 etc.) will be summarized separately. Summaries for radiation type (external beam, intensity-modulated radiation therapy [IMRT], photon beam, proton beam, stereotactic radiosurgery [SRS]), total radiation dose (Gy), and total number of fractions delivered will be summarized based on N = total number of target lesions treated or N = total number of non-target lesions treated.

All exposure data will also be provided in subject-level listings.

3.5.8 Safety Analyses

All safety analyses will be based on the FAS.

3.5.8.1 Safety Variables

<u>TEAEs</u>

TEAEs to be analyzed include Grade 3 (Severe) or above TEAEs, related TEAEs, and TEAEs that lead to discontinuation of trial product.

SAEs

AESIs (immune-mediated AE)

Injection site reactions events

Immunotherapy Toxicity Events (Tsimberidou et al., 2018)

Physical Examinations

Physical examinations or targeted physical examinations will be performed at screening and every visit during the trial. Any findings occurring after the signing of informed consent will be reported as baseline signs and symptoms on the AE form, and any findings discovered after start of trial treatment through the end of the trial will be reported as adverse events.

Neurological Assessment

- Type of examination (cranial nerve, motor, sensory, cerebellar, deep tendon reflex)
- Examination result (normal, abnormal)

Vital Signs

- Body temperature (°C)
- Pulse (beats/minute)
- Respiratory rate (breaths/minute)
- Blood pressure (mmHg)

Safety Laboratory Data

- Serum chemistry: Albumin, alkaline phosphatase, total bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, creatinine, blood urea nitrogen (BUN), calcium, phosphorus, bicarbonate, chloride, potassium, glucose, sodium, magnesium, free T3 and T4 (only if clinically indicated), and thyroid stimulating hormone (at screening and post baseline only if clinically indicated)
- Hematology: Hemoglobin, hematocrit, red blood cell (erythrocyte) count, total white blood cell (leukocyte) count, mean corpuscular/cell volume, mean corpuscular/cellular hemoglobin, red blood cell distribution width, platelet count, and differentials
- Anti-nuclear antibodies (ANA)

3.5.8.2 Adverse Events

All AEs observed by the investigator and/or reported by the subject will be recorded in the eCRF regardless of the assessment of relationship to the trial treatment. Verbatim descriptions of AEs will be mapped to MedDRA version 21.0 (or higher) and graded for severity per NCI-CTCAE, Version 4.0 or higher.

A TEAE is an adverse event that presents itself during or following initiation of trial treatment or worsens in severity after the initiation of trial treatment (Refer to General Definitions for details). The algorithm for the assignment of AEs as treatment emergent in the case of missing data can be found in Section 3.4.1. Non-TEAEs, including baseline signs and symptoms, will not be included in the table summary but will be flagged in the subject-level listings. TEAEs will be further assigned to the following treatment periods: Pre-radiation Vaccination Period, Radiation Therapy Period, Post-Radiation Vaccination Period 1 and Post-Radiation Vaccination Period 2.

All TEAEs will be summarized overall and by treatment periods, SOC, and PT, sorted by descending frequency. For each specific TEAE a subject will be counted only once within an SOC and PT. Also, two separate tables will summarize TEAEs by treatment period (including the overall treatment period), with the first table summarized further by PT sorted by descending frequency of PT, and the second table summarized further by SOC and High-Level Term (HLT), sorted by descending frequency of HLT. Similar summaries will be provided for all Grade 3 or above TEAEs, related TEAEs, Grade 3 or above related TEAEs, SAEs, related SAEs, AEs that lead to discontinuation of any trial product (MVA-BN-Brachyury, FPV-Brachyury, and Radiation), TEAEs leading to death, and non-serious TEAEs occurring at a frequency ≥5% any treatment group.

A separate table will summarize AEs related to MVA-BN-Brachyury or FPV-Brachyury, and AEs related to radiation therapy for the overall treatment period by SOC and PT.

Additional summaries by severity based on NCI-CTCAE grade in which a subject is presented at the maximum severity within the SOC, and PT categories will also be generated. Similarly, summaries based on causality will be created where a subject is counted at their maximum causality for each SOC and PT experienced. These additional summaries will be presented for the overall treatment period and sorted by descending frequency of SOC and PT (regardless severity or causality level).

AESIs are flagged on the general AE eCRF page, with additional information on the event of interest collected on an additional AESI/SAE-specific page. AESIs will be summarized overall and by treatment period and by SOC and PT sorted by descending frequency.

Injection site reaction AEs will be summarized by selecting AEs that have injection site reactions indicated as the AE high level term. Summary tables will be created overall and by treatment period, and by PT sorted by descending frequency.

Additionally, an immunotherapy toxicity table will be created by PT. It will include frequency summaries for treatment delay, treatment discontinuation, required hospitalization, death, complete resolution, incomplete resolution, high-dose steroids use and use of additional immune-suppressing agents. Summary statistics (median, minimum and maximum) will also be included for trial day of onset of the event and trial day of event resolution (Tsimberidou et al., 2018). All AEs will be included in the subject-level listings. Separate listings of SAEs, AESIs, AEs leading to death and AEs leading to discontinuation of any trial treatment will also be presented.

3.5.8.3 Laboratory Data

Laboratory toxicities will be defined based on local lab normal ranges and NCI-CTCAE, Version 4.03 or higher. The number and percentage of subjects will be summarized by grade, using the most severe grade over the treatment periods (Pre-Radiation Vaccination Period, Radiation Therapy Period, Post-Radiation Vaccination Period 1 and Post-Radiation Vaccination Period 2). For lab parameters with both higher than normal and lower than normal severity grades, each finding will be treated as a different lab parameter. Shift from baseline to worst grade will also be summarized by treatment periods. For labs not covered by NCI-CTCAE, data will be summarized by High or Low based on normal lab ranges.

In addition, laboratory values will be listed, with out of range and NCI-CTCAE Grade 3/4 values flagged. For women of child-bearing potential, pregnancy test results will be presented in a listing.

3.5.8.4 Vital Signs

Mean and standard deviation intervals for each vital sign will be plotted over time. A listing of vital signs will also be provided. If any abnormal trend is identified, further analyses will be performed.

3.6 Timing of Analyses

The first post-treatment (vaccination plus radiation therapy) imaging assessment for the OR endpoint by the investigator will occur approximately 14 weeks after completion of radiation therapy. The analysis at the end of stage 1 to make a go versus no-go decision by the BN team will occur when the first 10 subjects accrued have completed at least two post-baseline CT or MRI scans for tumor assessment or the minimum threshold for stage 2 enrollment (at least 1 OR in the first 10 subjects) has occurred. For subjects who have completed multiple scans, the best OR within 12 months after radiation therapy will be used. If at least one OR is observed prior to the end of stage 1 analysis, enrollment of stage 2 subjects will continue regardless of the timing of the end of stage 1 analysis.

A Data and Safety Monitoring Board (DSMB) will oversee the safety of subjects participating in the trial. The primary responsibility of the DSMB is to review and evaluate the accumulated trial data for safety, trial conduct, and the integrity of the trial. Tumor response data will also be

provided to the DSMB for benefit-risk assessment and for confirmation of tumor response. The DSMB may recommend to temporarily halt or terminate the trial based on safety information.

Stage 2 OR assessments will be reviewed continuously, once all subjects accrued have completed at least two post-baseline CT or MRI scans for tumor assessment. Because ORR may increase with further follow up, ORs will be followed until all subjects have reached the 12 months post-radiation time point or progressed. For subjects who have completed multiple scans, the best OR within 12 months after radiation therapy will be used.

Final analysis will occur when all of the subjects accrued have either completed the 2-year treatment period or have progressed.

4 Changes from Planned Analyses

Due to a few early ORs in stage 2 of the trial, a formal analysis of stage 2 results was not performed after the first two post-radiation scans for all subjects. Continual review of the responses is ongoing, and the formal analysis will be performed, at the earliest, after all subjects have completed 12 months of post-radiation therapy or progressed.

Analyses of exploratory efficacy endpoints based on Volumetric Criteria, Choi Criteria and standard RECIST 1.1 will not be performed for the final CSR. Reasons for not performing the analyses are listed in Section 3.5.3.5.

5 References

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6 Appendices

6.1 Appendix 1: Trial Procedure Schedule

	Screening/ Baseline	Day 0	Day 14	Day 28	Day 42-70 (approximate)	End Radiation[11] + 2 weeks	End Radiation + 6 weeks	End Radiation + 10 weeks	End Radiation + 14 weeks	End Radiation + 26 weeks	End Radiation + 38, 50, 62, 74, 86, 98, 110 weeks[12]	Post-treatment follow-up +30 days after last Treatment Visit
Visit Window			±2 days	±2 days		+7days	-4/+7days	-4/+7days	-4/+7days	±2 weeks	±2 weeks	±2 days
History and physical examination[1]	X											X
Medical assessments[2]	X	X	X	X	X	X	X	X	X	X	X	X
Serum HIV antibody[3]	X											
Serum hepatitis B & C[4]	X											
CBC with differential, platelet count	X		X	X	X	X	X	X	X	X	X	X
Chemistry[5]	X		X	X			X	X	X	X	X	X
Beta-HCG[6]	X		X	X	X	X	X	X	X	X	X	
TBNK	X			X		X	X					
ECG	X											
CT and MRI[7]	X								X	X	X	X
Correlative biomarker studies (blood)[8]	X			X		X	X					
Pulse oximetry	X											
MVA-BN-Brachyury		X	X									
FPV-Brachyury				X		X	X	X	X	X	X	
Radiotherapy[9]					X							
RECIST-basedAssessment[10]	X								X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
BPI-SF		X	X	X	X	X	X	X	X	X	X	X

[1]Baseline: History and physical and laboratory studies should be completed within 16 days of initiating treatment. Baseline radiographic and immunologic studies should be obtained within 28 days of initiating treatment. History and physical includes all components of medical assessments. Special attention should be paid to any history of vaccine allergies.

[2]Medical assessments include a complete neurologic examination including documentation of cranial nerve, motor, sensory, cerebellar, and deep tendon reflex examinations; interim history (since last visit); vital signs; physical

examination (at baseline); targeted physical exam (Day 0-28, End of Radiation +2-+110 weeks, and Post-treatment follow up visits) and ECOG performance status. To be performed within 3 days prior of each dose of vaccine. Repeat medical assessment is not required at baseline if history and physical has been performed within 3 days of vaccine administration on day 0.

[3]Serum HIV antibody should be completed within 6 months of initiating treatment.

[4]Serum hepatitis B & C antibody should be completed within 6 months of initiating treatment.

[5]Chemistry panel: Na+, K+, Cl–, CO2, glucose, Blood Urea Nitrogen (BUN), creatinine, albumin, alkaline phosphatase, ALT, AST, total bilirubin, thyroid stimulating hormone, calcium, and ANA to be performed within 16 days prior to screening/ baseline per protocol. TSH is optional after screening visit.

[6]In females of child-bearing potential, Beta-HCG to be done at baseline 48 hours prior to treatment and within 48 hours of any dose of vaccine or radiation.

[7]CT chest, abdomen, and pelvis and MRI (if target lesion is best visualized by MRI)

[8]Correlative biomarker studies (blood): 6 (10 mL) green top sodium heparin tubes for PBMC; 1 (8.5 mL) SST tubes for serum samples.

[9]Radiotherapy schedule and dose selected by treating radiation oncologist. Radiotherapy will begin at least 2 weeks and ideally not more than 4 weeks after first administration of FPV-Brachyury (Dose 3).

[10] RECIST based assessment includes using RECIST principles (refer to trial protocol Section 10.5 for the description of RECIST principles for the trial) to measure the “target” lesions, defined as those meeting RECIST requirements for measurability and those that will be treated with radiation as defined by minimum requirements of the protocol. “Non-target” lesions may include those that are not measurable by RECIST or those that are measurable and not treated with radiotherapy at the dose required by protocol

[11]Time noted is from end of radiation or until resolution of AEs related to radiation, whichever is later

[12]Vaccine doses will be administered in 12-week intervals through approximately 2 years of post-radiation treatment.

6.2 Appendix 2: Tables, Listings, and Figures Specifications

Mock tables, listings, and figures to support the clinical report will be specified in an additional document.